Opill (Norgestrel 0.075 mg Tablets) for Rx-to-OTC Switch

May 9, 2023

HRA Pharma / Perrigo

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee

Introduction

Helene Guillard, PharmD

Global Rx-to-OTC Switch Director, Women's Health

HRA Pharma / Perrigo

Most Women* Spend Most Reproductive Years Trying to Avoid Pregnancy

28-Tablet Blisters

*Not all people who can become pregnant use the term “women”. The term is used in this presentation to reflect HRA’s study participants and how they are generally described in published literature

Women Face Unnecessary Burdens Accessing Effective Contraception

Nonprescription contraceptive options limited to least effective methods; Opill more effective than all current nonprescription options

Using the label, women of all ages can use Opill safely and effectively without healthcare provider supervision

Opill has key characteristics of OTC drug

Improved access to Opill has potential to reduce unintended pregnancy in US

Opill (Norgestrel 0.075 mg): Daily Progestin-Only Oral Contraceptive Pill (POP)

POPs Approved ~50 Years in US

- Norgestrel POP marketed for > 30 years
- 17 million 28-tablet norgestrel blister packs sold in US

Well-characterized Efficacy and Safety Profiles

- POPs considered safe[1]

Mechanism of Action

- Thickening cervical mucus to inhibit sperm penetration
- Suppressing / disrupting ovulation

1. American College of Obstetricians and Gynecologists (ACOG), 2019

Establishing Benefit / Risk of Opill in OTC Setting

- Approved by FDA as safe and effective
- Inherent efficacy and safety same whether prescribed by physician or OTC

Incremental Benefits

- Improve access to effective contraception
- Reduce unintended pregnancy and its consequences

Incremental Risks

- Likelihood of incorrect self-selection and use and clinical impact?

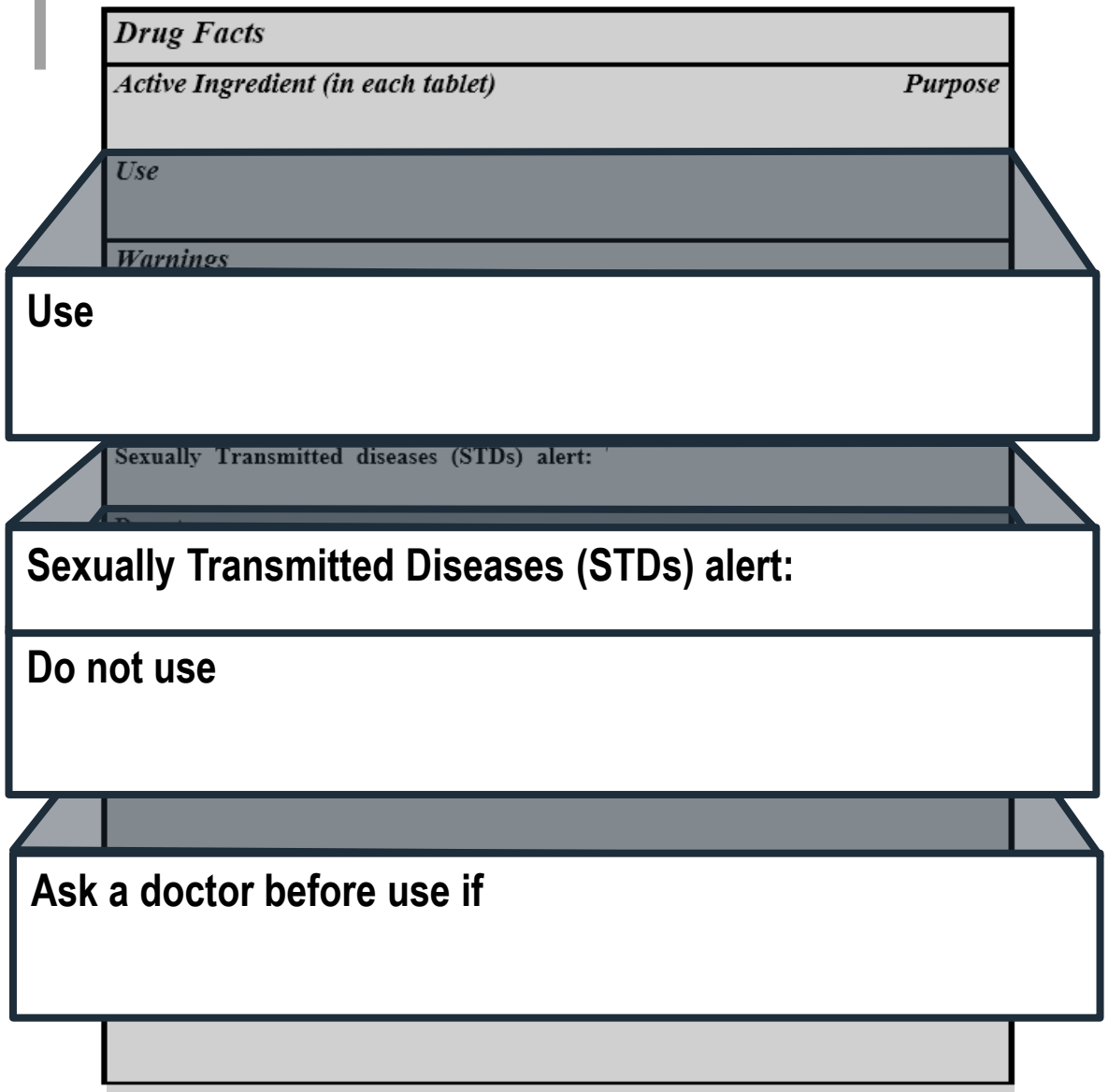
Can consumers, supported by label, select and use Opill safely and effectively in OTC setting so potential incremental benefits of consumers using Opill as guided by OTC labeling outweigh potential incremental risks?

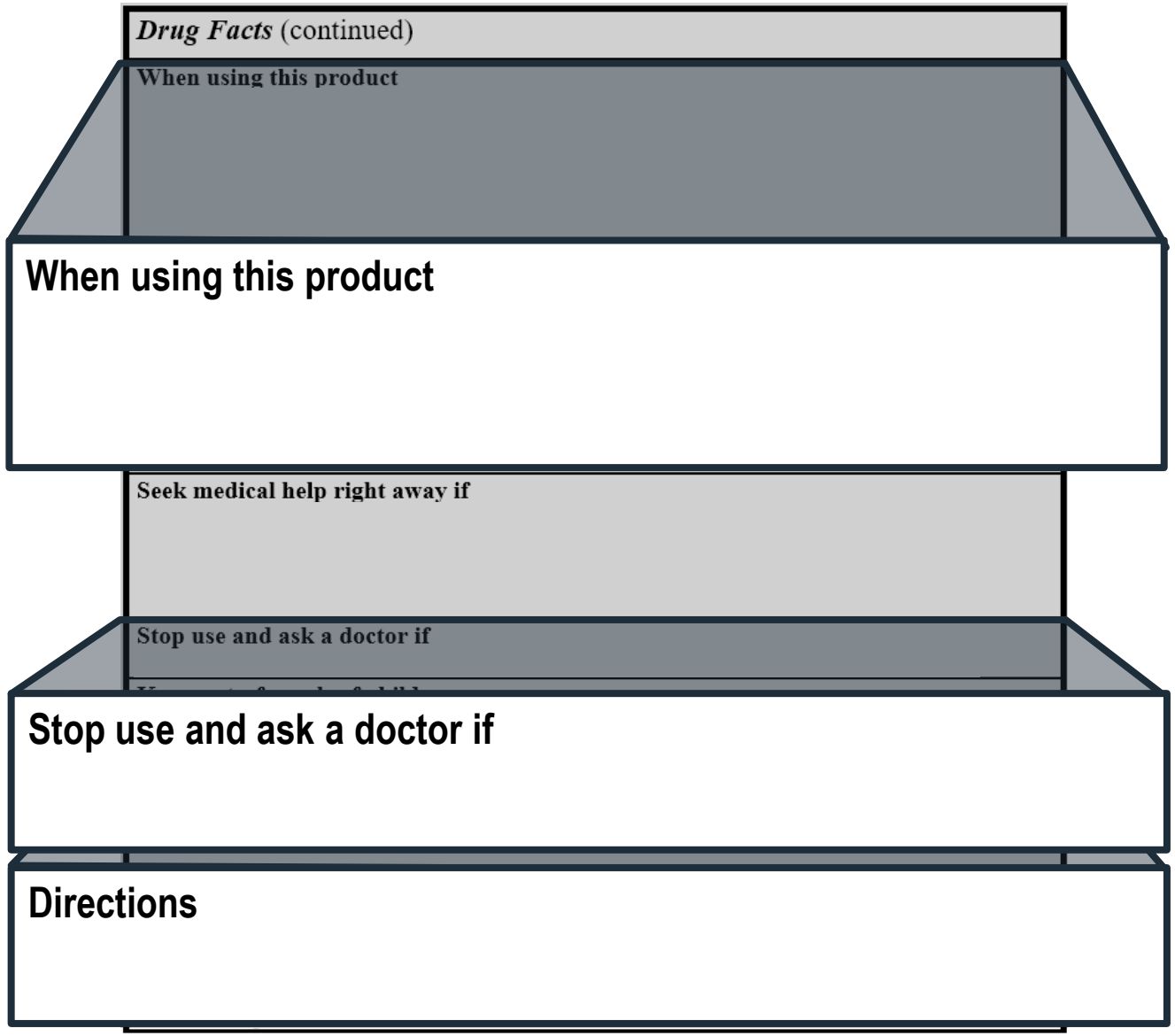
OTC Opill Labeling Optimized During Extensive, Iterative Label Development Process

- Adapted Opill Rx label and relevant national medical guidance[1,2] into consumer-friendly language, following standard OTC format
- Opill OTC labeling tested with consumers, revised multiple times, incorporates FDA feedback
- Final labeling after testing in 14 consumer studies over 7 years
- Labeling includes: Drug Facts Label (DFL), Consumer Information Leaflet (CIL), Reminder Card

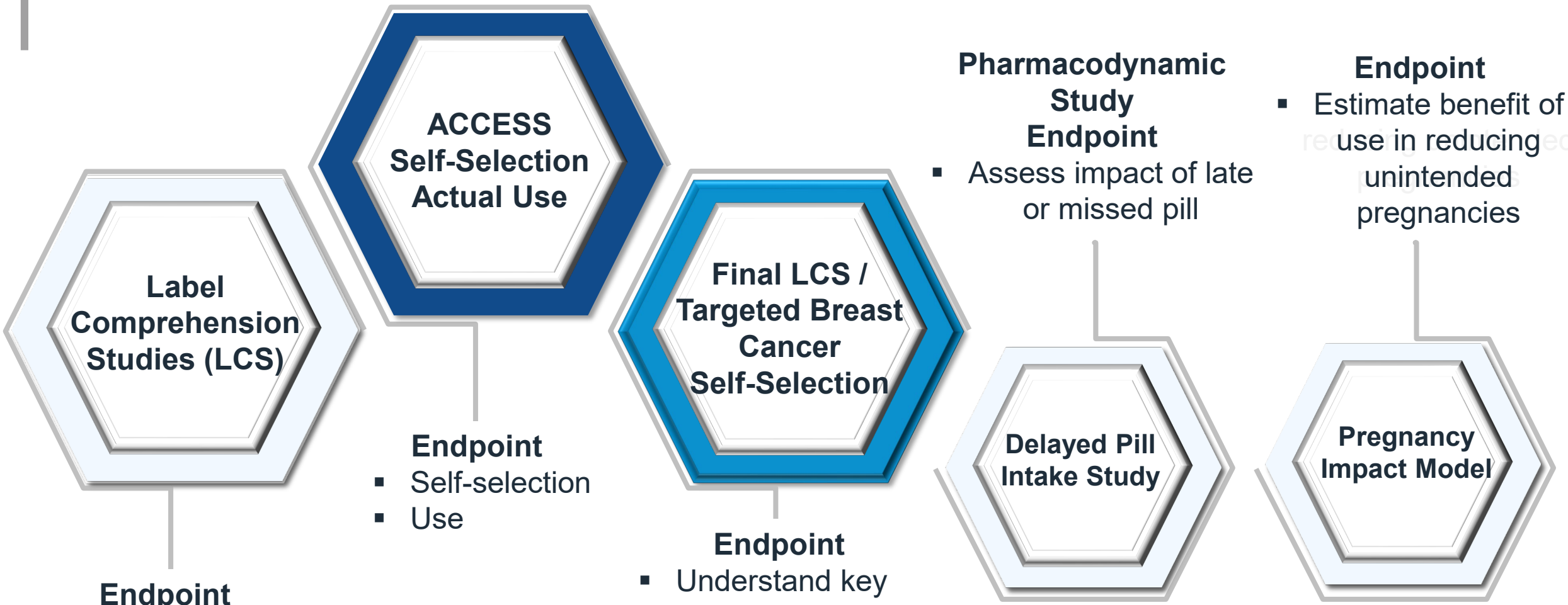
1. Curtis, 2016 [CDC Medical Eligibility Criteria for Contraception]; 2. Curtis, 2016 [US Selected Practice Recommendations]

DFL Structure and Content Highly Standardized





OTC Opill Development Program



ACCESS: Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use

Agenda

Need for Nonprescription Oral Contraception	**Carolyn Westhoff, MD, MSc** Sarah Billinghurst Solomon Professor of Reproductive Health Department of Obstetrics and Gynecology, Columbia University
Consumer Behavior Studies and ACCESS Study Design **Self-Selection Results**	**Russell Bradford, MD, MSPH** Senior Vice President, Medical Affairs PEGUS Research
Clinical Interpretation of Potential Risk of POP Use in Breast Cancer Survivors	**Pamela Goodwin, MD, MSc, FRCPC, FASCO** Senior Scientist, Lunenfeld-Tanenbaum Research Institute Sinai Health System; Professor of Medicine; University of Toronto
ACCESS Actual Use Adherence Results	**Irene Laurora, PharmD** Senior Director Scientific Affairs, Women's Health, HRA Pharma / Perrigo
Expert Interpretation of ACCESS Adherence Results	**Arthur Stone, PhD** Director, Center for Self-Report Science; Professor of Psychology, Economics, and Public Policy; University of Southern California
Clinical Interpretation of ACCESS Results	**Stephanie Sober, MD, MSHP** Global Lead Medical Affairs, Women's Health HRA Pharma / Perrigo
Clinical Perspective	**Anna Glasier, MD, DSc, OBE** Professor at Edinburgh and London Universities

Additional Experts

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Need for Nonprescription Oral Contraception

Carolyn Westhoff, MD, MSc

Sarah Billinghurst Solomon Professor of Reproductive Health
Department of Obstetrics and Gynecology
Professor of Population and Family Health and Epidemiology
Mailman School of Public Health, Columbia University

~ Half of All Pregnancies in US Are Unintended

Even with Wide Range of Available Contraceptive Methods

45% of 6.1 million pregnancies in US each year are unintended[1]

72% of pregnancies in adolescents 15 to 17 years are unintended[1]

50% of all US women will have experienced an unintended pregnancy by age 45[2]

1. Finer, 2016; 2. Sonfield, 2014

Unintended Pregnancies Have Significant Consequences

- Maternal risks[1]
  - Pregnancy loss, delayed prenatal care, two-fold higher postpartum depression
- Perinatal risks[2]
  - Prematurity, low birth weight, and greater infant mortality
- Increased risk of lower educational and economic attainment in women and children[3]
  - ~ 50% of teen mothers receive high school diploma by 22 years of age (vs ~ 90% in teens who do not give birth)[4]

1. Gipson, 2008; Cheng, 2009; Maxson, 2011; Assefa, 2012a; Dibaba, 2013; Fellenzer, 2014; Lindberg, 2015; Abajobir, 2016; 2. Maxson, 2011; Hall, 2017; Mohllajee, 2007; Logan, 2007; Lindberg, 2015; Kost, 2015; 3. Sonfield, 2014; Logan, 2007; Hoffman, 2006; 4. CDC, 2021; Perper, 2010

Healthy People 2030 – Improving Pregnancy Planning and Reducing Unintended Pregnancy

- Reducing
  - Proportion of unintended pregnancies
  - Pregnancies in adolescents
- Increasing
  - Proportion of women at risk for unintended pregnancy who use effective* birth control
  - Proportion of adolescent females at risk for unintended pregnancy who use effective* birth control

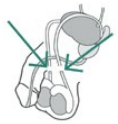
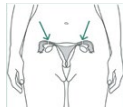
US Department of Health and Human Services Healthy People 2030 Initiative
*Defined by the CDC as most effective or moderately effective methods of contraception

Range of Contraceptives with Varying Failure Rates

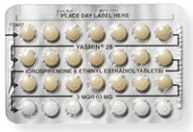
Failure Rate

More Effective

Most Effective
< 1 pregnancy per 100 women in 1 year

- 
  Implant
- 
  Vasectomy
- 
  Female Sterilization
- 
  IUD

Moderately Effective
4-7 pregnancies per 100 women in 1 year

- 
  Injectable
- 
  Pill
- 
  Patch
- 
  Ring

Less Effective
13-27 pregnancies per 100 women in 1 year

- 
  Male Condom
- 
  Diaphragm*
- 
  Sponge
- 
  Fertility Awareness-Based Methods
- 
  Female Condom
- 
  Spermicides
- Withdrawal

Less Effective

≥ 85 pregnancies per 100 women in 1 year

No birth control

*Diaphragms require a prescription but are recommended to be used with spermicides, most of which are available OTC. Adapted from Trussell, 2018

Only Less Effective Methods of Contraception Available Without Rx

Failure Rate

More Effective

Less Effective

Most Effective
< 1 pregnancy per 100 women in 1 year

- Implant
- Vasectomy
- Female Sterilization
- IUD

Moderately Effective
4-7 pregnancies per 100 women in 1 year

- Injectable
- Pill
- Patch
- Ring

Available Rx Only

Less Effective
13-27 pregnancies per 100 women in 1 year

- Male Condom
- Diaphragm*
- Female Condom
- Sponge
- Spermicides
- Fertility Awareness-Based Methods
- Withdrawal

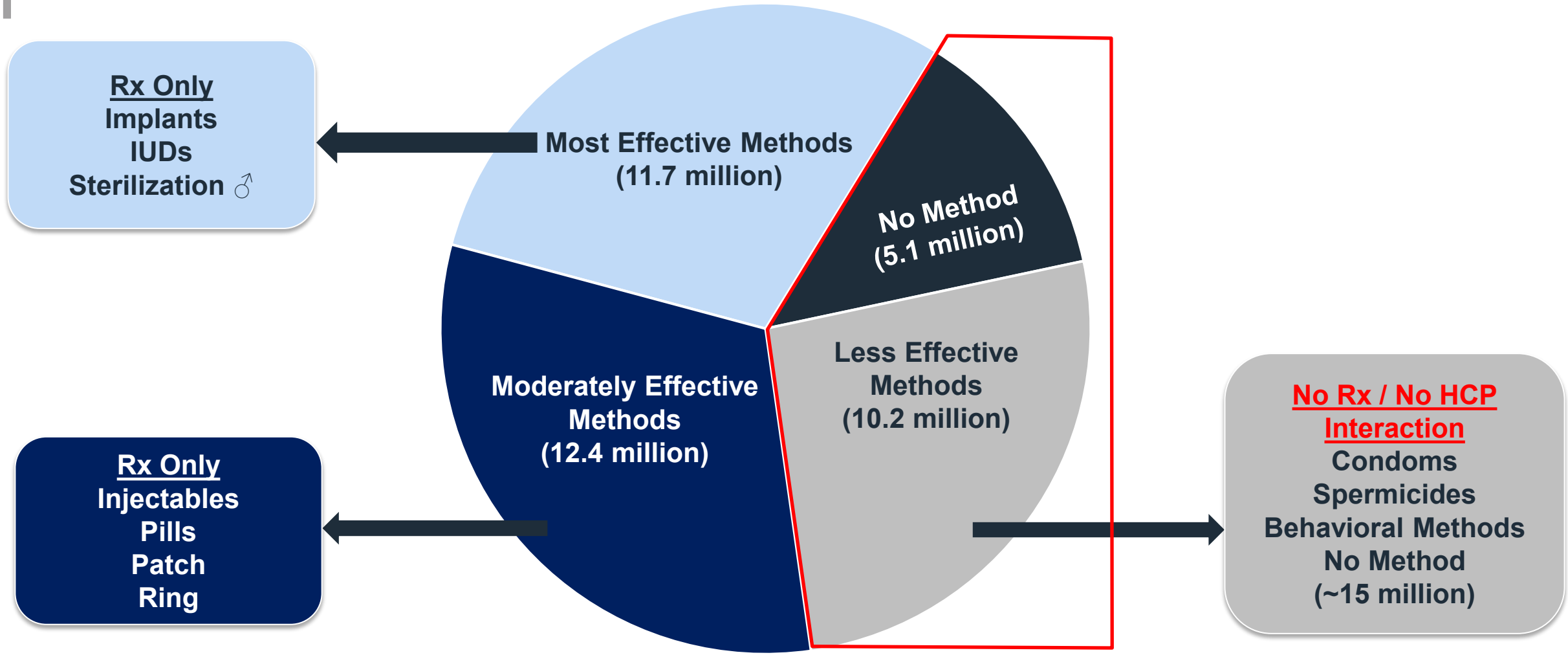
Available w/o Rx

≥ 85 pregnancies per 100 women in 1 year

No birth control

*Diaphragms require a prescription but are recommended to be used with spermicides, most of which are available OTC. Adapted from Trussell, 2018

15 Million Women Use Less Effective Methods or No Method at All



CDC Categories

Number of US women aged 15-49 at risk for unintended pregnancy according to NSFG 2017-2019 (Pinney Associates, 2022)

Women Face Barriers to Initiating and Refilling More Effective Options Only Available by Rx

- No regular medical provider
- Securing timely appointment
- Inconvenient hours for appointments

- Cost of doctor visit
- Lack of insurance

- Need to take time off work or school
- Must find childcare

- Transportation to / from appointment
- Cost of transportation

Adapted from Grindlay, 2016

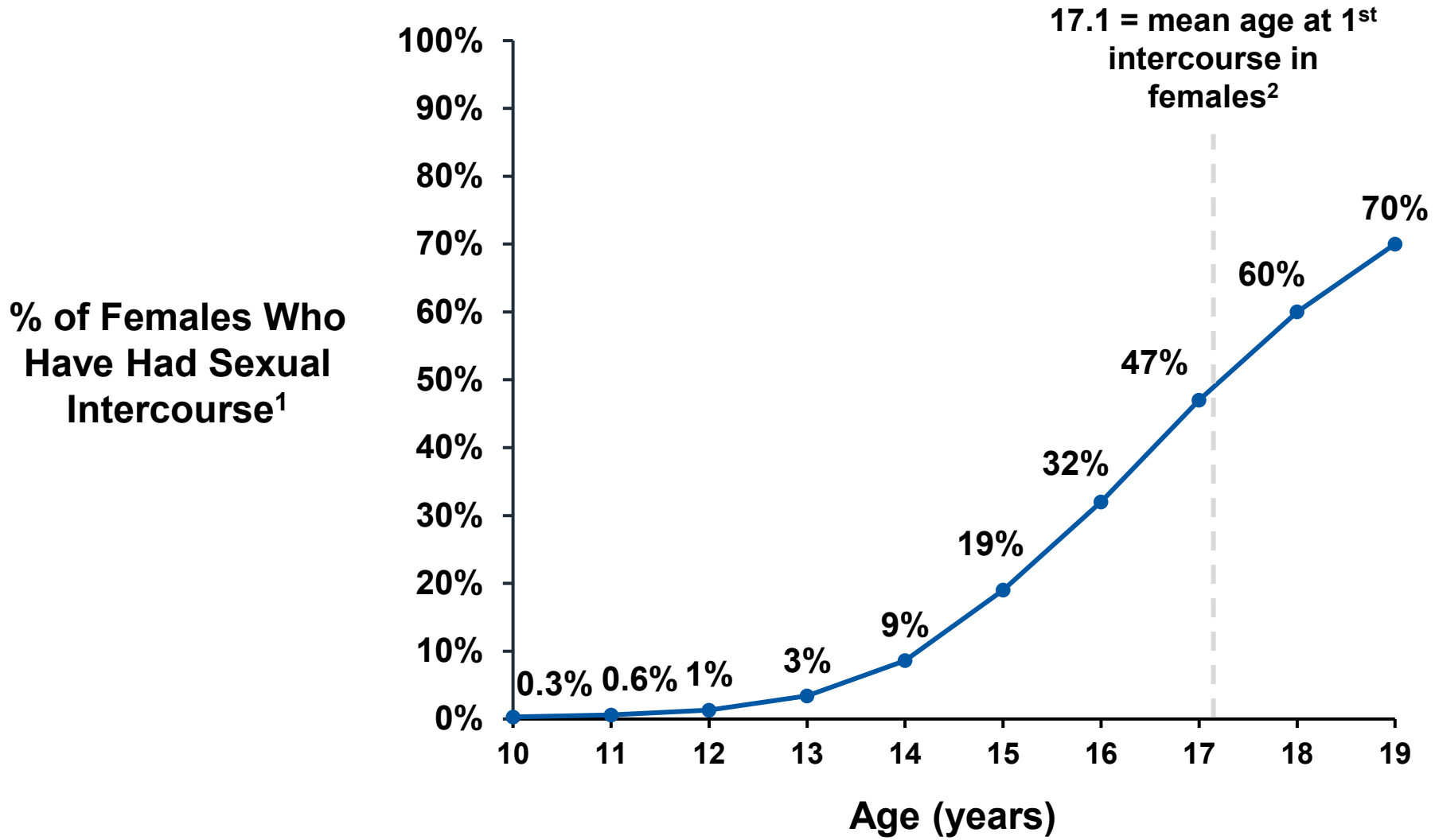
Barriers Are Real

- ~ 1/3 who ever tried to obtain Rx or refill for OC pill, patch, or ring reported difficulties[1]
- ~ 40-50% cite running out as primary reason for not using contraception[2]
- ~ 1/3 report non-adherence because unable to get next supply in time[3]

A woman who wants to avoid pregnancy needs easier access to effective contraceptives

1. Grindlay, 2016; 2. Biggs, 2012; Foster, 2012; 3. Frederiksen, 2022

~ 50% of US Females Are Sexually Active by Age 17



1. Finer, 2013; 2. NCHS, 2022

Adolescents Need Increased Access to More Effective Contraception

- ~ 88,000 pregnancies and 37,000 births in adolescents ≤ 17 years of age[1]
- 30% of first births in US occurred during teenage years[2]
- CDC allows oral contraceptive use *with no age restriction*[3]
- Professional organizations strongly endorse adolescent access to OTC oral contraception (ACOG, AMA, SAHM, NASPAG)

1. Maddow-Zimet, 2021; Hamilton, 2022; 2. Martinez, 2023; 3. Curtis, 2016 [CDC Medical Eligibility Criteria for Contraception]

ACOG: The American College of Obstetrics and Gynecology; AMA: American Medical Association; SAHM: Society for Adolescent Health and Medicine; NASPAG: North American Society for Pediatric Adolescent Gynecology

Leading Experts in Contraception and Adolescent Health Support OTC Oral Contraceptive Availability

ACOG
The American College of Obstetricians and Gynecologists

AMA
AMERICAN MEDICAL ASSOCIATION

AMERICAN ACADEMY OF FAMILY PHYSICIANS
STRONG MEDICINE FOR AMERICA

SAHM
SOCIETY FOR ADOLESCENT HEALTH AND MEDICINE

NASPAG
North American Society for Pediatric and Adolescent Gynecology

77% of reproductive aged women support making oral contraceptives available OTC[1]

1. 2022 KFF Women's Health Survey

Reality of Oral Contraceptive Prescribing

- Oral contraception easy to use, safe, and generally appropriate for most women
- Do not typically see patient again for a year after prescribing Rx OC and sometimes longer
- Usually do not provide level of counseling provided in Drug Facts Label
- Do not oversee our patients' use of product or adherence

Adherence to Daily Oral Contraceptive Use in Rx Setting

- Adherence to all types of daily prescription medications less than perfect despite involvement of healthcare provider[1-5]
  - Especially preventive medications including OCs
- Multiple studies show that ~15% of women may miss ≥ 3 active pills per cycle in Rx setting[3,4]
  - 3 of 21 active pills per cycle (15%)
- 7% of women report unintended pregnancies during first year of typical Rx OC use[6]

1. Bosworth, 2018; 2. Burnier, 2019; 3. Potter, 1996; 4. Fox, 2003; 5. Hou, 2010; 6. Trussell, 2018

POPs and COCs Have Same Typical Use Effectiveness but Some Differences

Progestin Only Pill (POP / Opill)	Combined Oral Contraception (COC)
▪ Typical use failure rate: 7%	▪ Typical use failure rate: 7%
▪ Less predictable bleeding pattern ▪ Not medically concerning	▪ More predictable bleeding pattern
▪ Pills to be taken at same time daily ▪ 3-hr window may be conservative	▪ Pills to be taken at same time daily
▪ Does not contain estrogen	▪ Contains estrogen ▪ Increased risk of VTE

▪ Only 1 absolute contraindication
  ▪ Current breast cancer
	▪ 16 absolute contraindications
	  ▪ Including breast cancer

CDC 2020: Medical Eligibility Criteria

POPs Carry Few Contraindications Making Appropriate for Broad Population of Women

Condition	POP		COC
	Initiation	Continued	
Stroke (history of cerebrovascular accident)	2	3	4
Ischemic heart disease (current and 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

Adapted from CDC, 2020

Need for OTC Oral Contraceptive

- Even with range of available contraceptive options, ~ half of pregnancies in US are unintended
- In 2023, women should have ready access to oral contraception
- OTC availability of effective oral contraceptive has potential to substantially improve individual and public health outcomes

POP ideal candidate for OTC

Consumer Behavior Studies and ACCESS Study Design

Russell Bradford, MD, MSPH

Senior Vice President

PEGUS Research

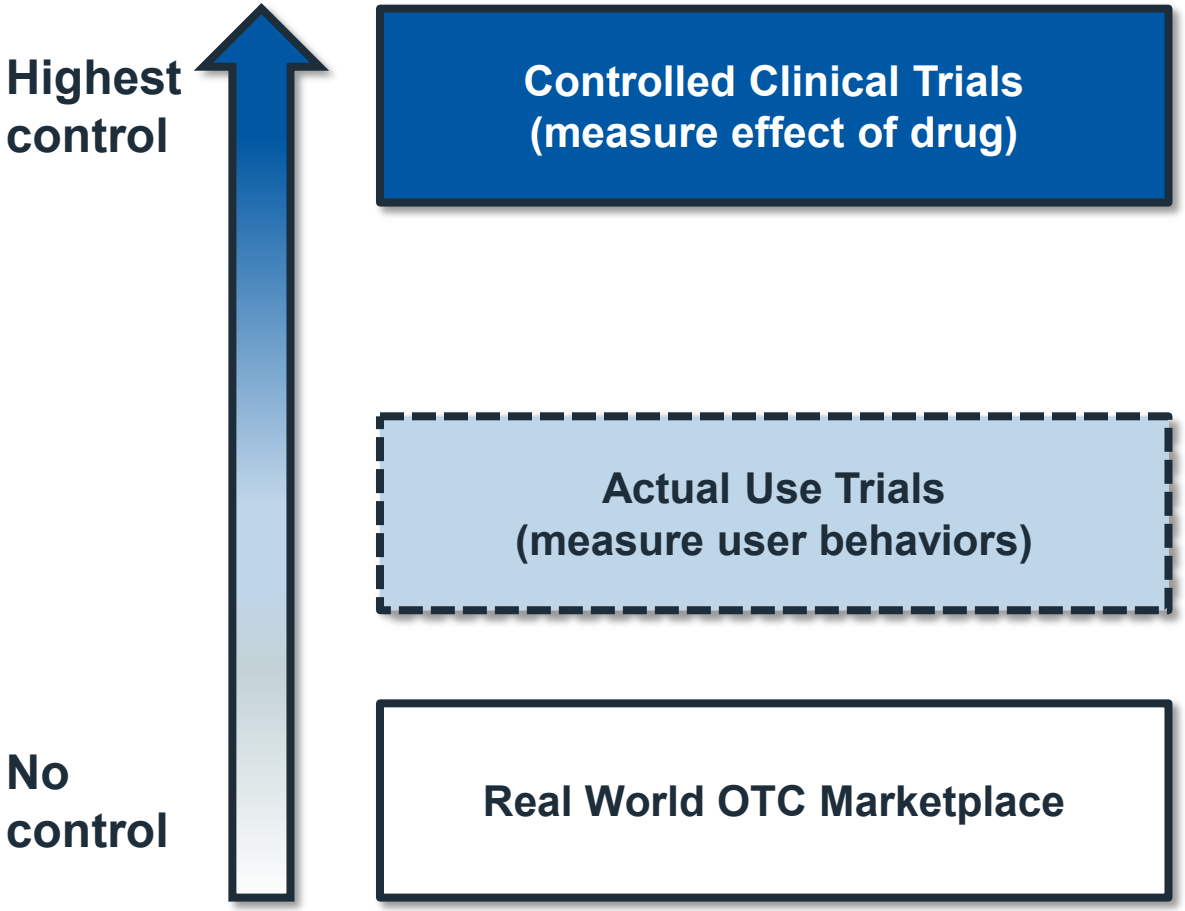
Introduction to Consumer Behavior Studies Supporting Rx-to-OTC Switch

- Products considered for switch to OTC status already approved for Rx use
  - Efficacy and safety already established
- OTC status relies on product labeling, principally DFL to guide consumers

Research Questions Addressed in Consumer Behavior Studies Supporting Rx-to-OTC Switch

Research Question	Mechanism to Assess
Do consumers understand messages in OTC labeling?	Label Comprehension Studies (LCS)
Does the DFL guide consumers as they decide if a product is appropriate for them?	Self-Selection Studies (SSS)
Do consumers use a product correctly in an OTC-like setting?	Actual Use Trials (AUT)

Actual Use Trials (AUTs) Less Controlled than Randomized Controlled Trials (RCTs)



Performance Thresholds Set for Consumer Comprehension and Behavior Studies

- Performance thresholds, set *a priori*
  - Guided by clinical assessment of risk of not following label
  - Outcomes must be considered in full benefit-risk assessment

In nonprescription consumer behavior studies, success thresholds are targets rather than 'hard stops'

Several Label Comprehension Studies Support Understanding of Opill OTC Labeling

- Final DFL comprehension study conducted after AUT completed
  - Label revised as recommended by FDA
- Messages on DFL generally well understood

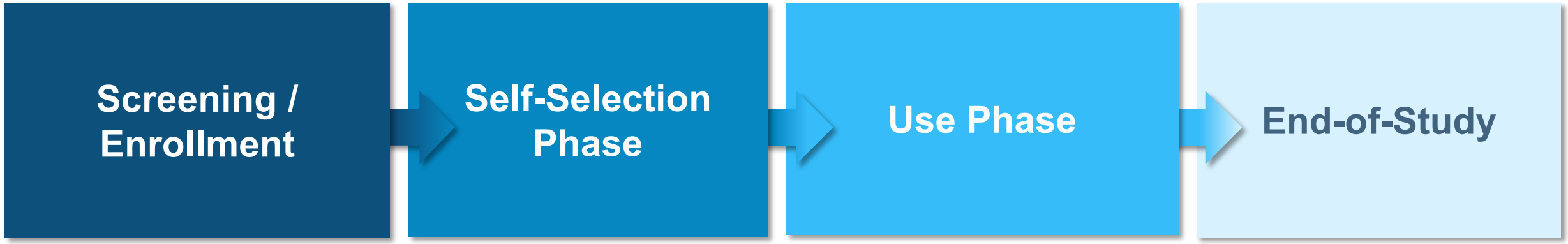
Ultimate test of label comprehension is how actual users translate OTC labeling into behavior

ACCESS: First of Its Kind Pivotal Consumer Study

- First OTC oral contraceptive intended for continuous, daily, preventative use
- Simulated OTC setting
  - Purchase and use daily oral contraceptive for up to 6 months
- Daily accounting of product use behaviors
- Do observed behaviors support intended benefit?
  - Prevention of unintended pregnancy
- Do observed behaviors incur unacceptable incremental risks?
  - Are these greater than if they took product in the Rx setting?

ACCESS: Evaluate Adequacy of Proposed OTC Labeling

- Appropriate self-selection and appropriate use of Opill in OTC-like setting



ACCESS: Screening / Enrollment Phase

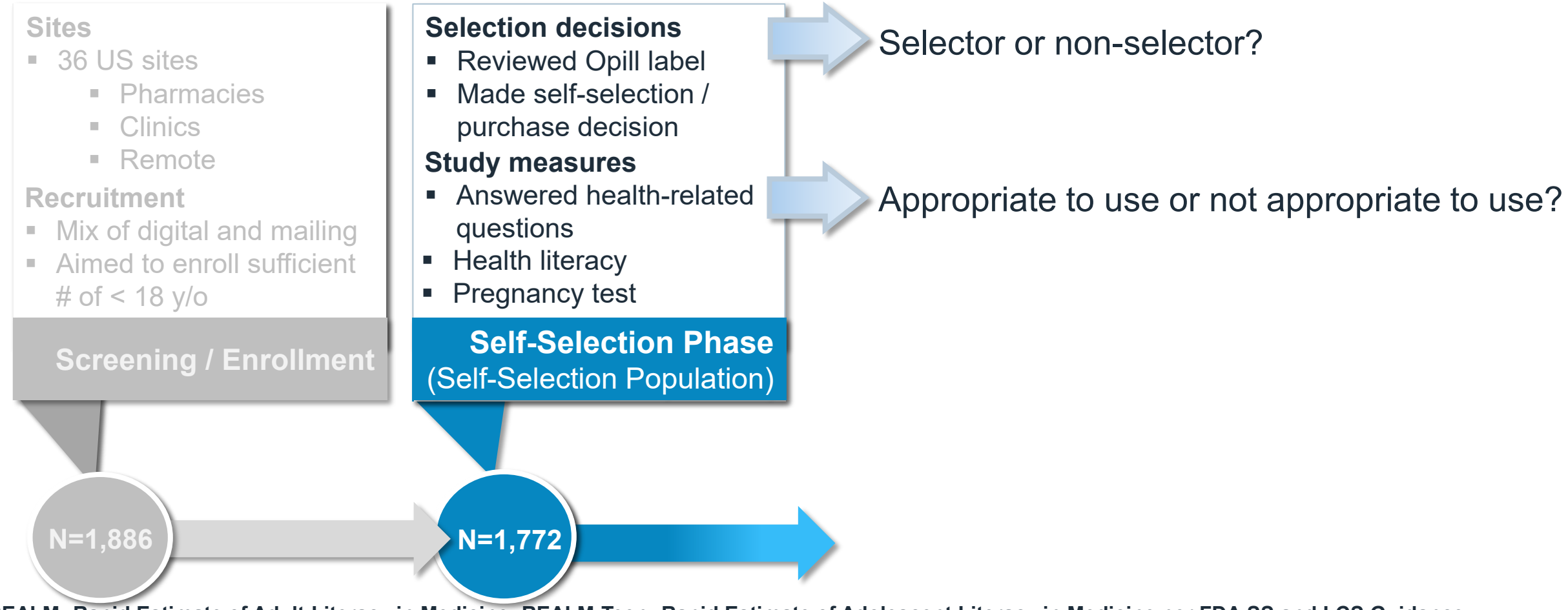
Sites
- 36 US sites
  - Pharmacies
  - Clinics
  - Remote

Recruitment
- Mix of digital and mailing
- Aimed to enroll sufficient # of < 18 y/o

Screening / Enrollment

N=1,886

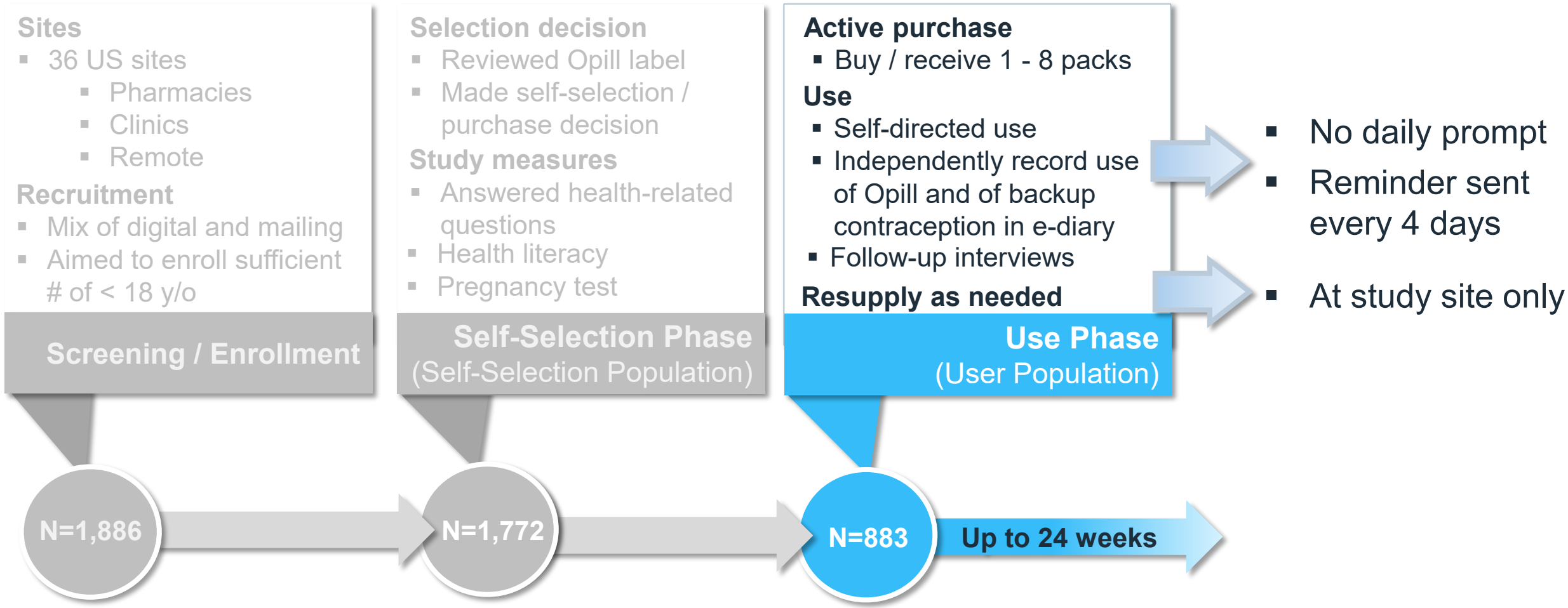
ACCESS: Self-Selection Phase



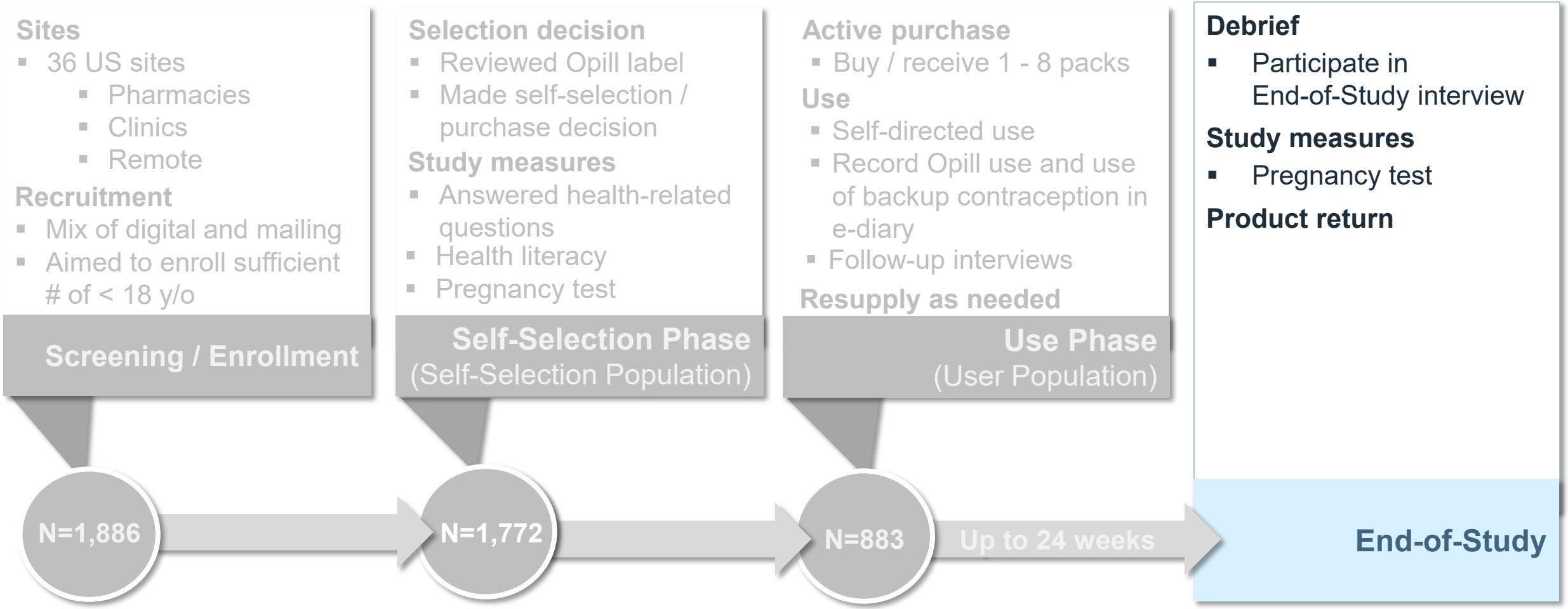
REALM: Rapid Estimate of Adult Literacy in Medicine; REALM-Teen: Rapid Estimate of Adolescent Literacy in Medicine per FDA SS and LCS Guidance

FDA, 2010. Guidance for industry: Label comprehension studies for nonprescription drug products. http://www.fda.gov; FDA, 2013. Guidance for industry: Self-selection studies for nonprescription drug products. http://www.fda.gov

ACCESS: Use Phase



ACCESS: End-of-Study



Self-Selection Results

Assesses ability of consumers to

- Apply drug labeling information to personal health situation
- Make correct decisions about whether Opill is appropriate to use

ACCESS: Self-Selection Population Represents Broad Range of Consumers

n (%)	Self-Selection Population N = 1,772	
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	226	13%
Race		
American Indian or Alaska Native	53	3%
Asian	106	6%
Black or African American	534	30%
Native Hawaiian or other Pacific Islander	25	1%
White	1057	60%
Other	105	6%
Hispanic ethnicity	306	17%

ACCESS: Consumer Decisions Based on Totality of Information

	Appropriateness to Use	
Selection	**Appropriate**	**Not Appropriate**
Selector		
Non-selector		

Questions	
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?"* ▪ *Follow-up questions: "Why or why not?"*
Purchase Question	*"Would you like to purchase Opill today to take home for your own use?"* ▪ *Follow-up questions: "Why or why not?"*

Verbatim Examples: 'Yes' Responders of Self-Selection Question and 'No' Responders of Purchase Question

	62-year-old female with history of colon cancer	25-year-old male	12-year-old premenarchal female
Self-selection question *Why / Why not?*	**Yes/Okay.** *I'm looking at it and it doesn't have estrogen in it, it seems simple…it explains thoroughly about the side effects…it seems very easy to use…I like how simple and to the point it is*	**Yes/Okay.** *It is very low maintenance and seems easy to use.*	**Yes/Okay.** *Everything looks ok to me except it might be hard to remember to take it everyday at the same time. I don't have any other conditions that would make it not ok to take it.*
Purchase question *Why / Why not?*	**No.** *I don't need it because I am menopausal…*	**No.** *I am a man*	**No.** *I don't need it*

ACCESS: Classified as Appropriate to Use Based on Responses to Medical History Questions and Physician Review

Selection	Appropriateness to Use	
	Appropriate	Not Appropriate
Selector		
Non-selector		

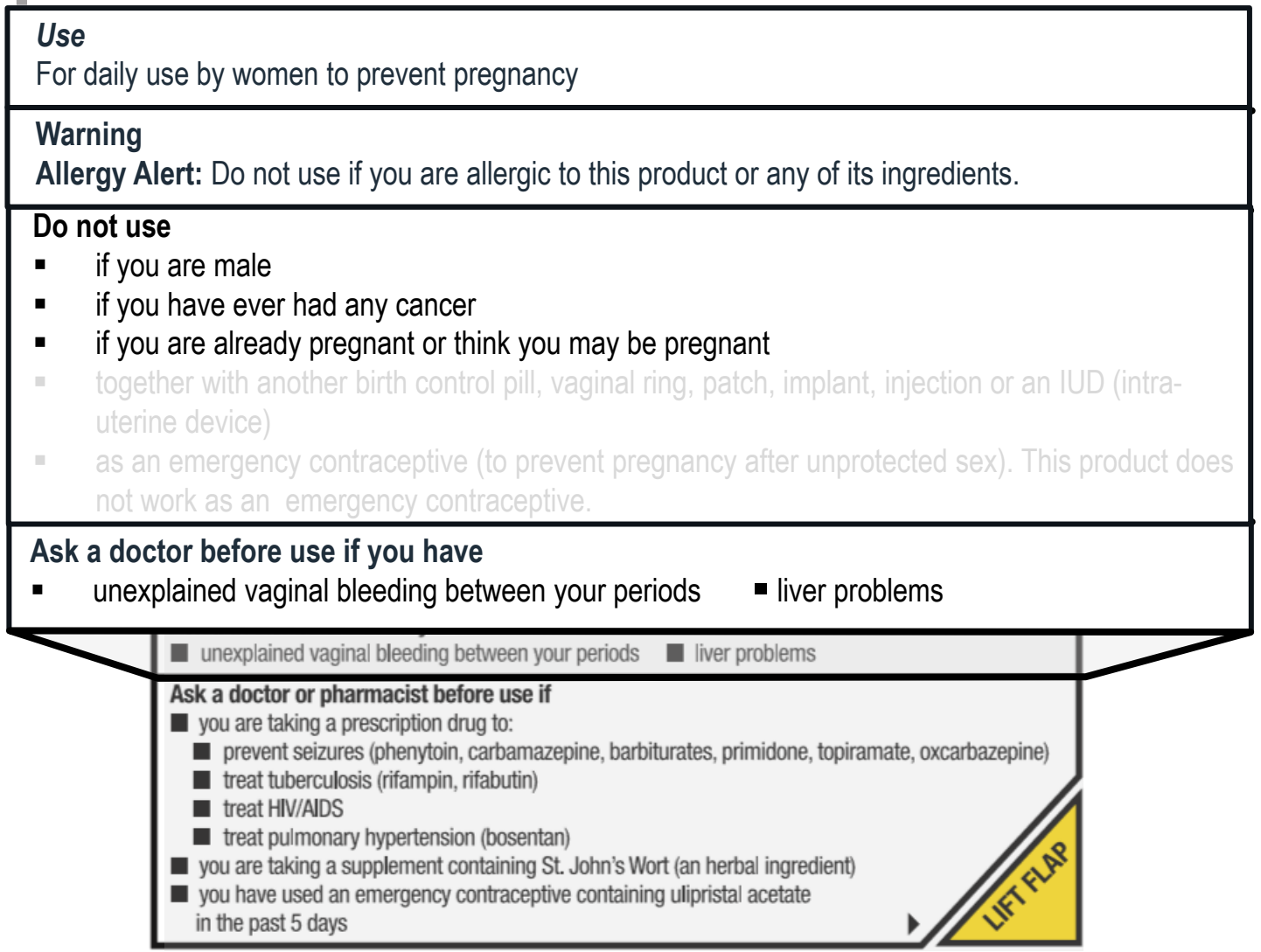
Scripted Targeted Medical History Questions

- Directed at understanding if particular label messages apply to participant

Physician Panel Review

- Directed at understanding clinical consequences of selection among those not appropriate to use
- Reclassified some participants from not appropriate to acceptable

ACCESS: Messages Assessed Related to Appropriateness to Use



Use
For daily use by women to prevent pregnancy

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

Do not use
- if you are male
- if you have ever had any cancer
- if you are already pregnant or think you may be pregnant
- 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

■ 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

Product indication for use

- not physically able to become pregnant

Allergy Alert

- allergic to norgestrel or other ingredients

Do not use

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

Ask a doctor before use if you have

- unexplained vaginal bleeding between your periods
- liver problems

ACCESS: Self-Selection Analysis Table

	Appropriateness to Use	
Selection	**Appropriate**	**Not Appropriate**
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

- **Group A:** Correct selection
- **Group B:** Incorrect selection – less favorable benefit/risk
- **Group C:** Appropriate to use, but did not select – neutral decision
- **Group D:** Correct non-selection

ACCESS: Calculation of Self-Selection Endpoints

	Appropriateness to Use	
Selection	**Appropriate**	**Not Appropriate**
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

Primary endpoint (Primary endpoint A)

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

$$\frac{A+D}{A+B+D}$$

Secondary endpoint (Secondary endpoint A)

- % Self-selection population not appropriate to use who did not select

$$\frac{D}{B+D}$$

ACCESS: Self-Selection Results Based on Per Protocol Classification

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

ACCESS: Comparative Self-Selection Results

Selection N = 1,772	*Based on totality of participants' responses*	**Appropriateness to Use** *Based on per-label classification plus review by panel of 3 physicians*	
		Appropriate + Acceptable N = 1,694	**Not Appropriate** N = 78
Selector	N = 1,180	**1,168**	**12**
Non-selector	N = 592	**526**	**66**

Selection N = 1,772	*Based primarily on initial SS question*	**Appropriateness to Use** *Based on FDA classification*	
		Appropriate + Acceptable N = 1,680	**Not Appropriate** N = 92
Selector	N = 1,550	**1,483**	**67**
Non-selector	N = 222	**197**	**25**

ACCESS: Selectors Not Appropriate to Use Per FDA (Group B)

	Participants FDA Classified as Selectors Not Appropriate to Use N = 67*
Do not use	
if you have ever had breast cancer**	**2**
if you have ever had any cancer	**8**
if you are already pregnant or think you may be pregnant	**8**
if you are allergic to norgestrel or other ingredients	**11**
if you are male	**6**
Ask a doctor before use if you have	
unexplained vaginal bleeding between your periods	**17**
liver problems	**4**
Product not indicated for use	
not physically able to become pregnant	**12**

*Participants could fall into multiple categories; ** message not tested in ACCESS

ACCESS: Selectors Not Appropriate to Use (Group B)

	FDA's 67 Selectors Not Appropriate to Use	
	Sponsor and FDA Classified as Selectors Not Appropriate to Use N = 12*	**Additional Participants FDA Classified as Selectors Not Appropriate to Use** N = 55*
Do not use		
if you have ever had breast cancer**	**1**	**1**
if you have ever had any cancer	**1**	**7**
if you are already pregnant or think you may be pregnant	**5**	**3**
if you are allergic to norgestrel or other ingredients	**0**	**11**
if you are male	**2**	**4**
Ask a doctor before use if you have		
unexplained vaginal bleeding between your periods	**0**	**17**
liver problems	**0**	**4**
Product not indicated for use		
not physically able to become pregnant	**3**	**9**

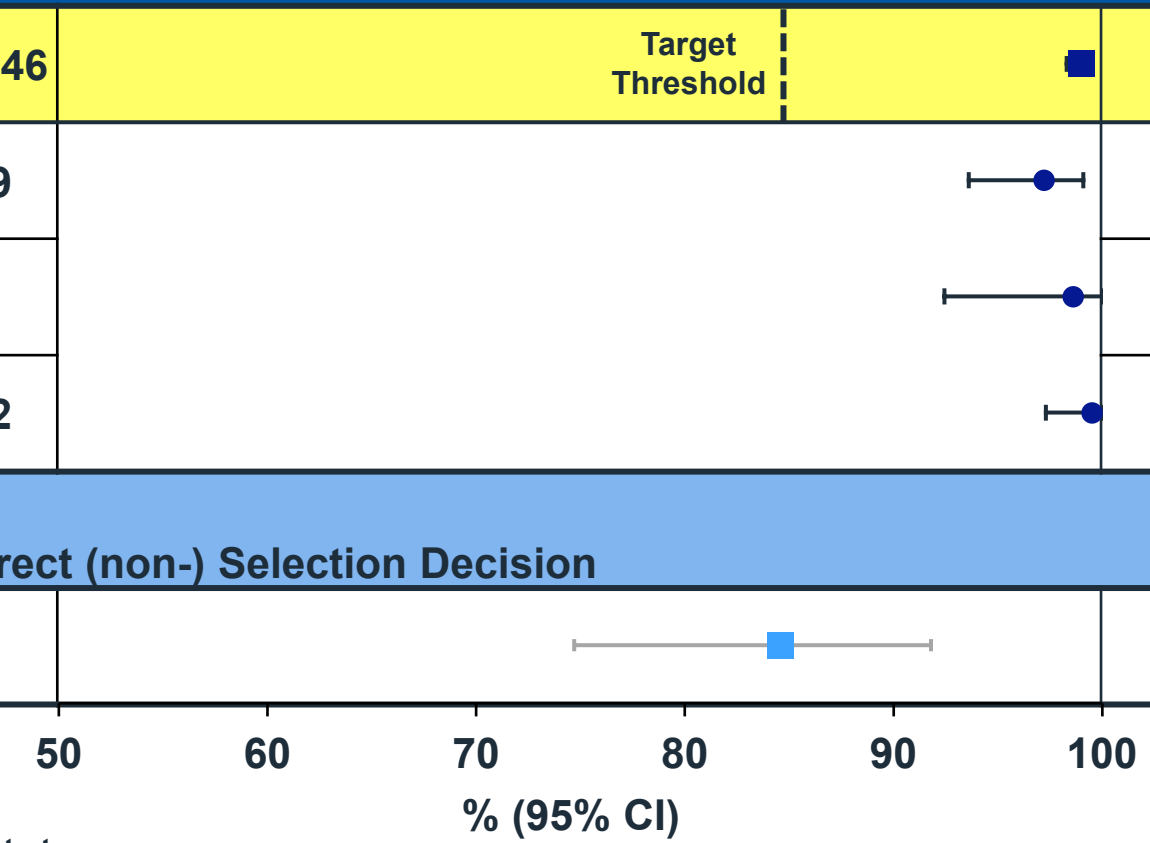
***Participants could fall into multiple categories; ** message not tested in ACCESS**

ACCESS: Self-Selection Results Based on Per Protocol Classification

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

ACCESS: Opill OTC Label Guides Appropriate Self-Selection

% Correct Selection Decision	Participants n / N	% (95% CI)
Primary endpoint*	**1,234 / 1,246**	**99.0%** (98.3, 99.5)
Low health literacy	174 / 179	**97.2%** (93.6, 99.1)
Adolescents (12-14 years)	70 / 71	**98.6 %** (92.4, 100)
Adolescents (15-17 years)	201 / 202	**99.5%** (97.3, 100)
% Not Appropriate to Use Who Made Correct (non-) Selection Decision		
Secondary endpoint**	**66 / 78**	**84.6%** (74.7, 91.8)



n = correct or acceptable selection decision
*N = all participants except non-selectors who are appropriate to use
**N = all participants who are not appropriate to use

Breast Cancer Warning Modified and Confirmed in Targeted Self-Selection Study

DFL Statement Tested in ACCESS Self-Selection / Actual Use	**Do not use** ▪ if you have ever had any cancer

Modified

DFL Statement Tested in Final LCS / Targeted Breast Cancer Self-Selection	**Do not use** ▪ if you **have or ever had** breast cancer **Ask a doctor before use if** ▪ you **have or ever had** any cancer

Targeted Breast Cancer Self-Selection Study: Supplements ACCESS Self-Selection Results

HRA Analysis

- **97.1%** (95% CI: 93.7-98.2%) (199/205) of women with history of breast cancer correctly did not select to use Opill
- 90% correct non-selection was *a priori* target threshold

FDA Worst-Case Analysis

- **92.3%** (95% CI: 87.6-95.6%) (179/194), excluding those who were not fertile and assuming responses about asking a doctor or not articulating breast cancer contraindication, are incorrect

Demonstrates that breast cancer warning on DFL successfully mitigates risk small subset of potential OTC population would select to use Opill

Conclusions Regarding Opill Self-Selection

Opill has few contraindications or other conditions for use

Proposed label guides appropriate self-selection, including women with current or past breast cancer

Clinical Interpretation of Potential Risk of POP Use in Breast Cancer Survivors

Pamela Goodwin, MD, MSc, FRCPC, FASCO

Senior Scientist

Lunenfeld-Tanenbaum Research Institute Sinai Health System

Professor of Medicine

University of Toronto

Breast Cancer Survivors – Clinician's Perspective

- POPs contraindicated in women who have ever had breast cancer (survivors)
  - Concerns that breast cancer growth would be stimulated
- Contraindication arises mainly from preclinical research
  - Some clinical evidence showing increased risk of recurrence in postmenopausal breast cancer survivors using estrogen
  - Limited clinical evidence with progestin

Evidence Regarding Hormonal Contraception in Breast Cancer Survivors Based on Limited Clinical Data

Oral Contraceptives (Ostroot, 2021)

Women 18-51 Years with Breast Cancer	N = 1,370	
	n	%
Hormonal contraception users	97	**7.1%**
Subset that used POP	8	**0.6%**

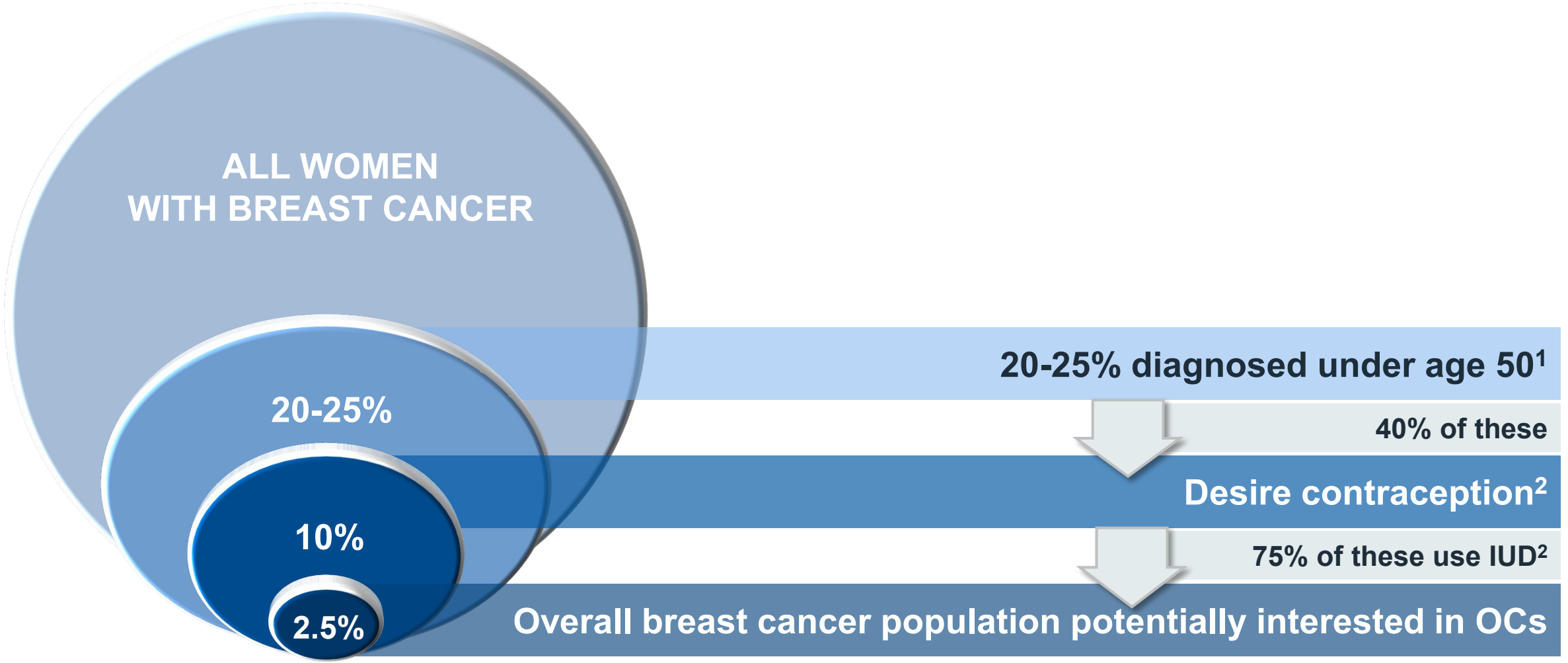
Breast Cancer Recurrence	n = 92 **(6.7%)**
Hormonal contraception users	6.2%
Non-hormonal contraception users	6.8%
p-value	**0.83**

- **No difference in all-cause mortality**
- **May not impact breast cancer recurrence**

All Patients with Breast Cancer Are Under Care of Physician

- Patients with breast cancer routinely told by doctors NOT to take hormonal agents, including OCs, at any time after their diagnosis
  - Recommendation reinforced by Opill label
- Potential concerns about use of POPs not relevant to all breast cancer survivors; concern restricted to subset interested in contraception

Small Subset of Patients with Breast Cancer Diagnosis Interested in Oral Contraceptives



1. Stapleton, 2018; 2. Lambertini, 2022

Breast Cancer Population Responded Correctly Regardless of Approach

"Do not use if you have or ever had breast cancer"

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

Correct response

- Sponsor: 97% (95% CI: 94-99)
- FDA: 95% (95% CI: 91-97)
  - Excluded 1 patient with hormone receptor negative BC who stated her doctor told her it was okay to take OCs
  - Excluded 4 who would ask their doctor before use

Conclusion

- Supportive of contraindication for women who have ever had breast cancer due to limited clinical data regarding safety
- Reassured 97% of breast cancer survivors made right decision
  - Real-world data from US and Europe – 3-7% of breast cancer survivors prescribed hormonal contraception after diagnosis[1]
- DFL guides breast cancer survivors to correct decision

Potential risk to breast cancer survivors needs to be balanced against benefits of OTC access in larger population of women without breast cancer

1. Ostroot, 2021; Morch, 2022; Lambertini, 2022

ACCESS Actual Use Adherence Results

Irene Laurora, PharmD

Senior Director, Scientific Affairs, Women's Health

HRA Pharma / Perrigo

Actual Use

- Assess whether consumers follow label instructions so they can use Opill as directed
    - Pre-specified results
    - Post-trial sensitivity analyses
    - Provide some perspective on FDA's analysis
    - Adherence conclusions

ACCESS: Population Reflective of Potential Users Sufficient Data in Special Populations

n (%)	User Population N = 883	
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	120	14%
Race		
American Indian or Alaska Native	24	3%
Asian	50	6%
Black or African American	267	30%
Native Hawaiian or other Pacific Islander	12	1%
White	527	60%
Other	57	6%
Hispanic ethnicity	161	18%

ACCESS: Distribution of Contraceptive Methods Used Prior to Enrollment

N (%)	User Population N = 883	Ages 12-17 N = 200
LARC	1.2%	1.5%
COC / POP / patch / vaginal ring	17.2%	11.5%
Injectable	0.8%	1.5%
Male condom	36.9%	24.0%
Diaphragm / sponge	0	0
Natural FP / rhythm method	2.9%	0
Spermicides / female condom	0.1%	0
Withdrawal	5.4%	1.5%
No method	35.3%	60.0%

More Effective ↑

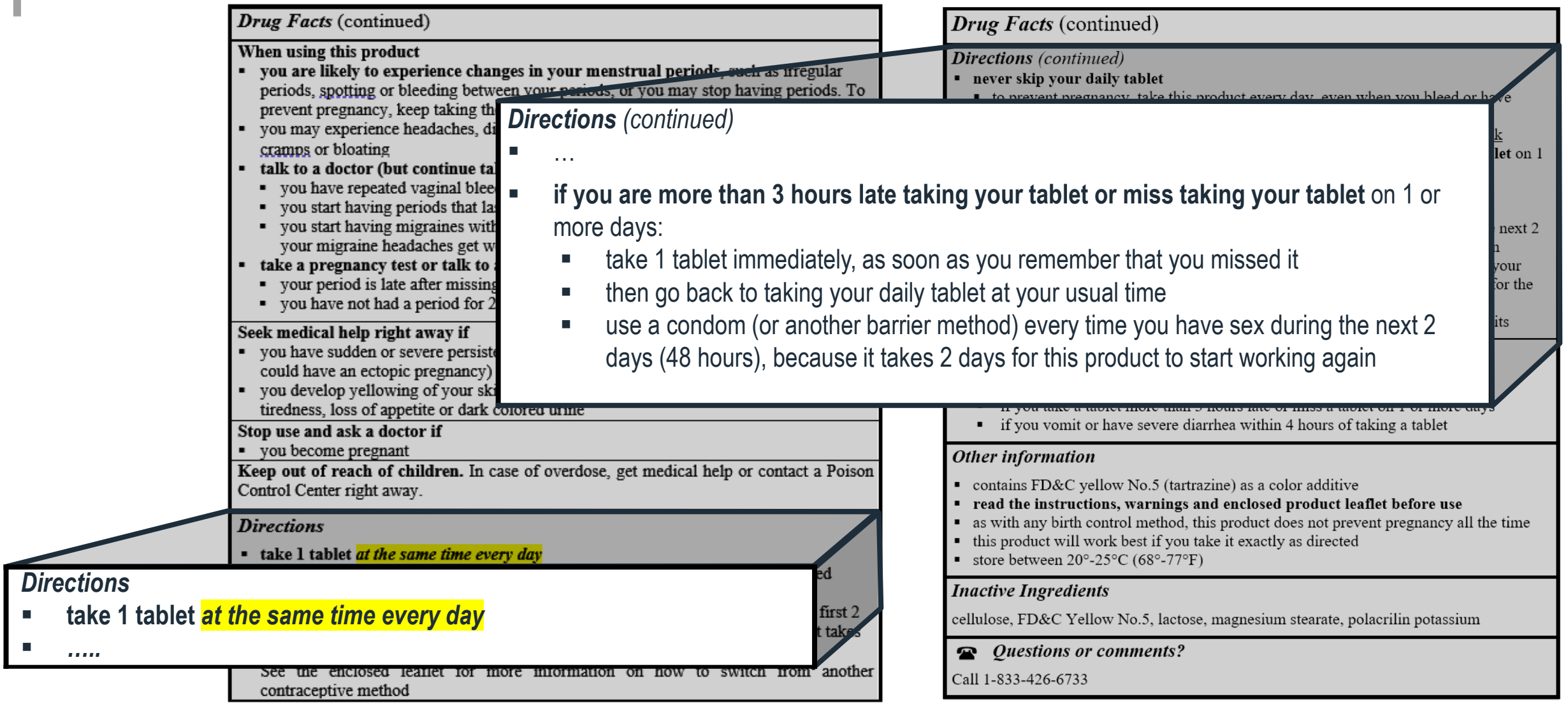
Less Effective ↓

↑ Available Rx Only

↓ Available w/o Rx

COC: combined oral contraception; POP: progestin-only oral contraceptive pill;
FP: family planning; LARC: Long-acting reversible contraceptive; N: number of participants

Label Directs Women to Take 1 Tablet at Same Time Every Day



ACCESS: OTC Adherence Based on Adherence in Rx Setting

- Typical OC prescription use
  - People take ~85% of active pills[1]

Therefore, acceptance threshold set at 85% adherence for OTC setting

- Thresholds inform our decision making
  - Consumer studies measure “how often” a behavior happens
- Clinical impact of this behavior is most important within benefit / risk framework

1. Fox, 2013; Potter, 1996; Huber, 2013; Hou, 2010; Aubeny, 2004

ACCESS: Overall Reported Daily Pill-Taking Adherence

Primary endpoint: daily adherence overall (Primary endpoint B)

- % of overall study days where Opill was reported as taken (threshold ≥ 85%)

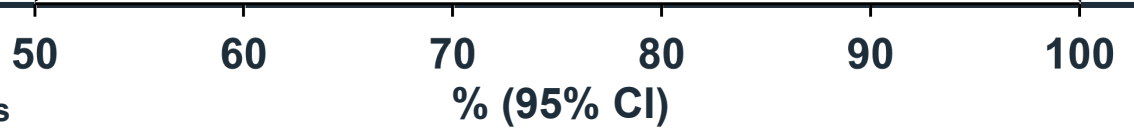
Secondary endpoint: daily adherence overall, allowing for mitigating behaviors* (Secondary endpoint B)

- % of days Opill was reported as taken, plus days where label-directed mitigating behaviors were followed when Opill was reported not taken

*Did not ask participants < 18 years of age about sexual behaviors; therefore, secondary endpoint does not include mitigating behaviors for this age group

ACCESS: DFL Guides Women in Taking Opill Daily (Overall Daily Adherence)

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)
Adolescents (12-14 years)	5,266 / 5,737		**91.8%** (91.0, 92.5)
Adolescents (15-17 years)	13,629 / 14,834		**91.9%** (91.4, 92.3)
Considering Mitigating Behaviors*			
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)



n = number of days participant reported taking Opill
N = total number of days
Assessed in 883 participants over course of up to six months
*Did not ask participants < 18 years of age about sexual behaviors; therefore, secondary endpoint does not include mitigating behaviors for this age group

ACCESS: Individual Participant-Reported Adherence to Daily Pill-Taking

Primary endpoint: daily adherence among individual participants (Primary endpoint C)

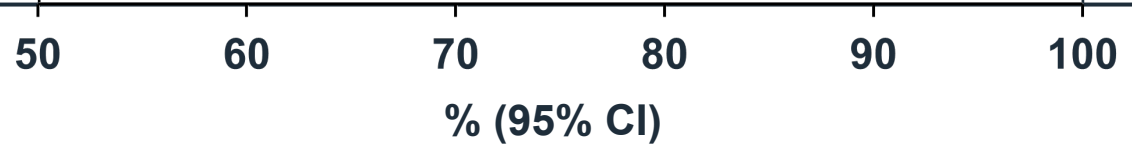
- % of participants who were adherent (reported taking Opill on ≥ 85% days; threshold ≥ 85% of participants)

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

- % of participants who were adherent (reported taking Opill or followed mitigating behavior when Opill was reported not taken on ≥ 85% days)

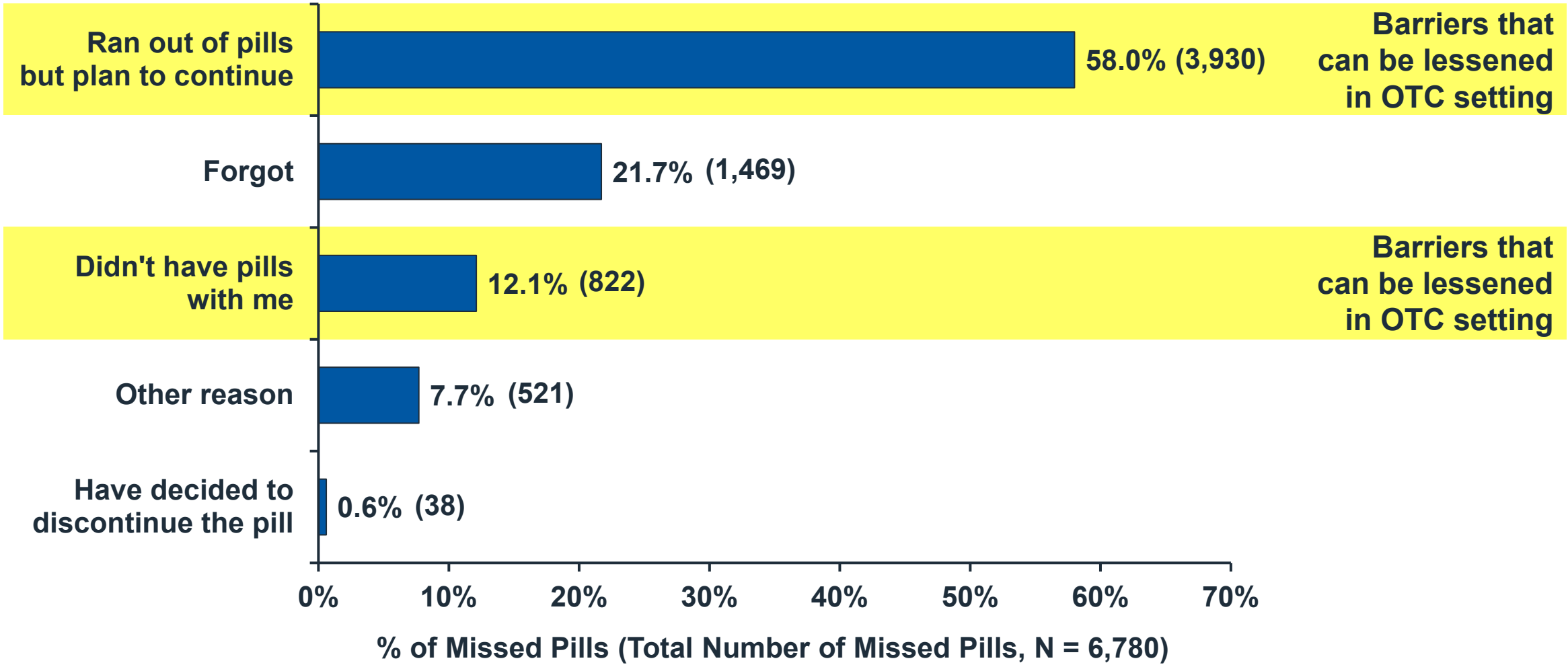
ACCESS: Most Users Reported Taking Opill Consistently (Individual Participant Daily Adherence)

≥ 85% Adherent to Daily Dosing	Participants n / N	Proportion of Participants	% (95% CI)
Primary endpoint	**747 / 883**	Target Threshold	**84.6%** (82.0, 86.9)
Low health literacy	98 / 120		**81.7%** (73.6, 88.1)
Adolescents (12-14 years)	40 / 49		**81.6%** (68.0, 91.2)
Adolescents (15-17 years)	125 / 151		**82.8%** (75.8, 88.4)
≥ 85% Adherent to Daily Dosing Considering Mitigating Behaviors*			
Secondary endpoint	**837 / 883**		**94.8%** (93.1, 96.2)
Low health literacy	109 / 120		**90.8%** (84.2, 95.3)



n = number of participants ≥ 85% adherent
N = number of participants in User Population
*Did not ask participants < 18 years of age about sexual behaviors; therefore, secondary endpoint does not include mitigating behaviors for this age group

ACCESS: Resupply Issues Main Reason for Missing Pills



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

Primary endpoint: intake at same time of day (Primary endpoint D)

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

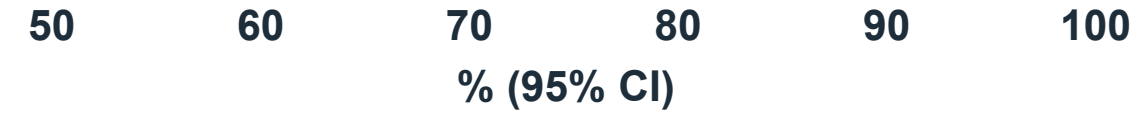
Secondary endpoint: intake within 27 hours,* allowing for mitigating behaviors (Secondary endpoint D)

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

*27 hours = 24 hours plus a max of 3 hours (maximum window of intake tolerated by label)

ACCESS: Users Report Taking Pill at Same Time of Day

Opill Used ± 3 Hours Since Time of Last Dose	Days n / N	Proportion of Days	% (95% CI)
Primary endpoint	**78,946 / 82,465**	Target Threshold	**95.7%** (95.6, 95.9)
Low health literacy	10,927 / 11,517		**94.9%** (94.5, 95.3)
Adolescents (12-14 years)	5,020 / 5,217		**96.2%** (95.7, 96.7)
Adolescents (15-17 years)	12,853 / 13,478		**95.4%** (95.0, 95.7)
Opill Used Within 27 Hours of Last Dose or Mitigating Action Taken*			
Secondary endpoint	**79,316 / 80,107**		**99.0%** (98.9, 99.1)
Low health literacy	11,070 / 11,231		**98.6%** (98.3, 98.8)



n = number of days Opill reported taken at correct time
N = number of days evaluable for timing of dose
*Did not ask participants < 18 years of age about sexual behaviors; therefore, secondary endpoint does not include mitigating behaviors for this age group

Additional FDA Analysis on Same Time of Dose

FDA Analyses (FDA Primary Endpoints)	n / N	% (95% CI)
D-1. Taking IP and at same time every day	78,946 / 89,245*	**89%** (88, 89)
D-2. % of participants with ≥ 85% same time adherence	648 / 877*	**74%** (71, 77)
Complementary HRA Analyses (Considering Mitigating Behaviors)		
D-1.Taking IP and at same time every day	82,605 / 89,239	**93%** (92, 93)
D-2. % of participants with ≥ 85% same time adherence	729 / 877	**83%** (80, 86)

*Estimate based on data provided in FDA's Briefing document

Over-Reporting and Its Impact on ACCESS Interpretation

- Over-reporter: anyone who reported in e-diary at least one dose more than drug supply available to them
- Occurred in 261 of 883 User participants
- Minimal intervention by study personnel, inherent risk in any actual use trial seeking to capture but not influence participant behaviors
- HRA has undertaken a number of steps to understand the over-reporting
  - Root Cause Analysis for etiology
  - Sensitivity analyses
  - Consulted experts in field of behavior research and self-reporting

ACCESS: Root Cause Analysis Identified Causes Related to Study Design and Study Conduct

- No systemic problems with study identified

Study Planning	Study Execution
No design elements in place to prevent over-reporting from happening	Pre-planned risk assessment did not identify over-reporting as a significant risk
Study design did not set to identify if and when participants reported taking more doses than possible	Over-reporting not identified during study – not flagged as protocol violation
Diary setup allowed participants to continue entering data after running out of drug supply	

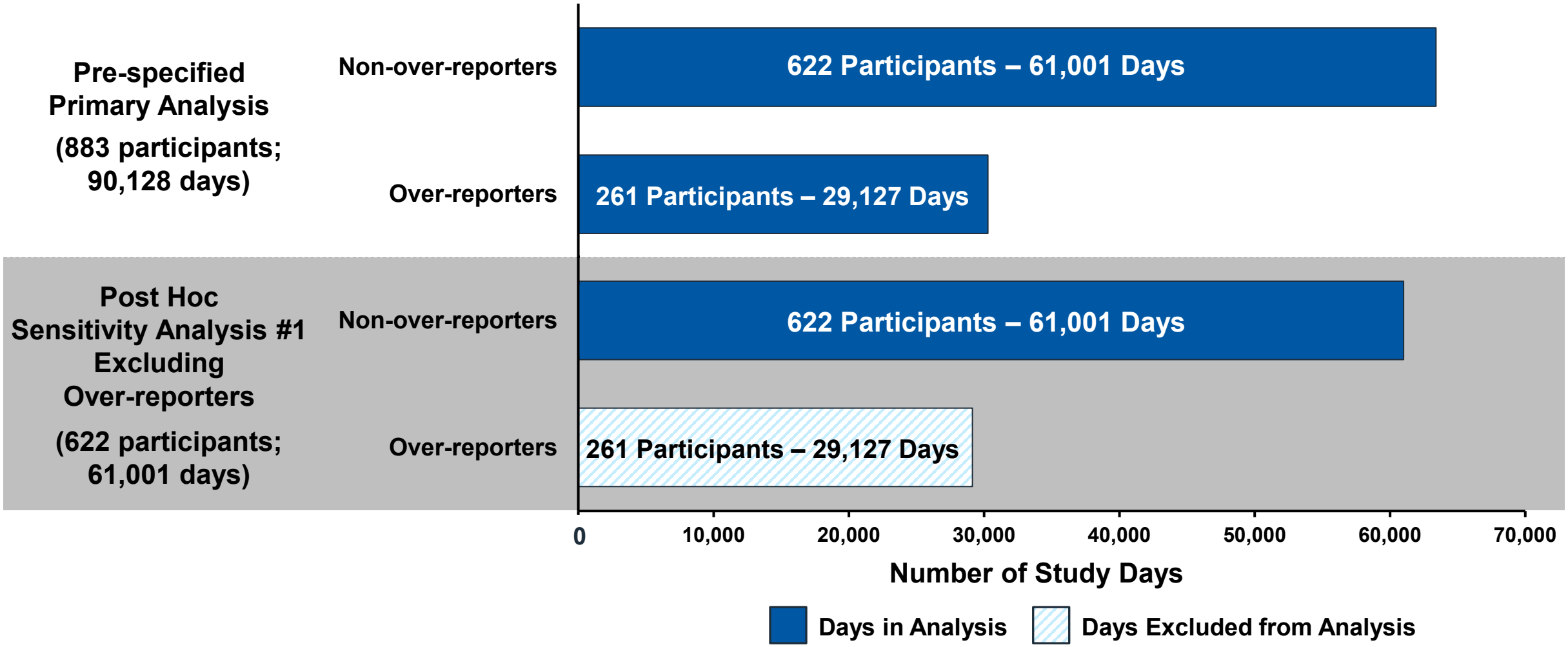
Over-Reporting in ACCESS

- Potential causal factor that could not be ruled out: participant incentive
  - Participants paid for each diary entry whether **yes/no**
- Few restrictions on reporting to allow to capture wide range of behaviors
  - Permitted participants to report taking more drug than feasible
- Some participants may have made inadvertent data entry mistakes
  - 89/261 participants (34%) reported taking maximum of 20% excess doses
- Participants who over-reported to large extent, most likely that reporting of excess doses was deliberate

ACCESS: Sensitivity Analyses Designed to Understand Impact of Over-Reporting

- Design elements allowing over-reporting necessary for 2 reasons
  - Allow participants' autonomy in decision-making
  - Minimize missing data
- Some data from over-reporters could not be reliably employed to assess adherence to Opill intake
- Two additional sensitivity analyses conducted to provide insight into potential impact of over-reporting on interpretation of adherence results

ACCESS: Sensitivity Analyses Designed to Challenge Results – Excluding Over-Reporters



ACCESS: Sensitivity Analysis Excluding "Over-Reporters" Consistent with Pre-Specified Primary Analysis

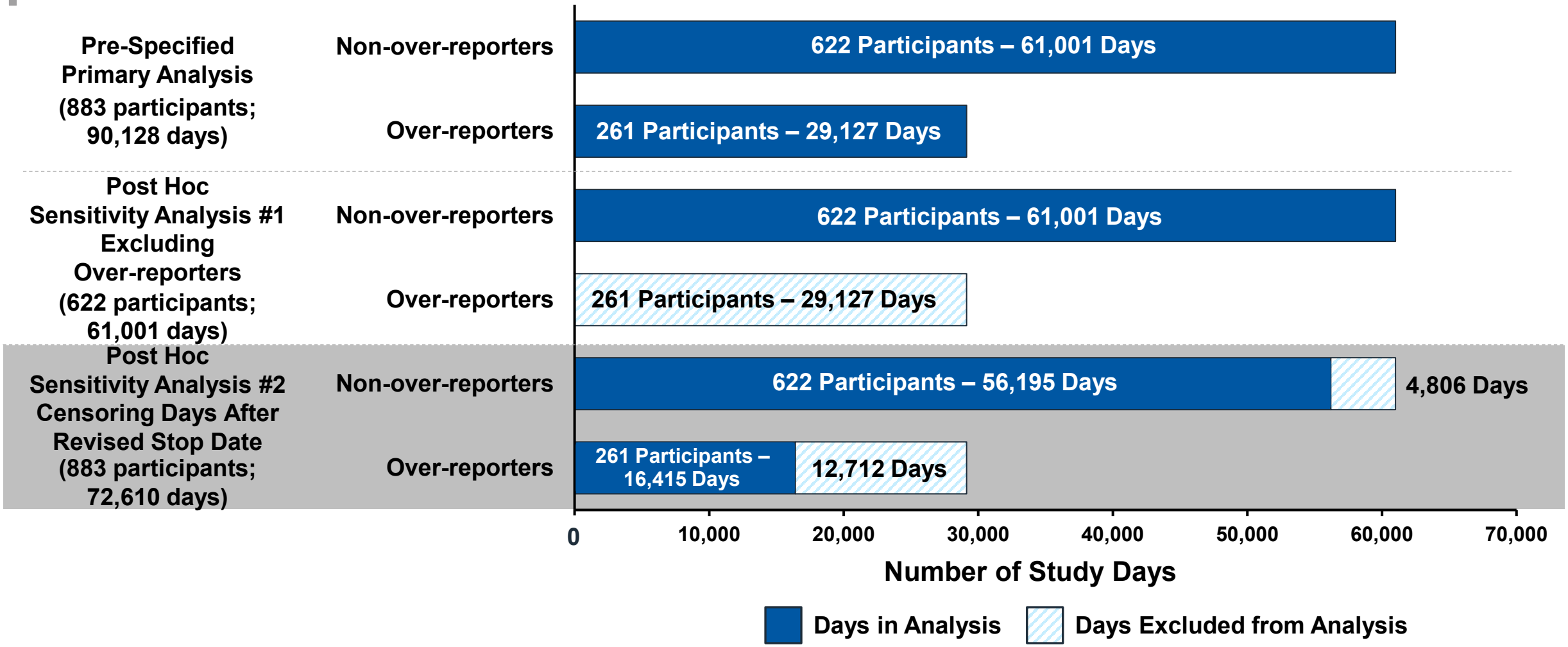
Taking Opill Every Day	Days n / N	Proportion of Days / Participants	% (95% CI)
Primary analysis	83,348 / 90,128	Target Threshold	**92.5%** (92.3, 92.6)
Sensitivity analysis #1, excluding over-reporters	55,967 / 61,001		**91.7%** (91.5, 92.0)
≥ 85% Adherent to Daily Dosing	**Participants**		
Primary analysis	747 / 883	Target Threshold	**84.6%** (82.0, 86.9)
Sensitivity analysis #1, excluding over-reporters	519 / 622		**83.4%** (80.3, 86.3)
Opill Used ± 3 Hours Since Time of Last Dose	**Days**		
Primary analysis	78,946 / 82,465	Target Threshold	**95.7%** (95.6, 95.9)
Sensitivity analysis #1, excluding over-reporters	52,692 / 55,345		**95.2%** (95.0, 95.4)

ACCESS: Sensitivity Analysis #2 Used Revised Stop Date

- Included all participants in User Population but censored their diary data after Revised Stop Date

Pre-specified Primary Analysis	Post Hoc Sensitivity Analysis #2 Censoring Days After Revised Stop Date
Stop Date is date of last day of use reported in e-diary	**Revised Stop Date** is earliest date among: → Date at which drug supply would have been exhausted based on recorded use → Last day of use reported in e-diary → Date participant reported stopping use in nurse interim interviews

ACCESS: Sensitivity Analyses Designed to Challenge Results – Revised Stop Date*



*Revised Stop Date: date at which drug supply ends or participant reported stop date to nurse interviewers, or last day of use reported in e-diary, whichever is earliest

ACCESS: Sensitivity Analysis Censoring Days After Revised Stop Date* Consistent with Pre-Specified Primary Analysis

Taking Opill Every Day	Days n / N	Proportion of Days / Participants	% (95% CI)
Primary analysis	83,348 / 90,128	Target Threshold	**92.5%** (92.3, 92.6)
Sensitivity analysis #2, censoring days after revised Stop Date*	69,061 / 72,610		**95.1%** (95.0, 95.3)
≥ 85% Adherent to Daily Dosing	**Participants**		
Primary analysis	747 / 883	Target Threshold	**84.6%** (82.0, 86.9)
Sensitivity analysis #2, censoring days after revised Stop Date*	793 / 883		**89.8%** (87.6, 91.7)
Opill used ± 3 Hours Since Time of Last Dose	**Days**		
Primary analysis	78,946 / 82,465	Target Threshold	**95.7%** (95.6, 95.9)
Sensitivity analysis #2, censoring days after revised Stop Date*	65,020 / 68,178		**95.4%** (95.2, 95.5)

*Revised Stop Date: date at which drug supply ends or participant reported stop date to nurse interviewers, or last day of use reported in e-diary, whichever is earliest

One FDA Sensitivity Analysis Classified All Over-Reporters as Incorrect

- Assumptions
  - All use days from all over-reporters imputed as failure to take Opill
    - All over-reporters did NOT take Opill on ANY day, however, includes all their days in analysis
- If one assumes participant did not take Opill at all, then participant should not be considered part of User Population

Table 8 FDA Briefing Document

Expert Interpretation of ACCESS Adherence Results

Arthur Stone, PhD

Professor of Psychology, Economics, and Public Policy

Director, Dornsife Center for Self-Report Science

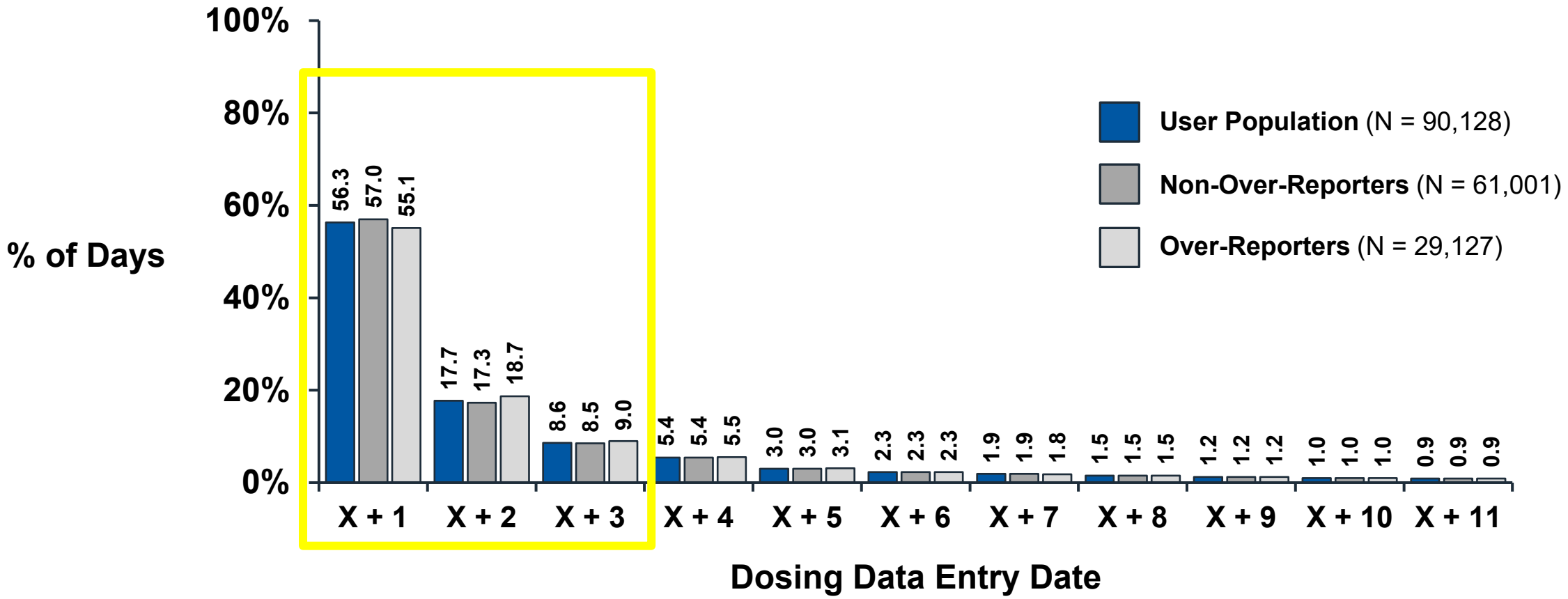
University of Southern California

Emeritus Distinguished Professor of Psychiatry & Behavioral Science, Stony Brook University School of Medicine

ACCESS Meets or Exceeds Standards of Most Other Studies Assessing Adherence

- Used time-stamped electronic diary
  - Form of self-report known to increase accuracy compared to methods such as retrospective questionnaire or paper diary
- Used relatively short recall period compared with published oral contraceptive adherence studies
- Data retrospectively reported up to 11 days in ACCESS
  - Contrasts typical retrospective reporting designs of oral contraceptive studies with recall periods of ≥ 3 months

ACCESS: 80% of Data Reported Within 3 Days in Both Non-Over-Reporters and Over-Reporters



Recall bias not significant issue and not linked to over-reporting

Day X = day participant was reporting on; Earliest possible reporting day is X +1 (i.e., no same day reporting)

Sponsor's Analyses Present Clear and Consistent Picture of Adequate Adherence to Opill

Over-reporting observed in ACCESS does not undermine study results

1. Self-report adherence measures: standard and most common method for assessing medication adherence in clinical research[1]
   - Including studies of oral contraceptive use[2]
     - Such measures convey important information
     - Known that errors in self-reporting occur
2. Over-reporting of adherence to medication occurs but only detected when extraordinary study design methods are incorporated

1. Stirratt, 2015; 2. Hall, 2010

Design Elements in ACCESS Reflect Reasonable and Frequently Encountered Compromises

- Compromises to balance need to minimize interference with participant behaviors with ability to optimally collect data
- Minimization of missing data critical to integrity of 6-month adherence study
- HRA took prudent steps to minimize missing data, some of which allowed over-reporting to occur
  - Reflects compromises in AUT study design

Exact Reasons for Over-Reporting in Self-Adherence Studies Not Clear

- Several potential reasons have been suggested in literature
  - Desire to stay in study[1]
  - Desire to please investigator[2]
- Similarly, specific reasons ACCESS participants over-reported not known
  - Design itself did not encourage over-reporting
  - Over-reporting appears to be function of decisions made by individual participants
- Not plausible DFL contributed to over-reporting

1. Verster, 2019; 2. Nelson, 2017

Totality of Evidence from ACCESS Supports Participants Are Adherent to Taking Opill

- Nothing in dataset nor my own review suggest a basis for questioning validity of data reported by non-over-reporters
- Sensitivity analyses can help understand impact of over-reporting

1 **Excluding over-reporters from analysis is reasonable**

2 **Data from all participants prior to the point they discontinued or ran out of drug is acceptable**

- Imputing over-reporters' complete datasets as failures does not seem reasonable

Totality of evidence from ACCESS supports conclusion that participants are adequately adherent to taking Opill

FDA Discussion Question #2

The ACCESS-UP had improbable dosing results for approximately 1/3 of participants. If FDA were to recommend the Applicant conduct another AUS, what changes to the AUS design would the committee recommend? Consider the following:

a. e-diary design
b. e-diary recall period
c. Participant compensation structure
d. Methods to ensure study instructions regarding e-diary data entry are adequately Comprehended by participants
e. Incorporating a pathway that allows participants to ask their doctor before deciding whether to purchase the study drug
f. Study questions to determine the timing of when participants spoke to a HCP during study

Perspective on FDA Discussion Question #2

e-diary design	▪ Continue using e-diary design to encourage timely and accurate reporting while minimizing cueing
e-diary recall	▪ Continue allowing degree of retrospective reporting to reduce missing data; effective without contributing to over-reporting
compensation	▪ Use similar compensation structure to help minimize missing data; emphasize in diary training that compensation based on diary completion and not pill taking
e-diary instructions	▪ Ensure participants observed using e-diary during training
HCP interaction	▪ Reluctant to ask about this given desire not to alter usual health-related behaviors
Addition	▪ Devise a way to know when pills not available for consumption to reduce possibility of overreporting

Some small design differences in ACCESS trial would not dramatically alter adherence conclusions

ACCESS Data Meets and Exceeds Standards of Most Oral Contraceptive Adherence Studies

- Over-reporting by some participants
  - Consistent with what is known about self-reported adherence
  - Does not appear to be impacted by duration of recall
  - Does not undermine reliability of self-reporting of other participants
  - Not a reason to treat all data from over-reporters as totally non-adherent
  - Does not indicate that confusion about DFL caused over-reporting

ACCESS data adequate to assess adherence to Opill intake

ACCESS Actual Use Adherence Conclusions

Irene Laurora, PharmD

Senior Director, Scientific Affairs, Women's Health

HRA Pharma / Perrigo

FDA Discussion Question #1

Discuss whether consumers are likely to use norgestrel tablet in a safe and effective manner, considering the possibility of unintended pregnancy with incorrect use.

Specifically, discuss whether consumers are likely to adhere to taking the tablet daily at the same time of day, based solely upon the nonprescription labeling without any assistance from a healthcare professional.

Please discuss for the following consumer populations:

a. General population of females of reproductive potential

b. Adolescents

c. Those with limited literacy

d. Those using concomitant products (e.g., anticonvulsant drugs) that may interact with and reduce efficacy of norgestrel tablet

ACCESS: Adolescents Adequately Adhere to Opill in OTC Setting

Taking Opill Every Day	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 to Daily Dosing		**Proportion of Participants ≥ 85% Adherent**	
Primary endpoint	**747 / 883**	Target Threshold	**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		**Proportion of Days**	
Primary endpoint	**78,946 / 82,465**	Target Threshold	**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)

Pre-specified Primary Analysis results

Good Representation of Low Health Literacy in Development Program

Consistent with Recently Switched OTC Products

n (%)	Pivotal DFL 1 LCS N = 624	Pivotal DFL 2 LCS N = 549	Pivotal CIL LCS N = 551	Targeted Cancer SS N = 164	ACCESS SS N = 1,772	ACCESS User N = 883	LCS Final N = 703	Targeted Breast Cancer SS N = 206
Low health literacy population	171 **(27%)**	144 **(26%)**	136 **(25%)**	13 **(8%)**	226 **(13%)**	120 **(14%)**	141 **(20%)**	10 **(5%)**

n (%)	Oxytrol Actual Use Trial Users N = 727	Differin Actual Use Trial Users N = 947
Low health literacy population	89 **(12.2%)**	125 **(13.2%)**

ACCESS: Those with Limited Health Literacy Adequately Adhere to Opill in OTC Setting

Taking Opill Every Day	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)
≥ 85% Adherent to Daily Dosing		**Proportion of Participants ≥ 85% Adherent**	
Primary endpoint	**747 / 883**	Target Threshold	**84.6%** (82.0, 86.9)
Low health literacy	**98 / 120**		**81.7%** (73.6, 88.1)
Opill used ± 3 hours since time of last dose		**Proportion of Days**	
Primary endpoint	**78,946 / 82,465**	Target Threshold	**95.7%** (95.6, 95.9)
Low health literacy	**10,927 / 11,517**		**94.9%** (94.5, 95.3)

Pre-specified Primary Analysis results

ACCESS Adherence Conclusion

Totality of evidence from ACCESS study demonstrates women adequately adhere to taking Opill in OTC setting

Involvement of HCP is not necessary to ensure good adherence

Supports that women would achieve intended benefit in OTC setting

Clinical Interpretation of ACCESS Results and Considerations Around Effectiveness

Stephanie Sober, MD, MSHP

Global Lead Medical Affairs, Women's Health

HRA Pharma / Perrigo

Perception of POP Effectiveness

- Data from 1970s and early 1980s
  - Showing that ovulation is less suppressed in POP users[1,2]
  - Small pharmacokinetic studies show low serum levels of progestin remain after 24 hours from intake[3,4]
    - Extrapolated to create concept of “three-hour window”

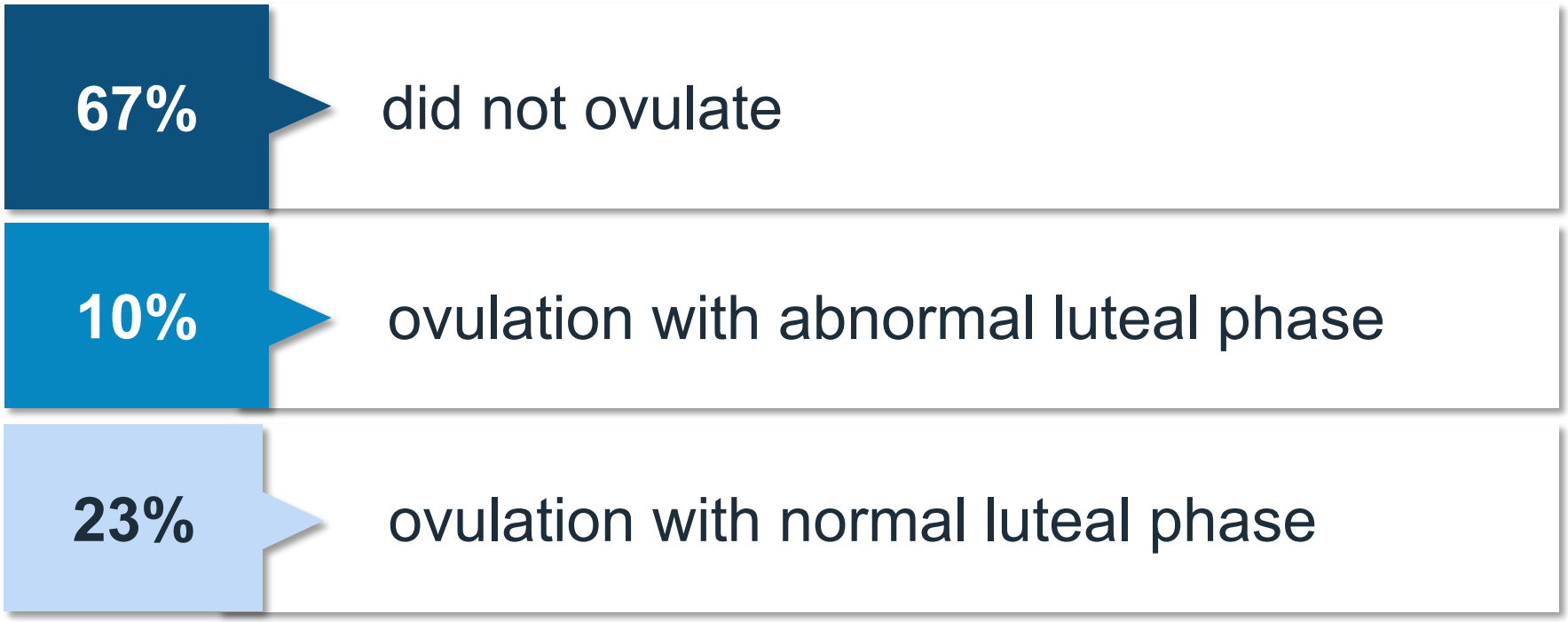
1. Landgren, 1980; 2. Landgren, 1981; 3. Prasad, 1979; 4. Weiner, 1976

Use of Well-Established Surrogate Markers to Measure Contraceptive Effectiveness in Delayed Pill Intake Study

- Deliberate non-adherence study with pregnancy endpoint not feasible
- Used two well-characterized tools to assess ovulation and cervical mucus
  - WHO cervical mucus score
  - Hoogland score for ovarian function
- Not validated with pregnancy as endpoint, but both widely used and accepted
  - Since 2008, PubMed lists many studies that employ Hoogland score
    - Studies on 9 different contraceptive methods[1]
    - 2 studies of effect of obesity[2]
    - 4 studies on drug-drug interactions on theoretical contraceptive efficacy[3]
  - Also used in several pharmacodynamic studies of deliberately missed COCs[4]

1. Duijkers, 2021; Klipping, 2012; Klipping, 2008; Duijkers, 2015; Duijkers, 2022; Endrikat, 2008; Seidman, 2015; Spona, 2010; Rible, 2009
2. Westhoff, 2014; Westhoff, 2010; 3. Schultze-Mosgau, 2021; Banh, 2020; Biswal, 2014; Heger-Mahn, 2014; 4. Zapata, 2013

Key Findings from Delayed Pill Intake Study: Ovulation and Cervical Mucus During Correct Use



Fertile cervical mucus absent throughout entire cycle of correct use

Glasier, 2022; Han, 2022; Glasier, 2023

Key Findings from Delayed Pill Intake Study: Ovulation and Cervical Mucus in Delayed and Missed Pill Cycles

- When pill intake delayed by 6 hours or missed altogether
  - % of women in whom ovulation was suppressed
  - Frequency of fertile cervical mucus

Not significantly different from correct use

Opill can be expected to effectively protect against pregnancy even if a woman takes her daily pill late or misses it entirely

Opill Expected to Effectively Protect Against Pregnancy Even After Delayed or Missed Pill

- Likely wider window exists for maintaining efficacy if pill is delayed or missed
- Proposed OTC label maintains 3-hour window language
- ACCESS data demonstrated excellent pill taking behavior
  - 97% either took Opill daily or took appropriate mitigating action
  - 68% of episodes of missed pills were a single missed day
- Potential clinical consequence of nonadherence in ACCESS would be expected to be further minimized

ACCESS: Few Pregnancies Observed During Opill Use

- Behavioral study related to consistent daily use of Opill
- Not an efficacy study

Participants in Safety Population	955
Pregnancies reported at any time during study	14
Conception occurred before enrollment / before participant took Opill	3
Conception occurred during use of Opill	6
Conception after discontinued use of Opill	5

- FDA Analysis included 9 pregnancies during use (included conception that occurred during use of Opill or within 7 days after discontinuation)

Safety population is all participants who enrolled in Use Phase and had access to study drug regardless of whether they used Opill

Available Evidence Suggests Effectiveness Is Not Affected by Body Weight or BMI

- Cochrane review concluded data did not indicate association between higher BMI or weight and effectiveness of hormonal contraceptives[1]
  - Evaluated 12 studies for impact of BMI/body weight on efficacy of hormonal contraceptives
- CDC MEC[2] have no restrictions for POP use among women with BMI ≥ 30 kg/m^2
- Healthcare providers do not prescribe different dose regimen for hormonal contraceptives, including POPs, to overweight or obese women

1. Lopez, 2016; 2. Curtis, 2016 [CDC Medical Eligibility Criteria for Contraception]

Data from Delayed Pill Intake Study and ACCESS Do Not Support Increased Risk of Pregnancy Among Overweight/Obese Women

- Delayed Pill Intake Study
  - No difference in effect of deliberate non-adherence on cervical mucus or ovarian activity in overweight or obese subjects (n = 18) compared with normal weight subjects (n = 28)
- ACCESS
  - Distribution of weight/BMI representative of that in general US female population
  - Higher BMI not associated with increased risk of pregnancy

Totality of evidence supports effectiveness of Opill is not affected by weight/BMI

Actual Use: When Consumer Should Take Action During Use

Other Information for Women During Use of Opill

When using this product

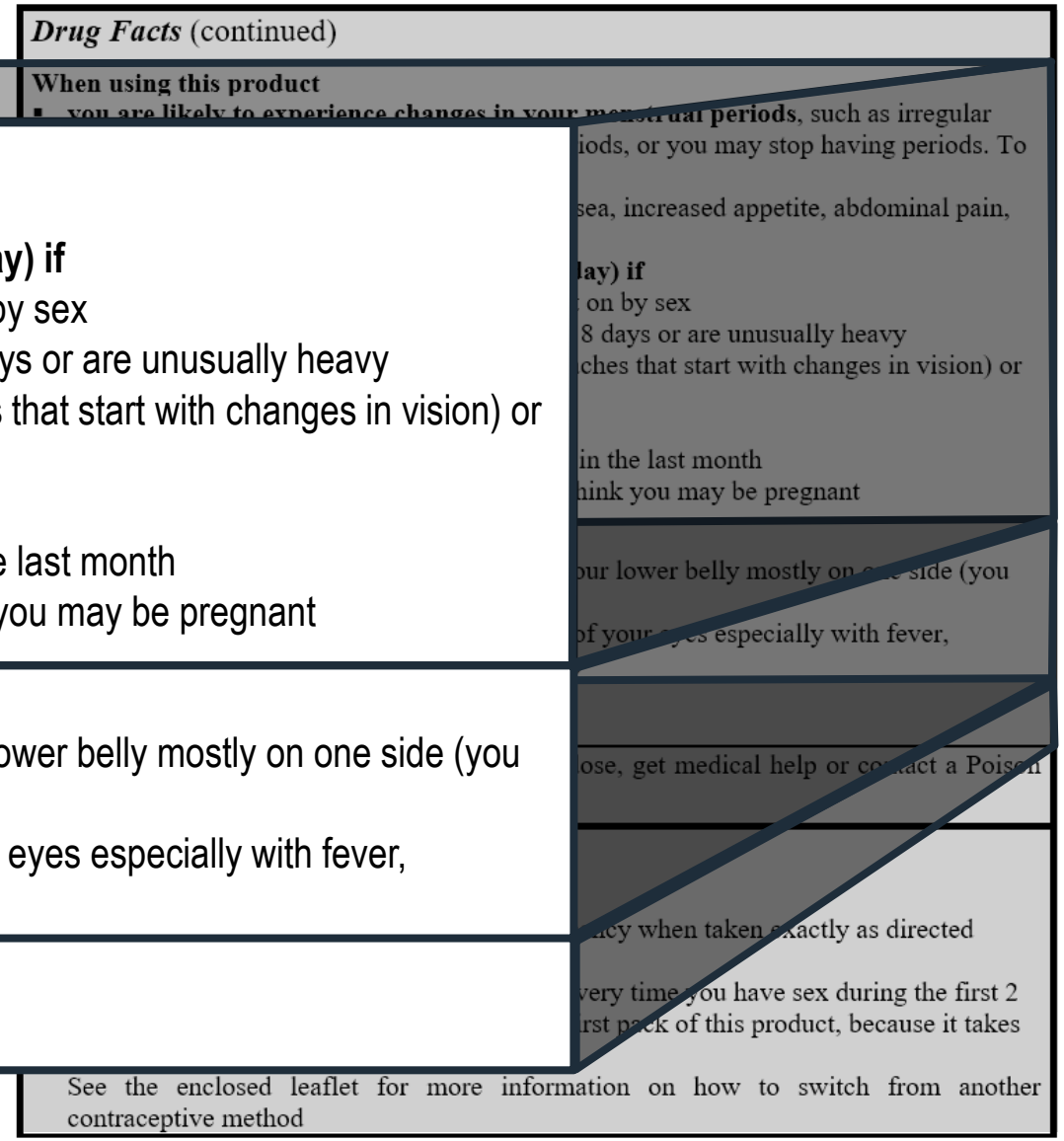
- …
- **talk to your doctor (but continue taking every day) if**
  - you have repeated vaginal bleeding brought on by sex
  - you start having periods that last more than 8 days or are unusually heavy
  - you start having migraines with aura (headaches that start with changes in vision) or migraine headaches 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



ACCESS: 'Ask a Doctor' Events Uncommon
No Signal of Clinical Concern for OTC Use

- Given inherent safety profile, situations in which consumers should take action during Opill use were uncommon in ACCESS
- In many instances, symptoms resolved spontaneously obviating need to contact HCP

Data show no signal of concern for use in OTC setting and consumers understand key messages

Women of Reproductive Age Can Use Opill as Directed in OTC Setting

- Appropriately self-select whether Opill is right for them
- Take Opill as directed every day at same time
- Few pregnancies occurred while taking Opill
- Consult healthcare provider, take pregnancy test, and/or stop use in response to certain new symptoms are uncommon situations

Opill is appropriate for OTC use

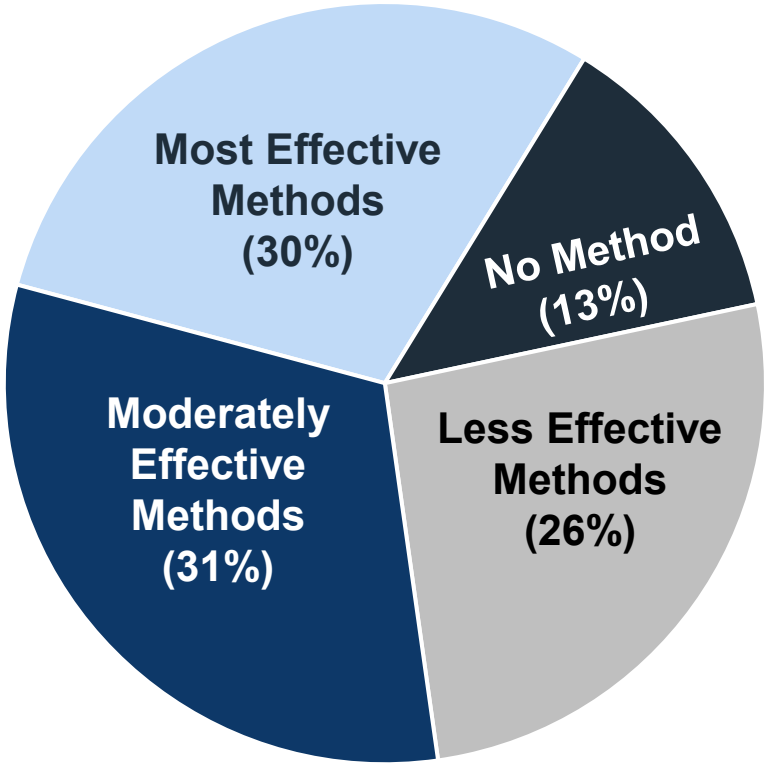
Clinical Perspective

Anna Glasier, MD, DSc, OBE

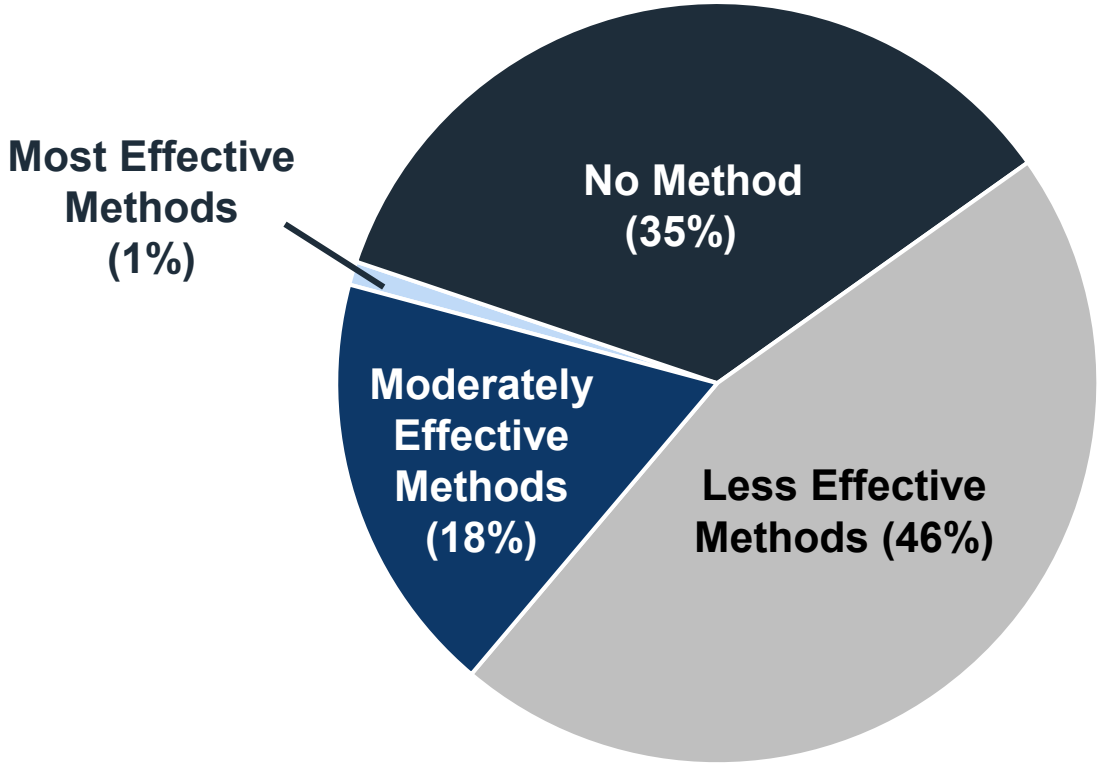
Professor at Edinburgh and London Universities

Women Using Less Effective Contraceptives Would Benefit Most From Opill OTC

US Population*

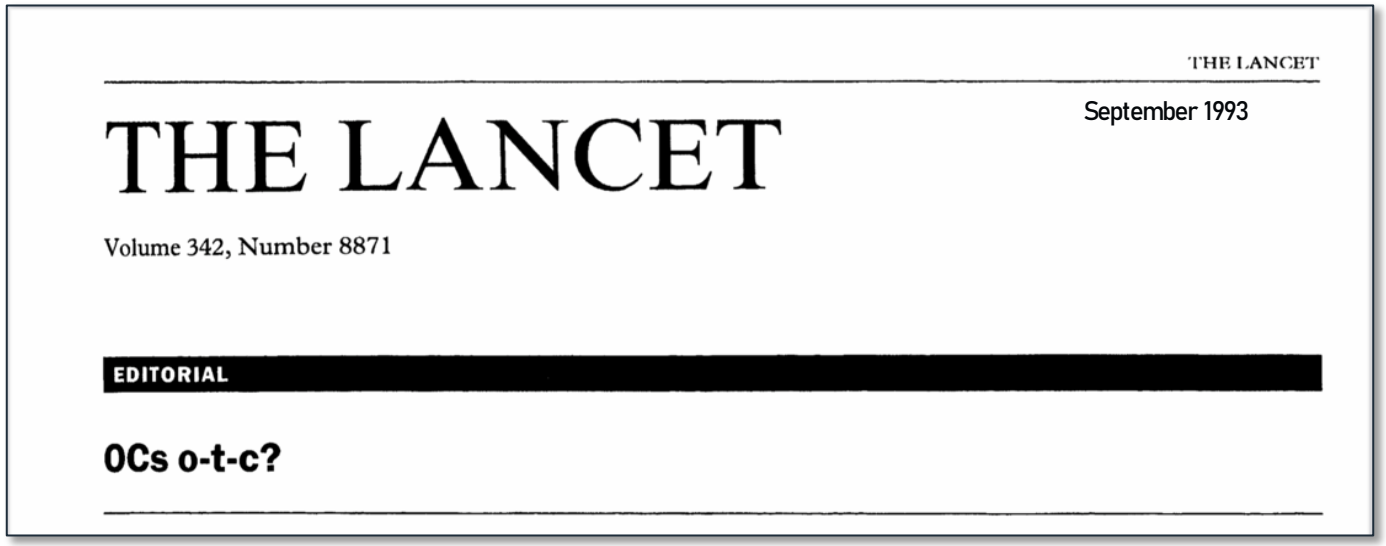


ACCESS User Population Before Enrollment



*Proportion of US women aged 15-49 using different contraceptive according to NSFG 2017-2019 (Pinney, 2022)

Idea of OTC Oral Contraception Not New



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EDITORIAL

OCs o-t-c?

ACOG
The American College of Obstetricians and Gynecologists

AMA
AMERICAN MEDICAL ASSOCIATION

AMERICAN ACADEMY OF FAMILY PHYSICIANS
STRONG MEDICINE FOR AMERICA

SAHM
SOCIETY FOR ADOLESCENT HEALTH AND MEDICINE

NASPAG
North American Society for Pediatric and Adolescent Gynecology

Incremental Benefits of OTC Opill Far Outweigh Potential Incremental Risks

Incremental Risks

Effective use?

- OTC adherence same as Rx adherence
- Opill use simple
- In ACCESS vast majority of women adhered to label directions and when not, took appropriate mitigating action
- Missed pills mainly due to supply issues at site
- Number of pregnancies in line with typical use failure rate

Incremental Benefits

Incremental Benefits of OTC Opill Far Outweigh Potential Incremental Risks

Incremental Risks

Safe use?

- Situations when women need to see doctor are uncommon
- OTC users make same decisions as Rx users
- Abnormal vaginal bleeding common, generally resolves, and women generally do not see HCP

Incremental Benefits

Incremental Benefits of OTC Opill Far Outweigh Potential Incremental Risks

Incremental Risks

Self-select?

- Very small number of women may use POP when should not
- Very few women with breast cancer likely to use hormonal contraception
- Almost all women with breast cancer made correct decision not to use

Incremental Benefits

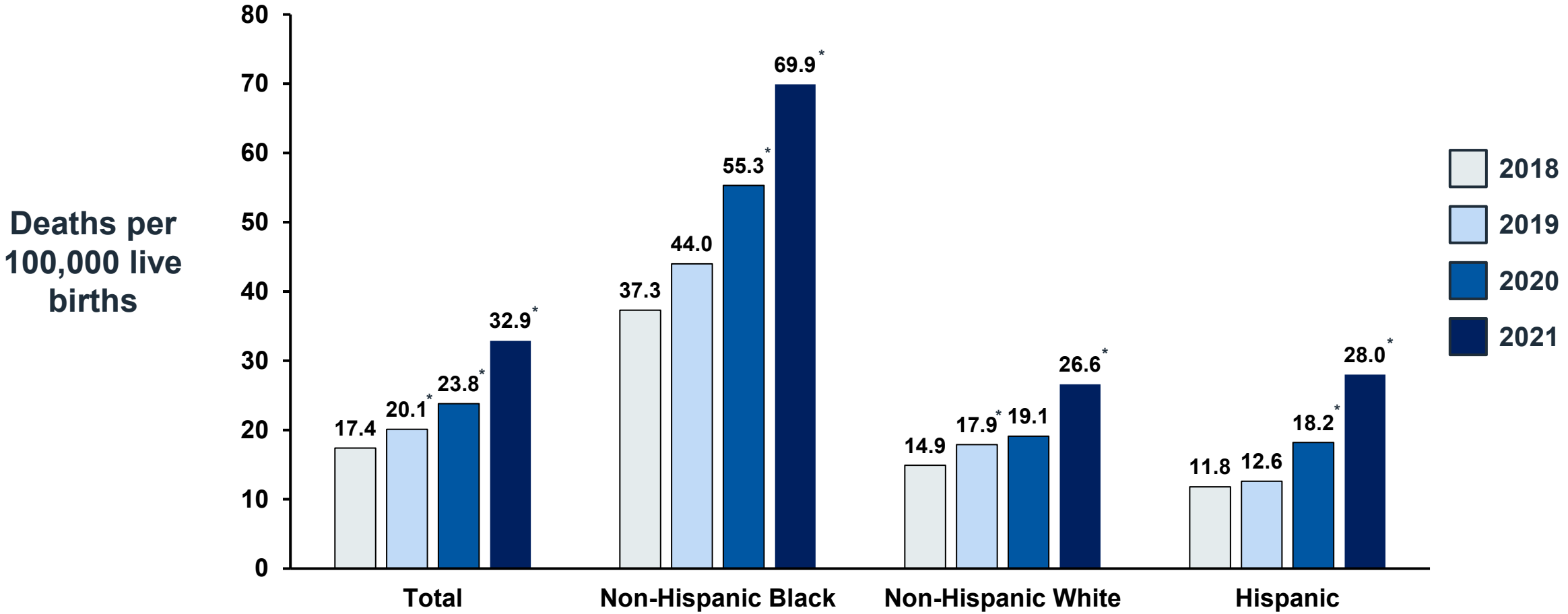
Increase access and reduces barriers

Provide women more effective choices and more autonomy

Prevent unintended pregnancy for large number of women

- Reduce maternal and neonatal morbidity
- Social and economic benefits

Maternal Mortality in US Significantly Rising Each Year



* Statistically significant increase from previous year ($p < 0.05$)

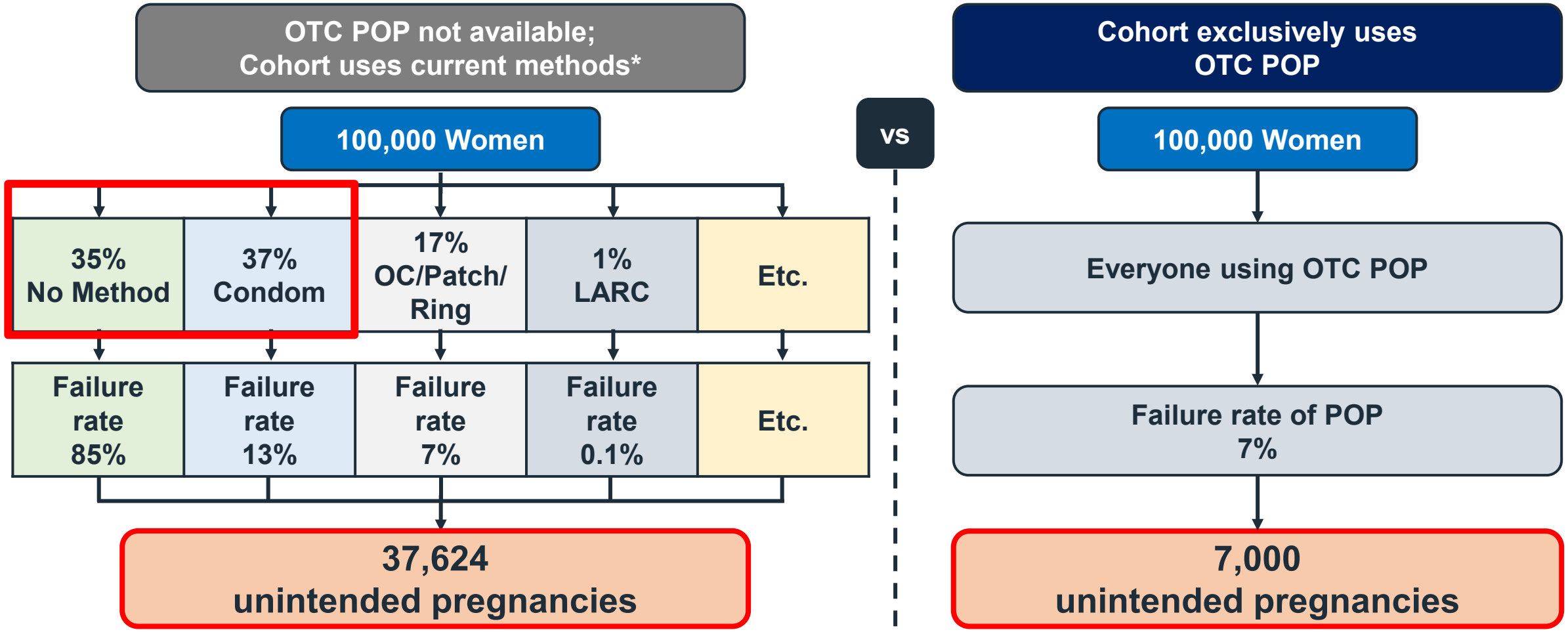
1. NCHS, 2023

Several Models of Impact of OTC Availability on Rate of Unintended Pregnancy

- All studies show positive public health impact[1]
- Data from ACCESS study to model potential impact on unintended pregnancy
  - For first time, our model incorporates characteristics of population who did purchase an OTC POP[2]
  - Model meant to estimate magnitude of impact on women who will elect to switch to Opill from their current methods

1. Wollum, 2020; Foster, 2015; 2. Guillard, 2023

Model Shows Significant Reduction in Unintended Pregnancies in Women Who Choose to Switch to OTC Opill



*Proportion of methods derived from ACCESS Guillard, 2023

81% reduction in unintended pregnancies in women who switch to OTC POP use

FDA Voting Question

Is there adequate information to conclude that consumers will be likely to properly use norgestrel tablet such that the benefits of making this available for nonprescription use (access without needing to interact with a healthcare professional), exceed the risks (contraceptive failure due to inadequate adherence, using this medication when they have a contraindication to its use, failure to see a health care professional when appropriate)?

Opill (Norgestrel 0.075 mg Tablets) for Rx-to-OTC Switch

May 9, 2023

HRA Pharma / Perrigo

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee

BACKUP SLIDES SHOWN

Risk of Breast Cancer Death With OC OTC Use is Lower Than Risk of Pregnancy Related Death Amongst Women Not Using OCs

- RR for current or recent users is of POPs or combined OCPs approximately 1.2[1]
- Current/recent users of OCs have 1 excess BC/7,690 years of use (13/100,000 person years)[1]
- BC case survival rates of 85%[2] translates ≈ 2 excess BC deaths/100,000 users annually
- Maternal death rates of 20/100,000 pregnancies[3] => avoiding 7.5 maternal deaths
- Plus additional benefit of preventing pregnancies

OC: oral contraception; BC: breast cancer

1. Morch et al. 2017; 2. ACS, 2022; 3. CDC, 2020

HRA 2019 Type C Meeting Briefing Book Submitted to the FDA

Selection Decision: Page 19

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

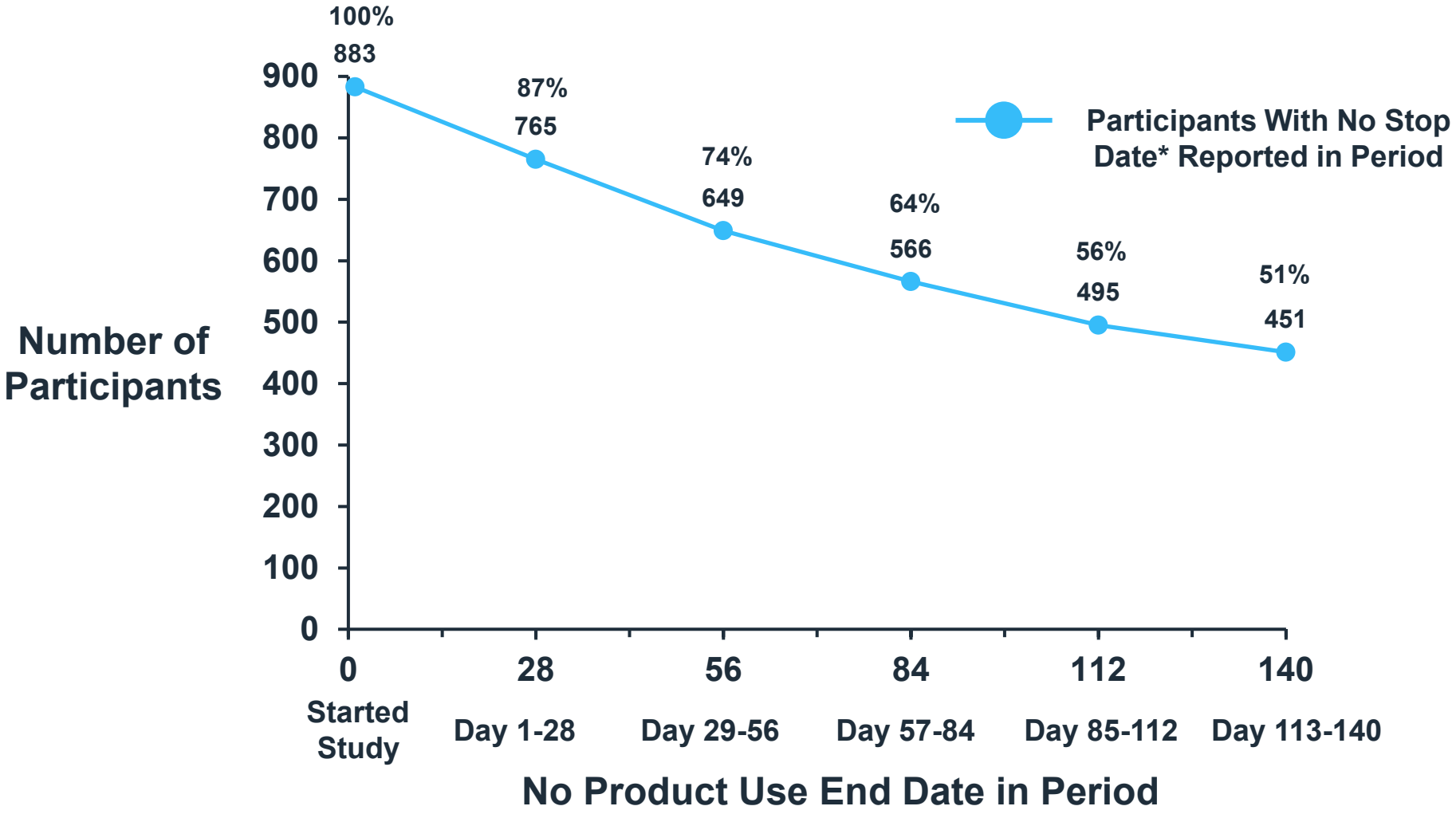
Question 2: Does the Agency have comments on the proposed definition of study endpoints of the CHOICE study as summarized in Section 15.3 and provided in full in the SAP in Appendix 16.2 (which includes the operationalized definition)?

CHOICE: AUT name used in Draft Protocol before study was renamed ACCESS

Opill OTC Label Iteratively Tested Throughout Comprehensive Label Development Program

*Final Pivotal DFL LCS = Final LCS

ACCESS: Half of Participants Reported Use of Opill at 6 Months in Study But Continuation Likely Lower in ACCESS vs Real OTC Setting Due to Barriers to Accessing New Packs



*Stop Date: last reported use of product in participant's E-diary

Continuing Use Rate of Opill Expected to be Higher in the OTC Marketplace vs ACCESS

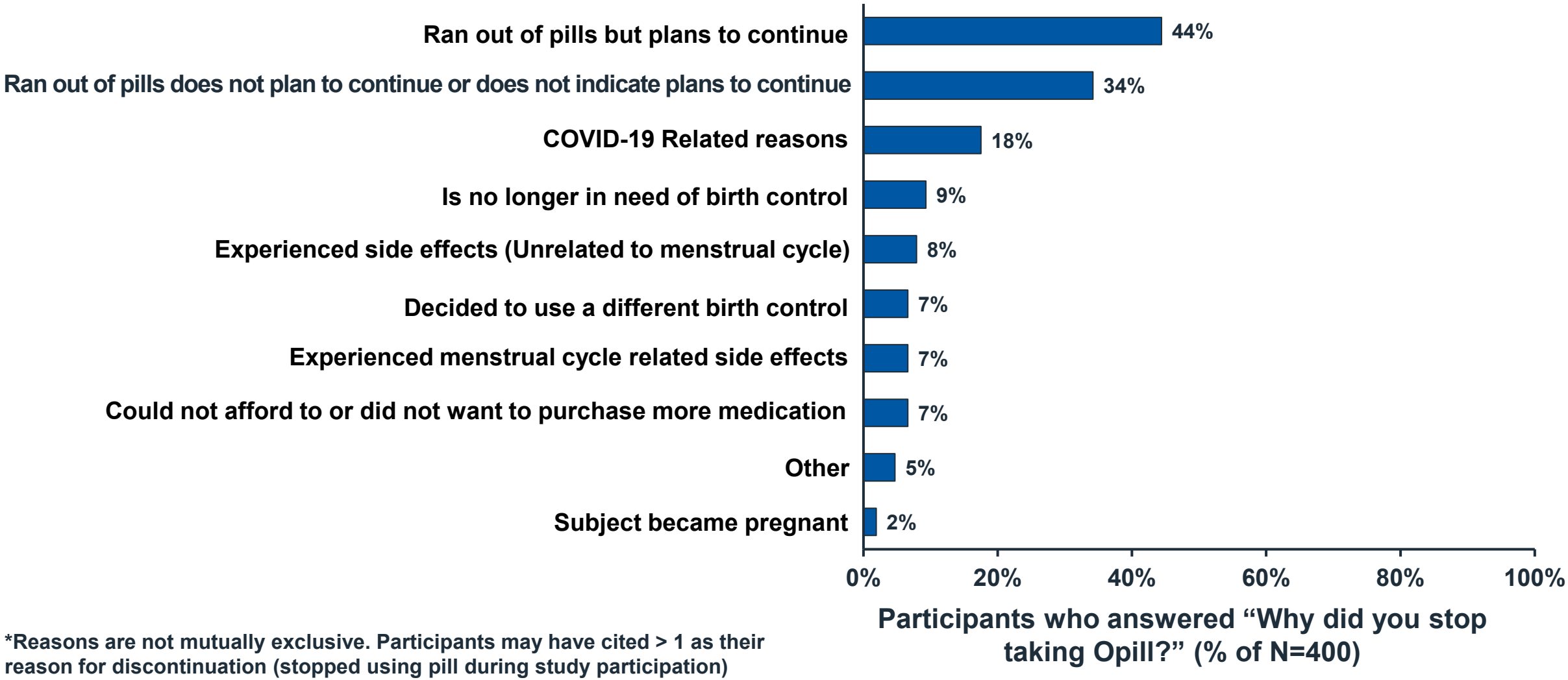
- Continuing use rate data:

Method	Timepoint	Percentage of Women[1]
Trussell, 2018	**1 year**	**67%**
ACCESS (user population)	**6 months**	**51%**
ACCESS (user population – probable dosing)	**6 months**	**50%**

- In ACCESS, 51% were still using the POP at the end of six months
  - Continuation was likely lower versus a real OTC setting as participants had to return to a single study site up to 35 miles from their home to purchase Opill vs the multiple retail sites that will exist in a real OTC marketplace

1. Raymond, 2018

ACCESS: Most Common Reason for Discontinuing Use Was Running Out of Pills



*Reasons are not mutually exclusive. Participants may have cited > 1 as their reason for discontinuation (stopped using pill during study participation)

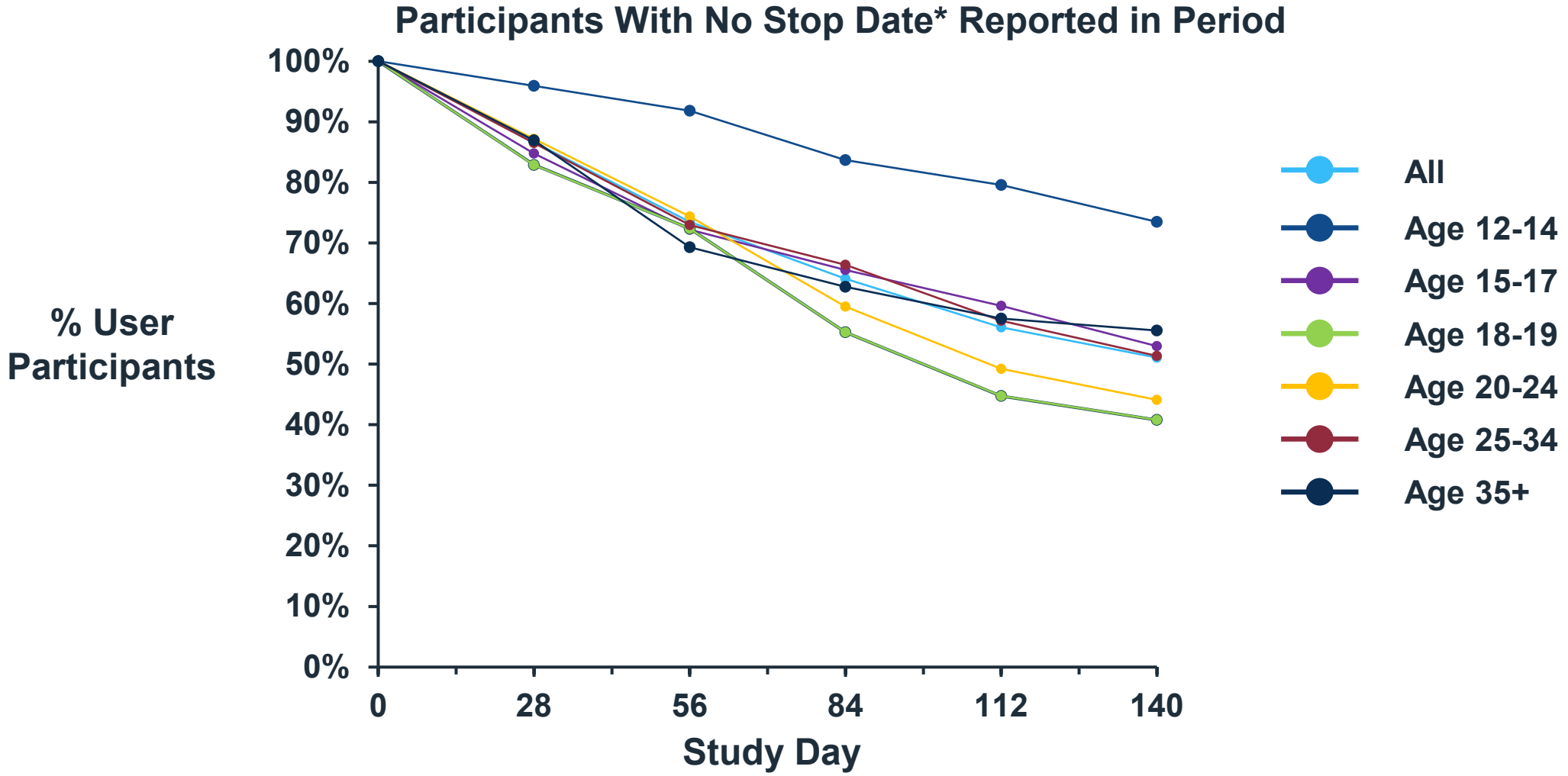
ACCESS: AEs Consistent with Known Safety Profile of Opill

Preferred Term	All Participants (Safety Population) N = 955
Participants with AEs	355 **(37%)**
Metrorrhagia	49 **(5%)**
Menorrhagia	49 **(5%)**
Menstruation irregular	30 **(3%)**
Menstruation delayed	29 **(3%)**
Off label use	24 **(3%)**
Urinary tract infection	22 **(2%)**
Polymenorrhea	19 **(2%)**
Influenza	16 **(2%)**
Nasopharyngitis	16 **(2%)**
Sinusitis	13 **(1%)**
Unintended pregnancy	13 **(1%)**
Acne	11 **(1%)**
Amenorrhea	10 **(1%)**

ACCESS: Most Common AEs Consistent With Known Safety Profile of Opill

Primary System Organ Class (SOC)	All Participants (Safety Population) N = 955
Participants with AEs	355 (37.2%)
Infections and infestations	99 (10.4%)
Nervous system disorders	30 (3.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1%)
Blood and lymphatic system disorders	1 (0.1%)
Immune system disorders	1 (0.1%)
Metabolism and nutrition disorders	4 (0.4%)
Psychiatric disorders	10 (1.0%)
Eye disorders	1 (0.1%)
Cardiac disorders	1 (0.1%)
Vascular disorders	2 (0.2%)
Respiratory, thoracic and mediastinal disorders	5 (0.5%)
Gastrointestinal disorders	31 (3.2%)
Skin and subcutaneous tissue disorders	16 (1.7%)
Musculoskeletal and connective tissue disorders	3 (0.3%)
Pregnancy, puerperium and perinatal conditions	13 (1.4%)
Reproductive system and breast disorders	185 (19.4%)
General disorders and administration site conditions	5 (0.5%)
Investigations	9 (0.9%)
Injury, poisoning and procedural complications	42 (4.4%)
Surgical and medical procedures	2 (0.2%)

ACCESS: Continuation Rate was Generally Consistent Across Age Subgroups With > 40% in Each Subgroup Reporting Use By 6 Months in Study



*Stop Date: last reported use of product in participant's E-diary