OPILL (NORGESTREL 0.075 MG TABLETS) FOR RX-TO-OTC SWITCH

SPONSOR BRIEFING DOCUMENT

JOINT MEETING OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND THE OBSTETRICS, REPRODUCTIVE, AND UROLOGIC DRUGS ADVISORY COMMITTEE

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List of Abbreviations

Abbreviation	Definition
AAFP	American Academy of Family Physicians
AAPCC	American Association of Poison Control Centers
ACCESS	Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use
ACOG	American College of Obstetricians and Gynecologists
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AMA	American Medical Association
AMI	acute myocardial infarction
AUT	actual use trial
BC	breast cancer
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIL	consumer information leaflet
COC	combined oral contraceptive
COVID-19	Coronavirus Disease 2019
CT	Computed tomography
DFL	drug facts label
DHHS	Department of Health and Human Services
DVT	deep vein thrombosis
EC	emergency contraception
e-diary	electronic diary
EOS	end of study
ER	emergency room
FDA	Food and Drug Administration
HCP	healthcare practitioner
HIV	human immunodeficiency virus
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
LCS	label comprehension study
MEC	Medical Eligibility Criteria for Contraceptive Use
NASPAG	North American Society for Pediatric and Adolescent Gynecology
NDA	New Drug Application

Abbreviation	Definition
NHANES	National Health and Nutrition Examination Survey
NSFG	National Survey of Family Growth
OB/GYN	Obstetrician and Gynecologist
OC	oral contraceptive
ODPHP	Office of Disease Prevention and Health Promotion
OTC	over-the-counter
POC	progestin-only contraceptive
POP	progestin-only oral contraceptive pill
PT	Preferred Term
RCA	root cause analysis
RCT	randomized controlled clinical trial
REALM	Rapid Estimate of Adult Literacy in Medicine
REALM-teen	Rapid Estimate of Adolescent Literacy in Medicine
Rx	prescription
Rx-to-OTC	prescription to over-the-counter
SAE	serious adverse event
SAHM	Society for Adolescent Health and Medicine
sNDA	supplemental New Drug Application
SOC	System Organ Class
SPR	Selected Practice Recommendations for Contraceptive Use
SSS	self-selection study
STI	sexually transmitted infection
TE	thromboembolism
US	United States
USAID	United States Agency for International Development
VTE	venous thromboembolism
WHO	World Health Organization

This document begins with an executive summary of key information, followed by a detailed review of the need for nonprescription oral contraceptives, background information on Opill Rx-to-OTC switch, key studies relevant to this switch, assessment of the self-selection and actual use in consumer studies (including assessment of the impact of not heeding the label instructions), overview of safety in the main clinical study conducted in this program (the ACCESS study), and finally assessment of the incremental benefit and risk of switching Opill to OTC.

We recognize that not all people who can become pregnant use the term "women". The term is used in this document to reflect the Sponsor's study participants and how they are generally described in the published literature.

1 EXECUTIVE SUMMARY

1.1 Introduction

HRA Pharma (HRA), a Perrigo company, is requesting a switch from prescription (Rx) to nonprescription (over-the-counter [OTC]) availability for Opill (norgestrel 0.075 mg tablets), a daily progestin-only oral contraceptive pill (POP). Opill was first approved for prescription use in the United States (US) in 1973 and marketed by Pfizer as the Rx product Ovrette® for more than 30 years. Marketing of Ovrette was discontinued in 2005 solely for business reasons (i.e., not safety or efficacy reasons). HRA acquired the rights to Opill in 2015 with the intent to generate the data necessary to support a full Rx-to-OTC switch application to market Opill as an OTC drug. See Section 3.2 for more information about the product.

Women, even those who want children at some point in their life, spend most of their reproductive life trying to avoid pregnancy (Sonfield et al 2014). However, women in the US face unnecessary burdens in accessing effective contraception. The contraceptive options currently available to women without a prescription are limited to methods which are less effective than alternatives available with a prescription. Opill is a more effective option than all current nonprescription contraceptives, and thus, improved access to Opill as an OTC drug has the potential to reduce unintended pregnancies in the US. As a POP, Opill does not contain estrogen and is generally considered safe (ACOG 2019), making it appropriate for a broader population of women.

As per Food and Drug Administration (FDA) regulation, to be nonprescription, a drug must be safe and effective for use without the supervision of a healthcare practitioner (HCP). In addition, the condition to be treated must be self-diagnosable and OTC products must be adequately labeled such that consumer can self-diagnose, self-treat, and self-manage the condition; the drug must have a low potential for misuse and abuse; and the benefits of OTC availability must outweigh the risks.

HRA has conducted an extensive, iterative label development program to develop OTC labeling that guides women in the safe and effective use of Opill. As described throughout this Briefing Document, data from the comprehensive development program demonstrate that using the label, women of all reproductive ages can both appropriately select Opill for their own use and use Opill safely and effectively without the supervision of an HCP. Importantly, for the context of the Rx-to-OTC switch, HRA carefully assessed the potential

incremental benefits of consumers using Opill as guided by the OTC labeling, as well as the potential incremental risks.

1.2 Need for Nonprescription Oral Contraceptives

Unintended pregnancies occur in women of all ages and all racial, ethnic, and socioeconomic backgrounds (Finer and Zolna 2016). In the US, even with a wide range of available contraceptive methods:

- 45% of the 6.1 million pregnancies annually in the US are unintended (Finer and Zolna 2016)
- 72% of pregnancies occurring in adolescents are unintended (Finer and Zolna 2016)
- More than 50% of all women will have experienced an unintended pregnancy by age 45 (Sonfield et al 2014)

Unintended pregnancies have been linked to a number of negative maternal and perinatal clinical outcomes, such as premature delivery and low birth weight, as well as an increased risk of lower educational and economic attainment in women and children (Cheng et al 2009; Dibaba et al 2013; Gipson et al 2008; Kost and Lindberg 2015; Lindberg et al 2015; Sonfield et al 2014). These risks are in addition to those inherent with any pregnancy, including maternal death. While most adolescents are not sexually active, those who are need access to effective contraception as the consequences of an unintended pregnancy may have life-long consequences. For example, only approximately 50% of teen mothers receive a high school diploma by 22 years of age (Perper et al 2010).

The significance of these consequences is reflected in the US Department of Health and Human Services' (DHHS) Healthy People 2030 initiative, which includes improving pregnancy planning and preventing unintended pregnancies in the US as one of their overall goals (ODPHP 2021). Specific objectives include reducing the proportion of pregnancies that are unintended, reducing pregnancies in adolescents, and increasing the proportion of women and adolescent females at risk for unintended pregnancy who use effective birth control.[1] Clearly, access to effective contraception is key to achieving these goals.

Contraceptive methods can be categorized based on their failure rates (Figure 1). Oral contraceptives (OCs) are classified as "moderately" effective, with a typical use failure rate of OCs (failure rate in real world use), estimated at 7% in the Rx setting, meaning that it is estimated that 7% of women will experience an unintended pregnancy during the first year of typical use (Trussell et al 2018).

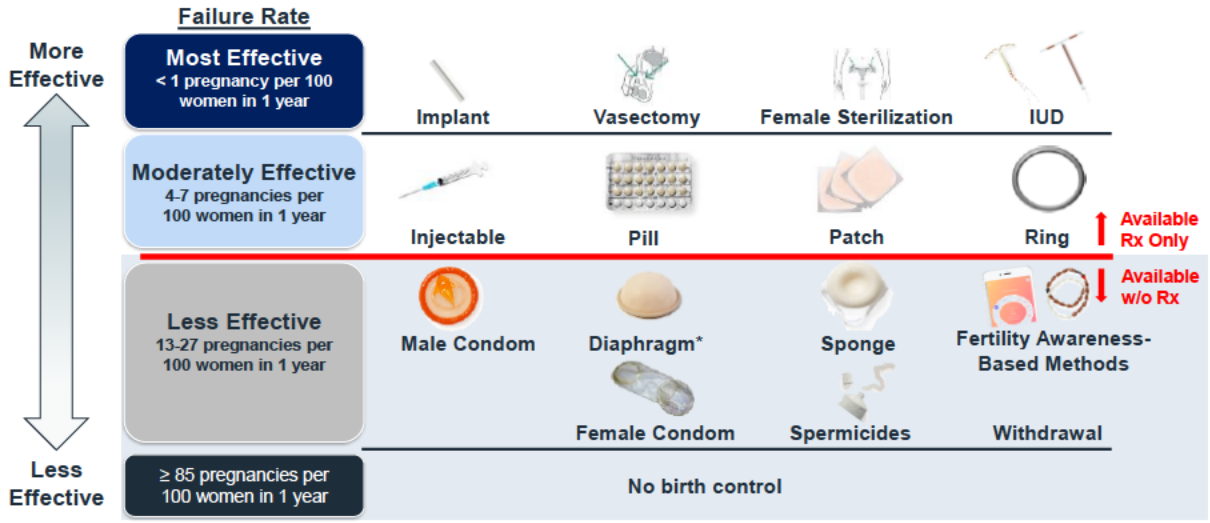
In the US, only those contraceptive methods categorized as "less" effective are available without a prescription, while the "moderately" and "most" effective contraceptive methods are only available by prescription. Most of the "less" effective methods require correct

[1] US DHHS provides the following specific detail around the objectives pertaining to increasing the use of effective birth control: Increase the proportion of women [and adolescents] at risk of unintended pregnancy who use most effective or moderately effective methods of contraception.

action at the time of every act of intercourse and may require experience and/or training for effective use. Additionally, male condoms, withdrawal, and fertility awareness-based methods require the active involvement of the woman's partner, and, in most cases, do not allow for discreet use by the woman.

Based on an analysis of data from the 2017-2019 National Survey of Family Growth (NSFG), approximately 40% of US women at risk for unintended pregnancy report current use of a "less" effective contraceptive method or no method at all (Pinney Associates 2022). For many women, access to effective contraceptives is limited by barriers such as lack of insurance and/or regular medical provider, difficulty taking time off work or school to get to an appointment, and transportation issues (Baum et al 2016; Biggs et al 2012; Foster et al 2012; Frederiksen et al 2022; Grindlay and Grossman 2016).

Figure 1: Effectiveness of Contraceptives Available With and Without Prescription in the US



IUD: intrauterine device; IUS: intrauterine system; OTC: over-the-counter; Rx: prescription; w/o: without
* Diaphragms require a prescription but are recommended to be used with spermicides, most of which are available OTC.
Failure rates displayed are for typical use failure rates for first year of use, from Trussell et al 2018.
Source: Adapted from Trussell et al 2018.

While adolescents make up a small proportion of those at risk of unintended pregnancy in the US (Pinney Associates 2022)[2], their need for increased access to effective contraceptives is particularly urgent. Currently, adolescents face the most significant barriers to accessing the more effective methods (Baum et al 2016; Biggs et al 2012; Foster et al 2012; Fuentes et al 2018). While very few young female adolescents have ever had sexual intercourse[3] (Finer and Philbin, 2013), by the age of 17, more than 50% are sexually active (Lindberg et al 2021). There were approximately 88,000 pregnancies in 2017 (Maddow-Zimet and Kost 2021) and approximately 37,000 births in 2021 (Hamilton et

[2] ~5% (4.9%) of those aged 15-49 at risk of unintended pregnancy in the US are aged 15-17, ~11% (10.9%) are aged 15-19 (National Survey of Family Growth 2017-2019, Pinney Associates 2022).
[3] 1.3% of females by age 12, 3.4% by age 13, and 8.6% by age 14 have had sex (Finer and Philbin 2013).

al 2022) in adolescents 17 and younger, while in 2015-2019, 29.7% of first births to US females occurred during the teenage years (≤ age 19) (Maddow-Zimet and Kost 2021). Pregnancies in adolescents result in significant individual and societal costs (Hoffman 2006; Perper et al 2010). For all these reasons, reducing pregnancies in adolescents and increasing their use of effective contraception are national health priorities (ODPHP 2021).

Key professional medical organizations in the US strongly support OTC availability of OCs (AAFP 2019; ACOG 2019; AMA 2022; NASPAG 2022; SAHM 2022), and most support OTC access to hormonal contraception without age restrictions (ACOG 2019; AMA 2022; NASPAG 2022; SAHM 2022). OTC availability of an OC, a more effective option than any method now available without an HCP interaction, has the potential to result in substantially improved individual clinical and public health outcomes. With their well-established safety profile and limited contraindications, a POP is an appropriate candidate for OTC availability.

1.3 OTC Label Development Process

The proposed OTC label includes the Drug Facts Label (DFL), as well as a Consumer Information Leaflet (CIL) and a Reminder Card to further support consumers in adhering to key label directions (see Section 3.3.2 and Appendix Section 11.1). The DFL uses a highly standardized and tightly regulated format established by the FDA that is the basis for all OTC drug labels (see Figure 12).

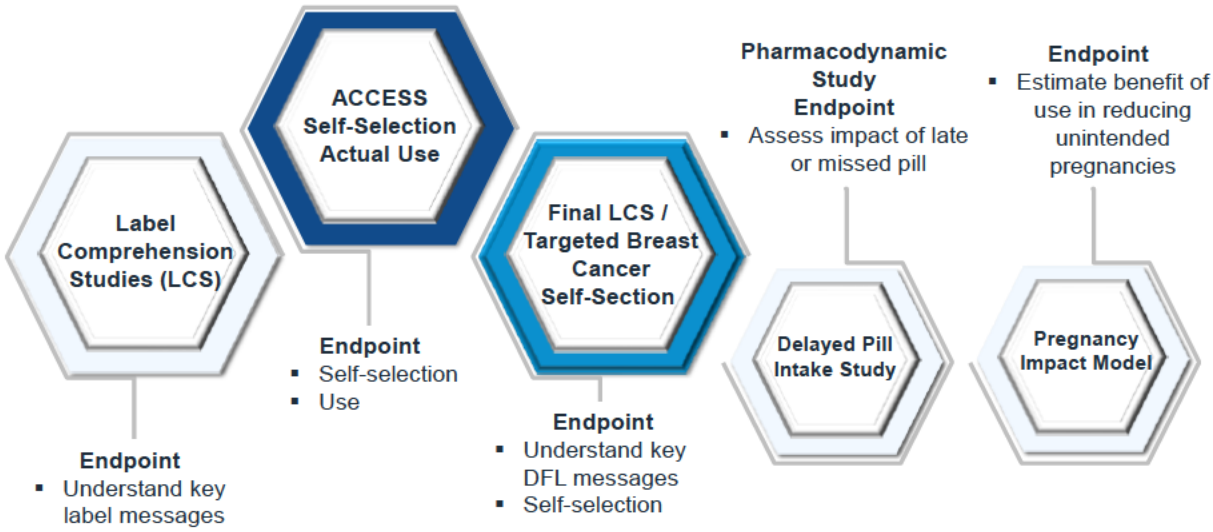
HRA developed the Opill OTC labeling through an extensive, iterative process, starting with adapting the approved Opill Rx labeling (Opill Rx labeling) into consumer-friendly language while considering relevant OTC regulatory requirements as well as national medical guidance [e.g., the Centers for Disease Control and Prevention (CDC) Selected Practice Recommendations for Contraceptive Use (SPR) (Curtis et al 2016a) and the CDC Medical Eligibility Criteria for Contraceptive Use (MEC) (Curtis et al 2016b)].

The proposed OTC labeling was tested over the course of a seven-year development program that comprised 14 consumer studies. Feedback from the FDA was incorporated throughout the development program in both the design of studies and content of the labeling.

To evaluate the labeling and consumers' use of the product, the clinical development program included studies assessing label comprehension, self-selection, and actual use (Figure 2). These studies were designed to answer key questions:

- Do consumers understand messages in the DFL? (Label Comprehension Studies [LCSs])
- Does the DFL appropriately guide consumers as they decide if a product is appropriate for them? (Self-Selection Studies [SSSs])
- Do consumers use a product correctly as guided by labeling without involvement of an HCP? (Actual Use Trials [AUTs])

Figure 2: Opill OTC Development Program



DFL: drug facts label; LCS: label comprehension study

See Section 4.1 for more information about the consumer studies typically done to support an Rx-to-OTC switch application.

The initial drafts of the Opill OTC labeling were assessed in and refined during several rounds of testing with consumers in LCSs. These studies demonstrated that the proposed DFL and key CIL messages were well understood.

Following the core labeling comprehension studies, two main consumer studies assessed the performance of the proposed Opill OTC labeling:

- The SSS / AUT 'Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use' (ACCESS) study evaluated whether consumers could correctly identify if Opill is right for them and if they could use it correctly based on the label, particularly how well they would follow the dosing instructions.
- The Final Label Comprehension Study / Targeted Breast Cancer Self-Selection Study (Final LCS/Targeted BC SSS) tested the comprehension of the final DFL in the general population as well as assessed, among the specific group of women with a history of breast cancer, whether they could appropriately determine that Opill was not right for them to use.

Overall, these studies demonstrated that consumers can:

- understand the key label messages,
- determine if Opill is right for them to use, and
- use Opill correctly based on the information on the label.

The development program also included the Delayed Pill Intake Study, a pharmacodynamic study which demonstrated that Opill-induced changes in cervical mucus and ovulation are maintained even if a pill is taken late or missed. A Pregnancy Impact Model was also developed which estimated the significant potential benefit of use of OTC Opill in reducing unintended pregnancies (Guillard et al 2023).

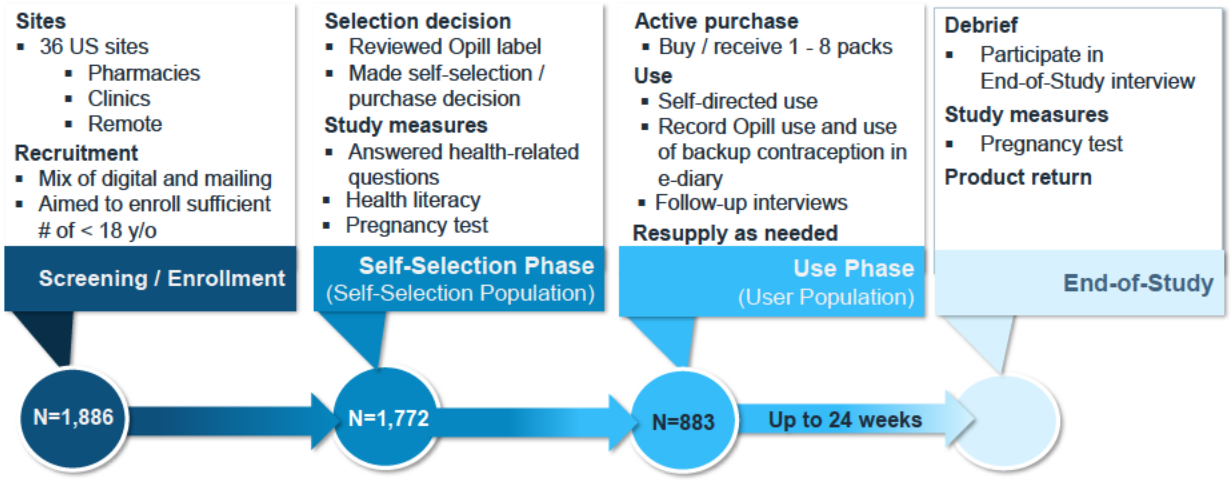
1.4 Key Results of the Opill Rx-to-OTC Switch Program: Self-Selection and Actual Use

ACCESS evaluated the ability of consumers to use the label to appropriately self-select (i.e., determine if Opill was right for them to use based on their own medical status) and use Opill according to the label in simulated OTC conditions.

Individuals interested in an OTC OC were recruited primarily via digital and print advertisements and enrolled at one of 36 sites in the US (N=1,886). To ensure adolescents can use Opill in the OTC setting, efforts were made to meet enrollment goals for participants under 18 years old that had been agreed on with FDA. The study population also included a robust subgroup of participants with low health literacy (determined by their score on the standardized Rapid Estimate of Adult Literacy in Medicine [REALM] or Rapid Estimate of Adolescent Literacy in Medicine [REALM-Teen]).

The ACCESS study design is illustrated in Figure 3 and fully described in Section 4.2.

Figure 3: ACCESS Study Design



US: United States; y/o: years old
Note: follow-up interviews at weeks 2, 4, 8, 12, 16, 20, and 24; Opill packs could be purchased throughout the Use Phase

The ACCESS study measured how well consumers followed the label directions. Pre-specified performance thresholds for the primary endpoints were determined based on an assessment of the potential clinical consequences if a consumer failed to follow the relevant label directions.

In the Self-Selection Phase, participants first reviewed the OTC labeling and were asked to decide whether Opill was right for them to use, per the label, and whether they would

purchase it for their own use (referred to as the selection decision). After making their selection decision, participants were asked a series of health and medical history questions to evaluate whether use of Opill was appropriate for them based on the proposed OTC label. Participants were also asked to complete a pregnancy test to confirm their pregnancy status, the result of which was not known until after participants made the selection decision. All participants who made a selection decision and provided answers to the relevant medical history questions were included in the Self-Selection Population (N=1,772).

For the Use Phase of ACCESS, eligible participants who selected Opill as appropriate for their own use were given the opportunity to purchase, paying out-of-pocket for Opill at study pharmacy sites to mimic an OTC environment. Participants with a history that included one of the “Do not use” conditions were not permitted to continue into the Use Phase of the trial. Participants meeting “Ask a doctor before use” conditions were not excluded from the Use Phase of the study.

Participants were reimbursed for the drug cost at the end of the study but were not aware of this at the time of initial or subsequent purchases. Some participants aged 17 and younger were enrolled at clinic sites (N=29) or remotely (N=99, enrolled during the Coronavirus Disease 2019 [COVID-19] pandemic) and were provided study drug for free. Participants obtaining Opill took the product home with them and were able to use it for up to 24 weeks (i.e., the Use Phase). The Opill package included the outer package with the DFL, a blister pack of 28 Opill tablets, the CIL, and the Reminder Card. Participants could obtain additional packs of Opill during the 24-week Use Phase. Participants were asked to record their use or non-use of the product daily in an electronic diary (e-diary), which served as the foundation of the adherence behavioral assessments. Participants also received interim telephone interviews during which a trained nurse asked pre-defined, non-leading questions about certain elements of use, followed-up on e-diary reporting, and solicited information to identify possible adverse events (AEs). These interim interviews intentionally avoided asking participants directly about whether they had complied with specific messages on the OTC labeling, so that subsequent behavior would remain unbiased.

A final, end-of-study (EOS) telephone interview was conducted at the end of the Use Phase, or when a participant elected to discontinue use of the product entirely and had no intention to restart, or when a participant withdrew from the study. At this interview, participants were asked direct questions about product use behaviors such as talking to an HCP or stopping the product as directed in labeling in response to certain events they experienced. Those participants who recorded using the product at least one time in their e-diary were included in the User Population and evaluated in use-related endpoints (N=883).

1.4.1 Self-Selection

Overall, the 1,772 participants in the ACCESS Self-Selection Population included a wide range of ages, levels of educational attainment, income levels, and racial and ethnic

diversity (Table 1). Subpopulations of special interest (adolescents and individuals with low health literacy) were well represented. Of note, participants under 18 years of age were purposely over-recruited to ensure an adequate sample size for analysis and therefore are over-represented in the study population versus the general population of US women 15–49 years of age at risk for unintended pregnancy.

Table 1: ACCESS Self-Selection Population

	Self-Selection Population (N = 1,772)	
	n	%
Age (years) – Mean [Range]	26.2 [12 – 68]	
Males	7	0.4%
Females	1,765	99.6%
Female 12-14	88	5%
Female 15-17	275	16%
Female 18-19	133	8%
Female 20-24	412	23%
Female 25-34	518	29%
Female 35+	339	19%
Low Health Literacy[1]	226	13%
Race[2]		
White	1,057	60%
Black or African American	534	30%
Asian	106	6%
American Indian or Alaska Native	53	3%
Native Hawaiian or other Pacific Islander	25	1%
Other	105	6%
Hispanic Ethnicity	306	17%

1 Scored ≤ 60 on the Rapid Estimate of Adult Literacy in Medicine (REALM) Test or Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) Test
2 Answers below are not mutually exclusive

To evaluate self-selection, each participant was classified on two variables: first, whether they selected to use the product, and second, whether they were appropriate to use the product.

Participants were classified regarding their selection decision based on responses to two questions:

> #1. Self-Selection Question*: "Given what you have read on the label and your own health history, is this product okay or not okay for you to take home today and start to use? Why/why not?"*
>
> #2. Purchase Question*: "Would you like to purchase Opill today to take home for your own use? Why/why not?"*

Both questions are important to understanding a consumer's selection of the product. While the Self-Selection Question is intended to ask a participant to apply the label information to their personal situation, in many cases participants interpret it as a question about the *general* appeal of the product. In these cases, responses to the Purchase Question are often very informative because it requires a more focused decision and

analysis by the participant regarding whether they would actually use the product. Verbatim responses to both the Self-Selection Question and Purchase Question were reviewed to classify participants as a Selector or Non-selector.

The second variable, appropriateness to use, was based on participant's responses to a series of scripted questions aimed at understanding whether any of the DFL messages of interest from the "Do Not Use" and "Ask a doctor before use" sections of the proposed DFL applied to them, namely,

> Do not use: if you have ever had any cancer, if you are already pregnant or think you may be pregnant, if you are allergic to any of the ingredients in Opill and if you are male.
>
> Ask a doctor before use if you have unexplained vaginal bleeding between periods or liver problems.

In addition to these label statements, as the product is intended to prevent pregnancy, participants had to report that they were physically able to become pregnant to be considered appropriate to use.

The risks associated with Opill OTC availability are determined not only by whether a consumer elects to purchase and use the drug contrary to DFL warnings, but also by what the actual clinical risks are for that specific consumer. To better understand this potential risk, a panel of three independent obstetrician/gynecologists (OB/GYNs) evaluated the casebooks of each of the participants who selected to use the product but who were classified as not appropriate to use per the label. The panel determined whether it was clinically acceptable for the participant to have used Opill (i.e., whether they would have prescribed it if requested). Their determination was factored into the analysis of appropriateness to use in ACCESS.

The selection and appropriateness to use classifications of participants can be visualized in a 2×2 table, as shown in Figure 4.

Figure 4: ACCESS Selection and Appropriateness to Use 2×2 Matrix

		Appropriateness to Use
Selection	**Appropriate to Use (or Acceptable to Use)**	**Not Appropriate to Use**
Selector	**A**: Selectors, appropriate to use	**B**: Selectors, not appropriate to use
Non-selector	**C**: Non-selectors, appropriate to use	**D**: Non-selectors, not appropriate to use

The primary self-selection analysis asked what proportion of the total Self-Selection Population made a correct selection decision, as noted below, where selectors who were both appropriate (per label) and acceptable (per physician review) to use were correct (Group A). Non-selectors who were not appropriate to use were also correct (Group D). Selectors who were not appropriate to use were incorrect (Group B). Non-selectors who

would have been appropriate to use (Group C) were not considered in the calculation, as their decision was neither correct nor incorrect.

Primary endpoint

- % Self-Selection Population who made correct selection decision regarding use of Opill (85% target threshold)

The selection decision specifically among the subset of participants who were inappropriate to use was also of interest. However, there are few clinical situations that preclude use of Opill, impacting a relatively low prevalence of women of reproductive age. Therefore, the size of this subgroup was expected to be small and thus, the assessment of appropriate non-selection for this subgroup would be expected to have a 95% confidence interval (CI) that is overly wide. This makes comparison to any threshold uninformative. Furthermore, there could be multiple reasons contributing to inappropriateness to use with highly variable levels of clinical importance (discussed in Section 5.3). Therefore, this assessment was designated as a secondary endpoint.

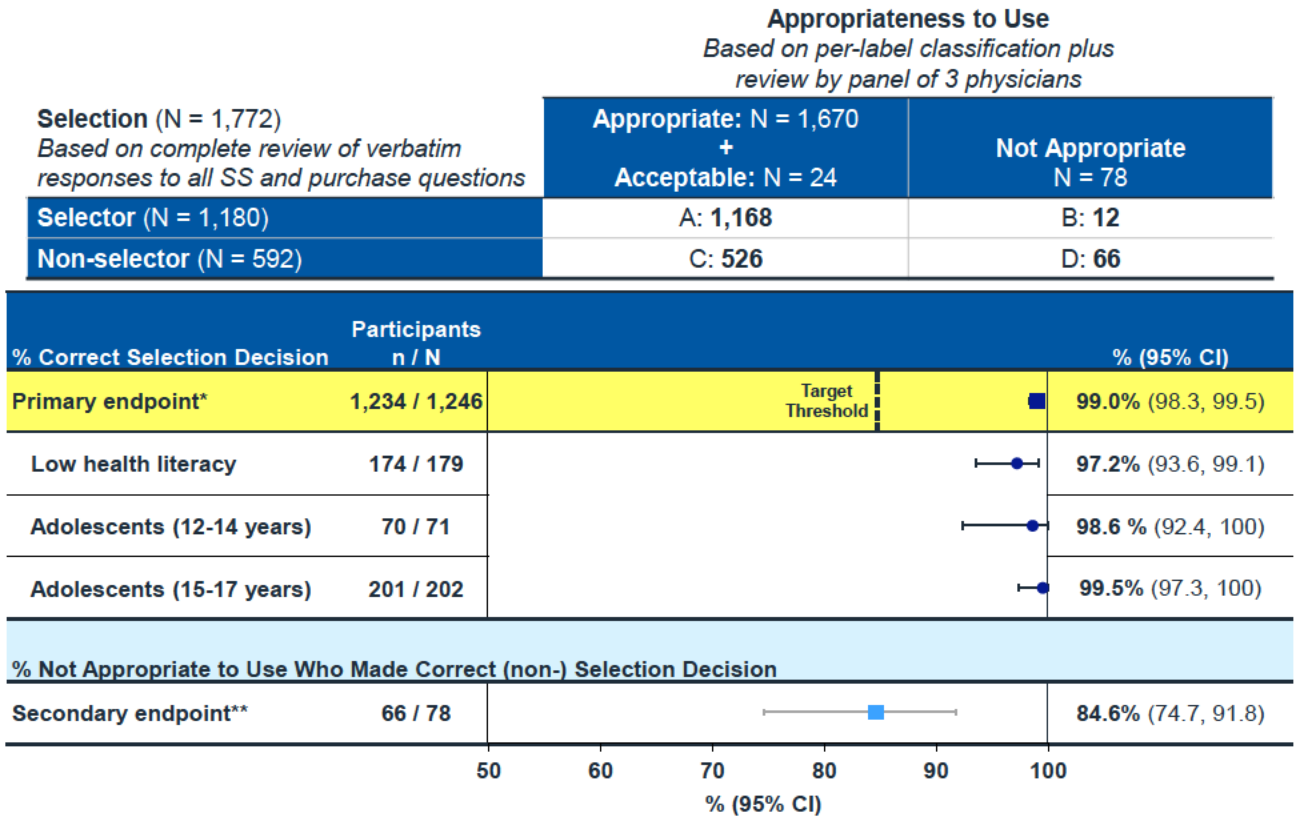
Secondary endpoint

- % Self-Selection Population not appropriate for use who did not select

The complete approach for classification of selectors and appropriateness to use is provided in Sections 5.1.2 and 5.1.3. For the primary self-selection endpoint in ACCESS, 99% of participants ([A+D] / [A+B+D], see n's in Figure 5) made a correct selection decision regarding use of Opill, which exceeded the pre-specified 85% target threshold (95% CI: 98.3, 99.5; Figure 5). Results were consistent across subgroups.

Of those who were not appropriate to use Opill (assessed in secondary endpoint D/ [B+D],), 84.6% (95% CI: 74.7, 91.8) correctly did not select the product.

Figure 5: ACCESS Key Self-Selection Results



CI: confidence interval; n: correct or acceptable selection decision; *N: all participants except non-selectors who are appropriate for use; **N: all participants who are not appropriate for use; SS: self-selection

Among the 12 participants who selected Opill but were not acceptable to use (after physician review), one reported a history of breast cancer, and one reported a history of "venereal cancer," which was not otherwise characterized. There were five participants who were pregnant, four of whom found out they were pregnant after having made the selection decision when they completed the enrollment pregnancy test and who recognized upon discovering their pregnancy that they should not use Opill, and one of whom planned to use the product after she was no longer pregnant. Two participants were male, and three reported that they were not physically able to become pregnant.

In total, only one participant may have some clinically important risk because she had a history of breast cancer. The impact of not heeding the various self-selection label messages is discussed in Section 5.3.

The warning of greatest clinical importance related to self-selection for Opill is the statement regarding breast cancer, which is the only condition listed in the CDC MEC as a Category 4 (i.e., a condition with unacceptable health risk) for POPs. The DFL used in the ACCESS study included a broad warning to not use the product if you have or ever had any cancer. This warning was included based on a concern that reproductive hormones may increase the likelihood of, or accelerate, recurrence of certain cancers, but with only breast cancer having biologic plausibility for concern (Catherino et al 1993; Gu et al 2019;

Jeng et al 1992; Liang et al 2007; Moreno 2016). The overall prevalence of breast cancer in women of reproductive age in the US is very low (0.25%) (SEER data at: https://seer.cancer.gov/explorer/), and thus the breast cancer warning will be relevant to a very small proportion of potential OTC Opill users. As anticipated, the number of participants in the ACCESS study with a history of breast cancer was very small (2/1,772).

Recognizing the importance of this message, a more specific warning not to use the product if you have or ever had breast cancer was added to the DFL based on the ACCESS results and feedback from the FDA. The revised label was tested in the **Targeted BC SSS** (see Section 5.2), which was better suited to evaluate the performance of that label element given the larger enrolled population of women with breast cancer.

In the **Targeted BC SSS**, 200 of 206 participants with current or past breast cancer made a correct selection decision regarding use of Opill (97.1%; 95% CI: 93.8, 98.9), which exceeded the 90% target threshold and demonstrated that the breast cancer warning on the DFL was well understood. Even among the six participants who made an incorrect selection decision, actual use in the OTC marketplace seems unlikely: one indicated that she would not actually use the product because she had an intrauterine device (IUD) in place, one indicated that her breast cancer diagnosis was so recent that she did not think of herself as having breast cancer, two indicated that they had not read the label carefully enough, but one of them ultimately noted that she would ask her doctor before purchasing, and two, when asked if there was anything on the label that would indicate that they should not use Opill, indicated their breast cancer. These results show that the revised label successfully mitigates risk for this small subset of the potential OTC consumer population.

Overall, there are few clinical situations that preclude use of Opill, and the data from the Self-Selection Phase of ACCESS and the Targeted BC SSS demonstrate that the DFL guides appropriate self-selection, including among women with current or past breast cancer.

1.4.2 Actual Use

The ACCESS User Population (N=883, those that elected to purchase/obtain the product and reported use of Opill in their diary) was generally reflective of those at risk of unintended pregnancy and likely to use Opill in the OTC setting, with the exception of those under 18 years of age that were enriched in the recruitment/enrollment for this study. This population represented those of all reproductive ages, and a wide range of educational attainment, income levels and race/ethnicity. Subpopulations of interest (e.g., adolescents, those of low health literacy) were well represented (Table 2).

Table 2: ACCESS User Population

	User Population (N = 883)	
	n	%
Age (years) – Mean [Range]	25.5 [12 - 61]	
Female 12-14	49	6%
Female 15-17	151	17%
Female 18-19	76	9%
Female 20-24	195	22%
Female 25-34	259	29%
Female 35+	153	17%
Low Health Literacy[1]	120	14%
Race[2]		
White	527	60%
Black or African American	267	30%
Asian	50	6%
American Indian or Alaska Native	24	3%
Native Hawaiian or other Pacific Islander	12	1%
Other	57	6%
Hispanic Ethnicity	161	18%

1 Scored at most 60 on the Rapid Estimate of Adult Literacy in Medicine (REALM) Test or Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) Test
2 Answers below are not mutually exclusive

The primary assessments of interest during the Use Phase were related to consistent daily intake of the product, as directed by the label. These directions are primarily focused on the part of the label entitled “directions” where consumers are instructed to take the product every day at the same time and which gives specific instructions to use a condom or other barrier method for two days (i.e., to take appropriate mitigating behavior) if a pill is taken late or missed.

Adherence to Directions to Use Daily

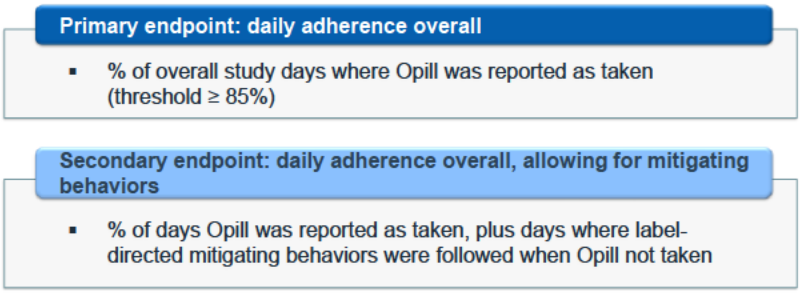
Adherence to daily pill taking was assessed over the course of up to six months using a daily e-diary. Each participant determined their own Opill use duration. Literature on OC adherence in studies conducted in the prescription environment and available for consideration, shows that up to 18% of women typically miss 15% or more of their active pills per cycle, or conversely, 82% of women typically take 85% or more of their active pills per cycle (Aubeny et al 2004; Fox et al 2003; Hou et al 2010; Huber et al 2013; Hughey et al 2010; Oakley et al 1991; Potter et al 1996; Wiegratz et al 2015; Woods et al 2006). These data provided estimates of adherence to OC in the prescription setting and were used to determine the 85% adherence endpoint threshold. The literature also shows that non-adherence varies widely between women and can vary substantially between cycles in the same woman (Aubeny et al 2004; Hou et al 2010). Therefore, several endpoints were created to measure adherence to daily pill intake, including two primary endpoints measuring:

- adherence to daily dosing overall, by calculating the proportion of all days where participants reported taking Opill (threshold ≥ 85% of days);

- proportion of participants who were adherent during the study as defined by reported Opill use on at least 85% of their participation days (threshold ≥ 85% of participants)

and each of these primary endpoints had a corresponding secondary endpoint measuring adherence with mitigating behaviors. Note that because participants younger than 18 years were not asked to report about their sexual behaviors, the secondary endpoints only included non-mitigated behaviors for this age group.

The primary and secondary endpoints evaluating daily intake overall included:

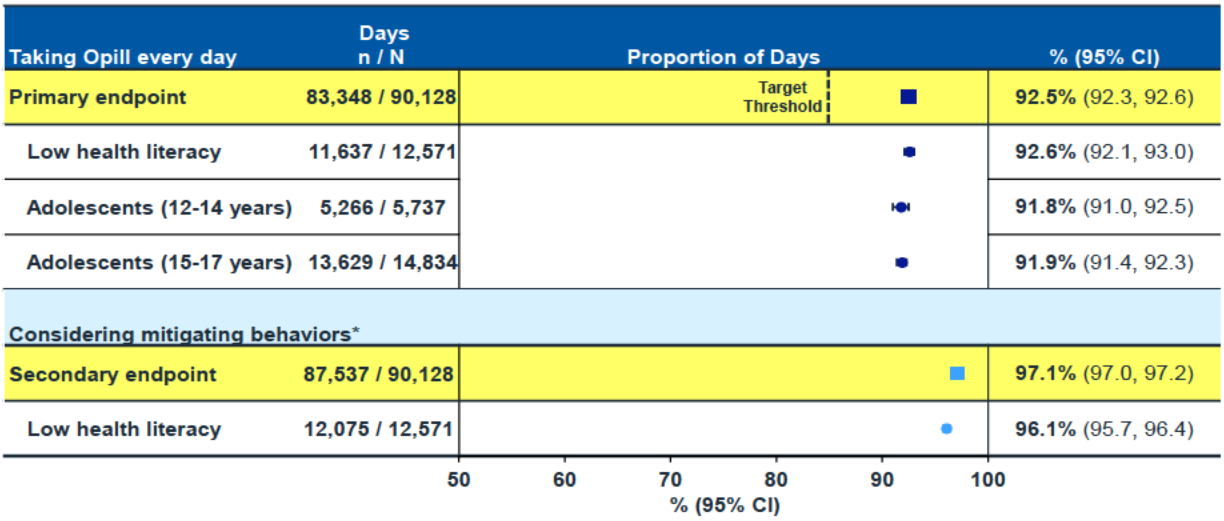


Presented below are the results for pre-specified endpoints, followed by a discussion addressing the behavior of over-reporting identified post-trial. Post hoc sensitivity analyses were performed to understand the impact of this reporting behavior on the interpretation of the study results.

Adherence to the label instruction to take the product every day was assessed in 883 participants (i.e., the User Population), providing information on more than 90,000 possible use days.

ACCESS demonstrated that the DFL is sufficient to guide women to correctly take Opill every day. Participants reported taking Opill on 92.5% of days overall (95% CI: 92.3, 92.6), which is above the target threshold of 85%. Consistent findings were observed for each of the subgroups of particular interest (Figure 6). When considering the label directed mitigating behavior when a tablet was missed, participants reported taking Opill or using a mitigating behavior (e.g., condom or other barrier method) when they missed a pill on 97.1% of days overall (95% CI: 97.0, 97.2). These mitigation behaviors are clinically relevant as they minimize pregnancy risk resulting from any potential loss of Opill effectiveness when a dose is missed.

Figure 6: ACCESS Pre-specified Primary Analysis for Overall Adherence to Taking a Pill Every Day (User Population, N=883)



CI: confidence interval; n: number of days participant reported taking Opill (primary endpoint) and/or used mitigating behaviour (secondary endpoint), N: total number of days
*Did not ask participants < 18 years of age about sexual behaviors; therefore, secondary endpoint includes non-mitigated adherence for this age group

The primary and secondary endpoints evaluating Opill daily intake at the participant level included:

Primary endpoint: daily adherence among individual participants

- % of participants who were adherent (took Opill on ≥ 85% days; threshold ≥ 85% of participants)

Secondary endpoint: daily adherence among individual participants, allowing for mitigating behaviors

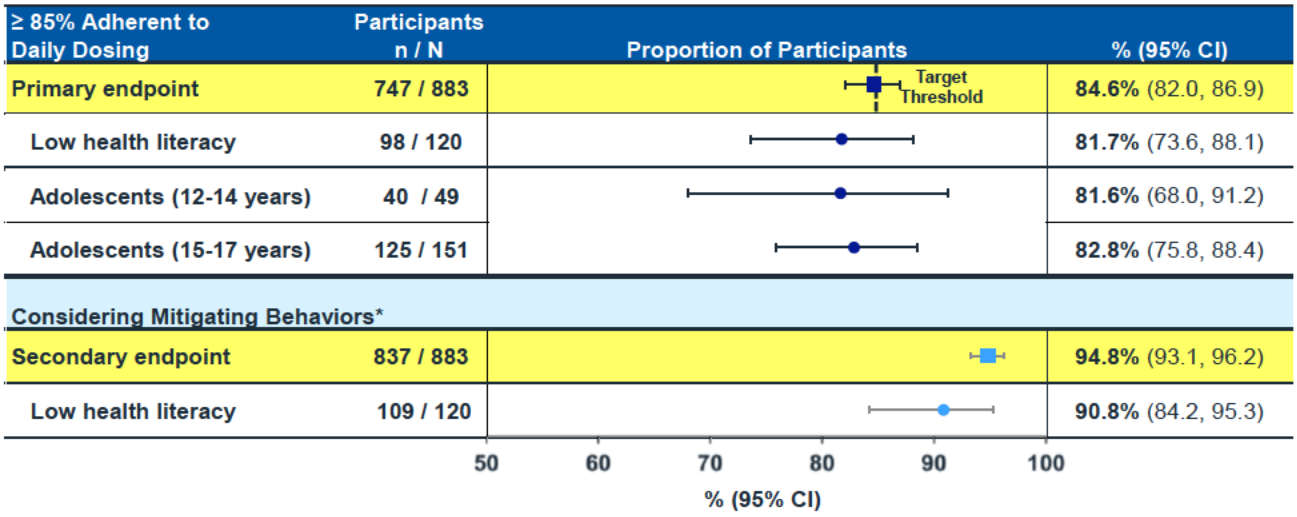
- % of participants who were adherent (took Opill or followed mitigating behavior on ≥ 85% days)

For the primary endpoint measuring adherence at the participant level, 84.6% (95% CI: 82.0, 86.9) of participants were adherent (defined as reported taking Opill ≥ 85% of the time), which did not meet the 85% threshold (Figure 7) but is similar to adherence reported for prescription OC users as discussed above in this section (Aubeny et al 2004; Fox et al 2003; Hou et al 2010; Huber et al 2013; Hughey et al 2010; Oakley et al 1991; Potter et al 1996; Wiegratz et al 2015; Woods et al 2006). For subgroups of interest (low health literacy, adolescents 12-17 years old) performance was generally consistent with the overall population, noted by the overlapping CIs (Figure 7). Overall, most participants were highly adherent to daily pill intake, with a mean participant-level adherence rate at 93.2%, and a median participant-level adherence rate at 99.4% (see Figure 25).

When accounting for label directed mitigating behaviors following a missed pill, 94.8% (95% CI: 93.1, 96.2) of participants were adherent (i.e., reported either taking Opill or taking mitigating action on ≥ 85% of days), demonstrating that even in the instances of

missed pills, users follow the label direction, which mitigate the clinical risk associated with missed pills.

Figure 7: ACCESS Pre-specified Primary Analysis for Participant-Level Adherence to Taking a Pill Every Day (User Population, N=883)



CI: confidence interval; n: number of participants ≥ 85% adherent (primary endpoint) and/or used mitigating behavior (secondary endpoint), N: number of participants in User Population
*Did not ask participants < 18 years of age about sexual behaviors; therefore, secondary endpoint includes non-mitigated adherence for this age group

In the study, 68% of episodes of missed pills reported were a single missed day (Figure 26). Interestingly, the data from the Sponsor's recent pharmacodynamic Delayed Pill Intake Study (see Section 6.2.4) demonstrate that Opill can be expected to effectively protect against pregnancy even if a woman misses a pill.

Importantly, the most common reason participants reported for missing pills in ACCESS appeared to be study-related barriers to accessing new pill packs, since study drug was available only at the enrolling study site (see Figure 27). These re-supply issues illustrate precisely the barriers to adherence that could be lessened by switching Opill to the OTC setting.

Adherence to Directions to Use at the Same Time of Day

ACCESS also examined the adherence to the instruction to take a pill at the same time every day through two endpoints:

Primary endpoint: intake at same time of day

- % of days Opill was taken ± 3 hours from time of day of last dose (80% target threshold)

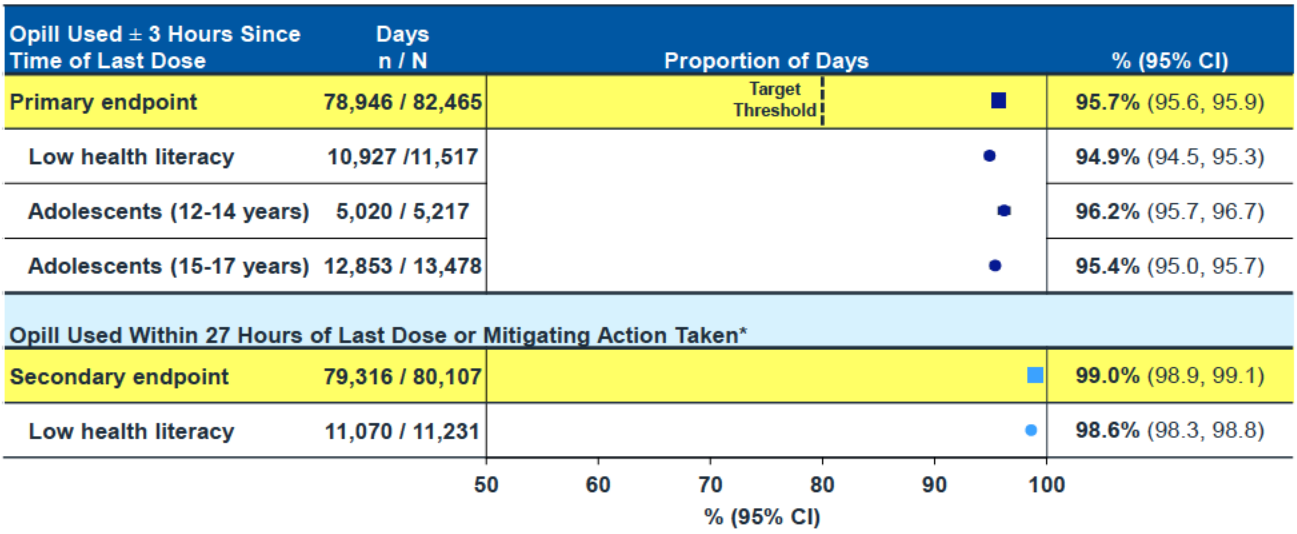
Secondary endpoint: intake within 27 hours, allowing for mitigating behaviors

- % of days Opill was taken no more than 27 hours since previous day's dose or appropriate mitigating behaviors

The primary endpoint provided a measure of consistency of time-of-day dosing and was evaluable for all doses where the time of day for the previous dose was known (even if it was not the preceding calendar day). The secondary endpoint was the more clinically relevant measure and was evaluable for all doses where the dose was taken and the timing was known for the immediate preceding day, assessing whether the current dose was taken no more than 24 hours + 3 hours after the previous dose (or appropriate mitigating behaviors were taken), which is a behavior thought to be needed to maintain sufficient effectiveness. While there are no direct data that define the incremental risk of pregnancy associated with taking a pill late, data from the Sponsor's recent pharmacodynamic Delayed Pill Intake Study (see Section 6.2.4) show Opill users are highly protected from conception, not only during perfect use, but also following a delayed (or even missed) pill.

In ACCESS, participants reported correctly taking their dose within 3 hours of the time of day of their last reported dose (primary endpoint) 95.7% (95% CI: 95.6, 95.9) of the time, exceeding the pre-specified target threshold of 80%. For the secondary endpoint, participants reported correctly taking their dose within 27 hours of the prior day's dose or taking label directed mitigating action 99.0% of the time (Figure 8).

Figure 8: ACCESS Pre-specified Primary Analysis for Adherence to Taking a Pill at the Same Time of Day (User Population, N=883)



CI: confidence interval; n: number of days Opill taken at the correct time (primary endpoint) and/or used mitigating behavior (secondary endpoint); N: number of days evaluable for timing of dose.
*Did not ask participants < 18 years of age about sexual behaviors; therefore, secondary endpoint includes non-mitigated behaviors for this age group

Sensitivity Analyses to Evaluate Impact of Missing Data

Pre-specified sensitivity analyses were conducted to evaluate the impact of missing diary data using both a "worst case" (imputing days with missing data as pill not taken) and a "best case" (imputing days with missing data as pill taken) scenario. All pre-specified sensitivity analyses were consistent with the primary analysis (see Section 6.2.3.3).

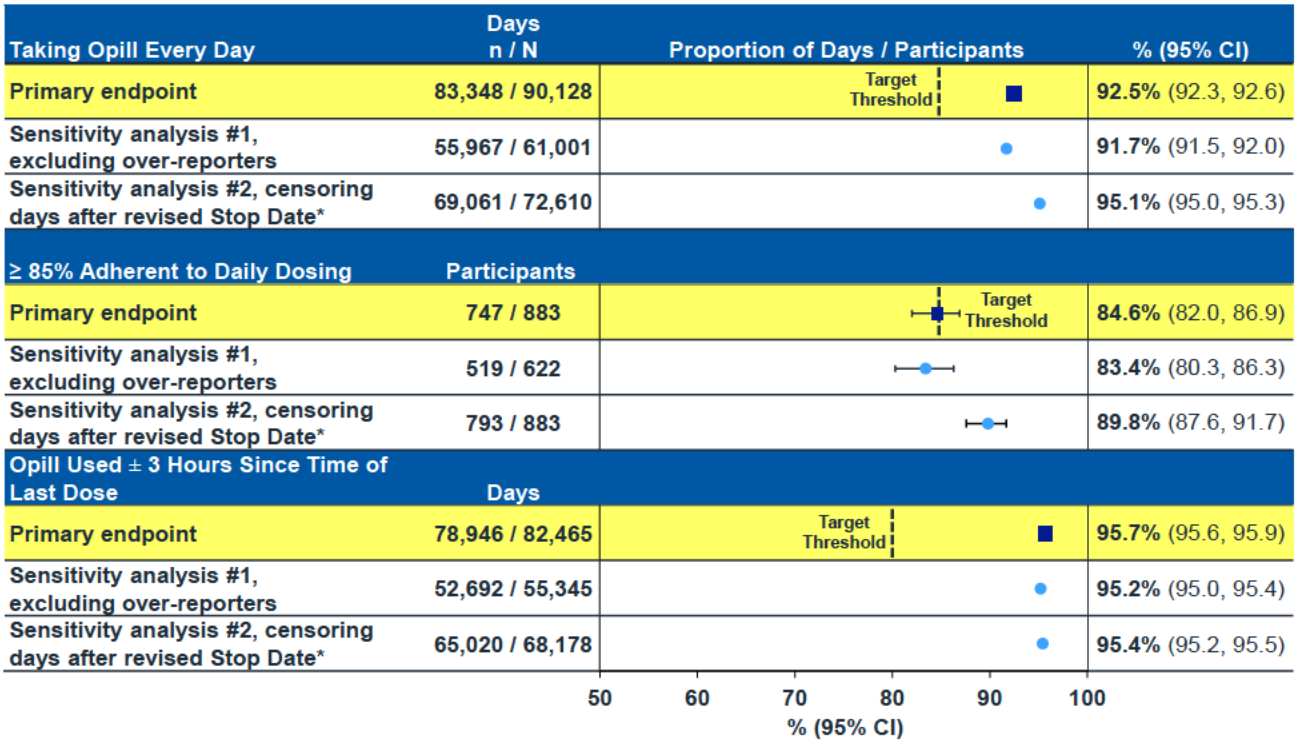
Actions to Assess Impact of Over-Reporting Behaviors

ACCESS collected adherence data using self-report, which is the most common method for assessing medication adherence in research and clinical care (Stirratt et al 2015). After the study was completed and under review by the FDA, HRA determined that 261 participants reported that they took Opill on more days than was possible given the number of tablets recorded as dispensed and/or returned. This behavior is referred to as over-reporting.

An extensive independent root cause analysis (RCA) was performed to better understand this over-reporting behavior. The RCA identified no systemic problems with the study planning or conduct, including concluding that the e-diary functioned as it was intended, allowing participants to enter data as they chose (see Section 6.2.3.4.1). Rather, decisions made during the study design allowed over-reporting to occur without being recognized while the trial was in progress. As a result, the over-reporting was likely caused by a combination of inadvertent data entry mistakes as well as deliberate over-reporting in some participants. Unintentional data entry errors were plausible for the 89 participants (34.1% of over-reporters; 89/261) who reported taking no more than 20% more doses than the number of tablets they had access to. In contrast, intentional over-reporting appeared more likely for those participants who reported larger number of use days when no Opill was available to them. The flexible nature of the e-diary design allowed over-reporting to occur, and participants may have had varied incentives to engage in over-reporting (see Section 6.2.3.4.1). Since AUTs are designed to capture a broad range of possible behaviors and do not control participants' behavior or their reporting of these behaviors, participants may report behaviors that are not possible. Study participants reporting taking more medication than available to them based on medication supply records has been seen in the few published adherence studies that allowed detection of this type of over-reporting (Fanaroff et al 2020; Lauffenburger et al 2020), including OC studies (Nelson et al 2017; Triebwasser et al 2015). Participants reporting doses beyond the supply available to them is likely present in adherence studies generally, although in most studies goes undetected (see Section 6.2.3.4).

Post hoc sensitivity analyses were conducted to better understand the impact of over-reporting behavior on the results and interpretation of the ACCESS data. To avoid bias of results due to those participants who over-reported Opill usage, one sensitivity analysis excluded them from the analysis, while another sensitivity analysis censored all participants' days after their "revised Stop Date" defined as the date at which drug supply would have been exhausted based on recorded use, the date that the participant reported stopping use to a nurse interviewer, or last day of use reported in the e-diary, whichever came first. As shown in Figure 9, excluding all participants who over-reported Opill usage and censoring the participants' days after their revised Stop Date did not change the overall study conclusions: participants were adequately adherent to daily and timely dosing when using Opill in the OTC setting (see Section 6.2.3.4.3).

Figure 9: ACCESS Post Hoc Sensitivity Analyses Excluding Participants Who Over-Reported (N=622 Participants) or Censoring Days After Revised Stop Date (N=883 Participants) Along With Pre-specified Primary Analysis (N=883 Participants) for Primary Adherence Endpoints



CI: confidence interval
For endpoint of taking Opill every day: n: number of days Opill was reported as taken, N:total number of days
For endpoint of ≥ 85% adherent to dosing: n: number of participants ≥ 85% adherent, N: number of participants
For endpoint of Opill used ± 3 hours since time of last dose: n: number of days Opill reported at the correct time, N: number of days evaluable for timing of dose
* Revised Stop Date: date at which drug supply exhausted based on reported use, participant reported stop date to nurse interviewers, or last day of use reported in the e-diary, whichever is the earliest

All these analyses, including the pre-specified primary analysis, the pre-specified sensitivity analyses and the post hoc sensitivity analyses, yield similar and markedly consistent conclusions that people adequately adhere to Opill directions in the OTC setting.

Clinical Impact of Missing or Delaying a Dose

The Rx dosing instructions focusing on Opill use at the same time every day were based on limited data. Therefore, HRA conducted the Delayed Pill Intake Study to assess the pharmacodynamic impact of one dose of Opill being taken late or missed altogether. In this study, no significant changes in cervical mucus score or ovulatory status were observed after delaying intake of a pill by six hours or missing one pill, indicating protection from conception likely persists even if a pill is taken late or missed (see Section 6.2.4.2.2). Thus, the adherence results presented above likely represent a conservative surrogate for estimated pregnancy risk in the OTC setting.

Overall, when considered along with these findings, the ACCESS data on Opill adherence demonstrate that the label clearly enables users to adhere to the Directions for Use in a way that achieves effectiveness in the OTC setting.

When Consumers Should Take Action During Use

The proposed Opill OTC labeling provides users with information on what to expect during use and when they need to take an action (such as to take a pregnancy test, stop use, or consult an HCP) while using Opill. Behaviors related to these statements in the DFL were assessed as secondary endpoints in ACCESS. As expected, such situations were uncommon in ACCESS, given the inherent safety profile of norgestrel, and in many instances, the symptoms resolved spontaneously, obviating the need to see an HCP. Overall, no signals of concern for use in the OTC setting were observed. These findings are supported by the Final LCS results that show that consumers understand these DFL messages. (Results are presented in Section 6.3)

Importantly, expected consumer behaviors reflected in these labeling statements are not unique to an OTC setting, meaning that users of OCs have to make the same decisions during use regardless of whether the POP is obtained by prescription or OTC.

Pregnancies in ACCESS

Although ACCESS was not an efficacy study, pregnancies in the study were documented. Among the 955 women in the Safety Population in ACCESS, which included all those who purchased / obtained the study medication, 14 pregnancies were reported during the study, although three of the 14 occurred in women who purchased but never used the product nor reported use in the diary (excluded from User Population). Among the 883 women in the User Population using the product for a total of 3,538 months, six participants reported pregnancies for which conception was estimated to have occurred during use of Opill. The remaining five occurred in women who had discontinued Opill prior to the estimated day of conception.

1.5 Benefit-Risk Summary

Norgestrel is effective at preventing pregnancy. Women in the US face unnecessary burdens in accessing effective contraception. The moderately and most effective methods are available only through an HCP, while the contraceptive options available without a prescription are limited to the less effective methods. Improved access to Opill, a more effective method than any now available without a prescription, has the potential to reduce unintended pregnancy in the US and positively impact individual women, their families and public health overall.

Across two pivotal studies that assessed self-selection (ACCESS and Targeted BC SSS), data show that consumers are able to appropriately self-select whether Opill is right for them to use. Of utmost importance, the Targeted BC SSS that specifically assessed self-selection among women with a history of breast cancer demonstrated that the DFL effectively communicated to these women that Opill was not appropriate for their use. Actual use data from ACCESS demonstrate that the DFL is sufficient to guide women to use Opill

appropriately, including to correctly take it every day at the same time. Given the inherent safety profile of norgestrel, the situations in which Opill users needed to stop use and/or consult an HCP in response to certain new symptoms that arise during use were uncommon in ACCESS and in many instances, the symptoms resolved spontaneously, obviating the need to see an HCP.

Overall, Opill has all the key characteristics of an OTC drug (Table 3). Contraception is a self-recognizable indication and an established OTC category in the US. The proposed DFL contains all the information consumers need to appropriately select and use Opill safely and effectively. Over the seven-year development program, it was demonstrated that the labeling is well understood, guiding appropriate self-selection and supporting safe and appropriate OTC use, with no need for HCP supervision. Furthermore, the results of the multiple, comprehensive assessments HRA completed demonstrate that Opill has a favorable benefit / risk profile for use in the OTC setting, with few incremental risks associated with consumer use as guided by OTC labeling while the prevention of unintended pregnancies provides clear benefits.

Table 3: Key OTC Drug Characteristics and their Applicability to Opill

OTC Drug Characteristics[1,2]	Opill	
Condition to be treated self-diagnosable	Women self-recognize when they want to prevent pregnancy	☑
Adequately labeled such that consumer can self-diagnose, self-treat, self-manage condition No health practitioner needed for safe and appropriate use	Studies demonstrate consumers can use Opill safely and appropriately without supervision of health practitioner	☑
Low potential for misuse and abuse	Low potential considering mechanism of action No signal of abuse identified in post-marketing data	☑
Benefits of OTC availability outweigh risks	Well-characterized efficacy & favorable safety profile Potential to reduce unintended pregnancy and consequences	☑

OTC: over-the-counter
[1] 503(b) of FD&C Act
[2] Adapted from Michele 2015

2 NEED FOR NONPRESCRIPTION ORAL CONTRACEPTIVES

2.1 Unintended Pregnancies in the United States

The Centers for Disease Control and Prevention (CDC) defines an unintended pregnancy as either unwanted, meaning that it occurred when no children or no more children were desired, or mistimed (e.g., occurred earlier than desired) (CDC 2021b). Even with a wide range of contraceptive methods available in the United States (US), almost half (45%; 2.8 million) of the more than 6.1 million pregnancies in the US each year are unintended (Finer and Zolna 2016). More than half of all US women will have experienced an unintended pregnancy by age 45 (Sonfield et al 2014). Notably, unintended pregnancies affect US women of all ages within the reproductive age range, racial and ethnic backgrounds, income levels, and levels of educational attainment (Finer and Zolna 2016).

While adolescents aged 15 to 17 years make up a relatively small proportion of those at risk of unintended pregnancy in the US (approximately 5% of those 15-49 at risk are aged 15-17; Pinney Associates 2022), an even higher proportion of pregnancies, 72% of pregnancies in adolescents 15 to 17 years, are unintended (Finer and Zolna 2016). While few very young adolescents have ever had sexual intercourse (e.g., 1.3% by age 12, 3.4% by age 13, and 8.6% by age 14; Finer and Philbin 2013), by age 15, approximately 20% have had intercourse and by age 17, approximately 50% have (Lindberg et al 2021). Approximately 88,000 pregnancies and 37,000 births occur annually among adolescents aged 17 and under.[4] Almost 30% (29.7%) of first births in US females occur in those aged 19 or younger (Martinez and Daniels 2023). Pregnancy and childbearing in adolescents result in significant individual and societal costs (Hoffman 2006; Perper et al 2010).

Unintended pregnancies are associated with substantial morbidity and mortality in women and represent both personal and public health burdens. Examples include:

- a reduced likelihood of receiving early prenatal care (Cheng et al 2009; Dibaba et al 2013; Gipson et al 2008; Kost and Lindberg 2015; Lindberg et al 2015),
- an increased risk of pre-term delivery (Mohllajee et al 2007; Shah et al 2011),
- an increased risk of low birth weight (Hall et al 2017; Kost and Lindberg 2015; Shah et al 2011),
- a reduced likelihood of breastfeeding (Gipson et al 2008; Kost and Lindberg 2015; Lindberg et al 2015),
- and an increased risk of maternal depression (Abajobir et al 2016; Cheng et al 2009; Fellenzer and Cibula 2014; Gariepy et al 2016; Gauthreaux et al 2017; Gipson et al 2008).

[4] Number of pregnancies is based on data from 2017 Maddow-Zimet I, Kost K. Pregnancies, Births and Abortions in the United States, 1973–2017: National and State Trends by Age. Guttmacher Institute; 2021. and number of births is based on data from 2021 Hamilton B, Martin J, Osterman M. Births: Provisional data for 2021. Vital Statistics Rapid Release [Internet]. 2022. (May).

An estimated 42% of US unintended pregnancies (excluding miscarriages) end in an induced abortion (Finer and Zolna 2016), contributing to more than 860,000 abortions annually (Jones et al 2019).

Unintended pregnancy is also associated with an increased risk of lower educational and economic attainment in women and their children (Logan et al 2007). For example, only approximately 50% of teen mothers receive a high school diploma by 22 years of age whereas approximately 90% of women who do not give birth during adolescence graduate from high school (Perper et al 2010). The public cost of unintended pregnancies nationwide has been estimated to total $21 billion in 2010 (Sonfield and Kost 2015). These negative sequalae are in addition to the inherent risks of any pregnancy, including maternal mortality.

Consistent with this burden, the US Department of Health and Human Services (DHHS), through its Healthy People 2030 initiative, which provides science-based 10-year national objectives for improving the health of all Americans, has an overall goal of improving pregnancy planning and preventing unintended pregnancy in the US (ODPHP 2021). To achieve that goal, the US DHHS established the following national family planning objectives for pregnancy and childbirth:

- Reducing:
    - the proportion of pregnancies that are unintended,
    - pregnancies in adolescents, and
    - the proportion of pregnancies conceived within 18 months of a previous birth.
- Increasing:
    - the proportion of women at risk for unintended pregnancy who use effective birth control,[5] and
    - the proportion of adolescent females at risk for unintended pregnancy who use effective birth control and, specifically, increasing the proportion of adolescent females who used effective birth control the last time they had sex.[6]

2.2 Prevention of Unintended Pregnancies: Currently Available Methods

The average US woman, who wants to have two children, spends more than 30 years trying to avoid pregnancy (Sonfield et al 2014). It is important for women who are at risk for unintended pregnancy and who want to avoid pregnancy to have access to effective contraception. Access to a range of methods and a range of ways to access contraception

[5] US DHHS provides the following specific detail around this objective: Increase the proportion of women at risk of unintended pregnancy who use most effective or moderately effective methods of contraception.
[6] US DHHS also includes the following Family Planning objective within the “Adolescent” sub-category in Healthy People 2030: Increase the proportion of adolescent females who used effective birth control the last time they had sex.

that meet people's needs will increase the likelihood that an individual will identify and use a method (Yeh et al 2022).

The vast majority of unintended pregnancies result from either not using contraception or using a contraceptive method inconsistently. Based on data from the 2006-2010 National Survey of Family Growth (NSFG)[7] and the Guttmacher Institute's 2008 Abortion Patient Survey, Sonfield and colleagues estimated that among the 3.4 million total unintended pregnancies that occurred in 2008 in the US (Sonfield et al 2014):

- 1.8 million (54%) were attributable to no contraceptive method having been used in the month of conception;
- 1.4 million (41%) were attributable to inconsistent method use[8]; and
- 184,000 (5%) were attributable to method failure among those who had used their method correctly.

Contraceptive methods can be categorized as "less", "moderately" or "most" effective based on their failure rates (Figure 10). While there is a wide range of contraceptive methods available in the US, only those contraceptive methods categorized as "less" effective are available without a prescription, while the "moderately" and "most" effective contraceptive methods are only available by prescription. Of note, acknowledging that typical adherence to contraceptives is less than perfect despite the involvement of a healthcare practitioner (HCP), a standard construct of "perfect use" and "typical use" effectiveness has been established for all contraceptives.

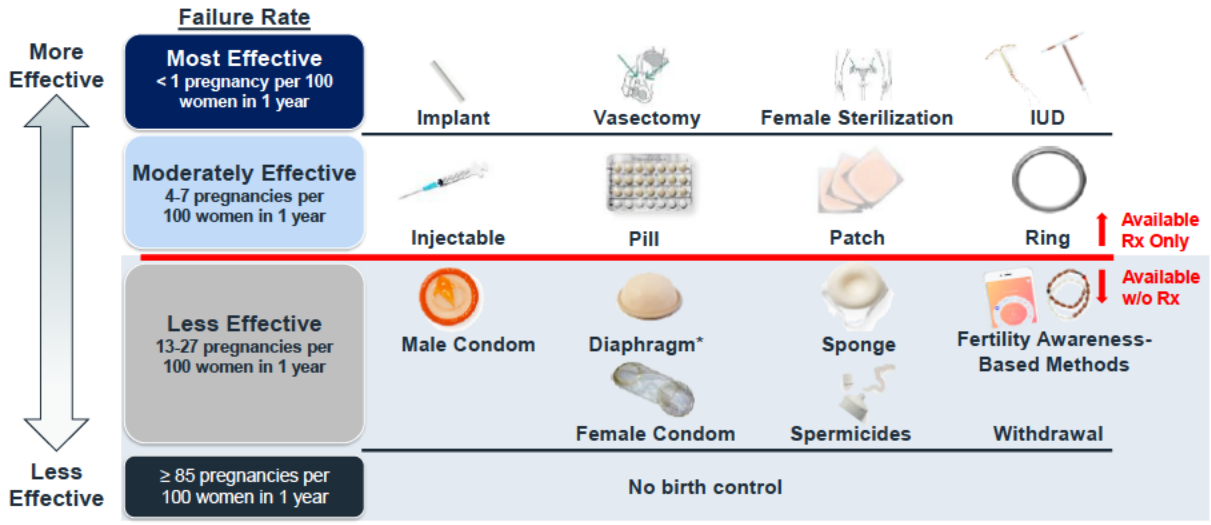
As illustrated in Figure 10, contraceptive methods currently available without a prescription or HCP interaction include over-the-counter (OTC) products (e.g., male condoms, some spermicides, female condoms) and behavioral-based methods (e.g., withdrawal and fertility awareness-based methods), all of which are classified as "less" effective contraceptive methods (i.e., with first year typical use failure rates ranging from 13%-27%, depending on the method) (Trussell et al 2018). These OTC and behavioral-based methods require correct action at the time of every act of intercourse; may require experience and/or training for effective use; require the active involvement of the woman's partner in the case of male condoms, withdrawal, and fertility awareness-based methods; and, in most cases, do not allow for discreet use by the woman.

In contrast, women can only access contraceptive methods classified as "most" effective (i.e., male sterilization, female sterilization, intrauterine device [IUD], intrauterine system [IUS] and implant) and "moderately" effective (i.e., oral contraceptives [OCs], patch, ring,

[7] The NSFG is a survey administered by the CDC's National Center for Health Statistics that provides nationally representative data on general and reproductive health, including pregnancies and births, and use of contraception.
[8] "Inconsistent use" includes women who used a method in all months that they were sexually active but missed taking some pills, or skipped use, or incorrectly used their barrier method or condom during some acts of intercourse.

and injectable) through an interaction with an HCP for a prescription, administration, or placement.

Figure 10: Effectiveness of Contraceptives Available With and Without Prescription in the US



IUD: intrauterine device; IUS: intrauterine system; OTC: over-the-counter; Rx: prescription; w/o: without
* Diaphragms require a prescription but are recommended to be used with spermicides, most of which are available OTC.
Failure rates displayed are for typical use failure rates for first year of use, from Trussell et al 2018.
Source: Adapted from Trussell et al 2018.

For many women, the requirement to obtain a prescription and/or for an HCP visit represents a barrier to initiating use of effective methods and continuing consistent use once started. A woman may face challenges related to obtaining an HCP appointment (e.g., appointment delay, not having a regular HCP); getting to an appointment (e.g., lack of physical proximity, inability to take time off from work/school, or inability to find time for an appointment); and not wanting to go to a clinic or see an HCP for contraception (Baum et al 2016; Biggs et al 2012; Foster et al 2012; Grindlay and Grossman 2016). According to two studies, approximately 40%-50% of women who report having unprotected sexual intercourse cite running out of contraceptive supplies and not being able to get birth control when needed as primary reasons for not using contraception (Biggs et al 2012; Foster et al 2012). Furthermore, data from the Kaiser Family Foundation's 2020 Women's Health Survey indicate that nearly one-third (31%) of hormonal contraceptive users report having missed taking their birth control (i.e., OC pills, patch, ring, or Depo Provera injection) because they were not able to get their next prescription-based supply in time (Frederiksen et al 2021).

Adolescents who need contraception face particular barriers to accessing it. While they can access the more effective methods available only through an HCP [without parental consent in Title X clinics in 49 states and in general practice in most states (Guttmacher Institute 2023; Shen 2023)], they face significant barriers to accessing the more effective contraceptive methods (Baum et al 2016; Biggs et al 2012; Fuentes et al 2018).

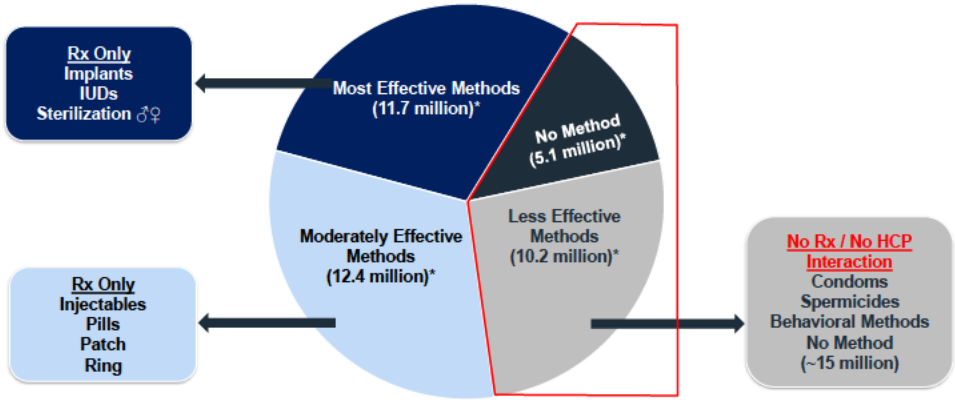
2.3 Unmet Need for Nonprescription Oral Contraceptives

The continued high rate of unintended pregnancies in the US within the current context of available contraceptive methods points to the need for additional contraceptive options, including improved access to effective contraceptives, for those at risk of unintended pregnancy.

Based on an analysis of data from the 2017-2019 NSFG using an approach adapted from CDC's National Center for Health Statistics (Jones et al 2012), nearly 40 million (39.4 million), or 54% of all US females aged 15-49, are considered to be at risk for unintended pregnancy (Pinney Associates 2022).[9] Those at risk include women who either report current use of a contraceptive method with some potential for failure or they report no current contraceptive method use despite being sexually active, able to become pregnant, and not seeking pregnancy. US women who are at risk for experiencing unintended pregnancy represent a wide range of reproductive ages, racial and ethnic backgrounds, income levels, and levels of educational attainment (Pinney Associates 2022).

Among the nearly 40 million US women at risk for unintended pregnancy, 15.3 million (4 out of 10) are at the highest risk for experiencing an unintended pregnancy either because they are not currently using contraception, or they are currently using a method classified as "less" effective (Figure 11). Of these 40 million at-risk women aged 15-49, approximately 5%, an estimated 1.9 million, are aged 15-17 (Pinney Associates 2022).

Figure 11: US Women Aged 15-49 at Risk for Unintended Pregnancy by Current Contraceptive Status



HCP: healthcare practitioner; IUDs: intrauterine devices; Rx: prescription; NSFG: National Survey of Family Growth
*Number of US women aged 15-49 at risk for unintended pregnancy according to NSFG 2017-2019 (Pinney Associates 2022)
Source: Annual typical use failure rates according to Trussell et al 2018

[9] Using an approach adapted from Jones et al (2012), women were considered to be at risk for unintended pregnancy if 1) they were using a method of contraception during the month of interview (i.e., current use) or 2) they were not using a method of contraception in the month of interview but had sexual intercourse in the prior 3 months. Women who were 1) pregnant, seeking to become pregnant or postpartum; 2) sterile for noncontraceptive reasons; or 3) not using contraception but had not had sexual intercourse since menarche or in the 3 months before the interview were not considered to be at risk for unintended pregnancy. Additionally, for purposes of this analysis, women who reported female sterilization as their current contraceptive method were not considered to be at risk for unintended pregnancy, as they are using a contraceptive method that is extremely effective at preventing pregnancy, although women whose partner was sterilized were considered to be at risk for unintended pregnancy as male partners can change over time.

Most women will use a variety of contraceptive methods throughout their reproductive lives. Data from interviews with over 12,000 US women indicate that the median number of different contraceptive methods ever used is three, with nearly 30% of women having used five or more different methods (Daniels and Mosher 2013). Preferences for contraceptive methods vary from woman to woman and for the same woman over the course of her reproductive life depending on her needs and priorities (Mansour 2014). Women choose their contraceptive methods for a variety of different reasons, such as effectiveness, lack of side effects, affordability, or mode of access to the method (Lessard et al 2012).

Any of the nearly 40 million US women at risk of unintended pregnancy could benefit from the use of an easily accessible and effective contraceptive option via an OTC OC at some point over the course of their reproductive lives. Those who could benefit the most from use of OTC OCs, however, are the estimated 15.3 million women at risk for unintended pregnancy who are either not currently using contraception (5.1 million) or relying on the "less" effective contraceptive methods, including those available OTC and behavioral-based methods (10.2 million) (Pinney Associates 2022). Shifting even some of those at risk for unintended pregnancy from use of no contraceptive method or the "less" effective methods has the potential to meaningfully reduce unintended pregnancies. For example, one published model designed to assess how changes in utilization of different contraceptive methods impacts unintended pregnancy at a population level suggests moving even a small proportion (5% in their model) of non-users of contraception and users of "less" effective methods (i.e., male condoms and withdrawal) to "moderately" effective hormonal methods (i.e., OCs, patch, or ring) could result in a 14% – 16% reduction in the national unintended pregnancy rate (Thomas and Karpilow 2016).

Acknowledging that unintended pregnancy is a major public health issue in the US and that barriers to accessing effective contraception contribute to nonuse or inconsistent use, key professional medical organizations have expressed strong support for OTC access to OCs (AAFP 2019; ACOG 2019; AMA 2022; NASPAG 2022; SAHM 2022):

- **American College of Obstetricians and Gynecologists (ACOG), 2019**: ACOG supports OTC access to hormonal contraception without age restrictions.
- **American Medical Association (AMA), 2022**: AMA supports removing the prescription access barrier to contraception and encourages the US FDA [Food and Drug Administration] to approve OTC access to oral contraceptives without an age restriction.
- **American Academy of Family Physicians (AAFP), 2019**: AAFP supports OTC access to oral contraception without a prescription.
- **Society for Adolescent Health and Medicine (SAHM), 2022:** SAHM supports over-the-counter access to oral contraceptive pills without an age restriction.
- **North American Society for Pediatric and Adolescent Gynecology (NASPAG), 2022:** NASPAG supports the availability of oral progesterone-only contraceptive pills to adolescents without a prescription.

Women who want to avoid pregnancy need easier access to safe and effective contraceptives. Nonprescription access to OC pills would offer women a new option that could help meet this need.

3 OPILL RX-TO-OTC SWITCH BACKGROUND

3.1 Purpose of Submission

HRA submitted a supplemental New Drug Application (sNDA) seeking approval for a full prescription (Rx) to OTC switch of Opill (norgestrel 0.075 mg tablets) without a change in the previously approved conditions of use under NDA#017031 (e.g., use by females of reproductive potential seeking to prevent pregnancy).

3.2 Norgestrel 0.075 mg Tablets – Product Description

3.2.1 Regulatory History

Both the efficacy and safety of norgestrel 0.075 mg tablets for use by females of reproductive potential seeking to prevent pregnancy were established based on data submitted when the product was initially approved for Rx use by FDA in 1973 (NDA#017031). Norgestrel 0.075 mg tablets were marketed in the US for more than 30 years (1974-2005; more than 17 million blisters of 28 tablets sold in the US and foreign distribution under the US Agency for International Development [USAID] program) under the tradename Ovrette® before sales were discontinued for business reasons (i.e., not for reasons of safety or efficacy; 82 FR 49380, Docket No. FDA-2017-P-0840, FR Doc. 2017-23125 Filed 10-24-17).

HRA acquired the NDA from Pfizer Inc. in 2015 with the intent to generate the data necessary to support an Rx-to-OTC switch. Norgestrel 0.075 mg tablets have not been remarketed in the US nor in any other country by HRA.

HRA intends to use the proprietary name Opill for OTC marketing. FDA has already approved this name for use in the Rx setting and found it conditionally acceptable for OTC marketing in August 2022.

3.2.2 Mechanism of Action

Opill prevents conception by thickening the cervical mucus to inhibit sperm penetration and suppressing or disrupting ovulation.

Pharmacokinetic evaluation from the 1970s demonstrated that serum progestin levels peak about two hours after oral administration of norgestrel 0.075 mg tablets, followed by rapid distribution and elimination (Brenner et al 1977; McCann and Potter 1994; Weiner et al 1976). By 24 hours after drug ingestion, serum levels are near baseline. This pharmacokinetic profile is the basis for the Rx label directions (Opill Rx labeling) recapitulated in the proposed OTC label, that Opill needs to be taken at the same time every day. Importantly, no clinical or pharmacodynamic studies were conducted for the original approval to evaluate the consequences of delayed/missed dosing.

Recognizing the importance of this topic to the effectiveness of Opill in the OTC environment, HRA conducted a pharmacodynamic study, the Delayed Pill Intake Study to further understand the impact on Opill contraceptive pharmacodynamics if users were to take a pill late or miss a pill. The results demonstrate that delaying a pill by 6 hours or

missing one pill entirely has no significant effect on cervical mucus thickening or disruption of ovarian activity. Thus, Opill is likely to maintain contraceptive effectiveness even if a woman takes her daily pill late or misses a dose (see Section 6.2.4.2 for full discussion of these data).

3.2.3 Established Efficacy and Safety of Norgestrel 0.075 mg Tablets

Opill is a daily progestin-only oral contraceptive pill (POP). POPs have been approved and marketed in the US for close to 50 years and have a well-characterized clinical profile. Since POPs do not contain estrogen, they have few contraindications (White et al 2012) and are considered safe (ACOG 2019). In particular, they present little or no risk of venous thromboembolism (VTE) (ACOG 2019).

Per the current Rx labeling, Opill is contraindicated for use in the following situations:

- Known or suspected pregnancy
- Known or suspected carcinoma of the breast, or other progestin-sensitive cancer, now or in the past
- Undiagnosed abnormal uterine bleeding
- Hypersensitivity to any component of the drug product
- Benign or malignant liver tumors (Opill Rx labeling).

Scientific and clinical research since the development of the Rx label has led to a reconsideration of these contraindications. The CDC Medical Eligibility Criteria for Contraceptive Use (MEC), which provides recommendations on safe use of contraceptive methods for women, identifies current breast cancer as the only Category 4 condition (i.e., unacceptable health risk) for POP use (Curtis 2016b)[10]. This is in contrast to the recommendations for combined oral contraceptives (COCs), which have Category 4 recommendations for each of the conditions listed in Table 4.

The contraindication against use of POPs by women with a history of breast cancer arises from a concern that reproductive hormones may increase the likelihood of, or accelerate, recurrence of certain cancers, most importantly breast cancer. The available preclinical data suggest that disease progression or recurrence among women with history of breast cancer using hormonal contraception is biologically plausible (Catherino et al 1993; Gu et al 2019; Jeng et al 1992; Liang et al 2007; Moreno 2016). Recent but limited clinical data have not confirmed an increased risk of progression or recurrence of breast cancer with use of hormonal contraception (Ostroot et al 2021; Trinh et al 2008).

[10] The CDC MEC provides recommendations on safe use of contraceptive methods for women with various medical conditions and other characteristics, which included the rigorous identification and critical appraisal of the scientific evidence through systematic reviews and input from national experts (Curtis, 2016b). The recommendations address the initiation and continued use of all methods evaluated.

Table 4: CDC Medical Eligibility Criteria Recommendations for Use of Progestin Only Oral Contraceptive Pills where Combined Oral Contraceptives are Contraindicated

Condition	POP		COC
	Initiation	Continued	
Stroke (history of cerebrovascular accident)	2	3	4
Ischemic heart disease (current or history of)	2	3	4
Hypertension (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg, vascular disease)	2		4
DVT/PE (history of or acute DVT/PE, major surgery with prolonged immobilization)	2		4
Valvular heart disease (complicated)	1		4
Peripartum cardiomyopathy (moderately or severely impaired cardiac function)	2		4
Known thrombogenic mutations	2		4
Headaches (migraine with aura)	1		4
Smoking (≥ 15 cigarettes/day after age 35 years)	1		4
Non-breastfeeding (< 21 days postpartum)	1		4
Breastfeeding (< 21 days postpartum)	2		4
Cirrhosis (severe decompensated)	3		4
Liver tumors (benign hepatocellular adenoma, malignant hepatoma)	3		4
Solid organ transplantation (complicated)	2		4
Systemic lupus erythematosus (positive or unknown antiphospholipid antibodies)	3		4
Breast cancer (current)	4		4

1 No restriction 2 Advantages outweigh risks 3 Risks outweigh advantages 4 Unacceptable health risk

CDC: Centers for Disease Control and Prevention; COC: combined oral contraceptive; DVT: deep vein thrombosis; PE: pulmonary embolism; POP: progestin only oral contraceptive pill
Adapted from Curtis 2016b

These contemporary recommendations, including conservative labeling on cancer, have been integrated into HRA's label development and its assessment of label performance.

3.2.3.1 Efficacy and Effectiveness

Since Opill has already been approved by FDA for Rx use by females of reproductive potential to prevent pregnancy, no new clinical trials assessing product efficacy were needed or have been conducted as part of this switch development program.

As described in the current Opill Rx labeling, its efficacy as an OC was evaluated in eight US clinical studies in which 2,173 participants completed at least one treatment cycle and 648 completed at least 13 cycles providing a total of 21,856 28-day cycles of exposure in

women aged 15 to 49 years (Opill Rx labeling). The pregnancy rate was approximately 2 per 100 woman-years in those studies.

HRA also conducted a meta-analysis of eight published clinical trials (different from the eight clinical studies on which the US approval was based) that assessed the efficacy of norgestrel 0.075 mg tablets. From a cumulative population of 7,584 participants across 66,409 cycles with 98 reported pregnancies, the calculated Pearl Index[11] was 1.96 (lower and upper bound of 95% confidence interval (CI): 1.09, 3.49) (Dunson et al 1993; Eckstein et al 1972; Hernandez-Torres 1970; Korba and Paulson 1974; Statzer 1972; Tejuja et al 1974; Tyler 1968; Vessey et al 1972). These results are consistent with the original NDA findings (Pearl Index of 2).

The typical use failure rate of OCs (failure rate in real world use), including POPs such as Opill, has been estimated at 7% in the Rx setting, meaning that it is estimated that 7% of women will experience an unintended pregnancy during the first year of typical use (Trussell et al 2018). This provides an important reference point for understanding the potential benefits of OTC Opill.

3.2.3.2 Safety

3.2.3.2.1 Safety from Clinical Studies Supporting Product Approval in 1973

As described in the current Opill Rx labeling, an increased risk of the following adverse reactions has been reported with the use of POPs: delayed follicular atresia/ovarian cysts; menstrual irregularity, changes in menstrual flow; breakthrough bleeding/spotting; amenorrhea, and prolonged bleeding.

The following adverse reactions were reported in ≥ 5% of participants in the norgestrel 0.075 mg tablets clinical studies that supported initial approval: • Headache • Dizziness • Nausea • Increased appetite • Abdominal pain, cramps and bloating • Fatigue • Vaginal discharge • Dysmenorrhea • Nervousness • Backache • Breast discomfort • Acne.

As with other continuously administered POPs, unpredictable and irregular bleeding episodes were the most frequently encountered adverse reaction and the main reason for discontinuation across the eight US clinical studies that supported initial approval. There were a total of 2,575 enrolled subjects, and approximately half of them experienced some menstrual changes.

Breakthrough bleeding occurred in 11.8% of all reported cycles and spotting in 12.2% (n=21,378 cycles). Breakthrough bleeding and spotting was reported by 48.6% and 47.3% of subjects, respectively. Amenorrhea occurred in 6.1% of subjects in their first cycle and 28.7% of all subjects during the studies. Participants reported no significant changes in menstrual cycle length or duration of menses. Duration of menses was greater than 8 days among 8.5% of the total reported 19,050 cycles. Three hundred and seventy-nine (379) participants (17.4%) discontinued treatment due to side effects. Sixty-eight percent of all

[11] The Pearl Index, a measure of contraceptive failure, represents the number of failures per 100 woman-years of exposure.

discontinuations were a result of menstrual cycle effects. Overall, 6.4% of participants discontinued treatment due to breakthrough bleeding and 2.7% due to amenorrhea.

3.2.3.2.2 Safety from Review of Post-marketing Databases and Published Literature

To support the overall evaluation of safety, HRA conducted an extensive review and analysis of data for norgestrel and levonorgestrel. Data on levonorgestrel were included because it is the levo-enantiomer of norgestrel and is responsible for norgestrel's biologic activity[12].

1) Post-marketing safety data for norgestrel and levonorgestrel (databases described in Table 29 of Appendix Section 11.5)

2) Published safety literature relevant to norgestrel and levonorgestrel for the period January 01, 1996, through September 30, 2021, and January 01, 2011, through September 30, 2021, respectively. The search of the literature databases (PubMed® and PubMed Central®) identified 8 norgestrel and 45 levonorgestrel publications relevant to assessing safety of these drugs. The publication types included randomized-controlled trials, open-label trials, case reports, case report reviews, clinical trial reviews and/or meta-analysis, case-controlled studies, population cohort studies, and in vitro or in vivo studies.

These reviews included a comprehensive review of all adverse events (AEs) related to Contraindications, Warnings, and Precautions listed in the current Rx labeling in addition to the general safety of norgestrel / levonorgestrel.

The analysis of these post-marketing safety databases identified reproductive system and breast disorders as the System Organ Class (SOC) with the highest frequency of AEs. The spectrum of reported terms reflected the recognized side effect profile for the drug as reflected in the current Rx labeling, namely bleeding pattern alterations and unintended pregnancy (Reproductive system and breast disorders SOC), and background events in the population of norgestrel/levonorgestrel users.

A structured literature review was conducted to assess the potential for thromboembolic (TE) AEs associated with norgestrel after a high case reporting rate was observed for TE AEs for norgestrel in the World Health Organization (WHO) VigiBase database for the ex-US cases (23%, 23 TE cases / 100 Total cases). No other post-marketing safety database reviewed had a similar case reporting rate. A number of small studies (Tepper et al 2016; Glisic et al 2018) have reported low rates of TEs with the use of progestin-only injectables and the use of progestins for non-contraceptive therapeutic indications (such as menstrual disorders or dysfunctional uterine bleeding) but lacked statistical power to draw firm conclusions. Systematic reviews and meta-analyses of published literature found no increased risk of VTE, stroke, or acute myocardial infarction (AMI) with POP use (Chakhtoura et al 2011; Chakhtoura et al 2009; Glisic et al 2018; Mantha et al 2012; Tepper et al 2016). The most recent review (which included studies incorporated in

[12] Levonorgestrel has been widely used and has been available as a mono-component oral product, as a subdermal implantable device, as an IUS, and as an oral tablet for emergency contraception (EC). Levonorgestrel oral tablet for EC has been available OTC in the US since 2007.

previous reviews) found no significant association of POP use (versus non-use) on the risk of VTE (pooled adjusted relative risk 1.06; 95% CI: 0.7-1.62), AMI (pooled adjusted relative risk 0.98; 95% CI: 0.66-1.47) or stroke (pooled adjusted relative risk 1.02; 95% CI: 0.72-1.44) (Glisic et al 2018). Overall, the majority of the evidence suggests that there is no increased TE risk with POPs, including norgestrel. This is reflected in the CDC MEC Category 2 recommendation for people with a history of deep vein thrombosis/pulmonary embolism (see Table 4).

Additionally, no unexpected safety findings emerged from the analysis of norgestrel or levonorgestrel used across a variety of dosage forms and exposures including when used orally as an emergency contraception (EC), or as an IUS or an implant. In this review, AEs including unintended pregnancies, menstrual irregularities, abdominal discomfort, and abdominal dysfunction were those reported with the greatest frequency for POPs in both the FDA and WHO VigiBase databases.

From the search of the literature databases for norgestrel, reports were consistent with its well-known safety profile, with menstrual bleeding disturbances most frequently reported. For levonorgestrel, the side effects of the levonorgestrel POP and levonorgestrel-EC regimens were consistent with their well-known safety profile. Events like nausea, headache, vomiting and dizziness were mild and of temporary duration with high recovery rate. Headache, abdominal pain, diarrhea, and menstrual cycle changes were the most common AEs occurring in > 10% of participants after levonorgestrel-EC dosing. Of the citations reviewed, none have raised any new safety issues.

Overall, given the extensive data from almost 50 years of post-marketing surveillance of both norgestrel and levonorgestrel, there is no indication of safety concerns not reflected in the current Rx labeling and in the proposed OTC labeling. Based on the totality of the safety data, HRA considers that Opill is an appropriate candidate for use as an OTC contraceptive option for women who want to prevent pregnancy.

3.3 Norgestrel 0.075 mg Tablets for OTC

As per regulation (503(b) of FD&C Act), to be nonprescription, a drug must be determined by FDA to be safe and effective for use without the supervision of an HCP. In addition, the condition to be treated must be self-diagnosable and OTC products must be adequately labeled such that consumer can self-diagnose, self-treat, and self-manage the condition; the drug must have a low potential for misuse and abuse and the benefits of OTC availability must outweigh the risks.

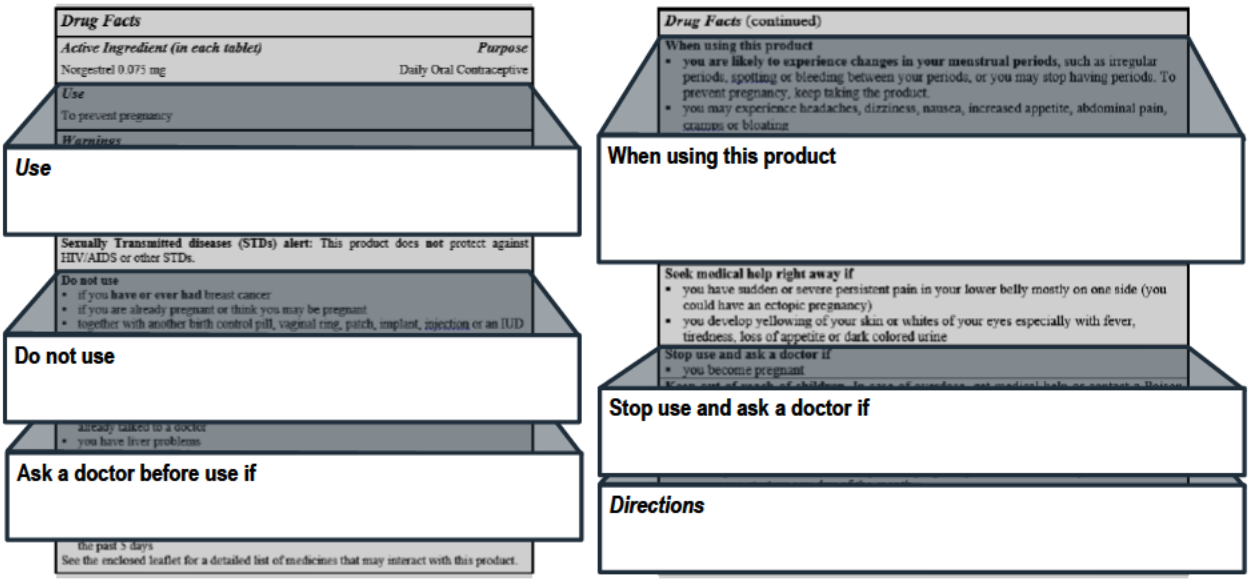
When considering an OTC switch, like that being proposed for Opill, it is important to recognize that the efficacy and safety have already been established for the Rx drug. Thus, one must determine what incremental benefits or risks result from moving the drug from Rx to OTC status. These incremental benefits and risks result from increased access to the drug, removal of the HCP prescribing of the drug, and the behaviors of the consumer using the drug as guided by the OTC label.

The central part of the OTC label, the Drug Facts Label (DFL), must adhere to a highly standardized, regulated format (21 CFR Part 201). Key sections of a standard DFL are illustrated in Figure 12. These sections are designed to allow a consumer to decide if the drug is appropriate for their own use (if they meet the indication and do not have contraindications), how to use the drug (directions), and how to respond over the course of therapy, including to any adverse reactions. Once a proposed DFL is developed, it is tested to determine whether consumers can understand and correctly use the label information. These are evaluated through an iterative process that includes:

- Label Comprehension Studies (LCSs), which focus on consumers ability to read and understand the information on the label,
- Self-Selection Studies (SSSs), which specifically assess whether consumers can use the label information to decide if the drug is right for them to use, and
- Actual Use Trials (AUTs), which evaluate consumers' ability to use the label information to use the drug as directed in a simulated OTC environment.

After completion of each study, the data are evaluated and the labeling may be further refined and tested to ensure the label supports safe and effective use of the product in the OTC setting.

Figure 12: Standardized Format of the Drug Facts Label for OTC Products



21 CFR 201.66(c)(1)-(9)

3.3.1 Proposed Use and Administration

The proprietary name (Opill), dosing regimen, and route of administration are the same as in the current Rx labeling: One tablet (0.075 mg norgestrel) taken orally at the same time every day.

The proposed OTC label (see Figure 13 to Figure 15 for proposed Opill OTC label) directs consumers to “take 1 tablet at the same time every day”.

The proposed indication for the OTC setting is:

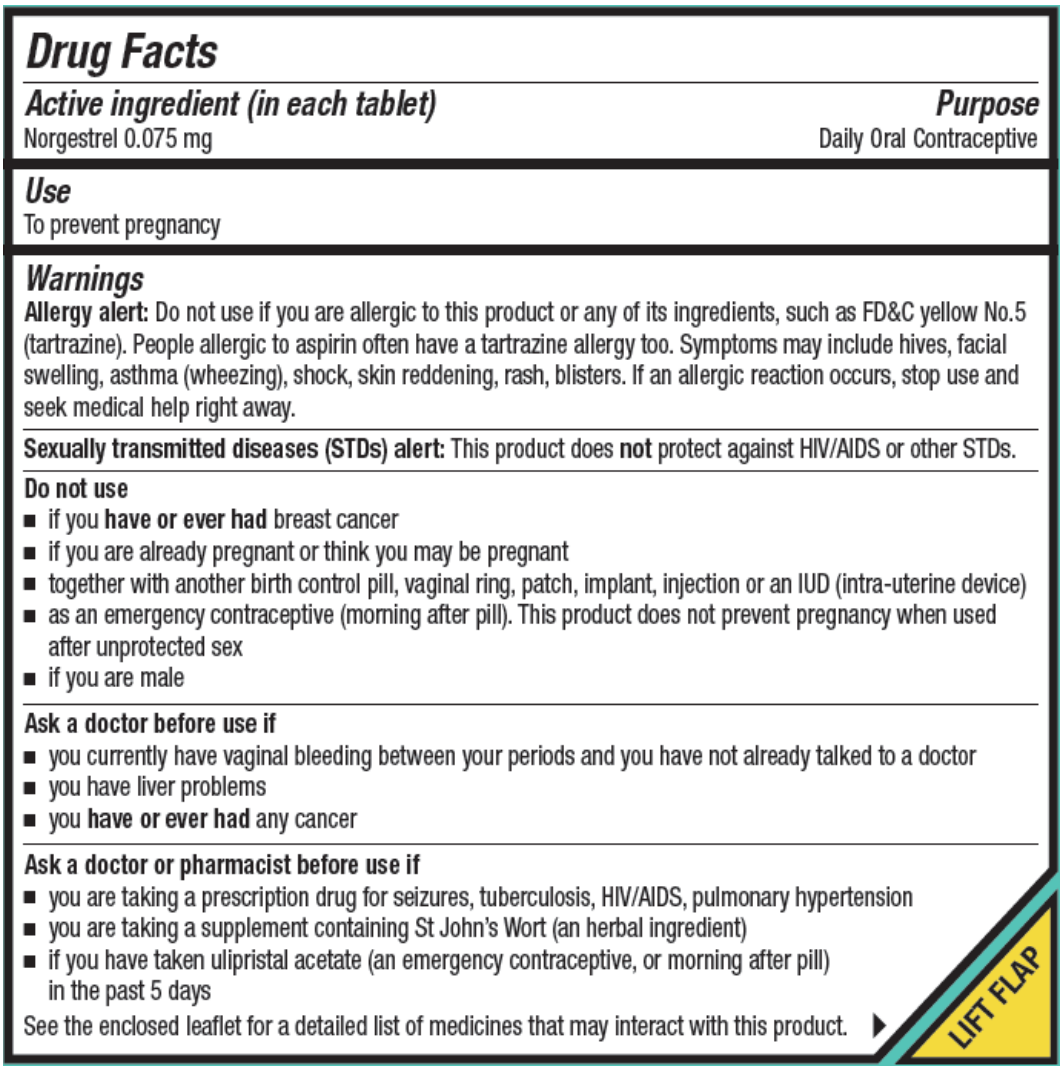
“Use: To prevent pregnancy” – “Purpose: Daily Oral Contraceptive”

3.3.2 Proposed OTC Labeling Components

The Opill proposed OTC labeling consists of three main components:

1. The outer carton containing the DFL, which incorporates all of the information from the Rx label that consumers need to appropriately select and use the product safely and effectively and presents that information in a way that is understood by consumers (Figure 13 to Figure 15).
2. The Consumer Information Leaflet (CIL), included inside the OTC package, provides more detailed information on key messages already on the DFL, as well as additional general educational information (e.g., reminders to obtain recommended preventive screenings). It also provides supportive information for consumers who are starting use of this product for the first time (e.g., suggested tips to help users remember to take one tablet every day, at the same time of day), and about possible scenarios that consumers may encounter once they are using this product (see Appendix Section 11.1.1);
3. A Reminder Card included inside the packaging to further support consumers in adhering to key label directions (see Appendix Section 11.1.2).

Figure 13: Proposed Drug Facts Label for OTC Opill – Panel 1 of 3



Drug Facts

Active ingredient (in each tablet)
Norgestrel 0.075 mg

Purpose
Daily Oral Contraceptive

Use
To prevent pregnancy

Warnings

Allergy alert: Do not use if you are allergic to this product or any of its ingredients, such as FD&C yellow No.5 (tartrazine). People allergic to aspirin often have a tartrazine allergy too. Symptoms may include hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

Sexually transmitted diseases (STDs) alert: This product does **not** protect against HIV/AIDS or other STDs.

Do not use

- if you **have or ever had** breast cancer
- if 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)
- as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex
- if you are male

Ask a doctor before use if

- you currently have vaginal bleeding between your periods and you have not already talked to a doctor
- you have liver problems
- you **have or ever had** any cancer

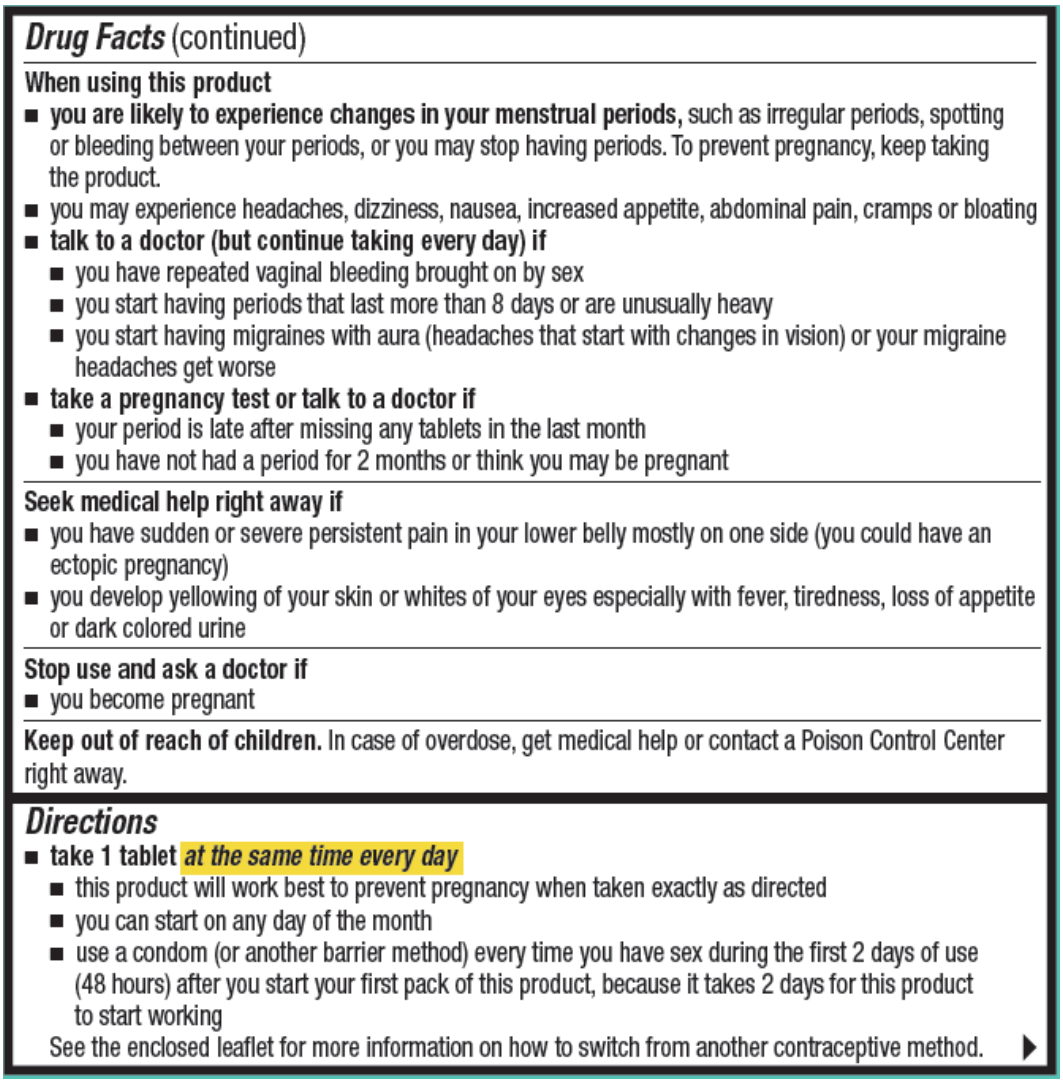
Ask a doctor or pharmacist before use if

- you are taking a prescription drug for seizures, tuberculosis, HIV/AIDS, pulmonary hypertension
- you are taking a supplement containing St John's Wort (an herbal ingredient)
- if you have taken ulipristal acetate (an emergency contraceptive, or morning after pill) in the past 5 days

See the enclosed leaflet for a detailed list of medicines that may interact with this product. ▶

LIFT FLAP

Figure 14: Proposed Drug Facts Label for OTC Opill – Panel 2 of 3



Drug Facts (continued)

When using this product

- **you are likely to experience changes in your menstrual periods,** such as irregular periods, spotting or bleeding between your periods, or you may stop having periods. To prevent pregnancy, keep taking the product.
- you may experience headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating
- **talk to a doctor (but continue taking every day) if**
  - you have repeated vaginal bleeding brought on by sex
  - you start having periods that last more than 8 days or are unusually heavy
  - you start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse
- **take a pregnancy test or talk to a doctor if**
  - your period is late after missing any tablets in the last month
  - you have not had a period for 2 months or think you may be pregnant

Seek medical help right away if

- you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy)
- you develop yellowing of your skin or whites of your eyes especially with fever, tiredness, loss of appetite or dark colored urine

Stop use and ask a doctor if

- you become pregnant

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

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

See the enclosed leaflet for more information on how to switch from another contraceptive method. ▶

Figure 15: Proposed Drug Facts Label for OTC Opill – Panel 3 of 3

Drug Facts (continued)

Directions (continued)

- **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 this product 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
- you should continue to see your healthcare provider(s) for routine healthcare visits

When to use a condom (or another barrier method)

- every time you have sex for the next 2 days (48 hours):
  - after you start your first pack of this product
  - if you take a tablet more than 3 hours late or miss a tablet on 1 or more days
  - if you vomit or have a severe diarrhea within 4 hours of taking a tablet

Other information

- contains FD&C yellow No.5 (tartrazine) as a color additive
- **read the instructions, warnings and enclosed product leaflet before use**
- 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
- store between 20°-25°C (68°-77°F)

Inactive ingredients

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

☎ ***Questions or comments?***

Call 1-833-426-6733

3.3.3 OTC Label Development Process and Components of Development Program Supporting Rx-to-OTC Switch

The key studies conducted to support the Rx-to-OTC switch are listed below in Table 5. HRA initiated an extensive, iterative label development process, which began by adapting the Opill Rx labeling into consumer-friendly language. The OTC label was also informed by relevant national medical guidance [e.g., the CDC Selected Practice Recommendations for Contraceptive Use (SPR) (Curtis et al 2016a) and the CDC MEC (Curtis et al 2016b)] and follows the standard format for all OTC products.

Between 2015 and 2021, HRA interacted with the FDA 13 times to discuss the proposed OTC labeling and the consumer studies. These discussions covered the LCSs and SS/AUTs that would be necessary to support an application to change the marketing status of Opill to OTC.

The proposed DFL and CIL, initially drafted in 2015 at the start of the development program, have been updated a number of times based on the results of consumer studies designed to optimize the labeling and several rounds of feedback from the FDA. The proposed DFL and CIL were tested in several qualitative, pilot and pivotal LCSs and a pilot SSS, over the course of 2015 to 2017, before the SS/AUTs were initiated in 2018. The ultimate study of this program that combined a final LCS on a general population of women, with a targeted SSS on women with a history of breast cancer (the Final LCS/Targeted BC SSS) was conducted in 2021 to test the final proposed DFL.

Overall, the proposed OTC label was tested over a seven-year development program, in label comprehension testing, self-selection testing, and in actual use testing in a simulated OTC environment, all of which comprised a total of 14 consumer studies, involving many thousand participants.

Of the 14 studies, the consumer studies listed in Table 5 provided the most robust assessment of the proposed Opill OTC labeling. This series of studies conclusively demonstrated that the proposed OTC labeling guides the appropriate consumer behavior, including selection or non-selection of the product, how to take the product, and when to stop use and/or consult an HCP. The focus of this Briefing Document is on the pivotal SS/AUT known as ACCESS and the Targeted BC SSS, but results on the Final LCS can also be found in Appendix Section 11.4.

A pharmacodynamic study was conducted to understand the impact of a delayed or missed dose (see Section 6.2.4). Additionally, a Pregnancy Impact Model was developed to estimate the magnitude of the benefit of OTC Opill use in reducing unintended pregnancies (Guillard et al 2023).

Table 5: Key Studies with Overall Results of HRA's Development Program Supporting the Rx-to-OTC Switch

Category	Studies / Period of Data Collection	Overall Results
Label Comprehension	LCSs of DFL 2015 – 2017	Demonstrated that most of the proposed DFL messages were well understood and identified the few proposed messages that needed further refinement prior to the label being used in subsequent consumer studies (SS / AUTs).
	LCS of CIL 2017	Demonstrated the key CIL messages were well understood. This study tested an earlier version of the CIL than that used in the pivotal ACCESS SS/AUT.
Self-Selection / Actual Use	ACCESS September 2019 to August 2021	Demonstrated that consumers can use the product as directed in labeling without an HCP. Participants were provided with DFL, CIL and Reminder Card.
Label Comprehension / Targeted Self-Selection	Final LCS/Targeted BC SSS August to September 2021	Demonstrated that consumers understand the key DFL messages and that women with breast cancer can correctly select not to use the product.
Pharmacodynamic	Delayed Pill Intake Study July 2018 to April 2020	Demonstrated Opill users are highly protected from conception even if they are late in taking one pill or miss one pill. This study was not a consumer behavioral study.

ACCESS: Adherence with Continuous dose Oral Contraceptive: Evaluation of Self-Selection and Use; AUT: actual use trial; BC: breast cancer; CIL: consumer information leaflet; DFL: drug facts label; HCP: healthcare practitioner; LCS: label comprehension study; Rx-to-OTC: prescription to over-the-counter; SS: self-selection; SSS: self-selection study

4 CONSUMER STUDIES BACKGROUND AND ACCESS STUDY DESIGN

This section introduces the consumer studies that are typically done to support an Rx-to-OTC switch application, as well as the design of the main study in this program, ACCESS.

4.1 Introduction to Consumer Behavior Studies to Support Rx-to-OTC Switch

Because products being considered for switch to OTC status are already approved for Rx use, their efficacy and safety are already established. OTC status allows access without requiring an HCP intermediary, and instead relies on product labeling, principally the DFL, to guide consumers. This drives the research questions that consumer behavior studies address, namely:

- Do consumers understand the OTC labeling?
- Does the DFL appropriately guide consumers as they decide if a product is appropriate for them?
- Do consumers use a product correctly in an OTC-like setting?

These questions are addressed through LCCs, SSSs, and AUTs.

LCSs address whether consumers understand the messages in the DFL. Multiple studies are often done to allow for messages to be refined in response to insights from consumers and feedback from the FDA. Participants are recruited members of the general population. However, in some cases, study participants with characteristics of expected eventual users or of special interest may be recruited. Also, specific subpopulations are tested to assess the potential impact of such variables as age or health literacy.

SSSs assess whether the DFL guides consumers to decide if a product is appropriate for them. In SSSs, participants who are potentially interested in the product are recruited to find out if they can decide on their own if a product is okay or not okay for them to use. In some cases, if there is concern about the ability of those with a specific contraindication to identify that the product is not appropriate for them, a targeted SSSs may be conducted in which participants with the contraindication are recruited.

AUTs are open-label studies conducted to evaluate whether a product can be used correctly as guided by the OTC labeling, without the supervision of an HCP. AUTs measure behaviors of interest during their use of the product and are designed to mimic the OTC environment as much as possible. Therefore, AUTs are less controlled than randomized controlled clinical trials (RCTs; Table 6). RCTs are designed to demonstrate the effect of a drug or intervention, and therefore take great pains to control variables like participant behavior. There are often restrictive inclusion/exclusion criteria and participants are regularly reminded to follow study procedures and are provided detailed instructions for the use, and measures are often put in place to ensure compliance and adherence. In contrast, AUTs are observational and minimally controlled, seeking to understand behavior relative to the directions on the label, in an uncontrolled setting. These studies are also all-comers, to the extent possible, so they involve minimal exclusion criteria. Recruitment is generally passive, meaning that participants must see advertising, decide that they are interested,

and initiate contact with the study team, similar to what a consumer might experience when selecting to use an OTC product in the real-world marketplace. Because use of the product is entirely left up to participants, study measures are designed to allow for a wide variety of participant behaviors and to minimize reactivity, or the likelihood of biasing behaviors by the very methods that are intended to measure them. So, to avoid cueing or guiding participant responses, methods often employed to confirm self-reported dosing in some clinical trials are not used, and detailed drug accountability during the course of the study is not done (in order to avoid biasing future behavior). Additionally, while participants are asked to return study drug and other materials, detailed per-pill end-of-study drug accountability is not feasible, as most participants do not return product that they feel they have purchased.

Table 6: Characteristics of Actual Use Trials Compared to Randomized Clinical Trials and Real-World OTC Marketplace

	Randomized Control Trial	Actual Use Trial	Real-World OTC Marketplace
IRB approved	YES	YES	NO
Follow Good Clinical Practices (ICH E6)	YES	YES	NO
Detailed instructions to participants on protocol and use of study drug	YES	NO	NO
Regular interaction with participants to ensure protocol compliance	YES	NO	NO
Frequent monitoring of adherence/compliance	YES	NO	NO
Qualified population	Restricted	Broad	Broad
Study participant/consumer pays out-of-pocket for drug	NO	YES	YES
Proposed marketing packaging to study participants/consumers	NO	YES	YES
Study participant/consumer access to information sources on drug	NO	NO	YES
Multiple locations to access additional drug	NO	NO	YES

ICH: International Council for Harmonisation; IRB: Institutional Review Board; OTC: over-the-counter

Additionally, consumer behavior studies are generally observational rather than hypothesis driven, and therefore success in these studies is not judged by strict statistical testing. Target performance thresholds are established *a priori* by a thoughtful appraisal of the clinical consequences if consumers do not follow the label instructions. Importantly, these target threshold act as a guidepost for decision making, to help understand if consumers will generally perform in a way consistent with the intent of the labeling. The specific thresholds for ACCESS and the Targeted BC SSS are referenced when discussing the endpoints and results in Sections 5.1.2, 5.2.2 and 6.2.1.

It is important to note that in nonprescription consumer behavior studies, success thresholds are targets, not automatic “hard stops.” If an objective fails to meet a threshold, the clinical impact is considered within the total risk-benefit assessment.

4.2 ACCESS Study Design

4.2.1 ACCESS Study Objectives

The **A**dherence with **C**ontinuous-dose Oral **C**ontraceptive**: E**valuation of **S**elf-**S**election and Use (ACCESS), the pivotal SS/AUT for the Opill Rx-to-OTC switch development program, was a single arm, non-randomized, open label, multicenter, 24-week prospective study. The study was designed to assess if, when, and how participants used Opill in an OTC-like environment. The objective of ACCESS was to evaluate the adequacy of the proposed OTC labeling to guide appropriate consumer selection and use behaviors using pre-specified endpoints.

4.2.2 ACCESS Participant Recruitment

Participants were recruited into the study based on their interest in a nonprescription OC pill. In order to mimic the OTC marketplace as much as possible, initial participant recruitment was based on consumer response to digital and print 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 Rx strength OTC birth control pill.”). Approximately 1.6 million print advertisement mailers were sent to households; digital ads were deployed which were collectively viewed over 98 million times. In this way, the study sample was generated in the same way that the potential users of an OTC OC would self-identify and purchase. This generated a sample that was most likely to be representative of a population who would be interested in using an OC if it was available OTC.

Adolescents were an important subgroup of interest to ensure this population could use the OTC labeling properly. Therefore, a sample of 175 user participants ages 17 and under including 50 aged 14 and under was planned. To meet this challenging target, staff within women’s health or adolescent clinic sites that specifically enrolled participants below the age of 18 were allowed to invite adolescents to participate in the study during a clinic visit if they identified a need for contraception and expressed a preference for an OC.

Respondents to digital or print advertisements either called the decentralized research site or visited a study website for initial screening during which data regarding age, gender, and minimal study exclusion criteria were collected. They then scheduled an in-person enrollment visit at a local participating research site.

A total of 36 sites were used, comprising 25 retail pharmacy research sites augmented by 10 women’s health clinics or adolescent clinics in geographically diverse locations. Additionally, a single (1) decentralized site was used during the Coronavirus Disease 2019 (COVID-19) pandemic for remote enrollment, when only participants below 18 were recruited to meet the target enrollment for users aged 17 and under.

4.2.3 ACCESS Enrollment Criteria

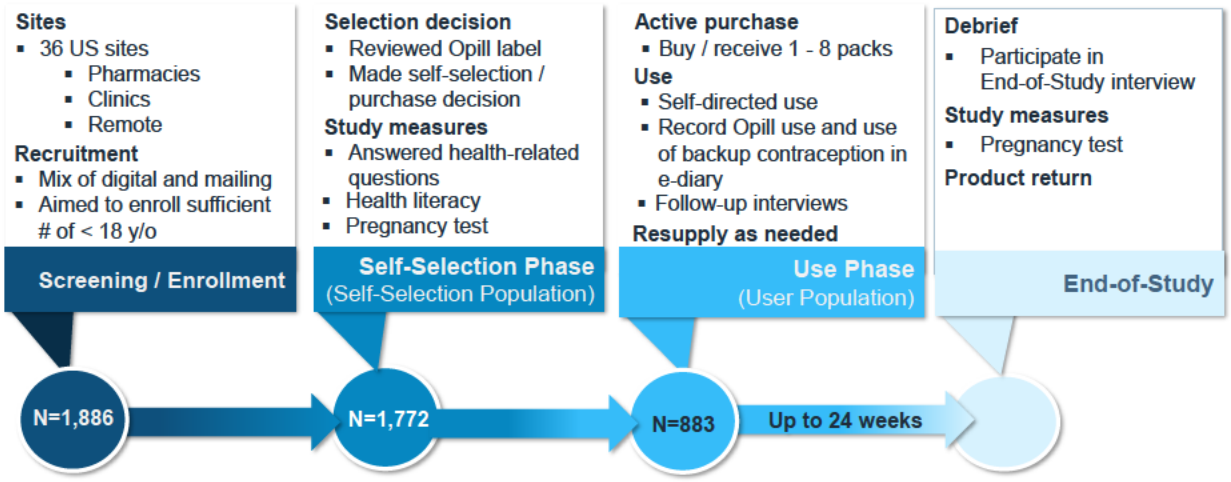
In order to enroll a sample as representative as possible of the likely OTC consumer population, the study inclusion criteria were defined as broadly as was feasible. Participants had to meet the following initial screening study inclusion criteria:

1. Able to read, speak and understand English
2. 11 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, nor anyone else, in the household does not work for a 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, and has not 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 OTC birth control medicines

4.2.4 Overview of Study Phases in ACCESS

The study included a Screening/Enrollment visit, followed by the Self-Selection Phase and then the Use Phase (Figure 16).

Figure 16: ACCESS Study Design



REALM: Rapid Estimate of Adult Literacy in Medicine; REALM-Teen: Rapid Estimate of Adolescent Literacy in Medicine; US: United States; y/o: years old
Note: follow-up interviews at weeks 2, 4, 8, 12, 16, 20, and 24

Following enrollment into the study, participants were asked to review the Opill packaging and were allowed as much time as they needed to review the information on the outside of

the entire package (including the DFL). Participants were then asked if the product was okay or not okay for them to use (the Self-Selection Question). Those who reported that it was okay for them to use were asked if they would like to purchase or obtain it for their own use (the Purchase Question). Reasons for responses to the Self-Selection Question or the Purchase Question that indicate that a participant would not select or purchase were recorded.

Following the Selection and Purchase Questions, in response to a structured questionnaire, participants provided limited medical history to determine whether individual label messages applied to them. Participants also provided current medication use, and demographic information. The Rapid Estimate of Adult Literacy in Medicine (REALM) or Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) was then administered (Davis et al 1993). Participants were asked to sign the informed consent only after the Selection and Purchase Questions to avoid biasing those decisions. The consent did not disclose the post-study reimbursement of out-of-pocket Opill costs but disclosed compensation to participate in various steps of the study. Participants who signed consent took a urine-based pregnancy test. Participants were excluded from the Use Phase of the study if they met any of the Use Phase exclusion criteria, including (1) elected not to purchase study medication (pharmacy sites); (2) declined to be dispensed study product for use (clinic sites); (3) did not to provide informed consent; (4) would not or unable to provide contact information; (5) would not state that the product is for their own use and no one else's; (6) premenarchal; (7) pregnant (based on self-report or enrollment pregnancy test); (8) male; (9) known allergy to norgestrel or inactive ingredients; (10) history of any cancer.

Additional Use Phase inclusion criteria included (1) evidence of a personally signed and dated informed consent form indicating that the participant (or a legal guardian) has been informed of all pertinent aspects of the study, and (2) willing and able to comply with the initial enrollment visit, planned phone calls and other study procedures, and the end of study (EOS) visit.

Qualified participants who elected to proceed to the Use Phase of the study were then allowed to purchase (pharmacy sites, comprising an actual out-of-pocket purchase transaction) or be given (clinic or remote enrollment sites) Opill to take home and use as guided by the label. They were informed that they could return to the site at any time for resupply. In pharmacy sites, participants paid $10 per one-month pack of product, or $20 for three packs. Participants were allowed to purchase/obtain up to 8 packages of 28 tablets during the study period, although that limit was not communicated to participants unless they attempted to purchase/obtain more than that. Participants recorded their use of the product and use of backup contraception along with use of other contraceptive measures using an online medication use diary (e-diary) and received regular periodic electronic reminders to complete their diary through the e-diary application, regardless of their diary completion rate.

Due to COVID-19, participants who enrolled after the pandemic began did so remotely via a telephone enrollment interview after responding to advertising. At the onset of the

COVID-19 pandemic, only enrollment of the adolescent subset remained to be completed. Informed consent was obtained via email (with an impartial witness present when necessary), with study materials (including study drug) delivered via next-day shipping. Similarly, participants who were enrolled before the pandemic began, but who had not yet exited the Use Phase, were resupplied with study product via next-day shipping upon their request.

After enrollment, participants were subsequently interviewed via telephone by trained nurse interviewers working from a central research site at weeks 2, 4, 8, 12, 16, 20 and 24. During those interviews, information was gathered on the product intake, diary entry, AEs, concomitant medications, and other actions the participant may have taken related to the product use. After 24 weeks of participation, or if the participant indicated earlier than 24 weeks that they had discontinued use of Opill and did not intend to restart, the end-of-study (EOS) interview was conducted. During the EOS interview, the participant was asked about other aspects of behavior, including whether they experienced any of the conditions where the label advises to talk to an HCP or stop use, and whether they did so. The participant was then asked to take a urine-based pregnancy test and return any unused study medication and/or packaging.

5 ASSESSMENT OF SELF-SELECTION: CONSUMERS CAN APPROPRIATELY SELECT OPILL IN THE OTC SETTING

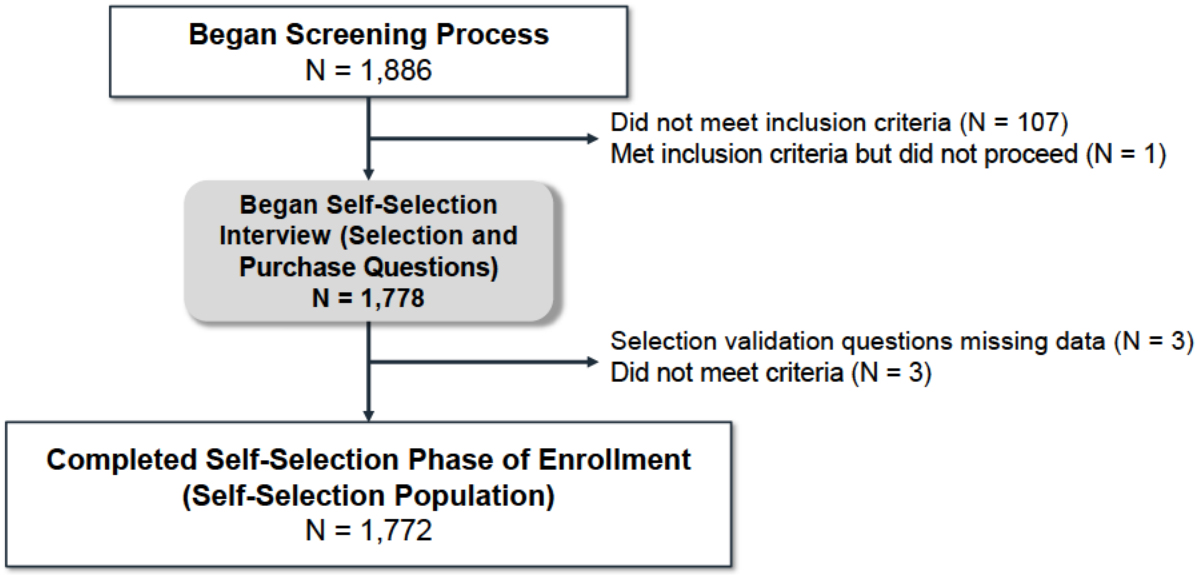
5.1 Assessment of Self-Selection in ACCESS

5.1.1 ACCESS Self-Selection Participants

5.1.1.1 ACCESS Self-Selection Population

All participants who scheduled an appointment and presented for an onsite or remote enrollment interview were re-asked initial screening questions to ensure that they qualified to participate in the study. Of the 1,886 participants who began the enrollment interview screening, 94.3% were qualified (see inclusion criteria listed in Section 4.2.3) after screening to proceed with the Self-Selection Phase of enrollment interview, and 1,772 completed the Self-Selection Phase of the enrollment interview, forming the Self-Selection Population (Figure 17).

Figure 17: ACCESS Self-Selection Flow Diagram



5.1.1.2 Demographics and Baseline Characteristics

The ACCESS study enrolled participants with a wide range of education levels and income levels and was racially and ethnically diverse (Table 7 and Table 8). Subpopulations of interest agreed upon with FDA (adolescents aged 17 and under, those of low health literacy, and those with prior hormonal birth control use) were well represented in each of these populations providing sufficiently precise estimates of the self-selection behaviors in those groups. Participants aged 17 and under were over-represented in the ACCESS study versus their proportion among US women at risk of unintended pregnancy to ensure an adequate sample of this subgroup.

Table 7: ACCESS Demographic Data – Self-Selection Population

	Self-Selection Population (N=1,772)	
	n	%
Sex		
Female	1,765	99.6%
Male	7	0.4%
Race [1]		
American Indian or Alaska Native	53	3.0%
Asian	106	6.0%
Black or African American	534	30.1%
Native Hawaiian or other Pacific Islander	25	1.4%
White	1,057	59.7%
Other	105	5.9%
Refused	16	0.9%
Ethnicity		
Hispanic or Latino/Latina	306	17.3%
Not Hispanic or Latino/Latina	1,464	82.6%
Refused	2	0.1%
Age Groups		
Female age 12-14	88	5.0%
Female age 15-17	275	15.5%
Female age 18-19	133	7.5%
Female age 20-24	412	23.3%
Female age 25-34	518	29.2%
Female age 35-45	283	16.0%
Female age 46-55	41	2.3%
Female age 56+	15	0.8%
Male age 14-37	7	0.4%
Age Distribution, years		
Mean	26.2	
SD	9.19	
Median	24.0	
Range	12, 68	
Female Participants Age 12-17 by Age		
Age 12	4	0.2%
Age 13	36	2.0%
Age 14	48	2.7%
Age 15	44	2.5%
Age 16	79	4.5%
Age 17	152	8.6%

SD: standard deviation
[1] Answers not mutually exclusive

Table 8: ACCESS Baseline Characteristics – Self-Selection Population

	Self-Selection Population (N=1,772)	
	n	%
Health Literacy		
Normal [1]	1,539	86.9%
Low [2]	226	12.8%
Refused [3]	7	0.4%
History of HBC Use (Females Only)		
History of HBC use	1,333	75.2%
History of oral contraceptive use	1,148	64.8%
No history of HBC use	439	24.8%
Education Level (18 yo+)		
8th grade or less	5	0.3%
Some high school	53	3.0%
High school graduate or GED	304	17.2%
Some college or technical school	571	32.2%
College graduate	384	21.7%
Post-graduate degree	89	5.0%
Education Level (12-17 yo)		
7th grade or less	37	2.1%
8th grade	47	2.7%
9th grade	54	3.0%
10th grade	83	4.7%
11th grade	109	6.2%
12th grade	14	0.8%
High school graduate, GED, or certificate	16	0.9%
Some college or technical school	6	0.3%
Estimated Annual Household Income		
Less than $25,000	540	30.5%
$25,001 - $50,000	551	31.1%
$50,001 - $75,000	263	14.8%
$75,001 - $100,000	127	7.2%
$100,001 - $150,000	114	6.4%
More than $150,000	53	3.0%
Don't know	120	6.8%
Refused	4	0.2%

HBC: hormonal birth control; GED: General Educational Development test; yo: year olds
[1] Scored at least 61 on the Rapid Estimate of Adult Literacy in Medicine (REALM) Test or Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) Test
[2] Scored at most 60 on the REALM Test or REALM-Teen Test
[3] Participant refused to take the REALM Test or REALM-Teen Test

5.1.2 ACCESS Self-Selection Endpoints

As noted in Section 4.1, SSSs assess how the DFL influences consumers' decisions about using a product. In ACCESS, each participant was classified on two variables: first, whether they selected to use the product, and second, whether they were appropriate (or acceptable) to use the product. These two independent variables were cross-tabulated to create a self-selection matrix (as shown in Table 9) which was used to assess both correct

selection (primary endpoint) and correct non-selection (secondary endpoint) described further below.

Table 9: ACCESS Self-Selection Matrix

Selection Classification	Appropriateness to Use Classification: Appropriate to Use (or Acceptable to Use)	Appropriateness to Use Classification: Not Appropriate to Use
Selector	**Group A:** represents a ***correct decision***, namely consumers for whom the study product was right to use and chose to use it.	**Group B:** represents an ***incorrect decision***, namely a consumer for whom the study product was not right to use and chose to use it.
Non-Selector	**Group C:** represents a consumer who *could* be correct to use the product, but did not select, therefore excluded from calculation. This decision accrues no health risk.	**Group D**: represents a ***correct decision***, namely a consumer for whom the study product was not right to use and chose not to use it.

Selection of the Product Classification:

Two questions were used to determine whether a participant selected the product:

> Self-Selection Question: *"Given what you have read on the label and your own health history, is this product okay or not okay for you to take home today and start to use? Why or why not?"*
>
> Purchase Question: *"Would you like to purchase Opill today to take home for your own use? Why or why not?"*.

In the ACCESS study, verbatim responses to the Self-Selection Question and Purchase Question, along with the associated follow-up questions were reviewed to determine each participant's selection status. This recognizes that the Self-Selection Question ("okay to use") is often interpreted in a non-specific general appeal manner, while the Purchase Question ("purchase and use") requires a more focused, real-world healthcare specific decision by the participant, and responses to both of these questions (and their response to why/why not follow-up questions) are informative in understanding each participant's selection decision.

Note that participants could respond affirmatively to the Purchase Question without ultimately deciding to purchase the study product and enroll in the Use Phase of the study.

Appropriateness to Use Classification:

To determine whether a participant was appropriate (or acceptable) to use Opill, the following seven health items were considered:

- Do not use:
    - if you have ever had any cancer (note: this warning was updated after ACCESS study and the final warning was re-assessed in the Targeted BC SSS)

  - if you are already pregnant or think you may be pregnant
  - if you are allergic to any of the ingredients in Opill
  - if you are male
- Ask a doctor before use (participant correctly followed this message if they did not select the product or if they selected the product and spoke to a doctor)
  - if you have unexplained vaginal bleeding between your periods
  - if you have liver problems
- Use to prevent pregnancy
  - Participants had to self-report as being physically able to become pregnant to be considered correct if they selected Opill for their own use.

Each health item was assessed using direct, closed-end questions (e.g., *"Have you ever been diagnosed with cancer?"* Yes/No) accompanied by open-end follow-up questions to further understand the condition (e.g., *"What type of cancer did you have?")*.

In the ACCESS study, an algorithm was used to determine an initial classification of "**Appropriateness to Use Per Label**" that only considered the responses provided in the initial, direct question addressing each health item.

Additionally, a classification of "**Appropriateness to Use Per Physician Review**" was determined by a three-physician panel (independent review; majority rules). The panel reviewed all the health information (e.g., the answer to the direct questions as well as the follow-up questions) provided by the participants who selected the product while being classified as non-appropriate to use per label, and reclassified selected participants based on their clinical judgement of the situation (identified as "acceptable to use").

Endpoint Evaluation:

The pre-specified endpoint analyses were made based on the participants' selection status as described above and the Appropriateness to Use inclusive of the Physician Review classification, because it represented the most complete assessment of each participant's intent to select the product for their own use and the likely clinical impact of these decisions.

The following self-selection endpoints of ACCESS were evaluated:

- **Primary Endpoint**: % Self-Selection Population who made a correct selection decision ([Group A + Group D] / [Group A + Group B + Group D]); 85% target threshold guided by clinical assessment of risk associated with not following the label.
  - Group C represents those who make a decision that poses no risk to the consumer and technically not an incorrect or correct decision, as deciding not to use a product that they are medically appropriate for is a matter of

personal choice. Thus, these participants are excluded from the percent correct calculation.

- The target threshold of 85% for overall self-selection was chosen to reflect the relative safety of this product and the relatively few limitations on use and the likely modest clinical consequences for failure to select appropriately.

- **Secondary Endpoint**: % Self-Selection Population who were not appropriate to use and correctly did not select the product for their own use (Group D / [Group B + Group D]).

  Note that there are few clinical situations that preclude use of Opill, impacting a relatively low prevalence of women of reproductive age. Therefore, the size of this subgroup was expected to be small and thus, the assessment of appropriate non-selection for this subgroup would be expected to have a 95% CI that is overly wide. This makes comparison to any threshold uninformative. Furthermore, there could be multiple reasons contributing to inappropriateness to use with highly variable levels of clinical importance (discussed in Section 5.3). Therefore, this assessment was designated as a secondary endpoint.

Additional statements that were also assessed as self-selection secondary endpoints in the ACCESS study are summarized in Appendix Section 11.3.

5.1.3 ACCESS Self-Selection Results

Figure 18 describes the classification of participants for the primary self-selection endpoint.

Of the 1,772 participants who took part in the Self-Selection Phase of the study, 1,597 said "okay" to the Self-Selection Question ("*Given what you have read on the label and your own health history, is this product okay or not okay for you to take home today and start to use?*").

However, classification of selection based on the Self-Selection Question alone does not reflect the complex nature of each participant's selection decision. When the decision to select is probed further with the Purchase Question, the complete review of responses makes clear which participants would actually select to use Opill for themselves. For example, many participants interpret the initial Self-Selection Question as a question about the general appeal of the product and answer affirmatively, but in response to the Purchase Question ("*Would you like to purchase Opill today to take home for your own use?*") make it clear that they would not personally select Opill. See Table 10 for examples of participants who said "okay" to the Self-Selection Question but were classified as non-selectors based on their complete responses to all questions in the selection section of the interview.

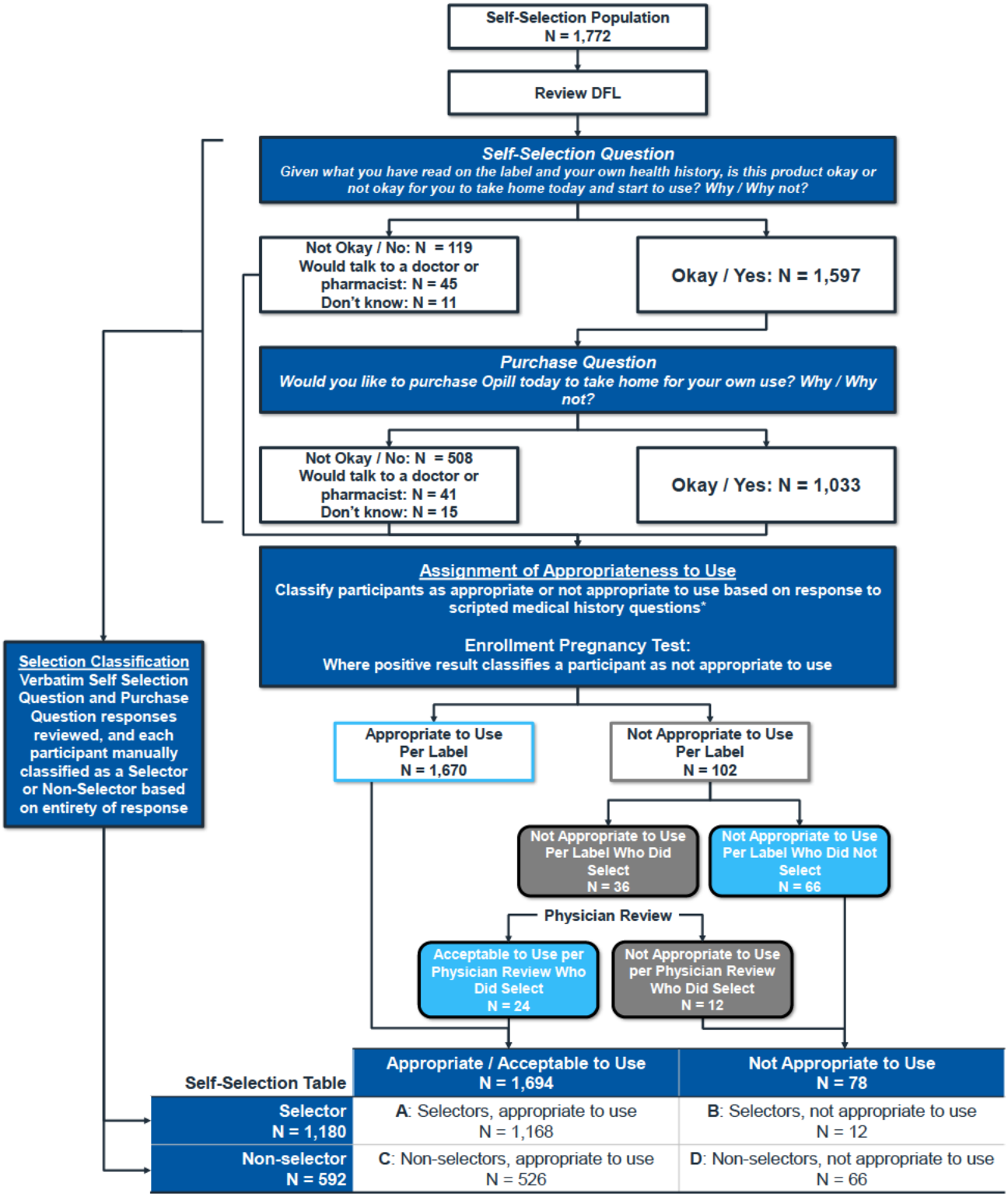
Table 10: Examples of Participants who Said "Okay" to the Self-Selection Question but Were Classified as Non-Selectors Based on their Complete Responses to All Questions Used to Determine Each Participant's Selection Status

Okay?	Why?	Purchase?	Why?
Yes	I'm looking at it and it doesn't have estrogen in it, it seems real simple and specific and it explains thoroughly the side effects, which seem to be mild compared to other birth control methods. It seems very easy to use. I like the reminder stickers.	No	I don't need it because I am menopausal, but I would purchase it for my granddaughter
Yes	Taking pills isn't as bad as going in to see a doctor regularly, this is something that can be controlled at home	No	Doesn't need birth control right now
Yes	Has basic information like the prescribed birth control. If over counter the information is simple to understand	No	Already using a birth control method and doesn't want to change

After classification of selection based on a complete review of responses to the questions in the selection section of the interview, 1,180 participants were classified as "selectors", while 592 were "non-selectors".

There were 102 participants considered not appropriate to use based on "Appropriateness to Use Per Label" classification. Of those, 36 participants selected to use Opill (i.e., classified as "selectors") despite reporting at least one of the seven health conditions incompatible with Opill use based on the label.

Figure 18: ACCESS Self-Selection Primary Endpoint Participant Flow Diagram



Self-Selection Table	Appropriate / Acceptable to Use N = 1,694	Not Appropriate to Use N = 78
Selector N = 1,180	A: Selectors, appropriate to use N = 1,168	B: Selectors, not appropriate to use N = 12
Non-selector N = 592	C: Non-selectors, appropriate to use N = 526	D: Non-selectors, not appropriate to use N = 66

*Scripted medical history questions include:
- "What was your sex assigned at birth?" where a "Male" response classifies a participant as not appropriate to use
- "Do you have a known allergy to norgestrel, the active ingredient in this product?"
- "Do you have a known allergy to any of these inactive ingredients?"

- "Have you ever been diagnosed with cancer?"
- "To the best of your knowledge, are you currently pregnant?" where "Yes" response classifies participant as not appropriate to use
- "Is your body physically capable of becoming pregnant?" where a "No" response classifies participant as not appropriate to use
- "Do you regularly experience unexplained vaginal bleeding between your menstrual periods?" where "Yes" response, together with no subsequent report of consultation with an HCP, classifies participant as not appropriate to use
- "Has a doctor ever told you that you have liver problems?" where "Yes" response, together with no subsequent report of consultation with an HCP, classifies participant as not appropriate to use

Reasons why these 36 participants were not appropriate to use Opill per the label are shown in Table 11.

Table 11: ACCESS: Reasons Selectors were Classified Not Appropriate to Use Per Label from Responses to Scripted Medical History Questions

	Selectors Not Appropriate to Use Per Label N = 36*
Do not use	
if you have ever had any cancer	6
if you are already pregnant or think you may be pregnant	5
if you are allergic to norgestrel or other ingredients	8
if you are male	2
Ask a doctor before use if you have	
unexplained vaginal bleeding between your periods	6
liver problems	4
Product not indicated for use	
not physically able to become pregnant	7

*Participants could fall into multiple categories

To better understand the potential clinical consequences among these participants who selected to use Opill but were classified as inappropriate to use per the label, three independent obstetrician/gynecologists (OB/GYNs) provided their clinical assessment based on the self-reported medical histories of the 36 participants. The panel assessed whether any of these participants were clinically "acceptable" to use, i.e., they would have prescribed Opill had the individual requested to use it. This analysis determined the participants' "Appropriateness to Use Per Physician Review" classification and is important as it ultimately helps to assess whether there would be a clinical impact from the use decision contrary to the label instructions.

Of the 36, the physician review identified 12 participants who they determined to be not appropriate to use, while 24 were deemed acceptable to use (Table 12). An examination of the 24 participants who were classified as clinically acceptable to use by the physician review panel shows:

- four participants with non-hormonally mediated cancers (in which use of Opill is not contraindicated per the Rx label),

- eight participants who reported allergy to an inactive ingredient (all lactose intolerance, not contraindicated and not the intent of the label message),
- six participants who reported unexplained bleeding between periods prior to enrollment (while advised to discuss with an HCP, not a contraindication to use),
- four participants who reported a history of liver problems (each considered not a contraindication to use),
- and four participants who reported not being physically able to become pregnant (but who might derive clinical benefit from use, such as for heavy menstrual bleeding).

These 24 participants, while not appropriate to use Opill per the label, were assessed as deriving potential benefit from Opill, without increased risk, maintaining a favorable benefit/risk ratio.

Among the remaining 12 participants, the benefit/risk ratio would not be favorable:

- because of no benefit from using Opill:
    - five participants were already pregnant (they learned/were confirmed they were pregnant from the test done after they made their selection decision; none of these participants thereafter indicated an intent to use during pregnancy),
    - two were males (one wanted the product for his female partner and one considered use for gender transition),
    - three were unable to become pregnant (with no other clinical benefit for use),
- because of a possibility of increased risk in one participant with a history of breast cancer and one participant with a history of “venereal” cancer (unlikely to be contraindicated, but not enough information available to assess).

In total, among all 36 participants who were classified not appropriate to use per the label who indicated they would select the product, only one participant may have some clinically important risk because she had a history of breast cancer.

Table 12: ACCESS Summary of Selectors Not Appropriate or Acceptable to Use per Physician Review

Criteria, n	Selectors Classified Not Appropriate to Use Per Physician Review N=12*	Selectors Re-classified Acceptable to Use Per Physician Review N=24*
Do not use		
if you have or ever had any cancer	2	4
if you are already pregnant or think you may be pregnant	5	0
if you are allergic to norgestrel or other ingredients	0	8
if you are male	2	0
Ask a doctor before use if you have		
unexplained vaginal bleeding between your periods	0	6
liver problems	0	4
Product not indicated for use		
not physically able to become pregnant	3	4

*Participants could fall into multiple categories

Overall, regardless of the final physician classification, this suggests that few people may incur clinically important consequences if they inappropriately select to use Opill. The impact of not heeding the self-selection label criteria is discussed in Section 5.3.

As explained above, the pre-specified self-selection endpoint results were calculated using the participants' appropriateness to use status based on the classification per the label *plus* the physician review.

In this analysis, 1,234 participants made a correct selection decision (1,168 + 66) and 12 inappropriately selected Opill (Figure 19). It is considered that the 526 participants who did not select Opill for their own use despite being considered appropriate for use made a neutral decision and were therefore not accounted for in the endpoint calculation.

Figure 19: ACCESS Self-Selection 2x2 Matrix Used for Pre-specified Self-Selection Endpoints

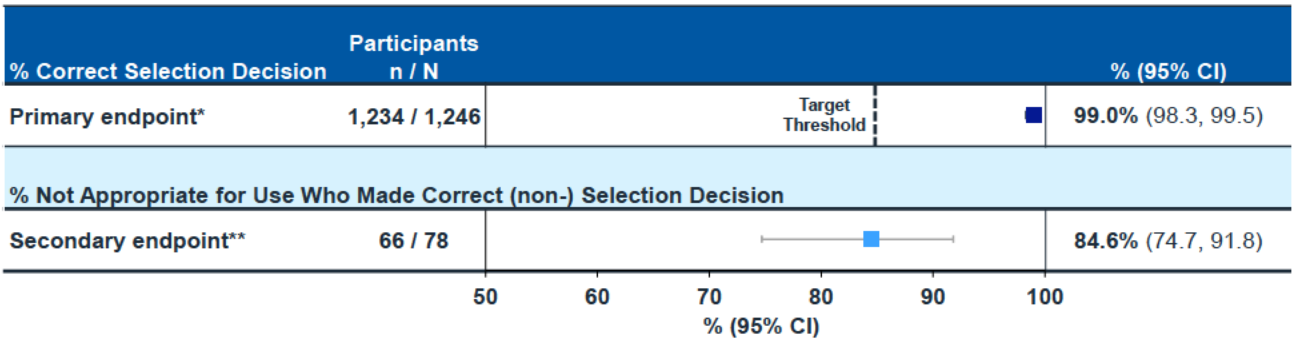
	Appropriateness to Use *Based on per-label classification plus review by panel of 3 physicians*	
Selection (N = 1,772) *Based on complete review of verbatim responses to all SS and Purchase Questions*	**Appropriate:** N = 1,670 + **Acceptable:** N = 24	**Not Appropriate** N = 78
Selector (N = 1,180)	**1,168**	**12**
Non-selector (N = 592)	**526**	**66**

SS: self-selection

Overall, 99% of participants (1,234/1,246) made a correct selection decision when judged against their appropriateness to use classification, exceeding the pre-specified target

threshold of 85% (Figure 20). For the secondary endpoint, 84.6% (66/78) of participants who were not appropriate to use correctly did not select.

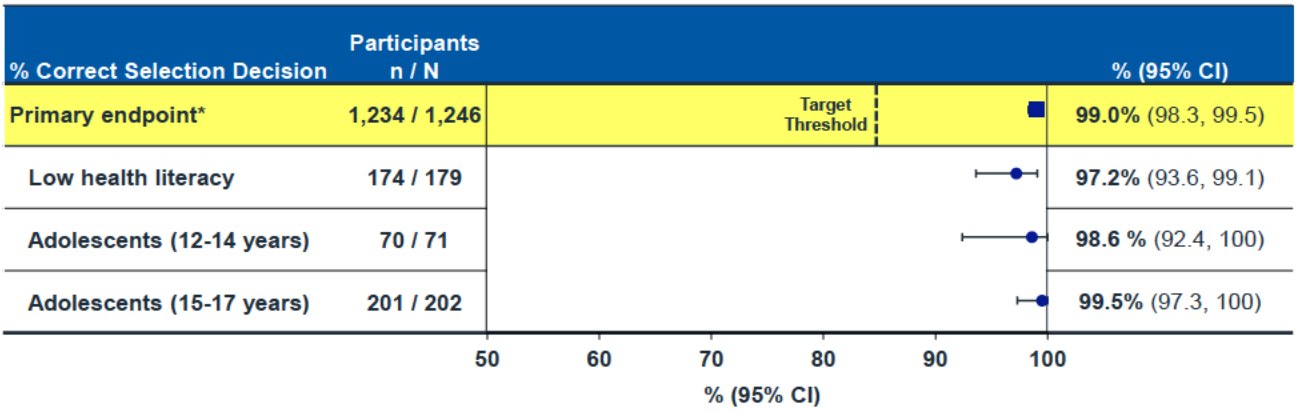
Figure 20: ACCESS Primary and Secondary Self-Selection Endpoint Results



CI: confidence interval; n: correct or acceptable selection decision; *N: all participants except non-selectors who are appropriate for use; **N: all participants who are not appropriate for use per physician review

As shown in Figure 21, performance was consistent across subgroups of participants with low health literacy and in adolescents below 18 years.

Figure 21: ACCESS Self-Selection Subgroup Results



CI: confidence interval; n: correct or acceptable selection decision; *N: all participants except non-selectors who are appropriate for use; **N: all participants who are not appropriate for use per physician review

5.2 Assessment of Self-Selection Among Women with a History of Breast Cancer in the Targeted BC SSS

With breast cancer being the only absolute contraindication for POP use in current clinical guidelines / recommendations which are based on a theoretical risk (see Section 5.3.1.1), the Sponsor conducted the Targeted BC SSS (as part of the Final LCS/Targeted BC SSS) aimed at assessing if women with current or past breast cancer could correctly determine whether Opill was or was not appropriate for their use based on their breast cancer.

In order to recruit participants of reproductive age with current or past breast cancer, invitations to participate in a study were mailed to many thousands of members of a pharmacy benefits manager (Express Scripts) who had a medication history or diagnosis

code suggestive of breast cancer (though they were not informed about why they were being invited to participate). Participation was dependent on recipients responding to mailed invitations. Further details on study procedures and enrollment criteria are provided in Appendix Section 11.4.

5.2.1 Targeted BC SSS Self-Selection Participants

The Self-Selection Population of the Targeted BC SSS included 206 women with current or past breast cancer (Table 13). While race and ethnicity are largely representative of the broader US population of women of reproductive age, this sample tended toward higher educational attainment (with a lower proportion of low health literacy participants), and higher household income. In the experience of the Contract Research Organization, this phenomenon is often seen in samples that are highly targeted for a particular medical condition.

Table 13: Targeted BC SSS: Self-Selection Population Demographics and Baseline Characteristics

	Self-Selection Population (N=206)	
	n	%
Sex		
Female	206	100%
Race [1]		
White	163	79.1%
Black or African American	35	17.0%
Asian	5	2.4%
Native Hawaiian or Other Pacific Islander	1	0.5%
American Indian or Alaska Native	3	1.5%
Other	5	2.4%
Ethnicity		
Hispanic or Latinx	23	11.2%
Not Hispanic or Latinx	183	88.8%
Age Distribution (years)		
Mean (SD)	44.2 (4.7)	
Median	45	
Range	31-50	
Age Groups		
11-24	0	0
25-45	109	52.9%
46-50	97	47.1%
Health Literacy		
Normal [2]	196	95.1%
Low [3]	10	4.9%
History of HBC Use		
History of HBC use and OC use	166	80.6%
History of HBC use but no OC use	22	10.7%
No history of HBC use	18	8.7%
Education		
Some high school or less	1	0.5%
High school graduate or GED	16	7.8%
Some college or technical school	30	14.6%
College graduate	96	46.6%
Post-graduate college degree	63	30.6%
Household Income		
Less than $25,000	3	1.5%
$25,001-$50,000	23	11.2%
$50,001-$75,000	44	21.4%
$75,001-$100,000	37	18.0%
$100,001-$150,000	57	27.7%
More than $150,000	40	19.4%
Refused	2	1.0%

BC SSS: breast cancer self-selection study; GED: General Educational Development test; HBC: hormonal birth control; OC: oral contraceptive; SD: standard deviation

[1] Answers not mutually exclusive

[2] Scored at least 61 on the Rapid Estimate of Adult Literacy in Medicine (REALM) Test or Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) Test

[3] Scored at most 60 on the REALM Test or REALM-Teen Test

5.2.2 Targeted BC SSS Self-Selection Endpoint

The selection and appropriateness to use elements of the Targeted BC SSS mirrored the processes described for ACCESS. To assess self-selection, after having participants with current or past breast cancer review the revised labeling, they were asked if the product was “okay or not okay" for them to use. In order to populate the self-selection matrix (Table 9), any participant who indicated it was “okay to use” was considered an incorrect selector (inappropriate use) based on their previously established breast cancer. However, the OB/GYN panel established for ACCESS reviewed the case reports of all participants who selected incorrectly to determine whether it was clinically appropriate for them to use Opill, i.e., whether they would have prescribed the pill had the participant requested it as a patient.

The sole primary endpoint of the Targeted BC SSS was defined as the proportion of respondents with current or past breast cancer in the Self-Selection Population who correctly did not select the product for their own use. The pre-specified performance threshold for this self-selection endpoint was set at 90%.

5.2.3 Targeted BC SSS Self-Selection Results

Seven participants indicated that the product was appropriate for their use. One of the seven was judged by the physician panel as being at no or minimal clinical risk and was re-classified as acceptable to use because she had been told by her doctor that her cancer was not hormone sensitive and that she could use any contraceptive method; she had also been in remission for nine years. Thus, overall, 97.1% of participants (200/206) made a correct decision to not select the product, with a 95% CI of ± 5.2% (93.7, 98.9). This exceeded the performance threshold of 90%.

Details on the reasons for the decisions of the six participants who responded that the product was okay for them to use are provided and discussed in Section 5.3.1.2.

Overall, these results demonstrate that the breast cancer warning on the DFL successfully mitigates risk that this subset of the potential OTC consumer population would select to use Opill.

5.3 Assessing the Impact of Not Heeding the Self-Selection Label Instructions

In every SSS, there are participants who make erroneous self-selection decisions, some of whom might be representative of consumers who might use the product when the labeling advises otherwise. This section presents the Sponsor’s interpretation of the clinical implications of failing to follow the proposed OTC label, based on the available literature, incorporating results from the Sponsors’ clinical studies and the Final LCS/Targeted BC SSS. The section also addresses the risk in the context of the OTC setting, supporting that the proposed OTC label is sufficient and adequate to mitigate associated risks.

The discussion is based on the ACCESS participants’ “Appropriateness to Use per Label” classification but includes when relevant the “Appropriateness to Use per Physician Review” classification.

5.3.1 Use in Women with Breast Cancer

5.3.1.1 Clinical Context

The warning against use of Opill by women with a history of breast cancer arises from a concern that reproductive hormones may increase the likelihood of, or accelerate, recurrence of breast cancer. The available preclinical data suggest that disease progression or recurrence among women with a history of breast cancer using hormonal contraception is biologically plausible (Catherino et al 1993; Gu et al 2019; Jeng et al 1992; Liang et al 2007; Moreno 2016). However, available clinical data have not confirmed an increased risk of progression or recurrence (Ostroot et al 2021; Trinh et al 2008).

The overall prevalence of breast cancer in women of reproductive age in the US is low [0.25% for women < 50 years; (NCI 2019a)], suggesting the breast cancer warning will be relevant to a small proportion of potential Opill users. Moreover, those women who have been diagnosed with breast cancer are generally under the regular care of a physician and informed that they should not take hormones.

5.3.1.2 Label Development

The DFL used in the ACCESS study included a broad cancer warning:

- Do not use if you have ever had any cancer

The broad warning tested in ACCESS that directed users not to use Opill in case they ever had any cancer was a conservative warning intended to include any cancers that may be hormone-sensitive, as consumers may not know whether their specific cancer is hormone-sensitive.

As anticipated, the number of participants who had ever had a breast cancer was small in ACCESS (2/1,772; 0.1% of the Self-Selection Population) and 14 reported that they had ever had any type of cancer.

Of those 14 participants, 8 made a correct non-selection decision. Four of the six participants who selected Opill for their own use were mitigated by the physician panel as being clinically acceptable for Opill use as their cancers were unlikely to be hormone-sensitive: one with thyroid cancer, two with skin cancer, and one with cervical pre-cancer. Two selectors were still considered not appropriate for use by the physician panel (an incorrect selection decision): one with breast cancer in remission for 1-4 years who justified her decision as “it doesn't seem to have any side effects that interfere with my type of cancer”, and one with “venereal” cancer diagnosed more than 5 years ago for which no further data was available to understand her decision or clinical situation.

A more specific DFL warning:

Do not use
- if you **have or ever had** breast cancer

replaced the original broad cancer “Do not use” warning after the ACCESS study based on feedback from the FDA, as well as an additional message to:

Ask a doctor before use if ▪ … ▪ you have or ever had any cancer

This additional message both reinforces the breast cancer warning and is intended to include any other cancers that may be hormone-sensitive as consumers may not know whether their specific cancer is hormone-sensitive. Given the insufficient sample of women with breast cancer in ACCESS to determine behavior of the breast cancer population and the modification of the cancer messages on the label after ACCESS, this modified label was tested in the Targeted BC SSS. In this study, 97% of participants (200/206) with history of breast cancer correctly determined whether Opill was appropriate for their use (95% CI: 93.8, 98.9%), which exceeded the 90% target threshold and demonstrated that the breast cancer warning on the DFL successfully mitigates risk for this small subset of the potential OTC consumer population.

The six participants in the Targeted BC SSS who responded that the product was okay for them to use were questioned about the reasons for their decisions. One participant reported that she would not purchase the product because she has an IUD. In response to a general question immediately following the selection decision questions about whether there were any label contraindications to taking Opill that applied to them, two participants stated that they could not take the product because of their history of breast cancer, suggesting that they would be unlikely to select (despite their classification as selectors). The remaining three participants did not realize that breast cancer was a contraindication until the debriefing question was asked at the end of the study interview. Of those three participants, one participant noted that she did not think of her own breast cancer as a contraindication because she had been diagnosed with breast cancer so recently (approximately one month before the study interview) and one participant indicated that she would talk to her doctor before purchasing the product.

Overall, results from ACCESS and the Targeted BC SSS show that the Opill DFL can guide appropriate self-selection for women with current or past breast cancer.

5.3.2 Use in Pregnant Women

The DFL used in the ACCESS study included the message:

- Do not use if you are already pregnant or think you may be pregnant

This warning is a conservative approach to the label given that per the CDC MEC, there is no known harm to the woman, the course of her pregnancy, or the fetus if progestin-only contraceptives (POCs) are inadvertently used during pregnancy (Curtis et al 2016b).

In ACCESS, of 1,765 female participants in the Self-Selection Population, 99.7% were correct in reporting their pregnancy status at baseline. Although 0.3% (5/1,765) of female participants were pregnant at the time of self-selection (and either did not know or were unsure if they were pregnant) and selected to use the product, those who were asked again after the positive study-site pregnancy test said they were not appropriate for use. Thus, the DFL was effective in guiding these women's self-selection decision. As noted, if they used the product in the absence of the on-site pregnancy test, no adverse clinical effects would have resulted.

5.3.3 Use in Case of Unexplained Vaginal Bleeding Between Periods

The DFL used in the ACCESS study included a message to:

- Ask a doctor before use if you have unexplained vaginal bleeding between your periods

The purpose of this direction regarding uninvestigated intermenstrual bleeding before initiation of OTC Opill use is to provide a safeguard that any condition requiring medical evaluation and treatment is ruled out prior to a woman's initiation of Opill use. This warning is based on the idea that once a woman begins to use the product, she might attribute her intermenstrual bleeding to the product rather than to a process that may need evaluation by an HCP. This could lead to a delay in diagnosis and treatment of an underlying condition, though the vast majority of causes of intermenstrual bleeding are benign (ACOG 2012). Thus, this warning does not represent a clinical contraindication to the use of Opill (Curtis et al 2016b), but rather, it is an effort to help guide self-triage to an HCP for a pre-existing condition and Opill is not expected to worsen these conditions.

Importantly, women to whom this warning applies had been experiencing intermenstrual bleeding prior to contemplating use of Opill and had not seen an HCP. Thus, the Opill DFL provides an opportunity to alert these women of the need to see an HCP. The risk of potential delayed diagnosis and treatment of endometrial or cervical cancer in those who had vaginal bleeding between periods before use is likely to be low given the low prevalence of these cancers in women of reproductive age < 50 [0.04% - uterine cancer (NCI 2019c); 0.05% - cervical cancer (NCI 2019b)]. Furthermore, use of the product in this population is not clinically contraindicated (Curtis et al 2016b).

In the ACCESS Self-Selection Population, 22 (1.2%, 22/1,765) female participants reported unexplained vaginal bleeding between their periods that they had not talked to an HCP about at enrollment. Seven of these participants selected to use the product, one of whom spoke with an HCP about their intermenstrual bleeding during the study. The remaining six did not, because their bleeding was not frequent and/or they considered it normal, and they were not worried. Of note, these six participants were considered clinically appropriate for use by the physician panel.

The proposed DFL includes language directing women to:

Ask a doctor before use if
- you currently have unexplained vaginal bleeding between your periods and you have not already talked to a doctor

This message was tested in the Final LCS and was well understood by consumers (see Appendix Section 11.4.6). This language is therefore considered sufficient to help women seek help for potential pre-existing gynecological pathology prior to their use of Opill.

5.3.4 Use If You Are Allergic To This Product Or Any Of Its Ingredients

There have been no published reports of hypersensitivity with the use of norgestrel POPs. Progestogen hypersensitivity appears to be rare, with just 113 reported cases, and there are no published estimates of incidence or prevalence (Foer et al 2016; Nguyen and Razzaque Ahmed 2016).

Opill contains tartrazine, a yellow dye used in foods and prescription and OTC medicines. Tartrazine is known to be associated with rare hypersensitivity reactions, and individuals who are sensitive to aspirin may also be sensitive to tartrazine (Miller 1982). The prevalence of tartrazine intolerance is estimated to be very low in the general population (less than 0.12%) (Elhkim et al 2007). While hypersensitivity to the product ingredients is rare, this may represent an important allergy for some consumers. Therefore, specific language regarding FD&C yellow No. 5 (tartrazine) allergy, potential side effects, and instructions to stop use and seek medical attention immediately if an allergic reaction occurs have been included in the proposed DFL.

In ACCESS, no participants reported a tartrazine allergy. However, two participants reported an allergy to norgestrel, and 25 reported an allergy to one of the inactive ingredients (lactose); of these, eight selected Opill for their own use. When asked why they selected Opill, all eight reported lactose intolerance, which is not an allergy, and were considered clinically appropriate for use by the physician review panel. There was no report of a hypersensitivity reaction related to use of Opill in the study.

Therefore, the proposed text for the OTC label is considered sufficient to mitigate the associated risks with hypersensitivity to any product ingredient.

5.3.5 Use in Case of Liver Problems

The Rx label for Opill lists “Benign or malignant liver tumors” and “Acute liver disease” as contraindications; these warnings are consistent with a series of recommendations made by the CDC SPR (Curtis et al 2016a) and CDC MEC (Curtis et al 2016b) related to use of COCs and extrapolated to POPs, both of which are metabolized in the liver. However, while estrogens act directly on the liver through specific receptor-mediated mechanisms, progestogens do not (Kapp et al 2009a). Thus, the use of POPs is preferred over COCs in patients with liver disease (Kapp 2009b). Furthermore, low dose progestins are not thought to be hepatoxic (LiverTox 2020).

Consistent with the prescription warning, the DFL for OTC Opill directs potential users of the product to:

Ask a doctor before use if
- …
- you have liver problems

This warning is deliberately broad in targeting "liver problems," as specific liver conditions may not be easily understandable in consumer language. This broad warning is also conservative given that POPs are safe to use in the presence of most liver diseases, including, for example, hepatitis and mild cirrhosis (Kapp 2009b; Kapp et al 2009a). The CDC SPR (Curtis et al 2016a) and CDC MEC (Curtis et al 2016b) indicate that POP use in those with a few specific liver conditions, including benign hepatocellular adenoma, malignant liver tumors, and severe (decompensated) cirrhosis, is of potential concern and these conditions have been designated by the MEC as Category 3 (i.e., theoretical or proven risks usually outweigh the advantages of use of the method). This rating for benign hepatocellular adenoma is due to an association between COC use and development and growth of hepatocellular adenoma. Whether other hormonal contraceptives, including POPs, have similar effects is not known (Curtis et al 2016b). Therefore, this rating may be overly conservative.

The proposed DFL warning reinforces the liver warning in providing an additional opportunity for anyone who has or ever had liver cancer to learn they should talk to a doctor before using OTC Opill:

Ask a doctor before use if
- …
- you **have or ever had** any cancer

It is important to note that the CDC MEC indicates the advantages generally outweigh the theoretical or proven risks for POP use by those with other liver conditions such as benign focal nodular hyperplasia and that there is no restriction for POP use by patients with hepatitis or mild, compensated cirrhosis (Curtis et al 2016b). The CDC SPR also concludes that screening for liver disease before initiation of POPs is not necessary given the low prevalence of contraindicated liver conditions and the high likelihood that women with liver disease already would have had the condition diagnosed and be under the care of an HCP (Curtis et al 2016a).

In the ACCESS Self-Selection Population, seven (0.4%: 7/1,765) female participants reported liver problems. Three correctly did not select to use the product. The remaining four selected Opill for their own use (three with fatty liver disease and one with history of Hepatitis C cured after treatment, neither of which is a contraindication to use) and were all determined to be clinically appropriate for use by the physician panel, which is in line with the conservative nature of that warning.

Therefore, based on the totality of the evidence, the proposed text for the OTC label is considered sufficient to mitigate any associated risks of use by women with liver problems.

5.3.6 Use by Males

The DFL used in the ACCESS study included the message:

- Do not use if you are male.

Use by males would represent a fundamental misunderstanding of the product and its indication. To avoid misunderstanding of the product and its indication, the label instructs that the product is not for use in males. However, if a male were to take a POP, the potential clinical consequences are reversible or merely theoretical. Importantly, based on studies of a variety of progestins in much higher doses tested in combination with testosterone as hormonal contraception for males, progestin use in males is considered safe (Bebb et al 1996; Herbst et al 2003; Roth et al 2016; Wu et al 1999).

There were seven male participants in the ACCESS Self-Selection Population. Two male participants inappropriately selected themselves as appropriate to use the product. When asked why they selected Opill when the label says it is not for use by males, one male stated he was considering a gender transition from male to female. As males were not offered the opportunity to purchase and use Opill in ACCESS, it is not clear if this participant would have actually used the drug. The second male stated that he was getting it for his wife.

Overall, use of Opill by males is not appropriate as it does not provide benefit but is also of limited clinical significance.

5.3.7 Use by Women Not Physically Able to Become Pregnant

The tested labeled “Purpose” and “Use” in ACCESS was “Daily Birth Control” and “for daily use by women to prevent pregnancy” respectively.

Seven female participants in the Self-Selection Population (0.4%; 7/1,665) selected Opill despite being not physically able to become pregnant: six because of tubal ligation and one because of congenital malformation / defect. Of note, all these participants, although having reported they were not physically able to become pregnant, explained that they selected Opill for their own use to prevent pregnancy. Four of these seven participants also indicated using the product for heavy bleeding/dysmenorrhea and were deemed acceptable for use by the physician panel because of a possible clinical benefit, in addition to possible additional contraceptive benefit. The other three participants with tubal ligation were considered not appropriate to use solely because they did not necessarily need a birth control method, as tubal ligation is 99.5% effective on its own at preventing pregnancy (Trussell et al 2018).

However, women who have had a tubal ligation can still use OC pills, as long as they do not report any of the contraindications listed for the OC pill they intend to use. In ACCESS, female participants who reported they were not physically able to become pregnant were offered to purchase and use the product in the study.

5.3.8 Ask a Doctor or Pharmacist Before Use: Drug-Drug Interactions

The DFL directs consumers to ask a doctor or pharmacist before use if they are taking a prescription drug for seizures, tuberculosis, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), pulmonary hypertension, or a supplement containing St. John's wort. This message is included on the label as the effectiveness of POPs is potentially reduced by use with hepatic enzyme (CYP3A) inducing drugs, such as anti-seizure drugs (e.g., barbiturates, carbamazepine, oxcarbazepine, phenytoin, topiramate, primidone); anti-tuberculosis drugs (e.g., rifampin, rifabutin); the pulmonary hypertension drug bosentan; antiretroviral drugs to treat HIV/AIDS (e.g., efavirenz); and herbal preparations containing St. John's wort (Opill Rx labeling). None of these medications/supplements are rated as Category 4 (i.e., unacceptable health risk) by the CDC MEC (Curtis et al 2016b), although certain anticonvulsants and the antimicrobials rifampin and rifabutin are rated as Category 3 (theoretical or proven risks outweigh the advantages), while St. John's wort and certain HIV/AIDS medications are rated as Category 2 (advantages generally outweigh theoretical or proven risks). The DFL also directs consumers to ask a doctor or pharmacist before use if they have taken ulipristal acetate, a prescription EC, or morning after pill, in the past five days. Failing to heed OTC labeling instructions to ask a doctor or pharmacist before use when taking these medications/supplements may result in an increased risk of pregnancy for the OTC norgestrel user, although this increased risk of pregnancy has not been quantified.

Findings from published research (Grossman et al 2008; Shotorbani et al 2006; White et al 2012) suggest that women can appropriately self-screen for use of certain medications/supplements for which a potential drug-drug interaction with norgestrel is possible.

In ACCESS, adherence to this label warning was tested as a distinct secondary endpoint (see Appendix Section 11.3). A small proportion of the ACCESS Self-Selection female Population, 1.1% (20/1,765), reported use of one of these relevant medications/ supplements. Of these 20 participants, 19 either appropriately selected not to use the product or spoke with an HCP during the study. These 19 comprise nine participants who did not select/purchase/use the product, four who selected and indicated speaking with their HCP specifically about the product, and six who selected and consulted an HCP for some other reason during the study. When asked why those who did not speak to an HCP specifically about use of Opill with their drug of interest did so, participants indicated that they did not think they needed to do so.

In summary, the ACCESS data support the conclusion from prior research that the proposed label warnings that address potential interactions with other products are considered sufficient to mitigate the associated potential risks.

5.4 Self-Selection Conclusions

There are few clinical situations that preclude use of Opill. The proposed label guides appropriate self-selection, including most importantly among women with breast cancer. The incremental risk associated with allowing women to self-select for POP in the OTC setting is unlikely to be clinically meaningful, particularly in the context of the large incremental benefit as discussed in Section 8.1.

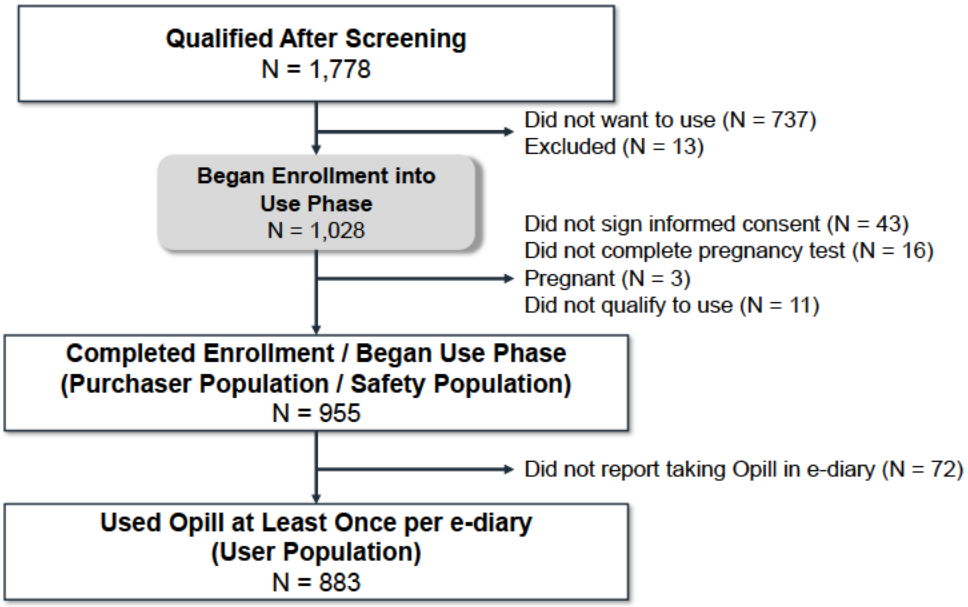
6 ASSESSMENT OF ACTUAL USE: CONSUMERS CAN APPROPRIATELY USE OPILL IN THE OTC SETTING

6.1 ACCESS Actual Use Participants

6.1.1 ACCESS User Population

As described in Section 4.2, qualified individuals from the Self-Selection Population were offered the opportunity to purchase Opill and take it home for use. Of the 955 participants who purchased Opill, 883 reported using it at least once in their e-diary, forming the User Population (Figure 22).

Figure 22: ACCESS Use Phase Flow Diagram



6.1.2 Demographics and Baseline Characteristics

As shown in Table 14 and Table 15, the User Population in ACCESS comprised a diverse group of participants that includes those most likely to use Opill in the OTC setting (i.e., US women at risk for unintended pregnancy; the table also presents data from the National Survey of Family Growth[13] for reference to US population at risk). The User Population reflected the diversity of the population of US women at risk for unintended pregnancy in terms of age, race, ethnicity, education level, income level, and prior experience with hormonal contraception. The population of adolescents was over-represented in ACCESS versus the proportion among US women at risk of unintended pregnancy according to the NSFG. The pre-specified recruitment goals for adolescents were exceeded with a total of 200 user participants below the age of 18, or 22.7% of the User Population in ACCESS. This contrasts with the percentage of US women at risk for unintended pregnancy in that

[13] The NSFG is a survey administered by the CDC's National Center for Health Statistics that provides national data on general and reproductive health, including pregnancies, births, and use of contraception.

age group of 4.9% (per the analysis of data from the 2017-2019 NSFG discussed above) (Pinney Associates 2022).

Table 14: ACCESS Demographic Data – User Population

	User Population		US Women at Risk for UIP per NSFG 2017-2019
Parameter	**N**	**%**	**%**
Total Population	883	100.0%	100.0%
Sex			
Female	883	100.0%	100.0%
Race [1]			
American Indian or Alaska Native	24	2.7%	NA
Asian	50	5.7%	NA
Black or African American	267	30.2%	15.7%
Native Hawaiian or other Pacific Islander	12	1.4%	
White	527	59.7%	75.0%
Other	57	6.5%	9.2%
Refused	8	0.9%	
Ethnicity			
Hispanic or Latino/Latina	161	18.2%	18.6%
Not Hispanic or Latino/Latina	722	81.8%	81.4%
Age Group			
Age 12-14	49	5.5%	
Age 15-17	151	17.1%	4.9%
Age 18-19	76	8.6%	6.0%
Age 20-24	195	22.1%	17.2%
Age 25-34	259	29.3%	36.3%
Age 35-45	139	15.7%	27.4%
Age 46-55	12	1.4%	8.3%
Age 56+	2	0.2%	
Age Distribution			
Mean	25.5		NA
SD	8.59		NA
Median	24.0		NA
Range	12, 61		NA
Participants Age 12-17 by Age			
Age 12	3	0.3%	NA
Age 13	16	1.8%	NA
Age 14	30	3.4%	NA
Age 15	22	2.5%	0.6%
Age 16	43	4.9%	1.9%
Age 17	86	9.7%	2.4%

NA: not applicable; NSFG: National Survey of Family Growth; SD: standard deviation; UIP: unintended pregnancy; US: United Sates

Note: All Ns (and other descriptive statistics) from NSFG are weighted unless otherwise noted.

[1] Answers below are not mutually exclusive.

Table 15: ACCESS Baseline Characteristics – User Population

Parameter	User Population N	User Population %	US Women at Risk for UIP per NSFG 2017-2019 %
Health Literacy			
Normal [1]	763	86.4%	NA
Low [2]	120	13.6%	NA
(Females Only) History of HBC Use			
History of HBC use	633	71.7%	89.2%
History of oral contraceptive use	543	61.5%	80.0%
No history of HBC use	250	28.3%	10.8%
Education Level (18+ years)			
8th grade or less	2	0.2%	NA
9th grade or less	NA	NA	3.2%
Some high school/other HS, no diploma/GED	21	2.4%	3.0%
High school graduate or GED	158	17.9%	20.5%
Some college or technical school	315	35.7%	22.1%
College graduate	156	17.7%	34.9%
Post-graduate degree	31	3.5%	11.4%
Education Level (< 18 years)			
7th grade or less	18	2.0%	NA
9th grade or less	72	8.2%	1.1%
8th grade	27	3.1%	NA
9th grade	27	3.1%	NA
10th grade	46	5,2%	NA
11th grade	60	6.8%	NA
12th grade	9	1.0%	NA
Other high school, no diploma/GED	NA	NA	3.5%
High school graduate, GED, or certificate	11	1.2%	0.3%
Some college or technical school	2	0.2%	0.0%
College graduate	0	0.0%	0.0%

GED: General Educational Development test; HBC: hormonal birth control; HS: high school; NA: data not available; NSFG: National Survey of Family Growth; UIP: unintended pregnancy; US: United States
Note: All Ns (and other descriptive statistics) from NSFG are weighted unless otherwise noted.
[1] Scored at least 61 on the Rapid Estimate of Adult Literacy in Medicine (REALM) Test or Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) Test
[2] Scored at most 60 on the REALM Test or REALM-Teen Test

6.2 Adherence to Directions for Use

6.2.1 ACCESS Adherence Endpoints

The OTC label directs users to take 1 tablet at the same time every day and provides instructions on what to do if a pill is missed or if a pill is taken more than 3 hours late. These specific behaviors in the face of a missed or late pill, also referred to as "label-directed mitigating behaviors" (i.e., the use of a barrier method for every act of sexual intercourse for the 2 following days) mitigate the risk of a pregnancy.

Endpoints measured adherence to (1) the intake of 1 tablet every day and (2) the medication intake at the same time each day.

The endpoints that measured adherence to daily medication intake were as follows:

Overall Daily Pill Taking Adherence

- Primary Endpoint: % of days Opill was taken (85% target threshold)
- Secondary Endpoint: % of days Opill was taken including days where label-directed mitigating behaviors were followed when a participant did not take Opill

Individual Participant Adherence to Daily Pill-Taking

- Primary Endpoint: % of participants ≥ 85% adherent defined as taking a pill on at least 85% of their participation days (85% target threshold)
- Secondary Endpoint: % of participants ≥ 85% adherent including days where label-directed mitigating behaviors were followed when the participant did not take Opill

Data on typical adherence with OCs in the Rx setting were used to determine the appropriate target threshold for adherence in an OTC setting. That is, a level of adherence that would reflect no incremental risk of pregnancy due to non-adherence versus use in the Rx setting. Studies using prospective daily diaries measuring intake of COCs showed that up to 18% of participants missed taking 15% or more of their prescribed active pills per pack (i.e., about 82% of women take at least 85% of their prescribed active pills based on observational clinical research) (Fox et al 2003; Potter et al 1996). Moreover, additional studies show that non-adherence varies widely between women and can vary substantially over time in the same woman (Aubeny et al 2004; Hou et al 2010). With that background, an adherence cutoff of pills taken on at least 85% of days was adopted for the population and for the participants.

Another set of endpoints measured adherence to medication intake at the same time each day:

Adherence to Pill Intake at Same Time Each Day (3-Hour Window)

- Primary Endpoint: % of days (evaluable time of intake) Opill was used ± 3 hours from time of day of last dose taken (80% target threshold). To be evaluable, a time of dosing had to be reported on both the day being evaluated and a previous dose (even if it was not the preceding calendar day).
- Secondary Endpoint: % of days (evaluable time of intake) Opill was used no more than 27 hours (i.e., no more than 24 hours plus 3 hours) since previous day's dose or appropriate mitigating behaviors were followed when a participant did not take Opill. To be evaluable, a time of dosing had to be reported on both the day being evaluated and the day prior.

In the various sets of adherence to daily and same time intake endpoints, the secondary endpoint is a clinically relevant measure designed to evaluate behavior thought to be needed to maintain sufficient effectiveness and in line with the label instructions for what to do in case of pills missed. Of note, while there are no direct data that define the

incremental risk of pregnancy associated with missing a pill or taking it late, data from the Sponsor's recent pharmacodynamic Delayed Pill Intake Study (see Section 6.2.4.2) show Opill users are highly protected from conception, not only during perfect use, but also following a delayed or even missed pill.

Additional secondary endpoints evaluated adherence to other label directions for use are listed in Appendix Section 11.3.

6.2.2 ACCESS Data Collection and Analyses on Adherence to Directions to Use

Adherence to daily pill taking was assessed over the course of up to six months using a daily e-diary. Each participant determined their own Opill use duration. Beginning the first day after the participant enrolled in the Use Phase, participants were asked to complete the diary with the prompt "did you take Opill on <date>". Participants were asked to report their previous day's use of the product (or non-use), time of dosing, and any sexual intercourse (participants under the age of 18 were not asked to report sexual intercourse daily).

For the purposes of analyzing the Actual Use endpoints in the ACCESS study that measure intake of Opill, the following terms were used:

> Possible Dosing Days: Every study day from the time the participant was dispensed Opill until the last day of the Use Phase or the participant withdrew/was withdrawn from the study or until the participant was lost to follow-up (whichever came first).
>
> Start Date: The date the participant reported beginning to take Opill in the e-diary.
>
> Stop Date: The date the participant reported stopping taking Opill in the e-diary.
>
> Study Days: All days in the period between the Start Date and the Stop Date (regardless of whether the participant took Opill on any specific day). A participant could report either Yes or No to the question "did you take Opill on <date>". Note that a "missed pill" (did you take Opill on <date>: "no") is not missing data, but rather is considered "incorrect" behavior. If the participant did not report "yes" or "no" to taking Opill, this information was considered missing.
>
> For ease of presentation, these "Study Days" are simply referred to as "days" in this briefing document.
>
> Non-Use Study Day: Any day after purchase but before a participant's first reported use of Opill (Start Date) and any day after a participant's last reported use of Opill in the e-diary (Stop Date) are not included in any pre-specified endpoint analyses. For example, the participant may have purchased the product but not taken the first dose until several days later (their Start Date). Hence, this period would be non-informative and is not included in the analysis.

Several strategies were employed to minimize missing data (specifically, days between the Start date and Stop Date where the participant did not report their actions regarding use of Opill). Because daily reminders to complete the e-diary could have potentially biased the data, all participants received a text, email, or push notification reminder every 4 days,

(e.g., “Time to fill in today’s diary!”) regardless of previous e-diary completion. Participants were allowed to complete a daily e-diary entry for up to ten days (ten-day look back period), with date and time of the diary entry recorded automatically by the system.

Sensitivity analyses for adherence endpoints were planned in the protocol and were undertaken to describe the potential impact of missing e-diary data on the endpoint outcomes. These included an analysis where all missing e-diary days were imputed to represent days on which the participant reported not taking Opill (worst-case scenario analysis or “Missing Imputed to ‘No’”) and an analysis where all missing e-diary days were imputed to represent days on which the participant reported taking Opill (best-case scenario analysis or “Missing Imputed to ‘Yes’”). Note that in each of these sensitivity analyses, the number of days increases since missing days are included in the analysis and imputed.

6.2.3 ACCESS Results for Adherence to Directions for Use

Note, in the subsequent sections, adherence results from ACCESS are presented first according to the pre-specified primary analysis from study protocol, then followed by the pre-specified sensitivity analyses, then followed by post hoc sensitivity analyses to understand the impact of a behavior of over-reporting identified post-trial on the results of the study.

6.2.3.1 Take One Tablet Every Day and Mitigating Behaviors

In the ACCESS study, adherence to the label instruction to take the product every day was assessed in 883 female participants over the course of up to six months, providing information on over 90,000 days.

ACCESS demonstrated that the DFL guides women in correctly taking Opill every day and in adopting appropriate, label-directed mitigating behaviors when the pill is missed.

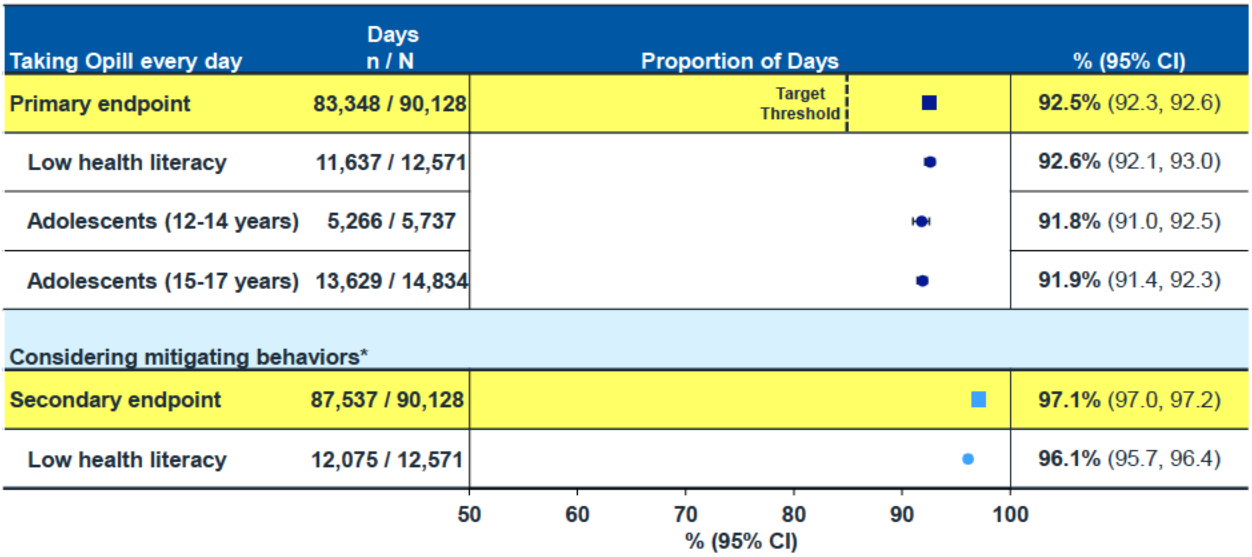
Overall adherence to daily pill intake was 92.5% of all days with a 95% CI lower limit of 92.3%, which exceeds the *a priori* defined threshold of 85% (Figure 23).

After considering mitigating behaviors, participants reported correctly taking the product or following the label directions in case of missed pill on 97.1% of all days analyzed.

Taking Opill every day was reported in similar proportions of study days in the low health literacy subgroup and adolescents below the age of 18, demonstrating that the DFL can guide women of diverse ages and abilities to use Opill appropriately.

Because sexual activity was not recorded for participants aged 17 or younger, the impact of adopting appropriate mitigating behaviors after a missed dose was not assessed in these participants, potentially underestimating the proportion of days where these behaviors were indeed adopted. That is, adolescents under 18 years contributed to the days in both the numerator and the denominator based on reported dosing only.

Figure 23: ACCESS Pre-specified Primary Analysis for Adherence to Taking a Pill Every Day (User Population, N=883)

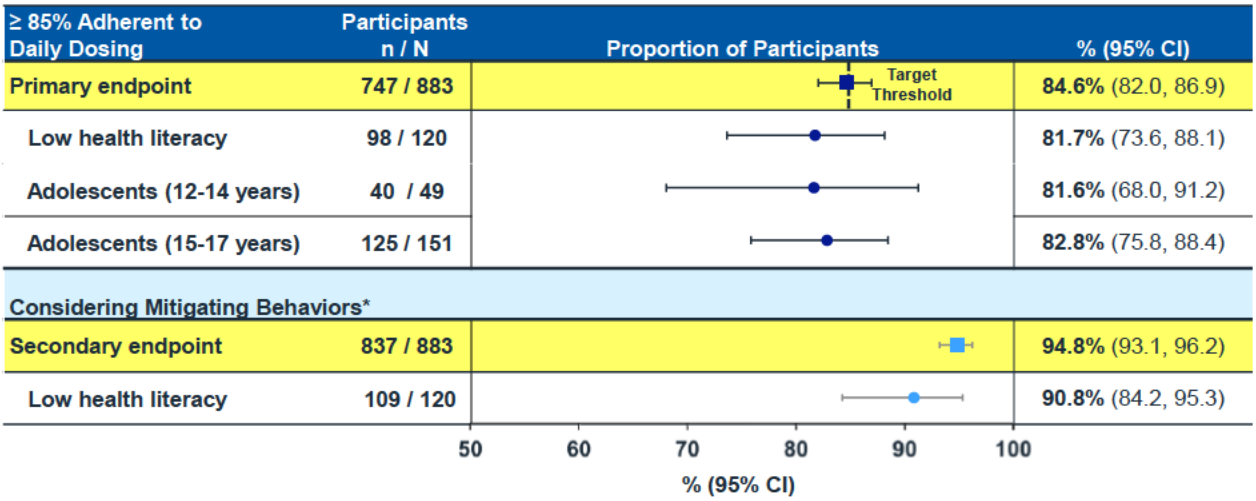


CI: confidence interval; n: number of days participant reported taking Opill (primary endpoint) and/or used mitigating behaviour (secondary endpoint), N: total number of days
*Did not ask participants < 18 years of age about sexual behaviors; therefore, secondary endpoint includes non-mitigated adherence for this age group

At the participant level, a total of 84.6% (747/883) of user participants were adherent based on the pre-specified criterion that they reported taking Opill on 85% or more of their study days (Figure 24). The lower limit of the 95% CI of this endpoint (82.0%) fell below the *a priori* defined threshold of 85% but was similar to adherence reported for Rx OC users. For subgroups of interest, including those aged 12-17 and those with low health literacy, performance was generally consistent with the overall population, noting the overlapping CIs.

After considering mitigating behaviors in case of missed pills, 94.8% (837/883) of participants behaved correctly on 85% or more of their study days, demonstrating that even in the instance of missed pills, women follow the label direction, which mitigates the clinical risk associated with missed pills. This secondary endpoint is clinically important as it minimizes the risk of conception despite the deviation from the label direction to take 1 tablet every day. Again, sexual activity was not recorded for participants aged 17 or younger, thus the impact of any appropriate mitigating behaviors after a missed dose is not reflected in the reported analysis.

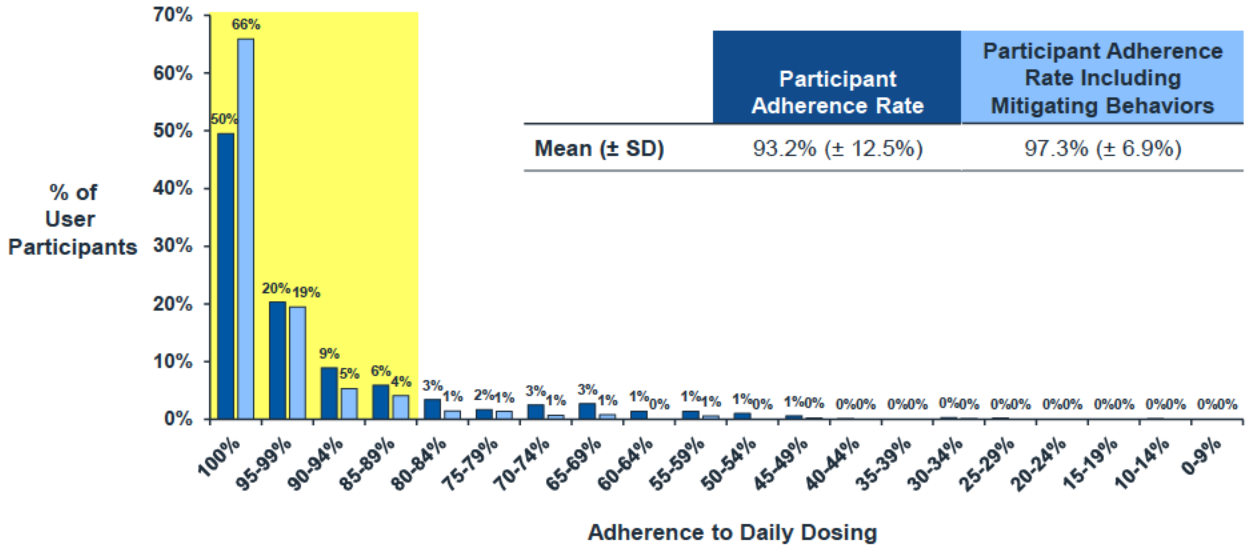
Figure 24: ACCESS Pre-specified Primary Analysis for Participant-Level Adherence to Taking a Pill Every Day (User Population, N=883)



CI: confidence interval; n: number of participants ≥ 85% adherent (primary endpoint) and/or used mitigating behavior (secondary endpoint), N: number of participants in User Population
*Did not ask participants <18 years of age about sexual behaviors; therefore, secondary endpoint includes non-mitigated adherence for this age group

Overall, most participants were highly adherent to taking the pill every day, with a median participant-level adherence rate to daily dosing over 99%. As shown by the highlighted columns in Figure 25, nearly 80% of participants reported taking Opill on at least 90% of days, and the mean participant-level adherence rate was 93.2%.

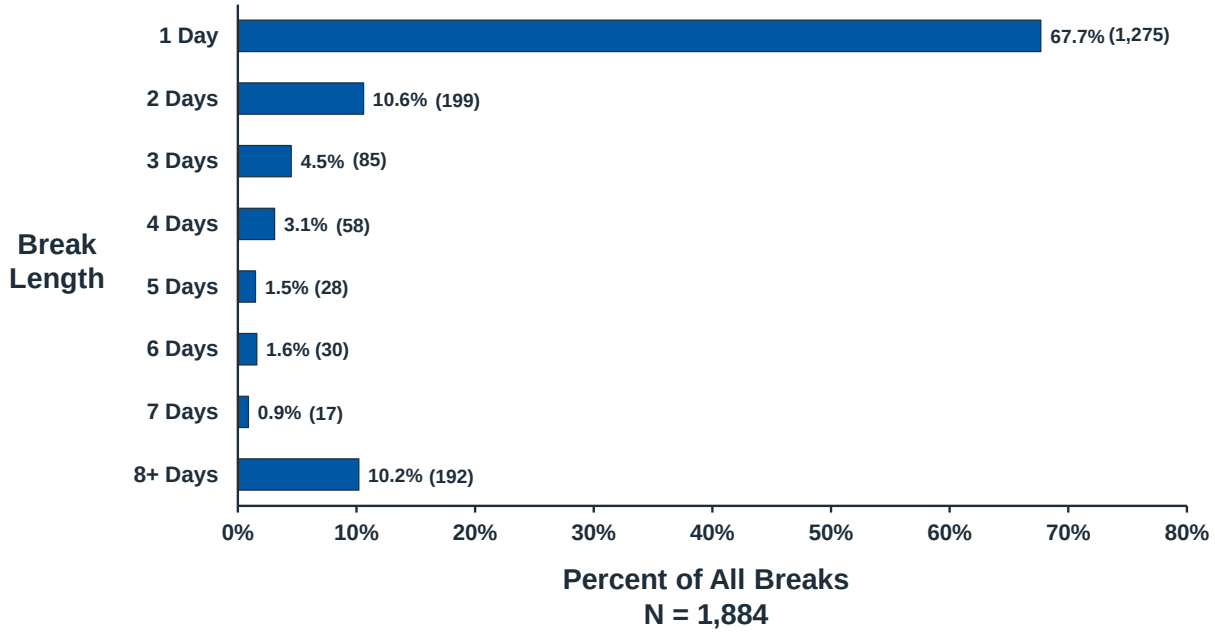
Figure 25: ACCESS Pre-specified Primary Analysis for Participant Adherence to Daily Dosing (User Population, N=883)



SD: standard deviation

In ACCESS, 68% (1,275/1,884) of episodes of missed pills (breaks) were a single missed day (i.e., where pills were taken the day before and the day after the missed day; Figure 26). As described in Section 6.2.4, Opill can be expected to effectively protect against pregnancy even if a woman misses one pill.

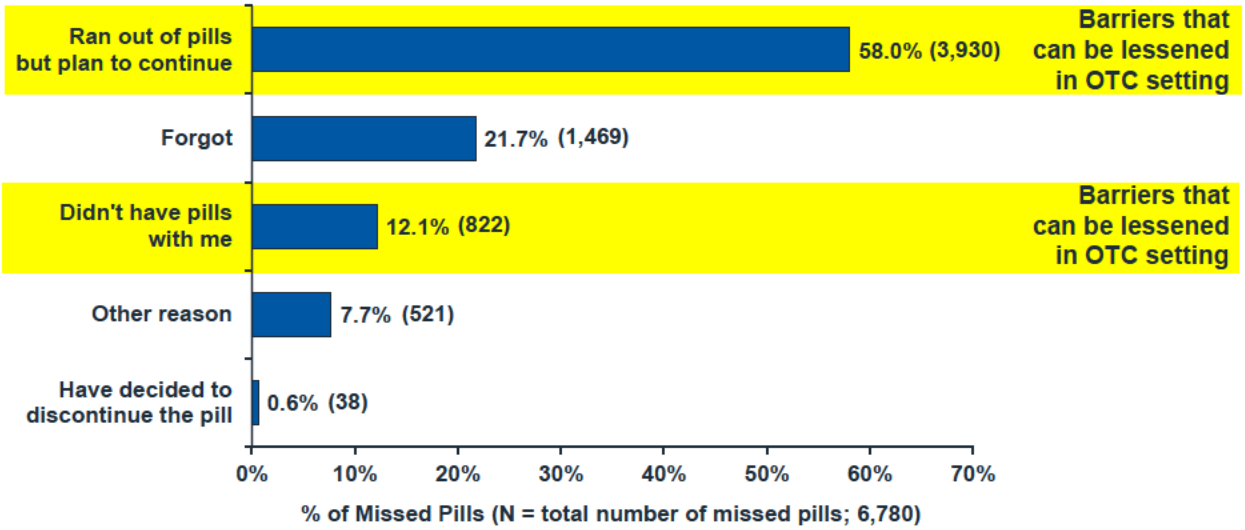
Figure 26: ACCESS Pre-specified Primary Analysis for Duration of Breaks At Any Time During Opill Use (User Population, N=883)



Break defined as one or more consecutive days a participant reported not taking Opill

Importantly, the most common reported reason participants missed pills was due to resupply issues which would be greatly reduced in the OTC setting (Figure 27). While ACCESS was intended to mimic an OTC environment as much as possible, as a clinical study, participants could only get new packs at the site where they enrolled (participants were discouraged from enrolling if they lived more than 35 miles from the site) and study staff had to be present for resupply. With this context, the fact that the majority of participants who missed pills reported that they ran out but planned to continue Opill, demonstrates the impact of barriers to accessing new packs. As indicated in Section 2.2, running out of pills and not being able to get a resupply in a timely manner is frequently reported in the Rx setting.

Figure 27: ACCESS Pre-specified Primary Analysis for Reasons for Missing Pills (User Population, N=883)



OTC: over-the-counter

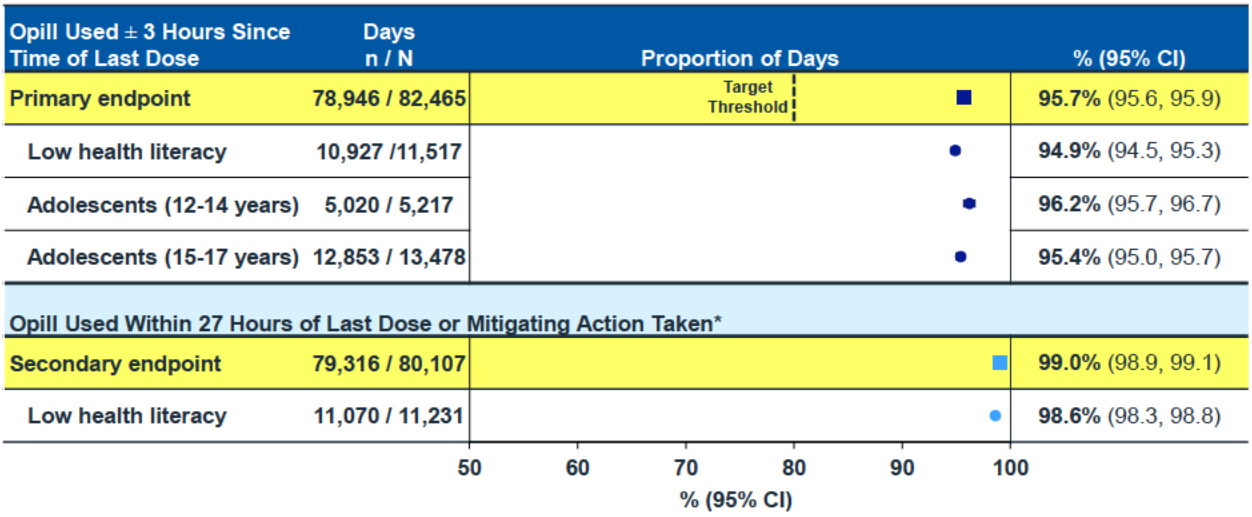
In summary, the evidence demonstrates that participants in the ACCESS study comprehended the label and followed the instructions with regard to the intake of Opill every day consistent with effective contraception. Importantly, if they missed a pill, they also behaved in a manner that maintained effective contraception through the label-directed mitigation. Thus, an HCP is not necessary to ensure adequate adherence in using this product every day. Furthermore, there is reason to believe that adherence with daily pill taking could be higher in a true OTC setting since the reason for most missed pills in the ACCESS study was related to participants not having access to the pill packs, which would be less of an issue in the true OTC setting in which pill packs would be readily available.

6.2.3.2 Take One Tablet at the Same Time of the Day and Mitigating Behaviors

Participants reported taking their dose within ± 3 hours from the time of their last reported dose 95.7% of the time (95% CI: 95.6, 95.9), exceeding the protocol target threshold of 80% (Figure 28). This endpoint demonstrates that the product labeling effectively guides users to establish a routine time to take the product at that same time each day during ongoing use.

The secondary endpoint supports this conclusion with 99.0% of doses evaluable for time of dose reported taken within 27 hours or less from the time of their last dose or the participant followed the appropriate mitigating behaviors. When the high adherence to this label direction is considered along with the probable nominal clinical impact of a single delayed or missed pill as an isolated circumstance, the label clearly enables users to adhere to the instruction in a way that effectively supports appropriate use in the OTC setting.

Figure 28: ACCESS Pre-specified Primary Analysis for Adherence to Taking a Pill at the Same Time of Day (User Population, N=883)



CI: confidence interval; n: number of days Opill taken at the correct time (primary endpoint) and/or used mitigating behavior (secondary endpoint); N: number of days evaluable for timing of dose.
*Did not ask participants < 18 years of age about sexual behaviors; therefore, secondary endpoint includes non-mitigated behaviors for this age group

6.2.3.3 Pre-specified Sensitivity Analyses

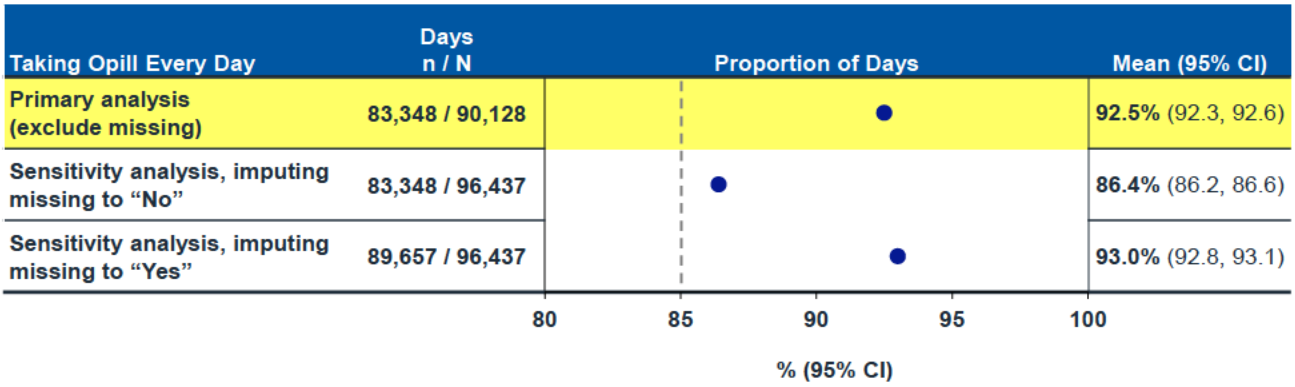
Pre-specified sensitivity analyses for adherence endpoints were undertaken to describe the potential impact of missing e-diary data on the endpoint outcomes. However, there was very little missing data overall (6.5% [6,309/96,437] of days).

Figure 29 and Figure 30 report the analyses of the different adherence primary endpoints when repeated as follows:

- Pre-specified Primary Analysis, as described above (where days with missing data are excluded);
- Pre-specified Sensitivity Analysis Imputing Missing to “No”, i.e., a scenario analysis where all missing days were imputed to represent days on which the participant reported not taking Opill (worst case analysis);
- Pre-specified Sensitivity Analysis Imputing Missing to “Yes”, i.e., a scenario where all missing days were imputed to represent days on which the participant reported taking Opill (best case analysis).

For adherence to daily pill intake overall, the sensitivity analyses for the primary endpoint (Figure 29) resulted in a range of the point estimate from 86.4% of days (Impute Missing to “No”) to 93.0% of days (Impute Missing to “Yes”).

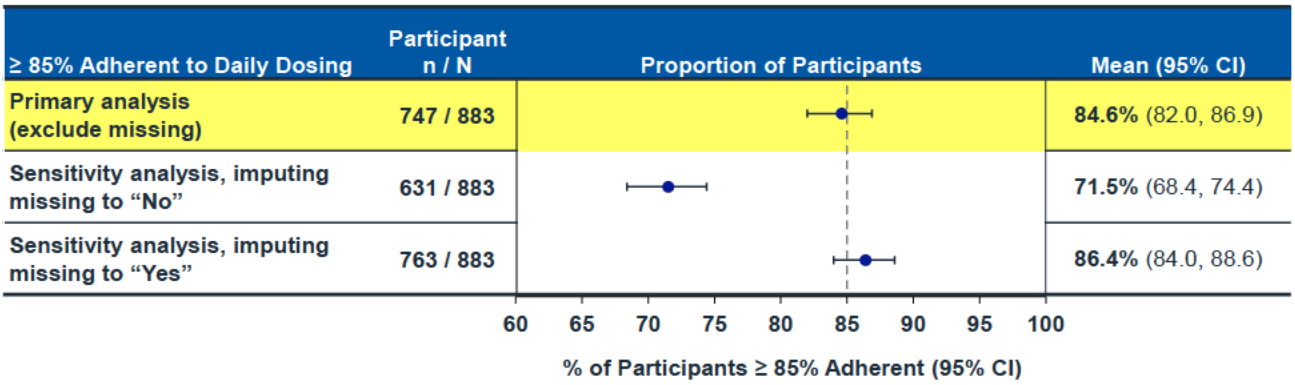
Figure 29: ACCESS Pre-specified Primary Analysis Along With Pre-specified Sensitivity Analyses – Adherence to Taking a Pill Every Day (User Population, N=883 Participants, Primary Endpoint for Overall Adherence)



CI: confidence interval; n: number of days Opill was reported as taken, N: total number of days

For adherence to daily pill intake at the participant level, the sensitivity analyses for the primary endpoint (Figure 30) resulted in a range of the point estimate from 71.5% (Impute Missing to "No") to 86.4% (Impute Missing to "Yes").

Figure 30: ACCESS Pre-specified Primary Analysis Along With Pre-specified Sensitivity Analyses – Adherence to Taking a Pill Every Day (User Population, N=883, Primary Endpoint for Participant-Level Adherence)



CI: confidence interval
N: number of participants ≥ 85% adherent, N: total number of participants in User Population

As in the primary analysis, the addition of mitigation behaviors improved measures of adherence in these sensitivity analyses.

6.2.3.4 Over-Reporting Behavior, Root Cause Analysis, and Post Hoc Sensitivity Analyses

After the study was completed, and while the sNDA was under review, FDA inquired and HRA determined that some participants reported in their diaries taking Opill that was incompatible with the amount of study drug available to them. Specifically, they reported that they took Opill on more days than was possible given the number of tablets recorded as dispensed and/or returned (i.e., participants over-reported taking Opill). This situation was referred to as “over-reporting” (or “improbable dosing”). Over-reporting is an inherent risk in any trial which seeks to simply capture, but not influence, participant behaviors, such as in AUTs.

Self-report is the most common method for assessing medication adherence in research and clinical care (Stirratt et al 2015). Self-report tends to overestimate adherence when compared with other assessment methods (Stirratt et al 2015). The rate of contraceptive pill adherence is likely over-estimated in OC adherence studies most of which rely on self-report only (Hou et al 2010).

Over-reporting of the kind observed in the ACCESS study (i.e., participants reporting taking medication when it was not available to them based on medication supply) can be detected only when certain conditions exist. These conditions are when study staff have information about participants’ medication supply and the study allows participants to report medication intake on more days than medication is available. Where both conditions apply, which is uncommon in adherence studies, over-reporting has been seen, including in published studies of adherence to cardiometabolic disease medications (Lauffenburger et al 2020; Fanaroff et al 2020) and OCs (Nelson et al 2017; Triebwasser et al 2015). In two OC studies which allowed for comparing self-report of medication intake with the medication supply available (per pharmacy claims), 8%-21% of participants reported taking more medication than was available to them based on pharmacy records (Nelson et al 2017; Triebwasser et al 2015). Therefore, while over-reporting of the type seen in ACCESS has been previously described, the conditions that allow detection of this type of over-reporting are uncommon. Participants over-reporting doses beyond the supply available to them (as seen in ACCESS) is likely present in adherence studies generally, although in most studies goes undetected because the required conditions did not exist.

To fully examine the situation, its implications, and the impact to the overall conclusions of the study, a formal and thorough root cause analysis (RCA) and additional post hoc sensitivity analyses were performed.

6.2.3.4.1 Root Cause Analysis

The RCA was conducted by an independent party experienced in the assessment of RCA in clinical trials (Clinical Pathways, LLC) who evaluated the critical processes linked to study design elements, as well as study conduct and oversight. A combination of well-accepted RCA methods was used, and the analysis included review of the design and functioning of the e-diary system, study data handling, clinical study site training and oversight.

The RCA did not identify any systemic problems with the study, including the functioning of the e-diary, systemic operational issues with the investigational sites, Contract Research Organization, or Sponsor. However, the analysis identified three major root causes with the study design (planning) and two major root causes related to conduct based on design limitations (execution) that may have inadvertently contributed to over-reporting.

Regarding study design:

1. There were no design elements in place to prevent over-reporting from happening,
2. The study design did not set out to identify if and when participants were reporting taking more doses than they could have, and
3. Diary set-up allowed participants to continue to enter data into their diaries and even receive reminders to complete their diary, even after they ran out of drug supply (the system did not automatically shut down when a participant "ran out of pills"). Specifically, the e-diary remained open for entry to allow participants to get resupply of study medication and diary deactivation was to occur only when a participant completed the study or was deemed lost to follow-up. Therefore, in some participants' diary, deactivation was delayed. For some participants this was just a few days, but for others it was longer.

Regarding study conduct:

1. The pre-planned risk assessment, while conducted as outlined in International Committee on Harmonization Good Clinical Practices (ICH E6), did not identify over-reporting as a risk.
2. Over-reporting was not identified during drug accountability and therefore not flagged as a protocol violation during the study.

In AUTs, detailed drug accountability is maintained at study sites, but in-trial ongoing detailed accountability with participants is not done. Importantly, this is inherent to AUTs, as the design tries to minimize interference with participant behavior (cueing, reactivity, etc.), while still encouraging data entry over a multi-month study. For example, asking a participant about their drug supply might cue them to engage in purchasing more drug when they otherwise would not have. Participants are asked to return study materials and any unused drug supply at the EOS, but typically the minority comply with that request. This is complicated by participants' perceptions that they "own" the drug as it was purchased out-of-pocket.

A potential causal factor built into the ACCESS design that could not be ruled out was the participant incentive provided. Participants knew they were paid for each diary entry they made, but this was the case even if they recorded no Opill was taken on the day in question. Additionally, they were also paid a "bonus" at the end of each month for which they made a diary entry for every day of the month. Notably, over-reporting was more frequent among participants with low household income, for whom this financial incentive might have played a role in the over-reporting behavior (see Table 17). This is despite the

fact that participants were reminded that the compensation would be made regardless of the actual entry (did or did not take Opill).

6.2.3.4.2 Extent of Over-Reporting and Demographics

There were 261 participants from the User Population who reported taking at least one more dose than their available supply, and these make up the over-reporting group. These 261 participants reported taking 27,381 total doses, of which 11,509 were in excess of their dispensed drug supply.

Approximately one-third (N=89, 34.1%) of the over-reporting group reported fewer than 20% more doses than their available supply (for example, for participants who had obtained just one 28-day pack, this would be one to five excess doses, meaning they reported taking 29 to 33 doses in the e-diary). These small number of excess doses may represent inadvertent data entry or other similar inadvertent errors, which could explain the over-reporting among this group.

However, among participants who over-reported to a larger extent (> 20% of available doses), it seems likely that reporting of excess doses was deliberate based on the large number of excess doses reported by these participants. The motives for such over-reporting in ACCESS are not fully understood, but may include the incentives discussed above, efforts to please the investigator by appearing adherent or an effort to complete the perceived study requirements.

Table 16 and Table 17 provide demographic data and other baseline characteristics in those that did and did over report study drug use in ACCESS.

Table 16: Demographic Data in ACCESS User Population for Total Population, Non-Over-Reporter Group, and Over-Reporter Group

	User Population (N=883)	User Population Non-Over-Reporters (N=622)	User Population Over-Reporters (N=261)
Sex			
Female	883 (100.0%)	622 (100.0%)	261 (100.0%)
Race [1]			
American Indian or Alaska Native	24 (2.7%)	19 (3.1%)	5 (1.9%)
Asian	50 (5.7%)	39 (6.3%)	11 (4.2%)
Black or African American	267 (30.2%)	153 (24.6%)	114 (43.7%)
Native Hawaiian or other Pacific Islander	12 (1.4%)	9 (1.4%)	3 (1.1%)
White	527 (59.7%)	413 (66.4%)	114 (43.7%)
Other	57 (6.5%)	34 (5.5%)	23 (8.8%)
Refused	8 (0.9%)	5 (0.8%)	3 (1.1%)
Ethnicity			
Hispanic or Latino/Latina	161 (18.2%)	108 (17.4%)	53 (20.3%)
Not Hispanic or Latino/Latina	722 (81.8%)	514 (82.6%)	208 (79.7%)
Age Group			
Age 12-14	49 (5.5%)	34 (5.5%)	15 (5.7%)
Age 15-17	151 (17.1%)	110 (17.7%)	41 (15.7%)
Age 18-19	76 (8.6%)	53 (8.5%)	23 (8.8%)
Age 20-24	195 (22.1%)	143 (23.0%)	52 (19.9%)
Age 25-34	259 (29.3%)	178 (28.6%)	81 (31.0%)
Age 35+	153 (17.3%)	104 (16.7%)	49 (18.8%)
Age 35-45	139 (15.7%)	95 (15.3%)	44 (16.9%)
Age 46-55	12 (1.4%)	7 (1.1%)	5 (1.9%)
Age 56+	2 (0.2%)	2 (0.3%)	0 (0.0%)
Age Distribution			
Mean	25.5	25.3	25.9
SD	8.59	8.56	8.66
Median	24.0	24.0	24.0
Range	12, 61	12, 61	12, 51

N: number of participants, SD: standard deviation, HBC: hormonal birth control
[1] Answers are not mutually exclusive

Table 17: Baseline Characteristics in ACCESS User Population for Total Population, Non-Over-Reporter Group, and Over-Reporter Group

	User Population (N=883)	User Population Non-Over-Reporters (N=622)	User Population Over-Reporters (N=261)
Health Literacy			
Normal	763 (86.4%)	555 (89.2%)	208 (79.7%)
Low	120 (13.6%)	67 (10.8%)	53 (20.3%)
History of HBC Use			
History of HBC use	633 (71.7%)	449 (72.2%)	184 (70.5%)
History of oral contraceptive use	543 (61.5%)	394 (63.3%)	149 (57.1%)
No history of HBC use	250 (28.3%)	173 (27.8%)	77 (29.5%)
Education Level (18+ yo)			
8th grade or less	2 (0.2%)	1 (0.2%)	1 (0.4%)
Some high school	21 (2.4%)	8 (1.3%)	13 (5.0%)
High school graduate or GED	158 (17.9%)	101 (16.2%)	57 (21.8%)
Some college or technical school	315 (35.7%)	224 (36.0%)	91 (34.9%)
College graduate	156 (17.7%)	121 (19.5%)	35 (13.4%)
Post-graduate degree	31 (3.5%)	23 (3.7%)	8 (3.1%)
Education Level (12-17 yo)			
7th grade or less	18 (2.0%)	13 (2.1%)	5 (1.9%)
8th grade	27 (3.1%)	20 (3.2%)	7 (2.7%)
9th grade	27 (3.1%)	21 (3.4%)	6 (2.3%)
10th grade	46 (5.2%)	32 (5.1%)	14 (5.4%)
11th grade	60 (6.8%)	39 (6.3%)	21 (8.0%)
12th grade	9 (1.0%)	7 (1.1%)	2 (0.8%)
High school graduate, GED, or certificate	11 (1.2%)	10 (1.6%)	1 (0.4%)
Some college or technical school	2 (0.2%)	2 (0.3%)	0 (0.0%)
College graduate	0 (0.0%)	0 (0.0%)	0 (0.0%)
Estimated Annual Household Income			
Less than $25,000	282 (31.9%)	181 (29.1%)	101 (38.7%)
$25,001 - $50,000	297 (33.6%)	209 (33.6%)	88 (33.7%)
$50,001 - $75,000	124 (14.0%)	91 (14.6%)	33 (12.6%)
$75,001 - $100,000	53 (6.0%)	41 (6.6%)	12 (4.6%)
$100,001 - $150,000	51 (5.8%)	42 (6.8%)	9 (3.4%)
More than $150,000	19 (2.2%)	18 (2.9%)	1 (0.4%)
Don't know	56 (6.3%)	39 (6.3%)	17 (6.5%)
Refused	1 (0.1%)	1 (0.2%)	0 (0.0%)

GED: general education development; HBC: hormonal birth control; N: number of participants; yo: year olds

6.2.3.4.3 Over-Reporting Post Hoc Sensitivity Analyses Methods and Results

For those participants who reported taking more doses than their available drug supply, it is reasonable to question how reliable their data are in the assessment of actual use of Opill, and how their data might impact the estimated adherence rate. Therefore, HRA conducted sensitivity analyses to examine the impact of this over-reporting behavior on the observed rates of adherence.

The two following post hoc sensitivity analyses were conducted (also illustrated in Figure 31):

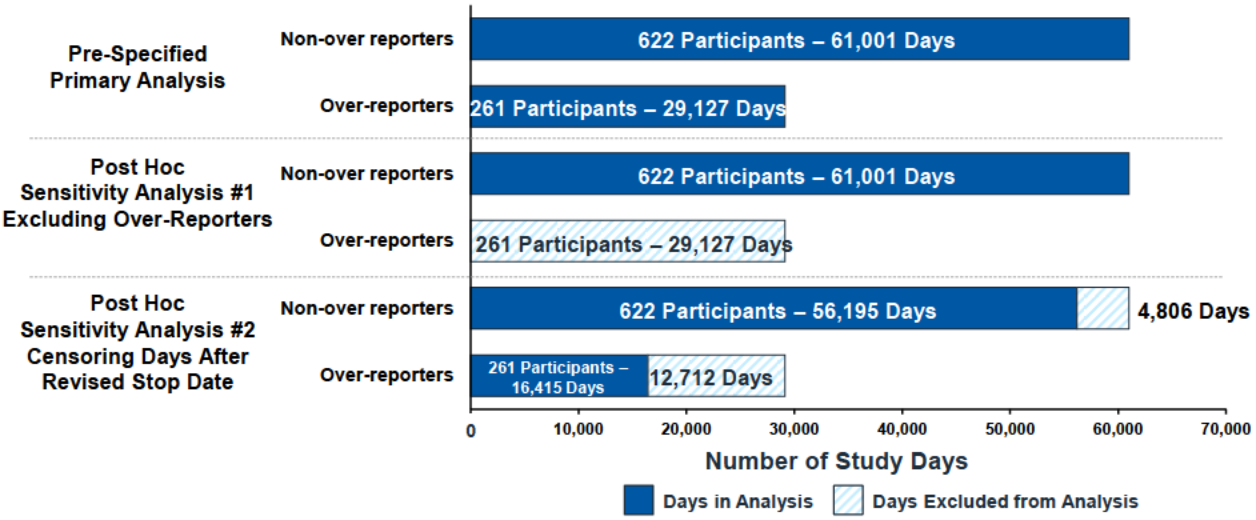
1. The first post hoc analysis excluded all participants who over-reported. In this manner, one could assume that data provided by the over-reporters was not a good representation of their use of Opill at any time during the study and this analysis allows understanding of the impact if their data were removed from consideration.

   This analysis is thus limited to the 622 non-over-reporting participants who reported on 61,001 days. Importantly this is a sample greater than that pre-planned in the protocol as being adequate to assess the study objectives.

2. The second post hoc analysis included all participants but censored the participants' diary data post an imputed "revised Stop Date" based on a conservative definition using all the available sources of data informing about participants' Opill use during the study. While the "Stop Date" used in the Pre-specified Primary Analysis was only based on e-diary data and defined as the date at which the participant reported stopping taking Opill in the e-diary, the "revised Stop Date" has been defined as the date at which drug supply would have been exhausted based on their recorded use, the date that the participant reported stopping use to nurse interviewers, or the last day of use reported in the e-diary, whichever is earliest. This analysis assumes that diary data provided by participants was accurate up until the earliest date when there is an indication that they could have stopped using Opill because they ran out of drug or told the nurse interviewer that they had stopped taking the medication or stopped reporting use in the e-diary. This results of censoring use data in non-over-reporters despite no evidence of mis-reporting and is thus considered conservative and less at risk of bias than the first post hoc analysis described above.

   This analysis included 883 participants who reported on 72,610 days but excluded 17,518 days exceeding the revised Stop Date from both non-over-reporting and over-reporting participants.

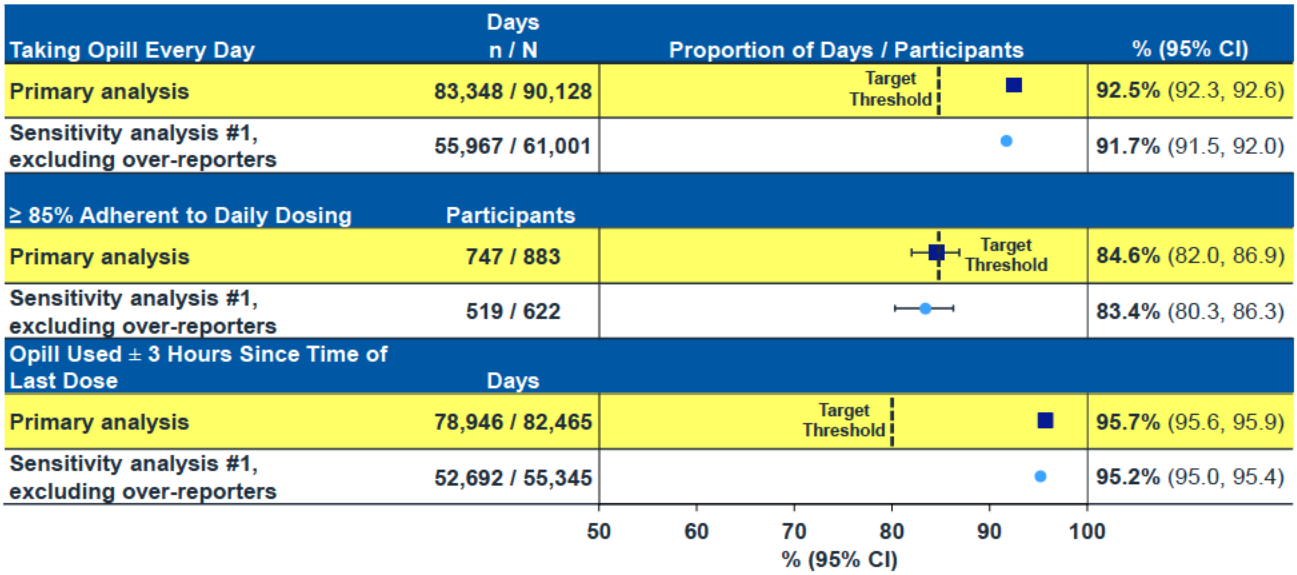
Figure 31: ACCESS Days Excluded in Each Post Hoc Sensitivity Analysis to Account for Over-Reporting in Comparison to the Pre-specified Primary Analysis



Importantly, the results of these sensitivity analyses support the overall conclusions drawn based on the pre-specified primary analyses.

As shown in Figure 32, the results for the various adherence primary endpoints assessed when excluding all data from the over-reporters (post hoc sensitivity analysis #1) are very similar to the results for the whole dataset, highlighted in yellow.

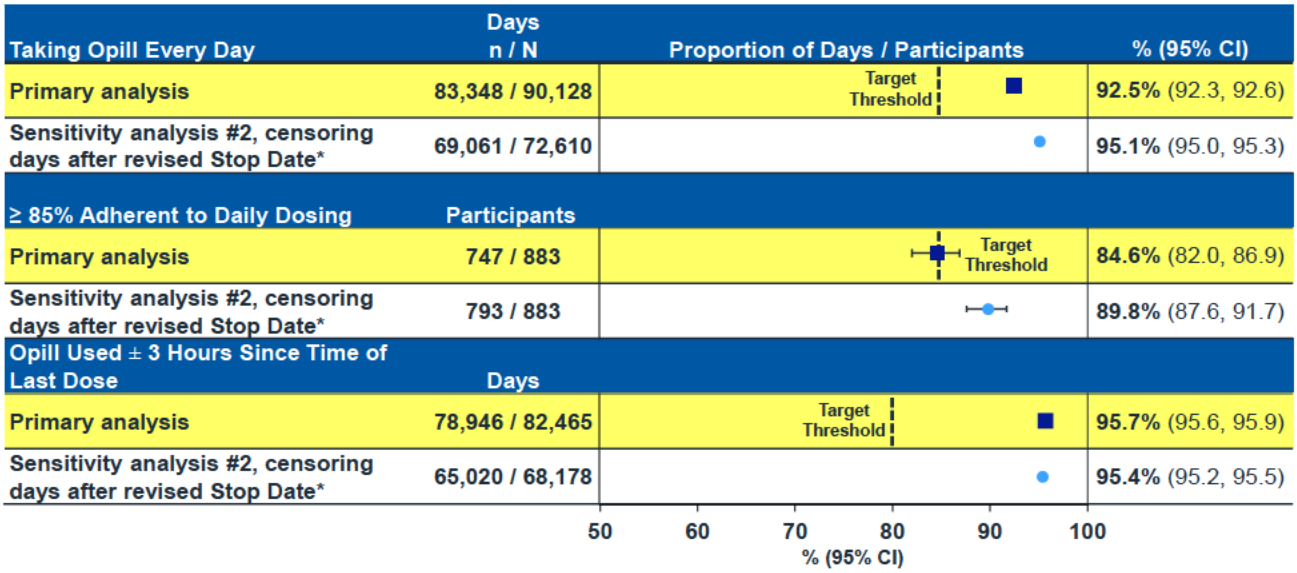
Figure 32: ACCESS Primary Adherence Endpoints Results: Post Hoc Sensitivity Analysis (#1) Excluding Participants Who Over-Reported (N=622 Participants) Along with Pre-specified Primary Analysis (N=883 Participants)



CI: confidence interval
For endpoint of taking Opill every day: n: number of days Opill was reported as taken, N: total number of days
For endpoint of ≥ 85% adherent to dosing: n:number of participants ≥ 85% adherent, N:number of participants For endpoint of Opill used ± 3 hours since time of last dose: n: number of days Opill reported at the correct time, N: number of days evaluable for timing of dose

Figure 33 presents the analysis that includes all participants but censors the participants' diary data after the revised Stop Date. Again, the results are very similar to the primary analysis results highlighted in yellow.

Figure 33: ACCESS Primary Adherence Endpoints Results: Post Hoc Sensitivity Analysis (#2) Censoring Days After Revised Stop Date (N=883 Participants) Along with Pre-specified Primary Analysis (N=883 Participants)



CI: confidence interval
For endpoint of taking Opill every day: n: number of days Opill was reported as taken, N: total number of days
For endpoint of ≥ 85% adherent to dosing: n: number of participants ≥ 85% adherent, N: number of participants
For endpoint of Opill used ± 3 hours since time of last dose: n: number of days Opill reported at the correct time, N: number of days evaluable for timing of dose
* Revised Stop Date: date at which drug supply exhausted based on reported use, participant reported stop date to nurse interviewers, or last day of use reported in the e-diary, whichever is the earliest

Thus, while the cause of the over-reporting of Opill use in ACCESS is incompletely understood, it reflects the design limitations inherent to an AUT that maximizes participants' autonomy and flexibility in decision making. However, it is nonetheless clear based on the totality of the data that the over-reporting did not affect the core conclusion from ACCESS: users were adequately adherent to daily and timely dosing when using Opill in an OTC setting.

6.2.3.5 ACCESS Adherence Conclusions

In conclusion, after careful review and consideration of all the ACCESS data, including the RCA and sensitivity analyses, the ACCESS study is informative of adherence behaviors during use of Opill in the OTC setting:

- ACCESS is an observational AUT designed specifically to assess adherence to Opill in the OTC setting.
- Importantly, the e-diary functioned as it was intended and allowed participants to enter data as they chose. Some participants chose to record that they used Opill when they had none available. Most research on medication adherence relies on self-report alone (Stirratt et al 2015), including adherence to OCs. Self-report tends to overestimate adherence when compared with other assessment methods (Stirratt et al 2015). Few adherence studies have included the

conditions necessary to observe the type of over-reporting seen in ACCESS. However, in those which did, this over-reporting has been seen (Lauffenburger et al 2020; Fanaroff et al 2020), including in studies of OC adherence (Nelson et al 2017; Triebwasser et al 2015).

- Multiple analyses were performed, which included the pre-specified primary analysis, the pre-specified sensitivity analyses designed to mitigate the impact of missing data, and the post hoc sensitivity analyses designed to mitigate the impact of over-reporting.

All these analyses yield similar and markedly consistent conclusions. The pre-specified analyses from ACCESS demonstrate that women can use Opill with adequate adherence without the aid of an HCP. When e-diary data are censored after a revised Stop Date determined based on all data sources available, or when participants who over-reported are excluded completely from analysis, the ACCESS data confirm that women of all ages can effectively use Opill in the OTC setting.

6.2.4 Assessing the Impact of Not Heeding the Adherence Label Directions for Use

In ACCESS, 68% (1,275/1,884) of episodes of missed pills were a single missed day (i.e., where pills were taken the day before and the day after the missed day). The Rx label dosing instructions for Opill indicating dosing should occur within a 3-hour dosing window were based solely on pharmacokinetic data. Thus, the true implications of a delayed or missed dose were uncertain.

To better understand the potential clinical consequence of nonadherence in ACCESS, results of the Delayed Pill Intake Study are provided below. (See Section 6.2.4.1 for study methodology.)

6.2.4.1 Delayed Pill Intake Study Design

HRA conducted a prospective, multicenter, randomized, crossover pharmacodynamic study, the Delayed Pill Intake Study, to determine the effects on cervical mucus characteristics and ovarian activity following one missed pill or a 6-hour delayed pill compared to “correct” daily use of norgestrel 0.075 mg tablets (Glasier et al 2023; Glasier et al 2022; Han et al 2022).

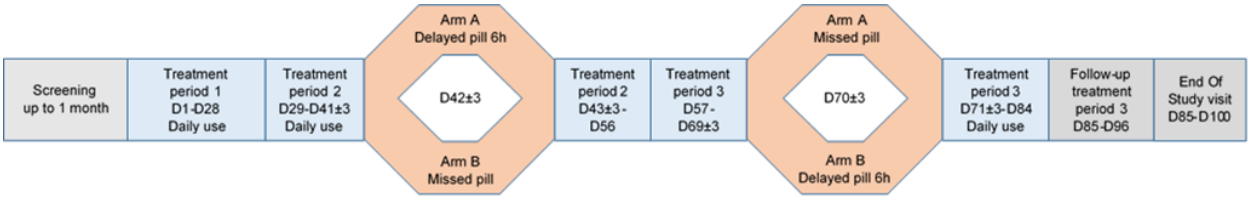
The Delayed Pill Intake Study was conducted at 2 sites in the US. Study participation lasted approximately 4.5 months including up to four weeks for screening, three 28-day treatment cycles, two weeks for follow up (if needed) and up to five days for End of Study processes (Figure 34). Reproductive-aged participants with regular menstrual cycles (21-35 days), body mass index less than 32 kg/m² and proven ovulation (screening luteal phase progesterone > 3 ng/mL [> 10 nmol/L]) were eligible to enroll.

Norgestrel 0.075 mg tablets were to be taken at the same time daily except for one specific day in each of treatment periods 2 and 3, when the pill was to be taken either six hours late (delayed pill) or omitted completely (missed pill) per the randomized assignment.

Participants were monitored every 3-4 days with transvaginal ultrasound examination for follicular activity and ovulation, cervical mucus evaluation and blood sampling for ovarian hormones and gonadotropins. Cervical mucus sampling and ovarian activity monitoring were increased to every other day once an ovarian follicle reached 15 mm in size, because this meant that ovulation was likely to occur within 7 days. Daily monitoring was undertaken for 3 days around the time of the delayed or missed pill.

The cervical mucus characteristics were determined based on a modified Insler score (WHO 2010). This score encompasses consistency (viscosity), ferning, spinnbarkeit, and cellularity, each scored on a 4-point scale (0-3), for a maximum of 12 points. The cervical mucus was considered protective (unfavorable to fertility) when the total score was ≤ 4 (versus 5-8 intermediate and ≥ 9 favoring fertility).

Figure 34: Delayed Pill Intake Study Design



6.2.4.2 Delayed Pill Intake Study Results

A total of 52 participants enrolled in the study, with 51 participants completing the "correct" use cycle and 46 participants completing each of the delayed or missed pill cycles.

6.2.4.2.1 "Correct" Daily Use (Baseline) Cycle Results

Data from the "correct" use cycle (i.e., where tablets were to be taken at the same time daily) confirm that Opill is very effective in thickening cervical mucus as daily administration in the 51 women who completed this cycle was associated with an absence of fertile cervical mucus. No participant had a cervical mucus score ≥ 9.

Of these 51 women:

- 67% of women did not ovulate
- 10% had a cycle in which ovulation occurred but with progesterone levels widely believed to be insufficient for conception to occur
- 23% had an apparently normal ovulatory cycle

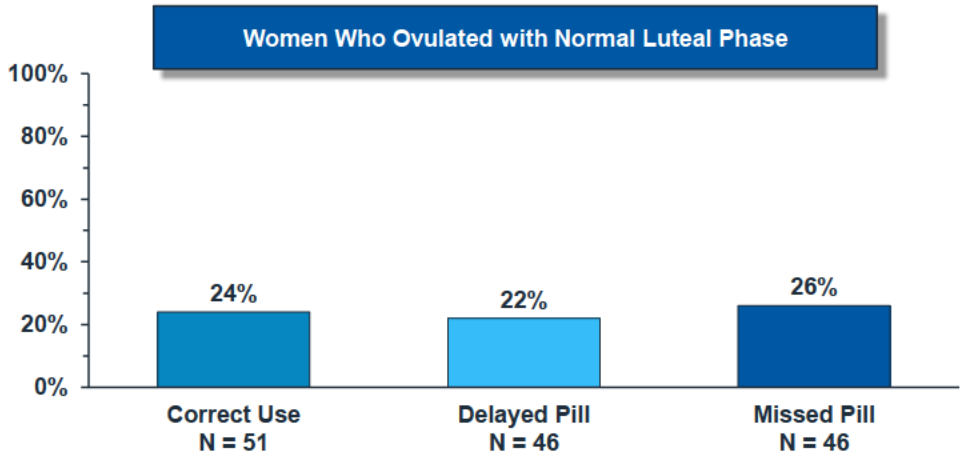
Although approximately one-third of users ovulated in this correct cycle of pill use, the contraceptive effect is maintained by hostile cervical mucus.

These data demonstrate that ovulation inhibition and follicle growth disturbance provide an important contribution to the mechanism of action of Opill in preventing pregnancy, in addition to its important effect on thickening cervical mucus.

6.2.4.2.2 Impact of Delaying or Missing a Pill

Figure 35 presents the ovarian status from the cycles in which a pill was taken 6 hours late or missed for an entire day compared to the correct use cycle. A similar percent of women ovulated with an apparently normal luteal phase in each of the three cycles.

Figure 35: Delayed Pill Intake Study – Effect of Delaying or Missing a Pill on Ovulatory Status



Only two women, one in the delayed pill cycle and one in the missed pill cycle, had a single cervical mucus score in the range considered favorable for fertility at any time in the cycle. Comparing the changes with the correct use cycle, there were no significant changes in cervical mucus score with either delaying intake by 6 hours or missing a pill entirely. Thus, Opill can be expected to effectively protect against pregnancy even if a woman takes her daily pill late or misses it.

6.2.4.3 Conclusion

The Delayed Pill Intake Study demonstrated that:

- Opill is very effective in thickening cervical mucus; cervical mucus does not become less protective after one missed pill or a 6-hour delayed pill, and
- Opill prevents ovulation in the majority of women and ovarian activity is not affected by one missed pill or a 6-hour delayed pill.

Overall, delaying or missing one Opill tablet appeared to have no significant effect on the two main mechanisms of contraceptive efficacy (i.e., cervical mucus thickening and disruption of ovarian activity), suggesting that the 3-hour window of intake in the label is overly conservative.

These new data are reassuring that there is likely a wider window for maintaining efficacy in the case that a pill is delayed or missed and that the clinical consequences of a late or missed pill would be less significant than previously thought. This has important clinical implications when considering the ACCESS use results. Nonetheless, HRA plans to keep the direction that Opill should be taken at the same time every day in the labeling as:

1) there are no data available to assess the impact of missing more than one pill on pregnancy risk and it is not known how many pills need to be missed before contraceptive efficacy is significantly reduced and 2) it remains wise to advise women to take a contraceptive pill (whether combined or progestin-only) every day and at the same time of day as they should be less likely to take the pill inconsistently (Rosenberg et al 1995).

6.2.5 Adherence to Directions for Use Conclusions

In ACCESS, 68% of episodes of missed pills were of one day duration. Overall, the ACCESS data together with the findings from the Delayed Pill Intake Study demonstrate that Opill can be expected to effectively protect against pregnancy in the OTC setting even if a woman takes her daily pill late or misses it.

6.3 When Consumer Should Take Action During Use

The proposed Opill OTC labeling includes information for women who choose to use a POP on what to expect during use and what to do while using Opill under specific circumstances.

6.3.1 ACCESS Endpoints for When Consumer Should Take Action During Use

Key DFL statements regarding actions consumers should take during Opill use that were evaluated in ACCESS as secondary endpoints included:

- Talk to a doctor if you have repeated vaginal bleeding brought on by sex
- Talk to a doctor if you have 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 tablets in the last month or if you have not had a period for 2 months or think you may be pregnant
- Talk to a doctor if you have sudden or severe pain in your lower belly
- Talk to a doctor if you 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
- Stop use and ask a doctor if you develop yellowing of your skin or whites of your eyes (especially with fever, tiredness, loss of appetite or dark colored urine)

The assessments of these endpoints were only made on participants who took part in an EOS interview (72.7%; 642/883 total User Population).

Due to the naturalistic study design of ACCESS as an AUT, the participants' actions were often reported either temporally distant from the issue in question (such as at EOS) or gathered through indirect methods in order to minimize reactivity (the likelihood that by asking the question, we influence the behavior we are trying to measure). As such, the information provided relied on recall of participants only, and their description of events (not corroborated with HCP records) and was often not detailed. Therefore, the standard

approach for assessing whether a participant had a discussion with an HCP for all relevant ACCESS secondary endpoints was to give credit for any interactions with an HCP at any point during study participation.

Additionally, some specific symptoms may occur infrequently in the study population making the drawing of firm conclusions impossible due to the small number of participants experiencing these symptoms. Of note as well, these symptoms often resolve spontaneously obviating the need to contact an HCP.

Because there were limited ACCESS data to assess the performance of the label in these specific uncommon scenarios, results from the Final LCS which inform about consumers' understanding of these label messages are summarized along with ACCESS results below (see also Appendix Section 11.4.6).

6.3.2 Assessment of the Impact of Not Heeding the Label Instructions

As expected, the situations in which consumers should take action during Opill use were uncommon in the ACCESS study given the inherent safety profile of norgestrel. Unsurprisingly, in many instances, the symptoms resolved spontaneously obviating the need to contact an HCP. However, the majority of participants reporting one of these events also reported speaking with an HCP at some point during the study. Overall, the data show no signal of concern for use in the OTC setting.

In addition, data from the Final LCS show that consumers understand these label messages.

Specific results in relation to the tested DFL statements for actions to be taken during Opill use are presented in more detail in the following sections along with a discussion on the impact of not heeding those statements.

Importantly, note that the action of a woman taking a POP should she experience any of these situations is not unique to the OTC setting; a woman in the Rx setting must also decide when to seek care in such circumstances.

6.3.2.1 Management of Bleeding Pattern Alterations During Product Use that Warrant Medical Evaluation

Some bleeding changes are expected to occur with Opill use and are a recognized side effect of use of the product. These are clearly described in the OTC labeling. The instruction to continue use despite certain changes in menstrual periods, specifically irregular periods, spotting or bleeding between periods, or amenorrhea is included in the labeling to ensure continued effective contraception. In contrast, the proposed DFL instructs users to continue use of the product but to also talk to a doctor if specific bleeding changes occur during use: repeated post-coital bleeding or newly prolonged periods or unusually heavy periods. These specific changes that are not a side effect of Opill should be medically evaluated to exclude underlying conditions, such as endometrial or cervical cancer, which are rare in women of reproductive age (see Section 5.3.3). Note that norgestrel use does not increase a woman's risk for any of these conditions (Park and Nam 2015).

In ACCESS, only two user participants (2/883; 0.2%) reported experiencing repeated vaginal bleeding brought on by sexual intercourse during Opill use. While one reported speaking to an HCP at some point during the study, she did so before she experienced her bleeding and did not ask specifically about bleeding brought on by sex. Both indicated they did not speak to an HCP about it because the symptoms resolved. However, the very low number of participants who experienced the symptom assessed in this endpoint precludes the ability to draw any conclusion. The label instruction to talk to a doctor if you have repeated vaginal bleeding brought on by sex tested well (95.3%) in the Final LCS.

Also in ACCESS, 50 (5.7%; 50/883) user participants reported experiencing unusually heavy periods or periods lasting more than 8 days during Opill use, including 45 who completed the study (45/50; 90%). Of these 45 evaluable participants, 71.1% (32/45) reported speaking to an HCP at some point during the study or decided to stop product use and were assessed as correct in the endpoint analysis. Those 32 participants included nine who spoke to an HCP specifically about their heavy or prolonged bleeding, 16 who stopped using the product, and seven who spoke with an HCP but not specifically about prolonged or heavy bleeding. Note that for two of these seven participants, the interaction with the HCP in question occurred before the onset of prolonged or heavy periods. Among those who did not speak to an HCP specifically about prolonged or heavy bleeding and/or who did not stop use, when asked why they did not do so, they generally responded that they attributed symptoms to the study medication (N=8) or the symptoms otherwise were not concerning to them (N=11). The label instruction to talk to a doctor if you start having periods that last more than 8 days or are unusually heavy tested well (93.5%) in the Final LCS.

6.3.2.2 Potential for Delayed Diagnosis of Ectopic Pregnancy During Product Use

No ectopic pregnancies were reported in ACCESS.

The best way to prevent an ectopic pregnancy is to use effective contraception as all contraceptive methods are associated with a lower absolute risk of ectopic pregnancy compared with no method of contraceptive use (WHO 2018). In the case of method failure, however, POCs, including POPs, may be more likely to result in ectopic pregnancies than some other contraceptive methods, such as combined hormonal contraceptives and barrier methods.

As an ectopic pregnancy may lead to clinically significant sequelae, women who could be pregnant should seek immediate medical attention in the event of an episode of acute severe persistent abdominal pain. Though ectopic pregnancy is uncommon, occurring in 1-2% of all pregnancies in the US (Callahan et al 2015), as it is a serious medical event with the possibility of significant morbidity and even mortality (in the case of a ruptured ectopic), the labeling errs on the conservative side, recommending consultation with an HCP should symptoms occur. It is also worth noting that a history of ectopic pregnancy is not a contraindication to use of POPs per the CDC MEC (Curtis et al 2016b).

In the ACCESS study, the DFL warning related to ectopic pregnancy read:

- 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).

Few user participants (1%; 9/883) reported sudden or severe abdominal pain while using Opill. All nine participants had self-limited pain that resolved and none were ectopic pregnancies or represented a clinically important issue requiring immediate evaluation or intervention. Of these, two thirds (66.7%; 6/9) spoke with an HCP at some point during the study and were assessed as correct in the endpoint analysis. Three of these participants spoke with an HCP specifically about their abdominal pain while three spoke with an HCP for some other reason (for two of these, the interaction in question occurred before the abdominal pain). Those who did not seek medical attention specifically about their episode of abdominal pain stated that they attributed the pain to a medication side effect or something non-serious and expected it to resolve on its own, which it did.

After the ACCESS study, this DFL warning was revised. The qualifiers of “persistent” pain “mostly on one side” were added to provide users of Opill with more specificity about the symptoms that might indicate an ectopic pregnancy and for which they should seek immediate medical attention. The more direct instruction to “seek medical help right away if…” was also added upon FDA latest recommendations. The final proposed DFL warning is:

“seek medical help right away if…you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy).”

This message was tested in the Final LCS and was well understood by 98.0% of participants (95% CI: 96.7, 98.9).

Among all instances of events that could be classified as “sudden or severe pain in the lower belly,” ectopic pregnancy is likely to represent a tiny fraction, which is what was observed in the ACCESS study where none of those situations were associated with an ectopic pregnancy. Therefore, it is reasonable that a person experiencing symptoms might draw upon their own life experience and circumstances to inform their decision whether or not to seek care. A short-lived episode of abdominal pain would not represent ectopic pregnancy and may not spur a consumer to consult an HCP, nor should it. Acknowledging that educating consumers about the (unlikely) possibility of ectopic pregnancy is important, strictly following this instruction to immediately seek medical care is not necessary for every consumer using the product who at some point develops self-limited abdominal pain, even if it appears to them as sudden and severe.

6.3.2.3 Use During Pregnancy and Delayed Diagnosis of Pregnancy

Although as per the CDC MEC, there is no known harm to the woman, the course of her pregnancy, or the fetus if POCs are inadvertently used during pregnancy (Curtis et al 2016b), the proposed DFL for Opill contains multiple warnings to limit its use by pregnant women. This includes language instructing women not to use the product if they are

already pregnant or think they may be pregnant and to discontinue using the product if they become pregnant. To minimize the risk of a delay in pregnancy diagnosis, there is also a specific instruction on the label to take a pregnancy test or talk to a doctor in the case of a late period after missing any tablets in the last month, in the case of amenorrhea for two months or if the woman thinks she may be pregnant.

Six ACCESS user participants (0.7%; 6/883) became pregnant while using Opill. All six reported taking the correct or acceptable action of stopping use of Opill and/or speaking to an HCP as instructed by the label. These six participants identified their pregnancies between 19-37 days (2.7-5.3 weeks) after their last menstrual period. The gestational age at pregnancy awareness for these six participants is consistent with, or earlier than, the US data for average gestational age at pregnancy awareness (5.5 weeks) (Branum and Ahrens 2017).

Fifty-eight (58) ACCESS user participants (6.6%; 58/883) reported having a late period after missing tablets in the last month or not having a period for two or more months; of this group, 70.7% correctly reported they took a pregnancy test, sought healthcare as directed by the label, or stopped using the product. Participants who did not heed the instruction to take a pregnancy test or talk to an HCP did so because irregular/missed periods were normal for them personally, because they knew they were not pregnant (i.e., did not have sex that month), or thought it was a normal side effect of the product. Importantly, none of these 58 participants became pregnant during their use of Opill.

Finally, the proposed DFL warnings related to use in pregnancy were well comprehended in the Final LCS. More than 93% of participants correctly understood the message “Do not use: if you are already pregnant or think you may be pregnant”; 94.7% correctly understood to “Stop use and ask a doctor if: you become pregnant”; 93.2% correctly understood “When using this product take a pregnancy test or talk to a doctor if you have not had a period for 2 months or think you may be pregnant”; and 82.6% correctly understood the message “When using this product take a pregnancy test or talk to a doctor if: your period is late after missing any tablets in the last month.”

Results from ACCESS and the Final LCS support the conclusion that the proposed text in the OTC label is sufficient to limit the potential for inadvertent use of Opill during pregnancy and the potential for delayed diagnosis of a pregnancy that may occur during use.

6.3.2.4 Use in Women in Case of Migraine

The CDC MEC categorizes migraine with aura as Category 1 (a condition for which there is no restriction for use) for all POC methods, including among women who develop migraine with aura after POC is initiated (Curtis, 2016b). As per Sponsor’s prior discussions with the FDA, the label includes messaging that new or worsening migraines should be evaluated but are not a criterion for discontinuing use of Opill given the documented safety of use of POPs in the setting of migraine with and without aura (Curtis, 2016b).

In ACCESS, 11 user participants (1.2%; 11/883) reported new migraines with aura or worsening migraines. Nine of these participants completed the EOS interview and the

majority (77.8%; 7/9) either spoke to an HCP during the study and/or stopped using Opill and were assessed as correct for the endpoint analysis.

In the Final LCS, the tested warning related to new or worsening migraines was understood by 95.2% of subjects.

Therefore, the proposed text for the OTC label is sufficient to encourage Opill users to get new or worsening migraines medically evaluated.

6.3.2.5 Use in Women in Case of Signs of Jaundice

The Opill Rx label instructs HCPs to discontinue use if the patient has signs of acute liver disease, and this warning is carried over to a parallel warning in the OTC labeling, written in easy-to-understand consumer language (“Seek medical help right away if you develop yellowing of your skin or whites of your eyes especially with fever, tiredness, loss of appetite or dark colored urine"). While the development of jaundice is likely to represent a significant medical event requiring urgent evaluation, it is unlikely to be related to use of Opill as low dose progestins are not thought to be hepatotoxic (LiverTox, 2020).

No user participants (0/883) reported yellowing of the skin or whites of the eyes during the ACCESS study and therefore heeding of this label message could not be assessed. In the Final LCS, the message to seek medical help in the face of onset of jaundice symptoms was understood by 97.9% of the 703 subjects.

Overall, the DFL for OTC Opill takes a conservative approach and results from the Final LCS support the conclusion that the proposed OTC labeling is sufficient to direct users of Opill to take action.

6.3.3 When Consumer Should Take Action During Use Conclusions

Given the inherent safety profile of norgestrel, situations in which Opill users need to consult an HCP, take a pregnancy test, and/or stop use in response to certain new symptoms are uncommon. However, the ACCESS data show no signal of concern for use in the OTC setting and the Final LCS data show that the relevant messages in the DFL are well understood.

Importantly, expected consumer behaviors reflected in these labeling statements are not unique to an OTC setting, meaning that users of OCs have to make the same decisions during use regardless of whether the POP is obtained by Rx or OTC.

7 OVERVIEW OF SAFETY IN ACCESS

Safety of Opill in ACCESS was assessed among the Safety Population which comprised 955 participants. It was larger than the User Population (N=883) as it included all those who purchased / obtained the study medication, including those who never reported use in their e-diary.

7.1 Pregnancies in ACCESS

The primary focus of the behavioral assessments in the ACCESS study was related to the consistent daily use of Opill, which is essential to achieve contraceptive effectiveness. Therefore, the study was designed to assess consumers' behaviors in the OTC setting rather than the effectiveness of the product as the product has already been approved by FDA for pregnancy prevention. All reports of pregnancy among the User Population were collected and classified by a panel of three independent OB/GYN physicians as occurring before, during, or after use of Opill.

Among the 955 women in the Safety Population in ACCESS, which included all those who purchased / obtained Opill in ACCESS, including those who never reported use in their e-diary, 14 pregnancies were reported during the study. Three of these 14 occurred in women who purchased but never used the product or never reported use in the diary (not included in User Population).

Among the 883 women in the User Population, there were six pregnancies that occurred while participants were using Opill (Table 18) in over 3,538 months of use. Five pregnancies occurred when the participant had discontinued Opill prior to the estimated day of conception.

Table 18: Pregnancies in ACCESS

Parameter	N
Safety Population (Participants)	955
Pregnancies reported at any time during study	14
Did not use Opill	2
Used Opill but reported use to nurse only (not included in User Population)*	1
User Population (Participants)	**883**
Pregnancies in User Population	11
Conception occurred before participant reported taking Opill [1]	0
Conception after discontinued use of Opill [2]	5
Conception while taking Opill [3]	**6**
Low health literacy (n = 120)	1
Adolescents 12-14 years (n = 49)	0
Adolescents 15-17 years (n = 151)	0

* Conception occurred before participant reported taking Opill
1 Majority of physician panel agrees that conception occurred before the Start Date
2 Majority of physician panel agrees that conception occurred after the Start Date and before the Stop Date
3 Majority of physician panel agrees that conception occurred after the Stop Date

7.2 Summary of Adverse Events and Serious Adverse Events in ACCESS

Overall, there were 507 AEs reported by 355 participants (37.2%; 355/955) in the Safety Population. The most frequently reported SOCs in the ACCESS study were Reproductive system and breast disorders (19.4%), Infections and infestations (10.4%), and Injury, poisoning and procedural complications (4.4%). The most common AEs were metrorrhagia, menorrhagia, menstruation irregular, and menstruation delayed (Table 19).

Table 19: ACCESS Summary of Participants with Adverse Events, ≥ 1% Incidence (Safety Population)

	Participants (N=955)	
Preferred Term	n	%
Participants with AEs:	355	37.2%
Metrorrhagia	49	5.1%
Menorrhagia	49	5.1%
Menstruation irregular	30	3.1%
Menstruation delayed	29	3.0%
Off label use	24	2.5%
Urinary tract infection	22	2.3%
Polymenorrhoea	19	2.0%
Influenza	16	1.7%
Nasopharyngitis	16	1.7%
Sinusitis	13	1.4%
Unintended pregnancy	13	1.4%
Acne	11	1.2%
Amenorrhoea	10	1.0%

AEs: adverse events
Off label use AEs were collected and reported for participants who used the product for a purpose that did not include contraception.
Note: Each participant who reported pregnancy may have been assigned an AE of "unintended pregnancy," "exposure during pregnancy" or both, depending on the timing of conception relative to signing of informed consent and the taking of Opill. In one case, conception was prior to enrollment (though it had not been identified at the time of enrollment by the enrollment pregnancy test), so that participant does not have an AE for "unintended pregnancy" (and therefore is not included in the AE tables on the corresponding rows)

Two participants (0.2%; 2/955) each experienced one severe AE (pharyngitis streptococcal and diabetic ketoacidosis, also classified as serious AEs). There were 24 serious AEs (SAEs, including pregnancies) reported in the study, occurring in 18 participants (1.9%; 18/955; Table 20). Of the 18 (1.9%) participants who reported a SAE, 14 (1.5%) reported a pregnancy, accounting for 20 SAEs (13: unintended pregnancy, 7: exposure during pregnancy). There were no deaths in the study.

There were four non-pregnancy-related SAEs among four participants reported in ACCESS, including cardiac failure congestive, pharyngitis streptococcal, diabetic ketoacidosis, and jugular vein thrombosis, all of which were judged by the medical monitor as not related or unlikely to be related to use of the study medication. Narratives for these events are provided in Appendix Section 11.7.

Table 20: ACCESS Serious Adverse Events (Safety Population)

	Participants (N=955)	
Preferred Term	n	%
Participants with SAEs:	18	1.9%
Unintended pregnancy	13	1.4%
Exposure during pregnancy	7	0.7%
Congestive heart failure	1	0.1%
Diabetic ketoacidosis	1	0.1%
Jugular vein thrombosis	1	0.1%
Pharyngitis streptococcal	1	0.1%

AE: adverse event; SAEs: serious adverse events
Note: Each participant who reported pregnancy may have been assigned an AE of "unintended pregnancy," "exposure during pregnancy" or both, depending on the timing of conception relative to signing of informed consent and the taking of Opill. In one case, conception was prior to enrollment (though it had not been identified at the time of enrollment by the enrollment pregnancy test), so that participant does not have an SAE for "unintended pregnancy".

Sixty-seven participants (7.0%; 67/955) experienced 89 AEs which led to temporary or permanent discontinuation of Opill (Table 21). Approximately half of the 89 AEs (44) were in the SOC of Reproductive system and breast disorders, primarily comprising menstrual changes.

Table 21: ACCESS Summary of Adverse Events Leading to Temporary or Permanent Discontinuation of Opill (Preferred Term Reported > 1) in the Safety Population (N=955)

Preferred Term	All AEs leading to discontinuation of Opill
AEs which led to discontinuation	89
Menorrhagia	14
Menstruation irregular	9
Unintended pregnancy	8
Metrorrhagia	7
Exposure during pregnancy	7
Polymenorrhoea	5
Weight increased	4
Acne	3
Premenstrual syndrome	2
Menstruation delayed	2
Nausea	2
Diarrhoea	2
Abdominal pain	2
Headache	2

AEs: adverse events

Overall, all AEs were consistent with the known side effect profile of Opill or were inherent to the study population, and all frequent AEs are listed in the Opill Rx labeling, as well as on the proposed OTC DFL. Bleeding irregularities, while common, are not clinically concerning.

8 INCREMENTAL BENEFIT-RISK ASSESSMENT

HRA thoroughly evaluated the potential incremental benefits and risks likely to be associated with the nonprescription availability of Opill. The focus on the *incremental* benefits and risks associated with consumers being able to access and use the product guided by the OTC labeling is what is most important as the drug is already recognized and FDA approved as safe and effective. Applying the approach as described by Brass et al (2011), HRA identified the important potential benefit and risk attributes specific to an Rx-to-OTC switch of Opill and then assessed the potential magnitude (frequency or likelihood of occurrence) and clinical significance (clinical impact) of each attribute through the available evidence. Evidence reviewed included data from HRA's consumer and other studies, post marketing surveillance safety data, as well as information and data from the published literature.

8.1 Summary of Benefits

OTC availability of Opill will address a significant unmet need among those at risk for unintended pregnancy for increased access to effective contraceptives, and the potential incremental benefits of making the product available OTC are clinically significant.

Those at risk of unintended pregnancy who need increased access to effective contraception include women of all reproductive ages, levels of educational attainment, income levels and racial and ethnic groups. Almost all women at risk of unintended pregnancy, who choose to, could benefit from use of Opill at some point in their reproductive lives. While adolescents aged 17 and under make up a relatively small proportion (~5%) of the approximately 40 million women at risk of unintended pregnancy in the US (Pinney Associates 2022), their need for increased access to effective contraceptives is particularly urgent given that 72% of pregnancies in adolescents are unintended (Finer and Zolna 2016). In addition, pregnancy and childbearing in adolescents 17 and under results in significant individual and societal costs (Hoffman 2006; Perper et al 2010). Adolescents now have ready access only to nonprescription methods (the least effective available). While they can access the more effective methods available through an HCP, adolescents face significant barriers to accessing these more effective methods (Alexander et al 2014; Baum et al 2016; Biggs et al 2012; Foster et al 2012; Fuentes et al 2018). Reducing pregnancies and increasing use of effective contraception in adolescents are national health priorities (ODPHP 2021). A number of leading medical organizations strongly support OTC access to OCs, including the American College of Obstetricians and Gynecologists, American Medical Association, American Academy of Family Physicians, North American Society for Pediatric and Adolescent Gynecology, and Society for Adolescent Health and Medicine (AAFP 2019; ACOG 2019; AMA 2022; NASPAG 2022; SAHM 2022), most of which explicitly support such access with no age limit (ACOG 2019; AMA 2022; NASPAG 2022; SAHM 2022). OTC Opill will provide all seeking to prevent pregnancy ready access to a safe and notably more effective method than is currently available without an HCP visit.

By removing unnecessary barriers to access to and therefore likely increasing use of this effective contraceptive, OTC availability of Opill also has the potential to decrease the negative outcomes associated with unintended pregnancies in the US. Moreover, all pregnancies, whether intended or unintended, are associated with an increased risk of morbidity and mortality (Grimes 1994) and reducing unintended pregnancies will circumvent these risks for many women.

Unintended pregnancy has been linked to an increased risk of adverse consequences for both mother and child, compared to intended pregnancies. This include a reduced likelihood of receiving early prenatal care (Cheng et al 2009; Dibaba et al 2013; Gipson et al 2008; Kost and Lindberg 2015; Lindberg et al 2015). Unintended pregnancy has also been found to be associated with an increased risk of pre-term delivery (Mohllajee et al 2007; Shah et al 2011) and an increased risk of low birth weight (Hall et al 2017; Kost and Lindberg 2015; Shah et al 2011). According to a meta-analysis of 17 studies (Hall et al 2017), the odds of having a baby with low birth weight are 1.41 times greater in women who have an unintended pregnancy. Low birth weight is an important determinant of child survival and development. It is the second leading cause of infant death in the US (Murphy et al 2021) and increases the risk for serious health problems (March of Dimes 2021).

Unintended pregnancy has also been found to be associated with an increased risk of maternal depression (Abajobir et al 2016; Cheng et al 2009; Fellenzer and Cibula 2014; Gariepy et al 2016; Gauthreaux et al 2017; Gipson et al 2008). One systematic review and meta-analysis concluded that the prevalence of perinatal depression is two-fold higher in women with an unintended pregnancy as compared to women with an intended pregnancy (Abajobir et al 2016).

Pregnancy intention has also been found to be associated with attitudes and behaviors in parenting (Logan et al 2007). For example, unintended pregnancies have been linked to a reduced likelihood of breastfeeding (Gipson et al 2008; Kost et al 2017; Lindberg et al 2015). Furthermore, children from unintended pregnancies have been reported to be more likely to experience poor mental and physical health during childhood, and to have lower educational attainment and more behavioral issues in their teen years (Logan et al 2007). Unwanted births may also cause poor mother−child relationships, from childhood through adulthood (Logan et al 2007). For women, reducing unintended pregnancies has been reported to reduce the risk of falling into poverty, improve maternal education and income, and increase women’s labor force participation (Bailey et al 2019; Bailey et al 2014; Fletcher and Wolfe 2009; Nuevo-Chiquero 2014).

Most pregnancies in adolescents (72% in those aged 15-17) are unintended (Finer and Zolna 2016). Adolescent pregnancy and childbearing in particular are associated with substantial individual and social costs (CDC 2021a). Pregnancy and birth are significant contributors to high school dropout rates among female adolescents. Only about 50% of adolescent mothers (those who give birth at age 19 or younger) receive a high school diploma by age 22, whereas approximately 90% of women who do not give birth during adolescence graduate from high school (Perper et al 2010). Children of adolescent mothers are more likely to have lower school achievement and to drop out of high school,

have more health problems, be incarcerated at some time during adolescence, give birth as a teenager, and face unemployment as a young adult (Hoffman 2006).

Making Opill available OTC would be an important step in helping to increase the proportion of women who use effective methods of contraception, a key US national health objective (ODPHP 2021). HRA created, and published, a Pregnancy Impact Model to estimate the magnitude of the potential incremental benefit that might be achieved from OTC availability of Opill (Guillard et al 2023). The model estimates the impact on the cohort of women who elect to switch to Opill from their current methods (or no method). Under a range of different assumptions, the model demonstrates that even under the most conservative assumptions, the use of an OTC POP instead of continued use of currently used methods is likely to meaningfully reduce unintended pregnancies. For example, comparing the number of pregnancies expected in a group of 100,000 women electing to using a POP for one year with the number of pregnancies expected if the women continued to use for one year the methods that those in the ACCESS User Population reported using before enrollment, could result in an 80% reduction in unintended pregnancies for the cohort. This significant reduction in unintended pregnancies is largely the result of shifting those who had been using nonprescription or behavioral methods, or no method, to use of a POP. Even under much more conservative assumptions, the model suggests that there could be a reduction in unintended pregnancies of approximately 10% over a year of contraceptive use. ACCESS confirmed the willingness of consumers using current OTC and behavioral methods or no method to pay out-of-pocket for and use Opill, reinforcing that there is an existing unmet need for OTC access to a more effective contraceptive. Substantial incremental benefit is expected to result from Opill availability OTC.

A thorough review of the relevant available data make clear that OTC access to Opill will result in substantive improved individual clinical outcomes and well-being as well as improved public health outcomes. OTC availability of a POP has the potential to meaningfully advance important national public health objectives and is supported by key professional medical societies.

8.2 Summary of Potential Risks

Opill has a well-characterized and acceptable safety profile. Because it contains progestin only, and does not contain estrogen, it has fewer and rare contraindications than a COC (White et al 2012), making it appropriate for a broad population of women. Opill has been demonstrated to be safe for use in women seeking to prevent pregnancy based on a thorough review of the available evidence. Overall, no safety signals relevant for a daily oral norgestrel contraceptive were observed in the data reviewed for this submission. The available data from these multiple data sources support the well-characterized and acceptable safety profile of Opill for OTC availability. Data from the ACCESS study demonstrate that women are able to use the product as directed by the OTC labeling, thereby minimizing any risks, in the OTC setting.

The typical use, real-world failure rate of OCs, including POPs such as Opill, has been estimated at 7% in the Rx setting (Trussell et al 2018). This means that it is estimated that

7% of women will experience an unintended pregnancy during the first year of typical use (Trussell et al 2018). There is a difference between efficacy as assessed in clinical trials (perfect use) and real-world effectiveness (typical use) which reflects how women actually use OCs prescribed by an HCP. For this reason, there should be no expectation of perfect use (i.e., the near 100% adherence seen in clinical trials) in the OTC setting. Rather, the goal is to achieve levels of adherence in the OTC setting that are similar to those seen in the prescription setting. As detailed above, adherence in ACCESS approximated that reported with Rx OCs.

Data from ACCESS demonstrate that women including adolescents are able to use the product as directed by the OTC labeling, including importantly taking their pill every day at the same time of day. Moreover, data from HRA's recent pharmacodynamic study (the Delayed Pill Intake Study) show that taking Opill late or missing one pill would be unlikely to result in an increased risk of pregnancy. Thus, the data from HRA's studies support that consumers who elect to use OTC Opill will achieve contraceptive effectiveness superior to existing OTC options and similar to that achieved with Rx OCs.

Where necessary, Opill users are encouraged in labeling (both DFL and CIL) to maintain or initiate interactions with HCPs. As noted above, the ACOG, AMA and other professional medical organizations support OTC access to OCs (AAFP 2019; ACOG 2019; AMA 2022; NASPAG 2022; SAHM 2022).

It has been suggested that initiation of an OC provides HCPs with an important opportunity to provide screenings and other preventive services. However, no exams (including pelvic and breast exams) or screenings (including those for cervical and breast cancer and sexually transmitted infection) are required before or during POP use (ACOG 2019; Curtis et al 2016a). Moreover, the ACOG clearly states that these exams and screenings "…should not be used as reasons to deny access to hormonal contraception". Opill users will be encouraged in labeling to get routine healthcare and important health screenings. Further, data support that cervical cancer and breast cancer screenings are likely in OTC POP users (Grindlay and Grossman 2018; Hopkins et al 2012), as are screenings for sexually transmitted infections for those who need them (Hopkins et al 2012).

The data from HRA's self-selection and actual use studies demonstrate that women, including those with a history of breast cancer, can correctly make the decision about whether Opill is right for their use, and that women can correctly and safely use Opill. Thus, OTC Opill will not present meaningful incremental risks when compared with the current prescription access. The net incremental benefit-risk is clearly favorable based on the totality of the evidence accumulated.

9 CONCLUSION: OPILL MEETS ALL KEY CHARACTERISTICS OF OTC DRUG

FDA has already determined that pregnancy prevention is an OTC indication (with a range of contraceptives available OTC today). Opill has been demonstrated to be effective and to be safe for use in women seeking to prevent pregnancy based on: clinical data from the original Rx NDA, literature published since Rx approval, HRA clinical trials, and post-marketing surveillance safety data from multiple safety databases for both norgestrel and its biologically active enantiomer levonorgestrel.

The Opill OTC label incorporates all of the information from the Rx label that consumers need to appropriately select and use the product safely and effectively and presents that information in a way that is understood by consumers. Through its LCSs, HRA has demonstrated that the proposed OTC labeling is well understood by consumers. Based on the findings from HRA's consumer development program, comprising multiple behavioral studies, the proposed OTC labeling guides appropriate selection and non-selection of the product, as well as safe and effective use of the product in the OTC setting without supervision of an HCP. Thus, Opill meets the key characteristics of OTC drugs (Table 22).

Table 22: Key OTC Drug Characteristics and their Applicability to Opill

OTC Drug Characteristics[1,2]	Opill	
Condition to be treated self-diagnosable	Women self-recognize when they want to prevent pregnancy	☑
Adequately labeled such that consumer can self-diagnose, self-treat, self-manage condition No health practitioner needed for safe and appropriate use	Studies demonstrate consumers can use Opill safely and appropriately without supervision of health practitioner	☑
Low potential for misuse and abuse	Low potential considering mechanism of action No signal of abuse identified in post-marketing data	☑
Benefits of OTC availability outweigh risks	Well-characterized efficacy and favorable safety profile Potential to reduce unintended pregnancy and consequences	☑

OTC: over-the-counter
[1] 503(b) of FD&C Act
[2] Adapted from Michele 2015

Overall, Opill has a favorable benefit / risk profile. There are few incremental risks associated with consumer use as guided by OTC labeling. And importantly, there are substantial incremental benefits in decreasing unintended pregnancies through use of this effective contraceptive in a population currently using no, or less effective, contraceptive methods.

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11 APPENDICES

11.1 Proposed Opill OTC Labeling

Note that the proposed DFL is presented in Section 3.3.2.

11.1.1 Proposed Consumer Information Leaflet for OTC Opill

What this leaflet covers

1 What is Opill®?

Opill® is a **daily oral contraceptive** (also called a **birth control pill**) used by women to prevent pregnancy.

Opill® is **NOT** an emergency contraceptive (morning after pill). You should not take Opill® to try to prevent pregnancy **after** unprotected sex because it will not work.

Opill® does **NOT** protect against HIV/AIDS or other sexually transmitted diseases (STDs). You should use condoms to protect against HIV/AIDS or other STDs.

2 Is Opill® right for you?

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

- If you have or ever had **breast cancer**, because some breast cancers are sensitive to hormones like the one 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).
- If you are **allergic to this product or any of its ingredients, such as the color additive FD&C yellow No.5 (tartrazine).** People allergic to aspirin often have a tartrazine allergy too. Symptoms may include: hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

Talk to a doctor before starting Opill® if:

- You currently have vaginal bleeding between your periods and you have not already talked to a doctor, because it could be the sign of a condition that should be treated.
- You have liver tumors or a liver disease.
- You have or ever had any cancer, because some cancers are sensitive to hormones like the one in Opill®.

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 tablet the day before).
Never skip your daily tablet.

- Never take a break between packs. When you finish one pack (all 28 tablets), 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 tablets 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 oral contraceptive, vaginal ring, or patch, start taking Opill® the day after you stop the other method.
- You must take your daily tablet 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)* because it takes 2 days to start working.

What if I am late taking my tablet?

Less than 3 hours late:

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

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

- Take 1 tablet immediately, as soon as you remember.
- Then, go back to taking your tablet at your usual time. This means you may take 2 tablets in 1 day.

  - For example, if you usually take your tablet at night, but forget and remember in the morning, take 1 tablet when you remember and take 1 tablet 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 tablets in the last month.

What if I vomit or have severe diarrhea within 4 hours of taking my 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.
- The next day, take your daily tablet at your usual time.

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 reminders. Consider using your smartphone to set a daily alarm, and put reminders in visible places such as bathroom mirror, phone or coffee machine.

Buy a new pack of Opill® before finishing the pack so you can start the next pack on time.

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 medications, as these may make Opill® less effective:

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

Your doctor or pharmacist may advise you to use another form of contraception.

What if I have taken an emergency contraceptive (morning after pill) 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.

What if I have sudden or severe persistent pain in my lower belly mostly on one side?

Seek medical help right away.

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

While ectopic pregnancy is unlikely if you are taking Opill® as directed, it is a serious risk if it occurs. Severe persistent belly pain may occur for a few reasons and should be assessed right away.

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 tablets 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 but continue taking every day. Some women with migraine may be at increased risk of stroke.

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

Seek medical help right away 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)*. These may be a sign of liver problems which can be a serious medical condition.

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 tablets in the last month, if you have not had a period for 2 months, or if you think you may be pregnant. Signs that you may be pregnant are listed in section 5, under « What if I become pregnant while taking Opill.

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

Talk to a doctor AND continue taking this product every day if you experience any of the following:

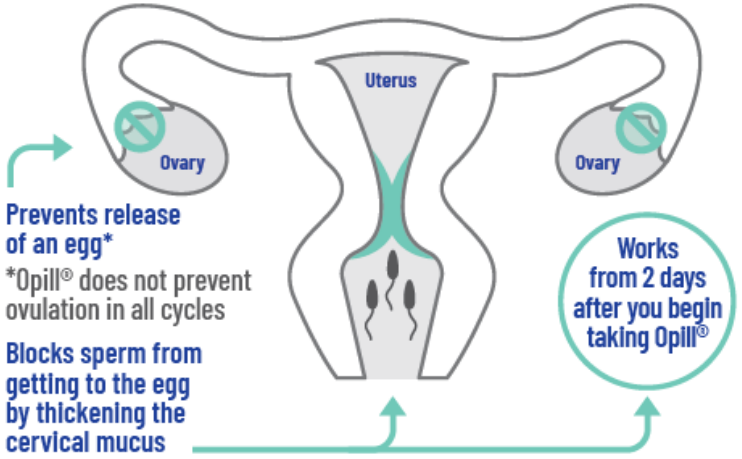
- You repeatedly have vaginal bleeding that is brought on by sex.
- You start having menstrual periods that last more than 8 days or are unusually heavy.

7 Other questions you may have

What type of oral contraceptive 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 oral contraceptive, which contains both estrogen and progestin.

  Opill® works mainly by thickening your cervical mucus which helps to block sperm from getting to the egg. You must take it every day to prevent pregnancy. In addition, Opill® may prevent your ovaries from releasing eggs.
- Every one of the 28 tablets in your blister pack contains the active ingredient so you must take one tablet 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 section 6.
- Less common side effects may include headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating.

Routine healthcare

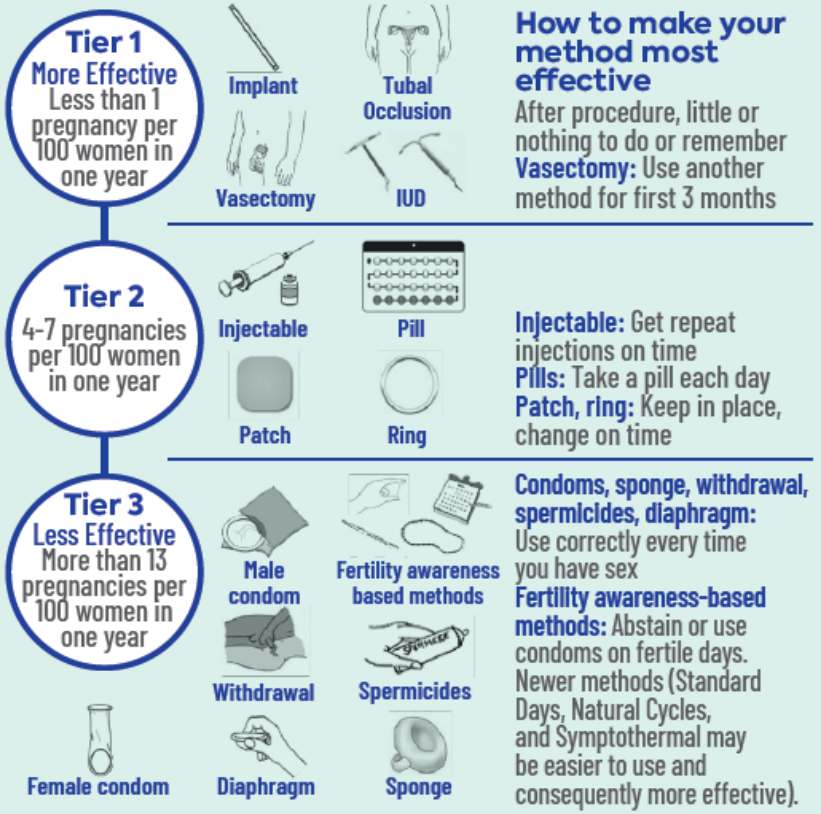
You should continue to see your healthcare provider(s) for routine healthcare visits.

- It is important that you continue to have regular Pap smear tests (cervical screening) while taking Opill®.
- Regular breast screening (mammography) is also recommended.
- If you are worried you may have a Sexually Transmitted Disease (STD) including HIV (AIDS), see your healthcare provider as soon as you can. Many STDs, like HIV, have no symptoms at all. The only way to know for sure that you do not have an STD is to get tested. Only barrier methods (such as condoms) can protect you from STD.

You should tell your healthcare provider(s) that you are taking Opill®.

Regular contraception

There are many different types of contraception available, and you should be able to find the right method for you. The different contraceptive options are listed below from the most effective to the least effective. You can ask your healthcare provider(s) for advice.



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More about routine healthcare and contraception

For further information on all methods of contraception or screening, go to

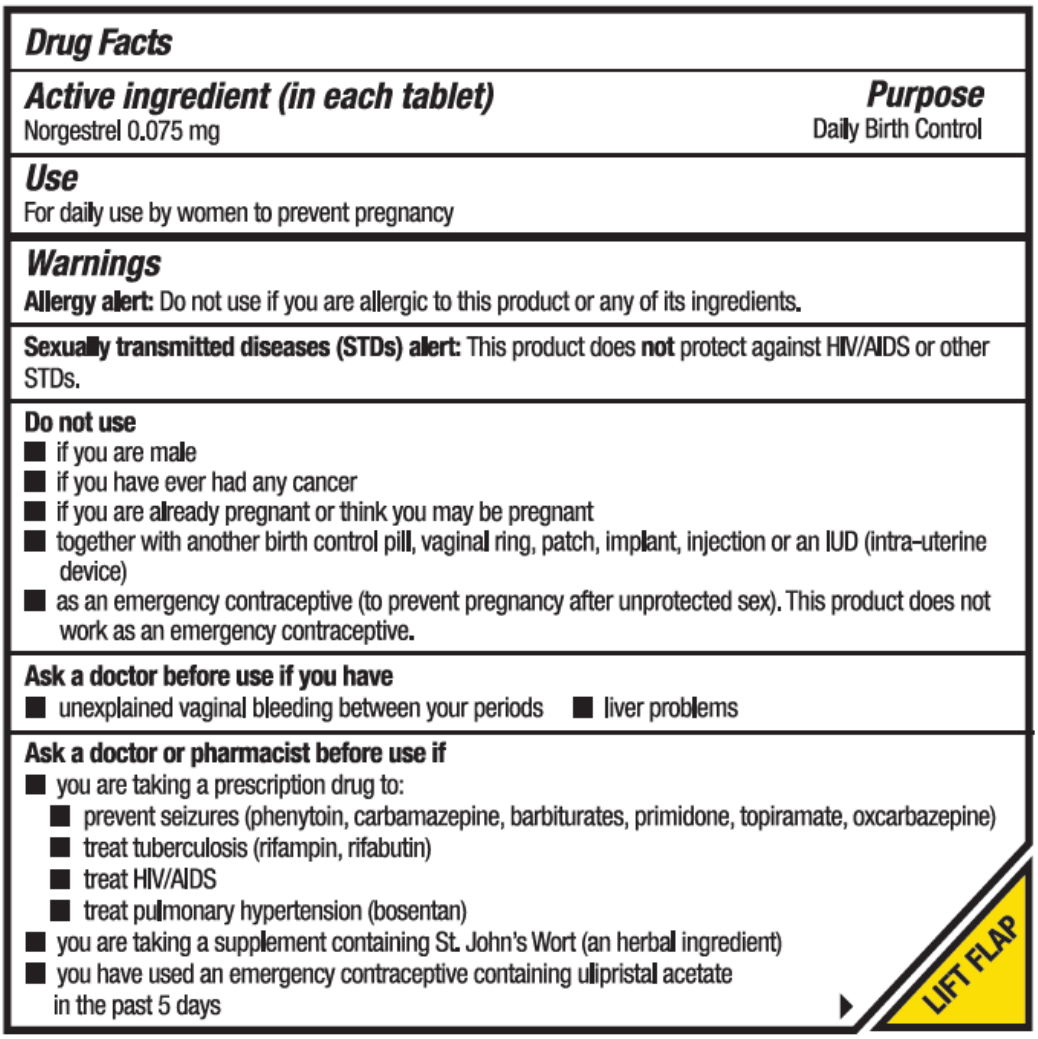
- https://www.cdc.gov/reproductivehealth/contraception/index.htm
- https://www.cdc.gov/cancer/breast/basic_info/screening.htm
- https://www.cdc.gov/cancer/cervical/basic_info/screening.htm

11.1.2 Proposed Reminder Card for OTC Opill

FRONT

BACK

11.2 Drug Facts Label Used in the ACCESS Study



Drug Facts

Active ingredient (in each tablet)
Norgestrel 0.075 mg

Purpose
Daily Birth Control

Use
For daily use by women to prevent pregnancy

Warnings
Allergy alert: Do not use if you are allergic to this product or any of its ingredients.

Sexually transmitted diseases (STDs) alert: This product does **not** protect against HIV/AIDS or other STDs.

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
- together with another birth control pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device)
- as an emergency contraceptive (to prevent pregnancy after unprotected sex). This product does not work as an emergency contraceptive.

Ask a doctor before use if you have
- unexplained vaginal bleeding between your periods
- liver problems

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

LIFT FLAP

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.

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

11.3 Summary of ACCESS Secondary Endpoints

Table 23: ACCESS Pre-specified Primary Analysis Results of All Secondary Endpoints

Secondary Endpoint A Self-Selection: Correct Non-Selection. Proportion of Self-Selection Population who are inappropriate for use who make a correct decision regarding non-selection of the Product	N=78
Non-selector	66 (84.6%)
95% CI	(74.7, 91.8)
Secondary Endpoint B Actual Use: Use of the study medication every day, accounting for appropriate mitigating behaviors (e-diary only)	N= 90,128
% Correct	87,527 (97.1%)
95% CI	(97.0, 97.2)
Secondary Endpoint C Actual Use: Proportion of participants who are adherent to daily dosing instructions, accounting for appropriate mitigating behaviors (e-diary only)	N=883
% Correct	837 (94.8%)
95% CI	(93.1, 96.2)
Secondary Endpoint D Actual Use: Use of the study medication within 27 hours of the previous dose, accounting for appropriate mitigating behaviors (e-diary only)	N=80,107
% Correct	79,316 (99.0%)
95% CI	(98.9, 99.1)
Secondary Endpoint E Actual Use: Use of the study medication without any break between packs (e-diary only)	N=2,225
% Correct	2,057 (92.3%)
95% CI	(91.1, 93.4)
Secondary Endpoint F Actual Use: Proportion of User Population who do not use study medication together with another form of hormone-containing birth control or an intra-uterine device	N=883
% Correct	872 (98.8%)
95% CI	(97.8, 99.4)

Secondary Endpoint G 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 (e-diary only)	N=681
% Correct	543 (79.7%)
95% CI	(76.5, 82.7)
Secondary Endpoint H Self-Selection/Actual Use: Proportion of Self-Selection Population who are taking one of the drugs/products listed in the "ask a doctor or pharmacist before use" section of the label 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	N=20
% Correct and acceptable	19 (95.0%)
95% CI	(75.1, 99.9)
Secondary Endpoint I Actual Use: Proportion of User Population who become pregnant during the course of the study who report stopping use and seeking healthcare as directed by the label	N=6
% Correct and acceptable	6 (100.0%)
95% CI	(54.1, 100.0)
Secondary Endpoint J Actual Use: Proportion of User Population who develop sudden or severe pain in their lower belly during the course of the study who report seeking healthcare as directed by the label	N=9
% Correct and acceptable	6 (66.7%)
95% CI	(29.9, 92.5)
Secondary Endpoint K Actual Use: Proportion of User Population who have a late period after missing any pills in the last month or who do not have a period for 2 months during the course of the study who report doing a pregnancy test or seeking healthcare as directed by the label or who stop use	N=58
% Correct	41 (70.7%)
95% CI	(57.3, 81.9)
Secondary Endpoint L Actual Use: Proportion of User Population who experience periods that last more than 8 days or are unusually heavy during the course of the study who report seeking healthcare as directed by the label or who stop use	N=45
% Correct	32 (71.1%)
95% CI	(55.7, 83.6)

Secondary Endpoint M Actual Use: Proportion of User Population who experience repeated vaginal bleeding brought on by sex during the course of the study who report seeking healthcare as directed by the label or who stop use	N=2
% Correct	1 (50.0%)
95% CI	(1.3, 98.7)
Secondary Endpoint N Actual Use: Proportion of User Population who start having migraines with aura or whose migraines get worse during the course of the study who report seeking healthcare as directed by the label or who stop use	N=9
% Correct	7 (77.8%)
95% CI	(40.0, 97.2)
Secondary Endpoint O Actual Use: Proportion of User Population who develop yellowing of the skin or whites of the eyes during the course of the study who report seeking healthcare as directed by the label	N=0
% Correct	NC
95% CI	(NC, NC)
Secondary Endpoint P Actual Use: Number of pregnancies reported by User Population during the course of the study	N=11
Conception occurred while participant was taking product	6 (54.5%)
Conception occurred after participant discontinued use of the product	5 (45.5%)

CI: confidence interval; NC: not calculated

11.4 Final LCS/Targeted BC SSS Design

11.4.1 Final LCS/Targeted BC SSS Study Objectives

While the ACCESS study was ongoing, the DFL was further revised in consultation with the FDA. The Sponsor decided to test this revised DFL (1) for self-selection among the specific group of women with a history of breast cancer and (2) for comprehension among a general population of reproductive-aged women. This study combining LCS with targeted SSS is referred to as the Final LCS/Targeted BC SSS.

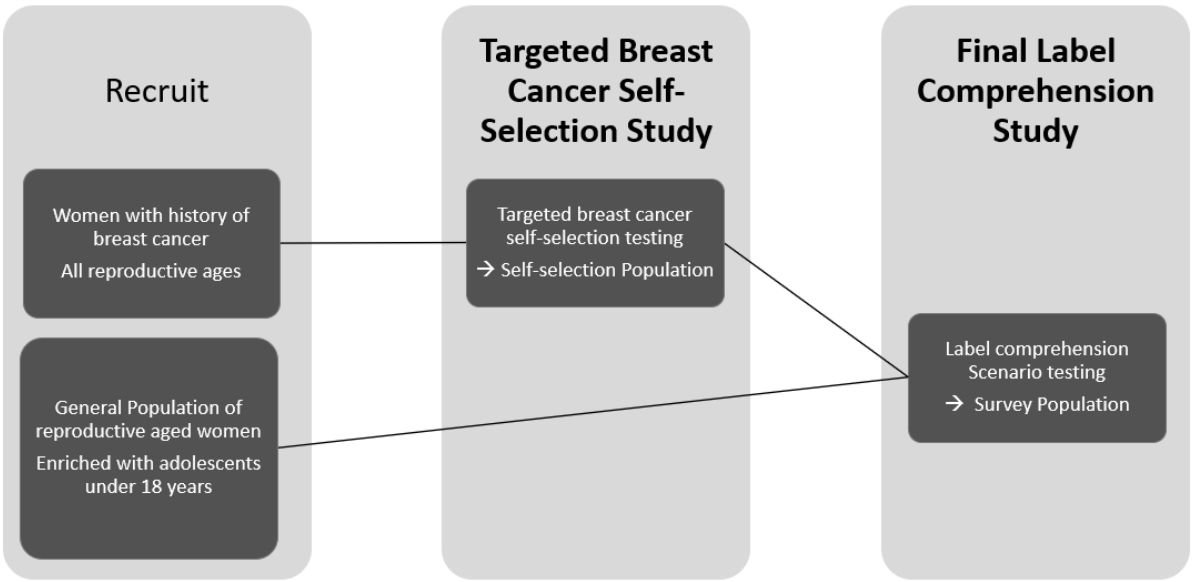
The objective of the self-selection portion of the Final LCS/Targeted BC SSS (referred to the **Targeted BC SSS**) was to assess if participants with a history of breast cancer correctly determined whether Opill was not appropriate for their use based on their history of breast cancer, as described in in Section 5.2.

The objective of the LCS portion of the study (referred to the **Final LCS**) was to assess comprehension of the Opill DFL among a general population of reproductive-aged women and to learn whether participants, including those at lower health literacy levels, adequately comprehended key messages from the label.

11.4.2 Overview of Final LCS/Targeted BC SSS Procedures

Overview of study recruitment in Final LCS / Targeted BC SSS is described in Figure 36.

Figure 36: Study Design of the Final LCS / Targeted BC SSS



The Final LCS/Targeted BC SSS was conducted remotely via video conference throughout the US, due to COVID-19 restrictions at the time. Participants aged 11-50 were recruited using digital advertising and consumer database panels. If they met the basic qualification criteria in an online self-screening questionnaire, they scheduled an appointment for a one-on-one video conference interview.

At the start of each one-on-one video conference interview, participants were again asked the screening questions to ensure they met the minimum eligibility requirements, after which literacy was assessed using the REALM or REALM Teen test.

Qualified participants were provided a link to view the mock Opill package and DFL online and asked to review all label information.

Based on the participants' answer (at self-screening) whether or not they had a history of breast cancer, the study interview proceeded as follows:

- Participants who said they had a history of breast cancer during self-screening were asked the self-selection question(s) before proceeding to the label comprehension portion of the study;
- Participants who said they had no current or past breast cancer during self-screening proceeded directly to the label comprehension questions.

During the label comprehension segment, participants responded to hypothetical scenarios about messages on the DFL to assess their comprehension of the label. Participants who said they had current or past breast cancer during self-screening were asked debriefing questions if applicable. Relevant health and demographic information was collected for all participants. All participants were compensated for their time.

- **Targeted BC SSS**: All participants who confirmed a current or past breast cancer during the study interview, who made a self-selection decision, and provided responses to all relevant medical history questions, formed the Self-Selection Population, on which self-selection was assessed.
- **Final LCS**: All participants who answered at least one comprehension question formed the Survey Population, on which label comprehension endpoints were primarily assessed.

11.4.3 Final LCS/Targeted BC SSS Enrollment Criteria

In order to enroll a sample as representative as possible of the likely OTC consumer, the inclusion criteria were defined as broadly as was feasible. Consumers were excluded only if they met one or more of the following criteria:

1. Younger than 11 years of age or over 50 years of age
2. Is male
3. Unable to read, speak, and understand English
4. Another member of the consumer's family has participated in this study
5. Consumer is a healthcare professional, or works as part of a health care practice or managed care company, or has been trained as a healthcare professional
6. Consumer or someone else in the household works for a marketing research or advertising company, public relations firm, or for a pharmaceutical company or medicine manufacturer (eliminated for reasons of confidentiality and increased awareness of drugs and their labels)
7. Participated in a health-related market research or product label study in the past 12 months
8. Participated in a clinical trial in the past 12 months
9. Participated in a study about OTC birth control at any time.

11.4.4 Final LCS Label Comprehension Endpoints

This section only describes the Final LCS label comprehension endpoints. See section 5.2.2 for the Targeted BC SSS self-selection endpoint.

The endpoint calculations for each key label message tested in the Final LCS were defined as the proportion of respondents who articulate acceptable comprehension of questions addressing each of the label messages. The primary endpoints related to these key label messages are outlined in Table 24. The key label messages listed here were all assigned a target threshold of 90% based on the clinical consequence of failure to heed. Comparisons to the pre-specified performance threshold were made on the basis of the lower bound of the 95% CI for each primary endpoint.

Table 24: Final LCS Label Comprehension Primary Endpoints

Primary Endpoint	Key Label Message
A	Do not use: if you have or ever had breast cancer
B	Do not use: together with another birth control pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device)
C	Ask a doctor before use if: you currently have vaginal bleeding between your periods and you have not already talked to a doctor
D	Seek medical help right away if: you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy)
E	Seek medical help right away if: you develop yellowing of your skin or whites of your eyes especially with fever, tiredness, loss of appetite or dark colored urine
F	Directions: take 1 tablet…every day
G	Directions: take…at the same time every day
H	Directions / When to use a condom (or another barrier method): 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
I	Directions: to prevent pregnancy, take this product every day, even when you bleed or have spotting
J	Directions: when you finish this pack, start the next one the following day without a break
K	Directions: 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
L	Directions: if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: then go back to taking your daily tablet at your usual time
M	Directions / When to use a condom (or another barrier method): if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: 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 this product to start working again
N	Directions / When to use a condom (or another barrier method): 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

The label messages having less potential for negative clinical consequences if misunderstood and not heeded, were tested in secondary endpoints (Table 25) and no performance thresholds were set for these endpoints, as suggested in the FDA's Guidance on Label Comprehension Studies.

Table 25: Final LCS Label Comprehension Secondary Endpoints

Secondary Endpoint	Label Message
A	Purpose and Use: Daily Oral Contraceptive to prevent pregnancy
B	Do not use if you are allergic to FD&C yellow No.5 (tartrazine)
C	Do not use: if you are already pregnant or think you may be pregnant
D	Do not use: as an emergency contraceptive (morning after pill)
E	Do not use: if you are male
F	Ask a doctor before use: if you have or ever had any cancer
G	Ask a doctor or pharmacist before use if: you are taking a prescription drug for seizures, tuberculosis, HIV/AIDS, pulmonary hypertension
H	Ask a doctor or pharmacist before use if: you are taking a supplement containing St. John's Wort (an herbal ingredient)
I	Ask a doctor or pharmacist before use if: you have used an emergency contraceptive (morning after pill) containing ulipristal acetate in the past 5 days
J	When using this product: you are likely to experience changes in your menstrual periods, such as irregular periods, spotting or bleeding between your periods, or you may stop having periods
K	When using this product: you may experience headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating
L	When using this product talk to a doctor (but continue taking every day) if: you have repeated vaginal bleeding brought on by sex
M	When using this product talk to a doctor (but continue taking every day) if: you start having periods that last more than 8 days or are unusually heavy
N	When using this product talk to a doctor (but continue taking every day) if: you start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse
O	When using this product take a pregnancy test or talk to a doctor if: your period is late after missing any tablets in the last month
P	When using this product take a pregnancy test or talk to a doctor if: you have not had a period for 2 months or think you may be pregnant
Q	Stop use and ask a doctor if: you become pregnant
R	Directions: never skip your daily tablet
S	Other information: as with any birth control method, this product does not prevent pregnancy all the time

11.4.5 Final LCS Label Comprehension Participants

This section only describes the Final LCS label comprehension participants. See Section 5.2.15.2.1 for Targeted BC SSS participants.

The Survey Population, on which the label comprehension results of the Final LCS are based, comprised 703 individuals (Table 26) including the Self-Selection participants presented in Section 5.2.1.

Table 26: Final LCS Label Comprehension Participant Demographics (Survey Population)

	Survey Population (N=703)
Age Distribution	
Mean (SD)	32.3 (12.3)
Median	35
Range	11-50
Age Groups, n (%)	
11-14	74 (10.5%)
15-17	78 (11.1%)
18-24	66 (9.4%)
25-45	368 (52.3%)
46+	117 (16.6%)
Education Level (18+), n (%)	
8th grade or less	0 (0.0%)
Some high school	4 (0.6%)
High school graduate or GED	41 (5.8%)
Some college or technical school	120 (17.1%)
College graduate	257 (36.6%)
Post-graduate college degree	129 (18.3%)
Education Level (11-17), n (%)	
7th grade or less	48 (6.8%)
8th grade	26 (3.7%)
9th grade (freshman in high school)	19 (2.7%)
10th grade (sophomore in high school)	16 (2.3%)
Health Literacy	
Normal	562 (79.9%)
Low	141 (20.1%)
History of HBC Use	
History of HBC use and OC use	406 (57.8%)
History of HBC use but no OC use	70 (10.0%)
No history of HBC use	227 (32.3%)

GED: General Educational Development test; HBC: hormonal birth control; OC: oral contraceptive

11.4.6 Final LCS Label Comprehension Results

This section only describes the Final LCS label comprehension results. See Section 5.2.3 for Targeted BC SSS results.

Results for Final LCS label comprehension Primary Endpoints are shown in Table 27.

Table 27: Final LCS Label Comprehension Primary Endpoint Results (Survey Population)

Primary Endpoint	Key Label Message	Point Estimate (95% CI)			
		Total N=703	Low Health Literacy N=141	Age 11-14 N=74	Age 15-17 N=78
A	Do not use: if you have or ever had breast cancer	90.3% (87.9, 92.4)	86.5% (79.8, 91.7)	95.9% (88.6, 99.2)	92.3% (84.0, 97.1)
B	Do not use: together with another birth control pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device)	94.6% (92.7, 96.1)	87.2% (80.6, 92.3)	87.8% (78.2, 94.3)	92.3% (84.0, 97.1)
C	Ask a doctor before use if: you currently have vaginal bleeding between your periods and you have not already talked to a doctor	93.5% (91.4, 95.2)	89.4% (83.1, 93.9)	87.8% (78.2, 94.3)	91.0% (82.4, 96.3)
D	Seek medical help right away if: you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy)	98.0% (96.7, 98.9)	95.7% (91.0, 98.4)	97.3% (90.6, 99.7)	94.9% (87.4, 98.6)
E	Seek medical help right away if: you develop yellowing of your skin or whites of your eyes especially with fever, tiredness, loss of appetite or dark colored urine	97.9% (96.5, 98.8)	92.9% (87.3, 96.5)	93.2% (84.9, 97.8)	98.7% (93.1,100.0)
F	Directions: take 1 tablet…every day	99.3% (98.3, 99.8)	98.6% (95.0, 99.8)	97.3% (90.6, 99.7)	100% (95.4, 100.0)
G	Directions: take…at the same time every day	98.0% (96.7, 98.9)	93.6% (88.2, 97.0)	93.2% (84.9, 97.8)	100% (95.4, 100.0)
H	Directions / When to use a condom (or another barrier method): 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	89.2% (86.7, 91.4)	81.6% (74.2, 87.6)	79.7% (68.8, 88.2)	93.6% (85.7, 97.9)
I	Directions: to prevent pregnancy, take this product every day	98.9% (97.8, 99.5)	96.5% (91.9, 98.8)	93.2% (84.9, 97.8)	100% (95.4, 100.0)
J	Directions: when you finish this pack, start the next one the following day without a break	92.9% (90.7, 94.7)	83.0% (75.7, 88.8)	78.4% (67.3, 87.1)	96.2% (89.2, 99.2)
K	Directions: 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	98.0% (96.7, 98.9)	93.6% (88.2, 97.0)	94.6% (86.7, 98.5)	98.7% (93.1, 100.0)
L	Directions: if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more	85.2% (82.4, 87.7)	75.2% (67.2, 82.1)	68.9% (57.1, 79.2)	82.1% (71.7, 89.8)

Primary Endpoint	Key Label Message	Point Estimate (95% CI) Total N=703	Low Health Literacy N=141	Age 11-14 N=74	Age 15-17 N=78
	days: then go back to taking your daily tablet at your usual time				
M	Directions / When to use a condom (or another barrier method): if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: 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 this product to start working again	84.9% (82.1, 87.5)	73.0% (64.9, 80.2)	66.2% (54.3, 76.8)	88.5% (79.2, 94.6)
N	Directions / When to use a condom (or another barrier method): 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	86.2% (83.4, 88.7)	72.3% (64.2, 79.5)	74.3% (62.8, 83.8)	92.3% (84.0, 97.1)

CI: confidence interval

For nine of the fourteen primary key label messages, the lower limit of the 95% CI for the associated endpoint measure met or exceeded the a priori threshold of 90%. The remaining five key label messages were also well understood, all with point estimates ≥ 84.9% and lower limits of the 95% CI > 82%:

1. Primary Endpoint A, *Do not use: if you have or ever had breast cancer,* was understood by 90.3% of participants. While the lower bound of the 95% CI (87.9%) did not meet the performance threshold of 90%, the subgroup most impacted by this label message (those with a personal history of breast cancer) better understood the label message (96.0%, 95% CI 92.6-98.2). This suggests that consumers for whom the label message applies and those who would need to heed the warning understood the label message well.
2. There were three key label messages from a group of directions on the label under the heading *When to use a condom (or another barrier method)*, which was added to the DFL at the FDA's request. Messages about when to use a condom or other barrier method were also given in a less consolidated fashion throughout the Directions section. These messages were evaluated independently with a series of questions beginning with "What are all the situations someone taking this product should use a condom or another barrier method during sex?" and are described as follows:
    a) Primary Endpoint H, *Directions / When to use a condom (or another barrier method): 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*, was

understood by 89.2% of participants (95% CI 86.7 - 91.4). In order to be correct, a participant needed to articulate two concepts, namely, “after initiating use” and “every time you have sex for the next 2 days”.

b) Primary Endpoint M, *Directions / When to use a condom (or another barrier method): if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: 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 this product to start working again*, was understood by 84.9% of participants (95% CI 82.1 - 87.5). In order to be correct, a participant needed to articulate two concepts, namely, either “when more than 3 hours late taking a tablet” or “after missing a tablet on 1 or more days,” AND “every time you have sex for the next 2 days”.

c) Primary Endpoint N, *Directions / When to use a condom (or another barrier method): 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*, was understood by 86.2% (95% CI 83.4 - 88.7) of participants. In order to be correct, a participant needed to articulate two concepts, namely, either “after vomiting within 4 hours of taking a tablet” or “after having severe diarrhea within 4 hours of taking a tablet,” AND “every time you have sex for the next 2 days”

Although these endpoints did not meet the performance threshold of 90%, the underlying label messages address back-up contraception methods advised in the face of what should be infrequent occurrences (initiating use, missed or late pill-taking, vomiting or severe diarrhea within 4 hours of taking a tablet). Furthermore, the vast majority of participants (97.2%) articulated the concept of using a condom “Every time you have sex for the next 2 days (48 hours)” in response to the primary question (coupled with one or more of the situations requiring backup barrier method use). This suggests that the concept was not difficult to understand. Rather, the question requires a compound response. Some participants did not provide a fully complete response for every one of the three key communication questions about condom use. Instead, they provided a response that was correct for one or two of the key label messages, but not all three. This was likely exacerbated by the fact that messages about condom or other barrier method use are found in multiple places on the label. Testing factors and the dual placement of messages on the label likely explain the lower results rather than fundamental comprehension of the messages.

3. Primary Endpoint L, *Directions: if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: then go back to taking your daily tablet at your usual time*, was understood by 85.2% (95% CI 82.4 - 87.7) of participants. Although this endpoint did not meet the performance threshold of 90%, Primary Endpoint K, *Directions: 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*, was understood by almost all participants (98%, 95% CI 96.7 - 98.9). Since Primary Endpoint K and

Primary Endpoint L are incorporated into the same label message and data collection instrument question, participants may not have provided a fully complete response to the question, impacting Primary Endpoint L.

Results for Final LCS label comprehension Secondary Endpoints are shown in Table 28.

Table 28: Final LCS Label Comprehension Secondary Endpoint Results (Survey Population)

Secondary Endpoint	Label Message	Point Estimate (95% CI)
A	Purpose and Use: Daily Oral Contraceptive to prevent pregnancy	99.1% (98.2, 99.7)
B	Do not use if you are allergic to FD&C yellow No.5 (tartrazine)	93.5% (91.4, 95.2)
C	Do not use: if you are already pregnant or think you may be pregnant	93.2% (91.0, 94.9)
D	Do not use: as an emergency contraceptive (morning after pill)	76.8% (73.5, 79.9)
E	Do not use: if you are male	96.9% (95.3, 98.0)
F	Ask a doctor before use: if you have or ever had any cancer	90.9% (88.5, 92.9)
G	Ask a doctor or pharmacist before use if: you are taking a prescription drug for seizures, tuberculosis, HIV/AIDS, pulmonary hypertension	92.6% (90.4, 94.4)
H	Ask a doctor or pharmacist before use if: you are taking a supplement containing St. John's Wort (an herbal ingredient)	96.3% (94.6, 97.6)
I	Ask a doctor or pharmacist before use if: you have used an emergency contraceptive (morning after pill) containing ulipristal acetate in the past 5 days	82.2% (79.2, 85.0)
J	When using this product: you are likely to experience changes in your menstrual periods, such as irregular periods, spotting or bleeding between your periods, or you may stop having periods	95.7% (94.0, 97.1)
K	When using this product: you may experience headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating	93.7% (91.7, 95.4)
L	When using this product talk to a doctor (but continue taking every day) if: you have repeated vaginal bleeding brought on by sex	95.3% (93.5, 96.7)
M	When using this product talk to a doctor (but continue taking every day) if: you start having periods that last more than 8 days or are unusually heavy	93.5% (91.4, 95.2)
N	When using this product talk to a doctor (but continue taking every day) if: you start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse	95.2% (93.3, 96.6)
O	When using this product take a pregnancy test or talk to a doctor if: your period is late after missing any tablets in the last month	82.6% (79.6, 85.4)
P	When using this product take a pregnancy test or talk to a doctor if: you have not had a period for 2 months or think you may be pregnant	93.2% (91.0, 94.9)
Q	Stop use and ask a doctor if: you become pregnant	94.7% (92.8, 96.3)
R	Directions: never skip your daily tablet	93.3% (91.2, 95.0)
S	Other information: as with any birth control method, this product does not prevent pregnancy all the time	93.3% (91.2, 95.0)

CI: confidence interval

Although there is no performance threshold set for secondary endpoints, sixteen of the secondary endpoints were understood by at least 90% of the Survey Population participants.

Below are the endpoints that were understood by less than 90% of the participants:

1. Secondary Endpoint D: *Do not use: as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex* was understood by 76.8% of participants. This may be explained by the fact that this label message may not seem to fit with the rest of the DFL messaging. Nothing about the product or its labeling suggests that it might be used as an emergency contraceptive, so to warn against such use may be difficult for participants to follow. Furthermore, the concept of EC is less familiar to participants.
2. Secondary Endpoint I: *Ask a doctor or pharmacist before use if: you have used an emergency contraceptive (morning after pill) containing ulipristal acetate in the past 5 days* was understood by 82.2% of participants. This message again references EC, and the medication name ulipristal acetate is difficult and unlikely to be recognized by most consumers. Moreover, when reviewing the verbatim responses, approximately 30 participants provided a response to not use the product, a more conservative interpretation of the warning to ask a doctor or pharmacist.
3. Secondary Endpoint O: *When using this product take a pregnancy test or talk to a doctor if: your period is late after missing any tablets in the last month* was understood by 82.6% of participants. Approximately 20% of participants provided a response for a different label message in the directions, namely, *if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days,* as evidenced by the responses “take a tablet as soon you remember / immediately” and “use a condom or other barrier method”. This indicates that the participants misunderstood the question being asked.

The results were consistent across subgroups of interest, namely adolescents and individuals with low health literacy.

Overall, the results of this study demonstrate that the Opill DFL was well comprehended by a diverse sample of potential consumers and support that the Opill DFL will appropriately guide correct decision-making among consumers.

11.5 Details on Safety Databases Reviewed

Table 29 provides a list of the safety databases reviewed and provides the review period, size of the dataset and the product(s) evaluated for each database.

Table 29: Listing of Safety Databases Reviewed

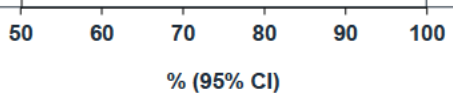
Medicinal Product Evaluated	Datasets	Database Review Period	Size of the Dataset
NG	HRA's dataset	29 Jun 1987 to 16 Apr 2012	33 cases involving 58 AEs
	FAERS/AERS	1 Oct 1969 to 30 Jun 2020	38 cases involving 82 AEs
	WHO exUS	1 Jan 1978 to 31 Dec 2005[1]	100 ex-US cases involving 141 AEs
	AAPCC NPDS	1 Jan 1999 to 31 Dec 2005[1]	18 cases
LNG oral	FAERS/AERS	1 Oct 1969 to 30 Jun 2020	37,410 cases involving 75,097 AEs
LNG implant			32,620 cases involving 84,986 AEs
LNG IUD			117,222 cases involving 306,383 AEs
LNG oral	WHO exUS	1 January 1978 to 30 Jun 2020	3,563 cases involving 6461 AEs
LNG implant			2,419 cases involving 4493 AEs
LNG IUD			54,669 cases involving 149,759 AEs

AAPCC NPDS: American Association of Poison Control Centers, National Poison Data System; AE: adverse event; AERS: Adverse Event Reporting System; exUS: outside the United States; FAERS: Food and Drug Administration Adverse Event Reporting System; IUD: intrauterine device; LNG: levonorgestrel; NG: norgestrel; WHO: World Health Organization
[1] discontinued from market in 2005.

11.6 ACCESS Adherence Endpoint Results in Subgroups of Interest

Figure 37: ACCESS Pre-specified Primary Analysis Results for Adherence Endpoints by Adolescents Below 18 Age Group (User Population, N=833)

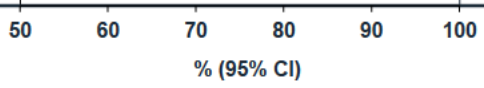
Taking Opill Every Day	Days (n / N)	Proportion of Days	% (95% CI)
Primary Endpoint	83,348 / 90,128	Target Threshold	**92.5%** (92.3, 92.6)
12-14 years	5,266 / 5,737		**91.8%** (91.0, 92.5)
15-17 years	13,629 / 14,834		**91.9%** (91.4, 92.3)
≥ 85% Adherent Daily Dosing	**Participants (n / N)**	**Proportion of Participants**	**% (95% CI)**
Primary Endpoint	747 / 883		**84.6%** (82.0, 86.9)
12-14 years	40 / 49		**81.6%** (68.0, 91.2)
15-17 years	125 / 151		**82.8%** (75.8, 88.4)
Opill used ± 3 hours since time of last dose	**Days (n / N)**	**Proportion of Days**	**% (95% CI)**
Primary Endpoint	78,946 / 82,465		**95.7%** (95.6, 95.9)
12-14 years	5,020 / 5,217		**96.2%** (95.7, 96.7)
15-17 years	12,853 / 13,478		**95.4%** (95.0, 95.7)



CI: confidence interval; HBC: hormonal birth control; OC: oral contraceptive
For endpoint of taking Opill every day: n: number of days Opill was reported as taken, N: total number of days
For endpoint of ≥ 85% adherent to dosing: n: number of participants ≥ 85% adherent, N: number of participants
For endpoint of Opill used ± 3 hours since time of last dose: n: number of days Opill reported at the correct time, N: number of days evaluable for timing of dose
Note: secondary endpoints not presented for adolescents below 18 years as sexual activity therefore mitigating behaviors were not collected in this age group.

Figure 38: ACCESS Pre-specified Primary Analysis Results for Adherence Endpoints by Health Literacy Status (User Population, N=833)

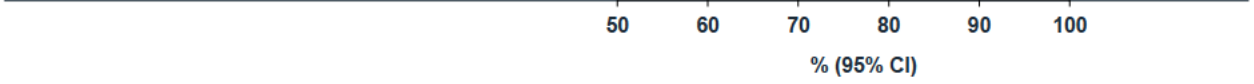
Taking Opill Every Day	Days (n / N)	Proportion of Days	% (95% CI)
Primary Endpoint	**83,348 / 90,128**	Target Threshold	**92.5%** (92.3, 92.6)
Low Health Literacy	11,637 / 12,571		**92.6%** (92.1, 93.0)
Normal Health Literacy	71,711 / 77,557		**92.5%** (92.3, 92.6)
Secondary Endpoint	**87,527 / 90,128**		**97.1%** (97.0, 97.2)
Low Health Literacy	12,075 / 12,571		**96.1%** (95.7, 96.4)
Normal Health Literacy	75,452 / 77,557		**97.3%** (97.2, 97.4)
≥ 85% Adherent to Daily Dosing	**Participants (n / N)**	**Proportion of Participants**	**% (95% CI)**
Primary Endpoint	**747 / 883**		**84.6%** (82.0, 86.9)
Low Health Literacy	98 / 120		**81.7%** (73.6, 88.1)
Normal Health Literacy	649 / 763		**85.1%** (82.3, 87.5)
Secondary	**837 / 883**		**94.8%** (93.1, 96.2)
Low Health Literacy	109 / 120		**90.8%** (84.2, 95.3)
Normal Health Literacy	728 / 763		**95.4%** (93.7, 96.8)
Opill used ± 3 hours since time of last dose	**Days (n / N)**	**Proportion of Days**	**% (95% CI)**
Primary Endpoint	**78,946 / 82,465**		**95.7%** (95.6, 95.9)
Low Health Literacy	10,927 / 11,517		**94.9%** (94.5, 95.3)
Normal Health Literacy	68,019 / 70,948		**95.9%** (95.7, 96.0)
Secondary	**79,316 / 80,107**		**99.0%** (98.9, 99.1)
Low Health Literacy	11,070 / 11,231		**98.6%** (98.3, 98.8)
Normal Health Literacy	68,246 / 68,876		**99.1%** (99.0, 99.2)



CI: confidence interval
For endpoint of taking Opill every day: n: number of days Opill was reported as taken, N: total number of days
For endpoint of ≥ 85% adherent to dosing: n: number of participants ≥ 85% adherent, N: number of participants
For endpoint of Opill used ± 3 hours since time of last dose: n: number of days Opill reported at the correct time, N: number of days evaluable for timing of dose

Figure 39: ACCESS Pre-specified Primary Analysis Results for Adherence Endpoints by Prior Hormonal Birth Control Use (User Population, N=833)

Taking Opill Every Day	Days (n / N)	Proportion of Days	% (95% CI)
Primary Endpoint	**83,348 / 90,128**	Target Threshold	**92.5%** (92.3, 92.6)
History of HBC – OC Use	51,518 / 55,344		**93.1%** (92.9, 93.3)
History of HBC – No OC Use	7,402 / 8,274		**89.5%** (88.8, 90.1)
No History of HBC Use	24,428 / 26,510		**92.1%** (91.8, 92.5)
Secondary Endpoint	**87,527 / 90,128**		**97.1%** (97.0, 97.2)
History of HBC – OC Use	54,285 / 55,344		**98.1%** (98.0, 98.2)
History of HBC – No OC Use	7,934 / 8,274		**95.9%** (95.4, 96.3)
No History of HBC Use	25,308 / 26,510		**95.5%** (95.2, 95.7)
≥ 85% Adherent to Daily Dosing	**Participants (n / N)**	**Proportion of Participants**	**% (95% CI)**
Primary Endpoint	**747 / 883**		**84.6%** (82.0, 86.9)
History of HBC – OC Use	465 / 543		**85.6%** (82.4, 88.5)
History of HBC – No OC Use	72 / 90		**80.0%** (70.2, 87.7)
No History of HBC Use	210 / 250		**84.0%** (78.9, 88.3)
Secondary	**837 / 883**		**94.8%** (93.1, 96.2)
History of HBC – OC Use	529 / 543		**97.4%** (95.7, 98.6)
History of HBC – No OC Use	82 / 90		**91.1%** (83.2, 96.1)
No History of HBC Use	226 / 250		**90.4%** (86.1, 93.8)
Opill used ± 3 hours since time of last dose	**Days (n / N)**	**Proportion of Days**	**% (95% CI)**
Primary Endpoint	**78,946 / 82,465**		**95.7%** (95.6, 95.9)
History of HBC – OC Use	48,802 / 50,975		**95.7%** (95.6, 95.9)
History of HBC – No OC Use	7,142 / 7,312		**97.7%** (97.3, 98.0)
No History of HBC Use	23,002 / 24,178		**95.1%** (94.9, 95.4)
Secondary	**79,316 / 80,107**		**99.0%** (98.9, 99.1)
History of HBC – OC Use	49,124 / 49,583		**99.1%** (99.0, 99.2)
History of HBC – No OC Use	7,050 / 7,080		**99.6%** (99.4, 99.7)
No History of HBC Use	23,142 / 23,444		**98.7%** (98.6, 98.9)



CI: confidence interval; HBC: hormonal birth control; OC: oral contraceptive
For endpoint of taking Opill every day: n: number of days Opill was reported as taken, N: total number of days
For endpoint of ≥ 85% adherent to dosing: n: number of participants ≥ 85% adherent, N: number of participants
For endpoint of Opill used ± 3 hours since time of last dose: n: number of days Opill reported at the correct time, N: number of days evaluable for timing of dose

11.7 Non-Pregnancy-Related Serious Adverse Event Narratives

- Cardiac failure congestive in a 32-year-old White female (65 inches, 202 pounds). Her past medical history at enrollment included diabetes mellitus type 2 (diagnosed ~16 years before enrollment, treated with Levemir and Novolog), depression (diagnosed ~5 years before enrollment, treated with Effexor), hypertension (diagnosed 14 months before enrollment, treated with lisinopril), gastroparesis (diagnosed 13 months before enrollment, treated with Reglan), acid reflux (diagnosed 13 months before enrollment, treated with omeprazole), and anemia (diagnosed 13 months before enrollment, treated with iron).

  Two days after enrollment she woke up feeling unwell and went to the emergency room (ER). She underwent an evaluation that included chest X-ray, echocardiogram, magnetic resonance imaging and blood tests (specific results unknown). She was diagnosed with congestive heart failure and admitted to the hospital. Additional testing in the hospital included blood tests and echocardiograms, and treatments included spironolactone, hydralazine, metoprolol, and intravenous (IV) furosemide. She was discharged from the hospital after 6 days with new prescriptions for spironolactone, hydralazine, metoprolol and furosemide. She had a follow-up appointment with her cardiologist 1 week later where she received additional education on disease management and returned to her normal daily activities. She did not report further episodes of decompensation during her participation in the study.

  The participant took her first dose of study medication on the day of enrollment, and a second dose on the day after enrollment. She did not take the study medication between the day she went to ER and 5 days later during her hospitalization. She started taking the study medication again the day after she was discharged from the hospital.

- Pharyngitis streptococcal in a 21-year-old African American Hispanic/Latina female (66 inches, 160 pounds). Her past medical history at enrollment included taking acetaminophen for cramps.

  The participant reported that she began having symptoms of a sore throat 1 day before enrolling. Her symptoms became worse, and she went to the ER 4 days after enrolment where she was diagnosed with strep throat and admitted from the ER to the hospital due to the severity of her symptoms. During her hospital stay, she had a computed tomography (CT) scan which was negative for a tonsillar abscess. Participant received unknown IV antibiotics and IV dexamethasone while in the hospital. She was discharged home from the hospital after 3 days with a prescription for amoxicillin and dexamethasone. She began using the study drug on her enrollment date and reports that she did not take the study drug for 2 days while in the hospital because she did not have it with her. She resumed the study drug the day after being discharged and completed the course of amoxicillin and dexamethasone. Her symptoms resolved by 7 days after discharge.

- Diabetic ketoacidosis (30-year-old African American female (62 inches, 145 pounds) and began daily use of the study drug on 1 day after enrollment). Her past medical history at enrollment included diabetes mellitus Type 1 (diagnosed ~25 years before

enrollment, treated with continuous insulin infusion pump), migraine headaches (diagnosed ~5 years before enrollment, treated with topiramate), seizures of an unknown cause (diagnosed ~5 years before enrollment), hypertension (diagnosed ~6 years before enrollment and treated with hydrochlorothiazide), depression (diagnosed ~8 years before enrollment, treated with Effexor), anemia (diagnosed ~10 years before enrollment, treated with iron) and constipation (diagnosed ~10 years before enrollment, treated with Colace). She was hospitalized for ketoacidosis approximately six months prior to enrollment.

Eight days after enrollment she began experiencing symptoms of ketoacidosis (which she thinks may have been due to a crimp in the tubing of her insulin pump), and she went to the ER for treatment. In the ER her blood glucose was 663 mg/dl, and she was spilling ketones in her urine. She was placed on an insulin drip, given IV fluids, and admitted to the hospital. The next day, her blood glucose was 190 mg/dl. She was discharged from the hospital after 2 days. Participant did not take study medication on the next day after she was admitted to the hospital, while she was in the hospital. She resumed taking study medication the day after.

- Jugular vein thrombosis in a 32-year-old White female (68 inches, 220 pounds). Her past medical history at enrollment included depression (treated with sertraline and aripiprazole) and attention-deficit/hyperactivity disorder (treated with lisdexamfetamine). She took her first dose of study medication on the day of enrollment and last dose 55 days later.

  Fifty days after she took her first dose of study medication, she reported that a pain started in her neck which did not resolve after nearly a week. She contacted her doctor 4 days later. She underwent ultrasound and CT testing and was diagnosed that same day with an eccentric mural thrombosis of the internal jugular and was started on a prescription anticoagulant that same day.

  Over the following months, she was diagnosed with a number of pre-existing medical conditions, including familial hypercholesterolemia, premature atherosclerosis, high blood pressure, and paroxysmal ventricular tachycardia. Her cardiologist and hematologist attributed the jugular vein thrombosis to her baseline medical conditions.