Agile Patch (AG200-15)

October 30, 2019

Agile Therapeutics, Inc.

Bone, Reproductive, and Urologic Drugs Advisory Committee

Introduction

Geoffrey Gilmore

Senior Vice President

Agile Therapeutics, Inc.

Need for More Contraceptive Options to Fit Individual Lifestyles, Evolving Needs

- Unintended pregnancy: significant public health problem
- Another transdermal system could provide women new, non-invasive method
- Data show many women want a contraceptive patch[1]
  - Only available patch delivers ~56 mcg of estrogen
- Lower-dose patch benefits women seeking transdermal option

Focus on approvability of Agile Patch as that new option

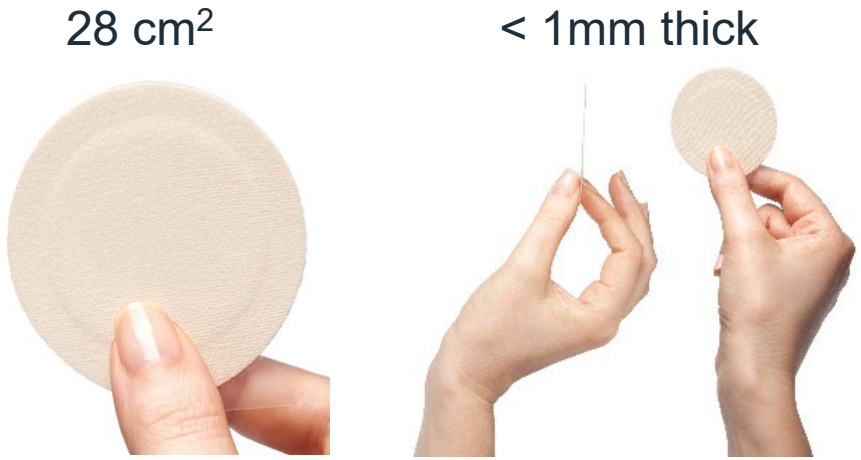
1. IMS National Prescription Audit

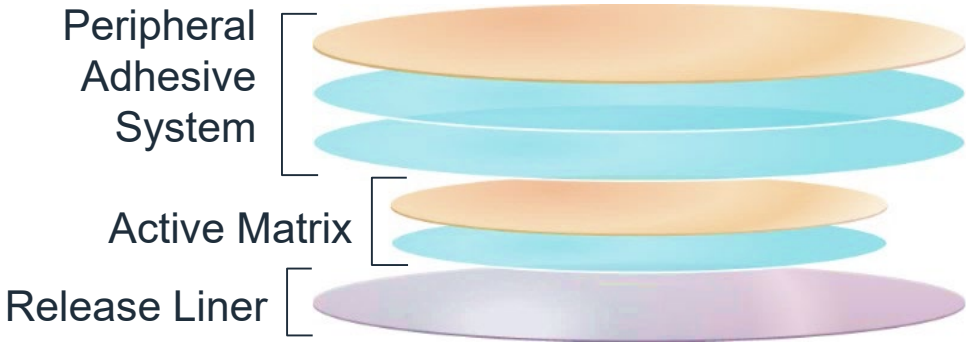
Key Topics for Discussion

Topics	Points to Consider
1. Low-dose CHC	• Varying definitions of low-dose estrogen • Agile Patch delivers ~30 mcg daily of ethinyl estradiol (EE) • Only contraceptive patch available delivers ~56 mcg daily EE
2. Unmet Need	• FDA considers an unmet need in terms of serious conditions • Contraception needs defined by gaps in options
3. Prespecified Criterion in Contraceptive Trials	• Contraceptive trials not designed to meet a specific objective • Study 23 designed to estimate Pearl Index, regulatory standard for evaluating efficacy with tight confidence interval
4. Pearl Index: Upper Bound of 95% CI	• UB ≤ 5 based on historical contraceptive studies • Limited utility for evaluating more contemporary trials, like Study 23

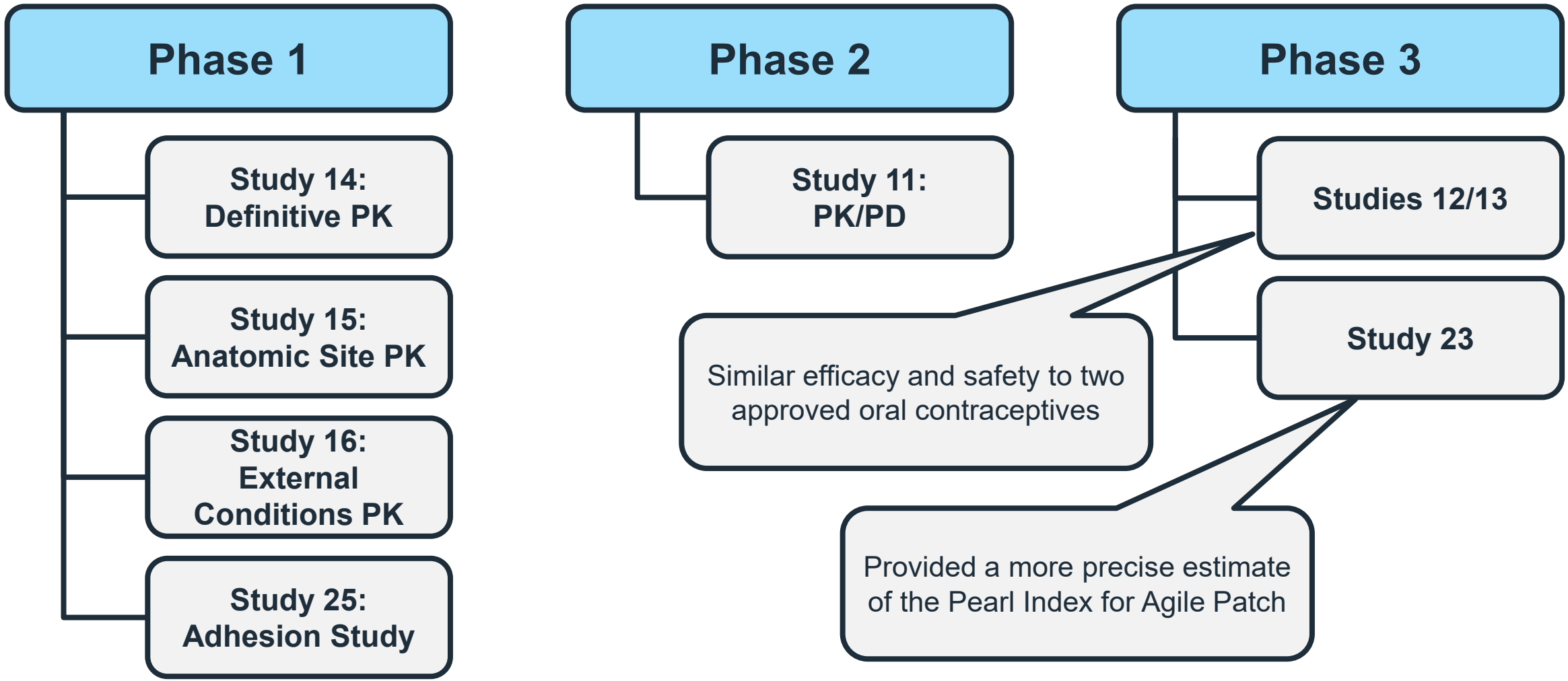
Combination Hormonal Contraceptive (CHC) with Levonorgestrel (LNG) + Ethinyl Estradiol (EE)

- Multi-layered transdermal system
- Well-known ingredients with long history and demonstrated safety profiles
- Daily hormone exposures
  - ~30 mcg EE, 120 mcg LNG
- Applied, changed weekly for 3 consecutive weeks, followed by 4th week of no patch





Robust Clinical Development Program



Study 23: Efficacy and Safety by BMI

Category	BMI (kg/m^2)	Study Population	Pearl Index	Upper Bound 95% CI	VTEs
Overall	**15.1 – 63.0**	**100%**	**5.83**	**7.21**	**4**
Non-obese	< 30	65%	4.34	5.82	0
Obese	≥ 30	35%	8.64	11.50	4

Proposed Indication

- *For use by females of reproductive potential to prevent pregnancy*
  - Limitation of Use: Agile Patch has demonstrated reduced effectiveness in women who weigh 202 lbs (92 kg) or more and/or have a BMI of 30 kg/m^2 or more

Agenda

Introduction	**Geoffrey Gilmore** Senior Vice President Agile Therapeutics, Inc.
Need for More Contraceptive Options and Evolving Clinical Trial Environment	**David Portman, MD** CEO and CMO, Sermonix Pharmaceuticals Founder, Director Emeritus, Columbus Center for Women's Health Research and Adjunct Instructor, Department of OBGYN, Wexner Medical Center, The Ohio State University
Study Design, Efficacy and Safety	**Elizabeth Onyemelukwe Garner, MD, MPH** Chief Medical Officer 2014-2019 Consultant Agile Therapeutics, Inc.
Clinical Perspective	**David Portman, MD**

Additional Experts

Janet Wittes, PhD
Statistics Collaborative, Inc.
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Brian Furmanski, PhD
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Nuventra, Inc.

Need for More Contraceptive Options and Evolving Clinical Trial Environment

David Portman, MD

CEO and CMO, Sermonix Pharmaceuticals
Founder, Director Emeritus, Columbus Center for Women's Health Research and Adjunct Instructor, Department of OBGYN, Wexner Medical Center, The Ohio State University

Seminal Paper on Contraceptive Clinical Trials, "The Creeping Pearl"

ELSEVIER

Contraception

Contraception 88 (2013) 604–610

Review Article

The creeping pearl: why has the rate of contraceptive failure increased in clinical trials of combined hormonal contraceptive pills?☆,☆☆,★,★★

James Trussell[a,b,*], David Portman[c,d]

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[b]The Hull York Medical School, Hull, England HU6 7RX
[c]Columbus Center for Women's Health Research, Columbus, OH 43213
[d]Department of Obstetrics and Gynecology, Ohio State University College of Medicine, Columbus, OH 43213

Received 7 February 2013; revised 4 April 2013; accepted 7 April 2013

Abstract

Background: Despite several drawbacks, the Pearl Index continues to be the most widely used statistical measure of contraceptive failure. However, Pearl indices reported in studies of newer hormonal contraceptives appear to be increasing.
Study Design: We searched PubMed and Medical Intelligence Solutions databases for prospective trials evaluating oral contraceptive (OC) efficacy to examine potential factors that could contribute to increasing Pearl indices.
Results: Numerous potential factors were identified, including an increased rate of failures of newer OCs, deficiencies in methods of calculating contraceptive failure rates, differences in study design and changes in patient populations resulting in increased rates of contraceptive failures due to the inappropriate or inconsistent use of the method.
Conclusion: The two most likely important contributors to the increase in Pearl indices are more frequent pregnancy testing with more

Contraception and Clinical Trials

1. Discuss needs of women and health care providers when exploring contraceptive options
2. Review evolving contraceptive clinical trial environment

Nearly All US Women Will Use Contraception at Some Point in Lifetime[1]

- Women weigh various factors when selecting a contraceptive method[2]
  - Effectiveness
  - Dose
  - Hormonal vs non-hormonal methods
  - Delivery route and level of invasiveness
  - Frequency of administration
- No single method for all women[3]
  - Choices vary person-to-person, within a woman's reproductive years
- Consistency more likely when contraceptive choice fits a woman's lifestyle[4]

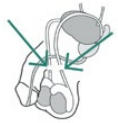
1. CDC National Survey of Family Growth 2011-2015; 2. Chen et al., 2019; 3. Mansour, 2014; 4. Grady et al., 2002

Contraceptive Options Tiered Based on Effectiveness

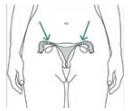
More Effective

TIER 1
< 1 pregnancy per 100 women in one year
(Sterilization, LARC)

Implant



Vasectomy

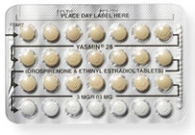


Tubal Occlusion

IUD

TIER 2
4-7 pregnancies per 100 women in one year
(Hormonal)

Injectable



Pill

Patch

Ring

TIER 3
> 13 pregnancies per 100 women in one year
(Barrier / Non-Hormonal)

Male Condom

Diaphragm

Female Condom

Sponge

Spermicides

Fertility Awareness-Based Methods

Withdrawal

Less Effective

≥ 85 pregnancies per 100 women in 1 year

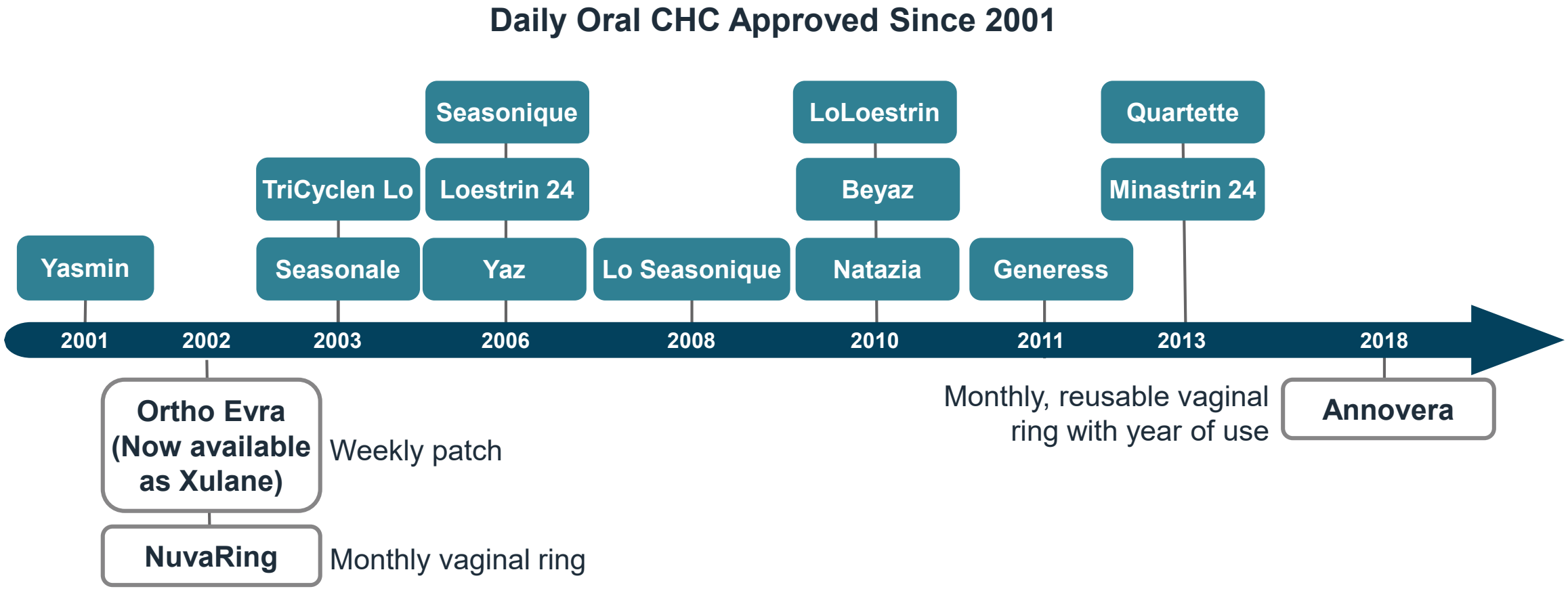
No birth control

Adapted from Contraceptive Technology, 2018

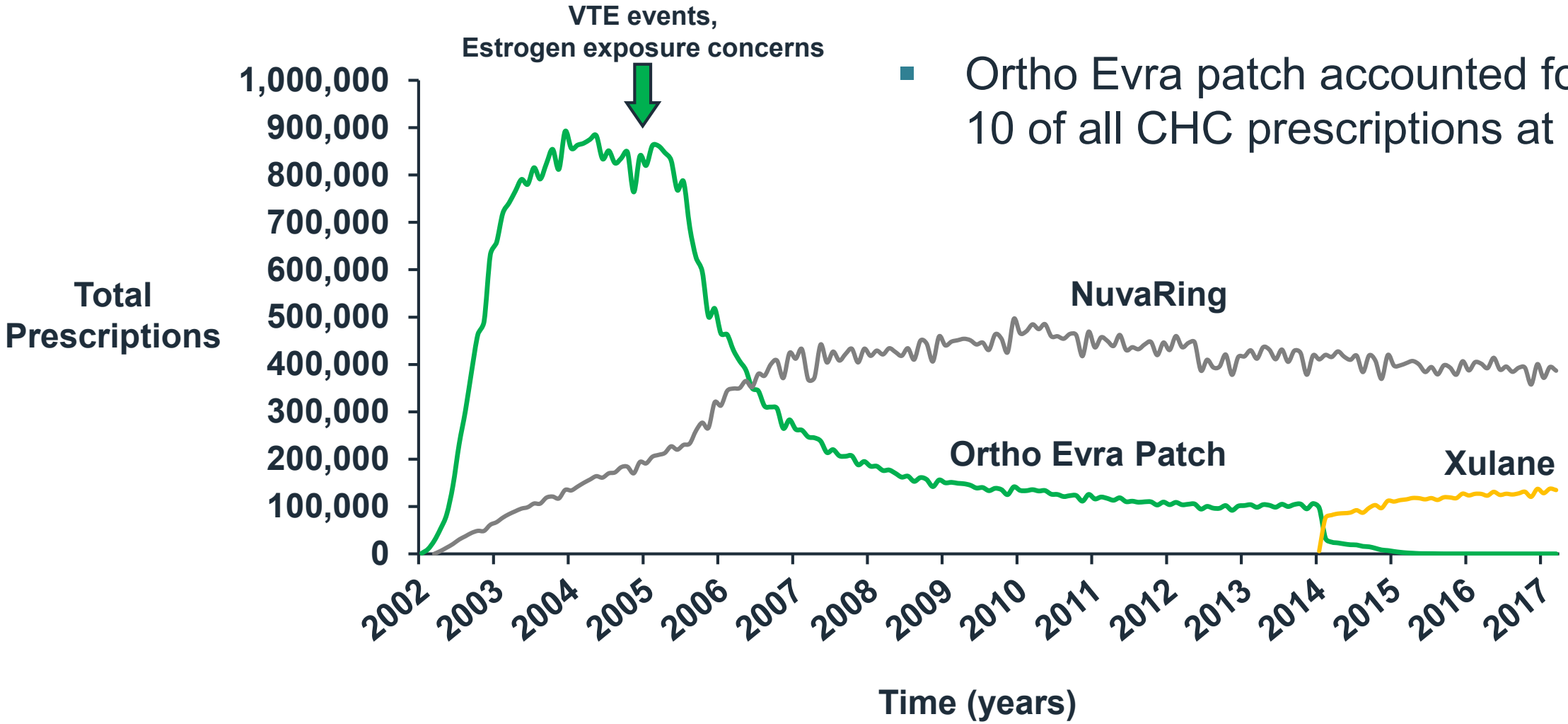
Combined Hormonal Contraceptives (CHCs) Contain Progestin and Estrogen Components

- Levonorgestrel + ethinyl estradiol commonly-used combination
- Progestin prevents pregnancy
  - Differing pharmacologic, tolerability issues
- Estrogen added for cycle control, optimize bleeding profile
  - Most contain ≤ 35 mcg
- Lower estrogen minimizes side effects such as breast tenderness, headache, nausea
- Doctors seldom prescribe CHCs with 50 mcg/day of estrogen

Only Three Non-Daily CHC Methods Available



CHC Use Patterns Demonstrate Interest in Non-Oral, Non-Daily Methods



- Ortho Evra patch accounted for > 1 in 10 of all CHC prescriptions at peak

IMS National Prescription Audit

Advantages of Transdermal Drug Delivery for Some Women

- Controlled release offers potential to reduce incidence, severity of side effects
- Avoids reduced bioavailability with oral administration
- May help women who have difficulty or avoid taking oral medication
- Potential to reduce burden associated with daily OCs
  - 49% contraception users prefer non-daily method[1]
  - 52% frustrated with taking pill daily[1]

1. Mansour, 2014

Pearl Index (PI): Most Common Regulatory Endpoint for Contraceptive Efficacy

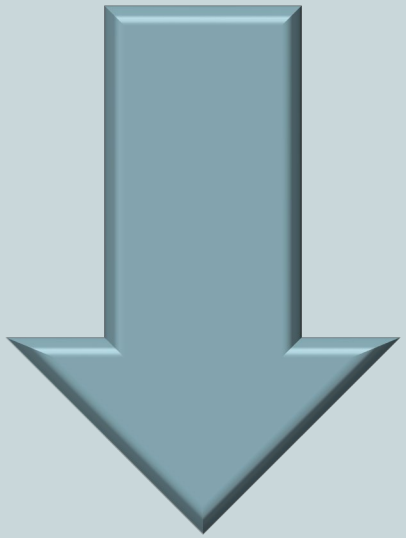
$$\text{Pearl Index} = \frac{\text{Number of on-treatment pregnancies x 13 cycles}}{\text{Number of on-treatment cycles}} \times 100$$

→ Number of pregnancies per 100 woman-years of product use

- Number of cycles in denominator directly impacts Pearl Index and resulting width of 95% confidence interval

Pearl Index: Highly Sensitive to Study Design, Duration, Population Factors

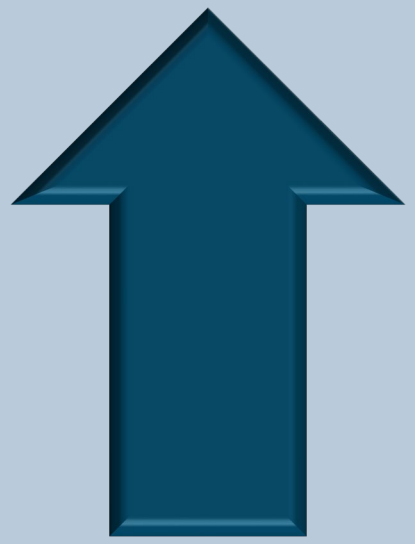
Historical CHC trials include factors known to yield low pearl indices



- ✓ Enrolling women in EU trial sites
- ✓ Restricting enrollment based on BMI or weight
- ✓ Recruiting more affluent, educated women
- ✓ No requirement to anticipate, record sexual activity
- ✓ No accounting for lack of sexual activity

Produced ungeneralizable results
Wide gap between trial efficacy and actual-use effectiveness

Pearl Indices of CHCs Rising in Contemporary Clinical Trials, Referred to as “Creeping Pearl”

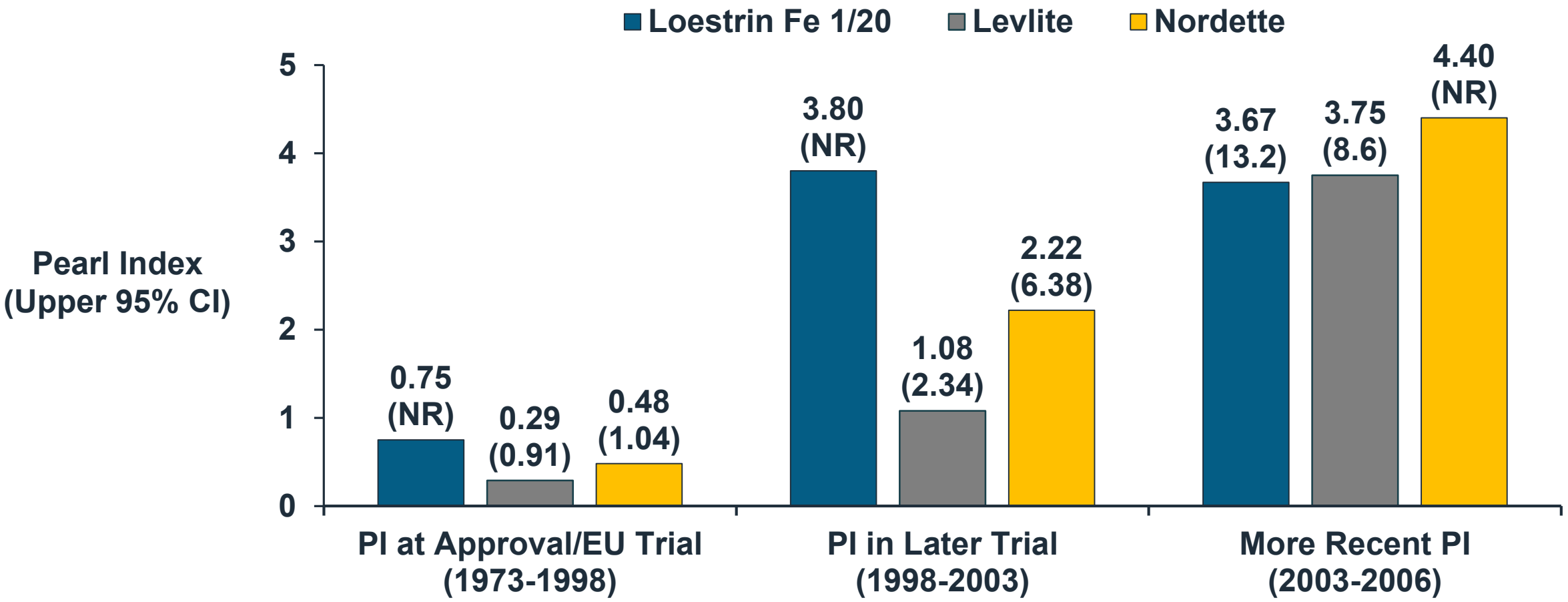


Contemporary CHC trials include multiple factors known to increase Pearl Indices

- ✓ Limiting enrollment to women in US
- ✓ Fewer to no restrictions on weight or BMI
- ✓ Documenting, removing sexually inactive cycles
- ✓ More frequent pregnancy testing
- ✓ More sensitive pregnancy tests

More inclusive, representative populations
Pearl Index more reflective of actual-use effectiveness

Pearl Indices in Initial FDA Registration Studies Increased In Later Trials

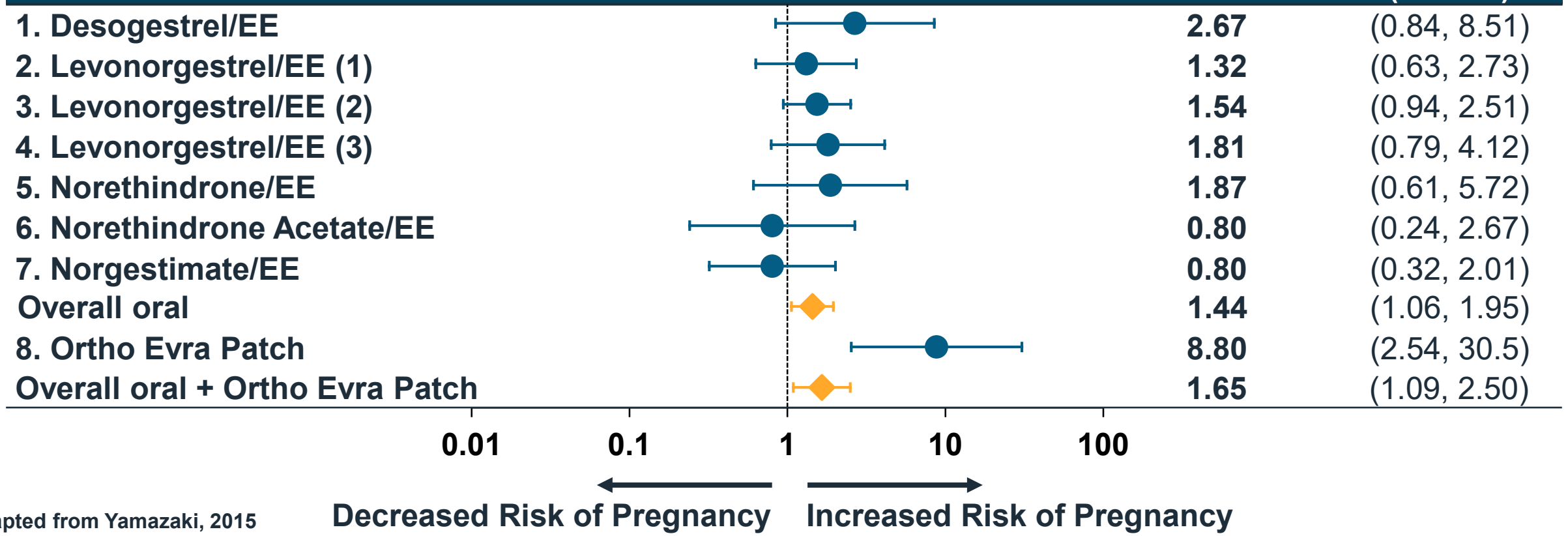


Upper 95% CI not reported for all studies; NR: not reported
Adapted from Edelman et al, 2018

FDA Meta-Analysis: Relationship Between Obesity and Contraceptive Effectiveness

Effect of Obesity (BMI ≥ 30 kg/m^2) on Risk of Pregnancy

COC / Patch Trials	Adjusted* Hazard Ratio	(95% CI)
1. Desogestrel/EE	2.67	(0.84, 8.51)
2. Levonorgestrel/EE (1)	1.32	(0.63, 2.73)
3. Levonorgestrel/EE (2)	1.54	(0.94, 2.51)
4. Levonorgestrel/EE (3)	1.81	(0.79, 4.12)
5. Norethindrone/EE	1.87	(0.61, 5.72)
6. Norethindrone Acetate/EE	0.80	(0.24, 2.67)
7. Norgestimate/EE	0.80	(0.32, 2.01)
Overall oral	1.44	(1.06, 1.95)
8. Ortho Evra Patch	8.80	(2.54, 30.5)
Overall oral + Ortho Evra Patch	1.65	(1.09, 2.50)



Adapted from Yamazaki, 2015
*Age and race adjusted

2007 BRUDAC Provided Recommendations on Trial Design, Risks and Benefits, Labeling

- Panel delivered clear recommendations
  - Change entry criteria to reflect real-world prescribing
  - Active comparator
  - Modify trial designs to reflect real-world effectiveness
  - Avoid arbitrary limits for upper bound of 95% CI to bring widest range of new contraceptive options
  - Ensure all relevant information provided to prescribers
    - Including data on subgroups

2019 FDA Draft Guidance Supports Broadening Contraceptive Populations, Updating Analyses

	Population	BMI / Weight	Sexual Activity	Pearl Index Analyses	Single Arm Studies
FDA Draft Guidance	Enroll representative population pertinent to US	No restrictions on BMI or weight	Enroll sexually active women (≥ once per month)	Exclude all sexually inactive cycles	Single arm studies generally sufficient

2007 BRUDAC Recommended Avoiding Arbitrary Limits for Upper Bound

- FDA guidance does not set limit, but expresses discomfort with upper bound > 5 for CHCs based on historical trials
  - Acknowledges population/design factors (particularly women with obesity) may yield higher Pearl Indices
  - Notes no CHC approved with upper bound > 5

Competing Forces at Cross Purposes

Narrow, historical studies that generate artificially low pearls

Inclusive, contemporary trials reflective of and generalizable to current US population

Diverse Population Needs Range of Contraceptive Options to Meet Diverse Needs

- Accurate generalizable information
- Labels that fully inform prescribers, users of risks/benefits
- Most effective method fits a woman's lifestyle with acceptable side effect/risk profile and preferred route of administration
- Current need for non-daily, transdermal, lower-dose estrogen, suitable progestin option

Agile Patch Clinical Program

Elizabeth Onyemelukwe Garner MD, MPH

Chief Medical Officer 2014-2019
Consultant
Agile Therapeutics, Inc.

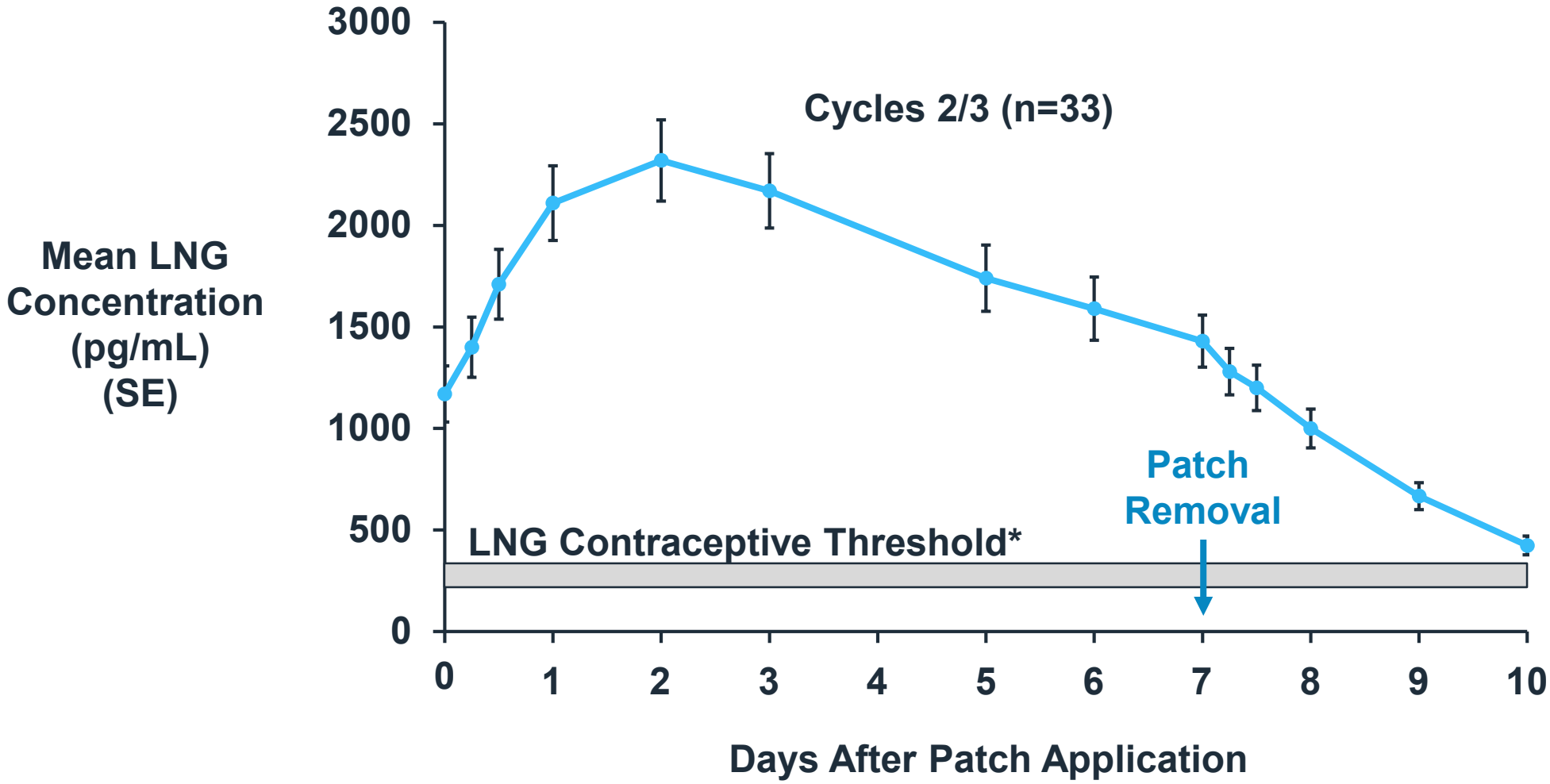
Results Overview

- PK
- Adhesion profile
- Studies 12/13
- Study 23 design, efficacy, and safety
- Postmarketing plans

Data from Agile Patch Clinical Program

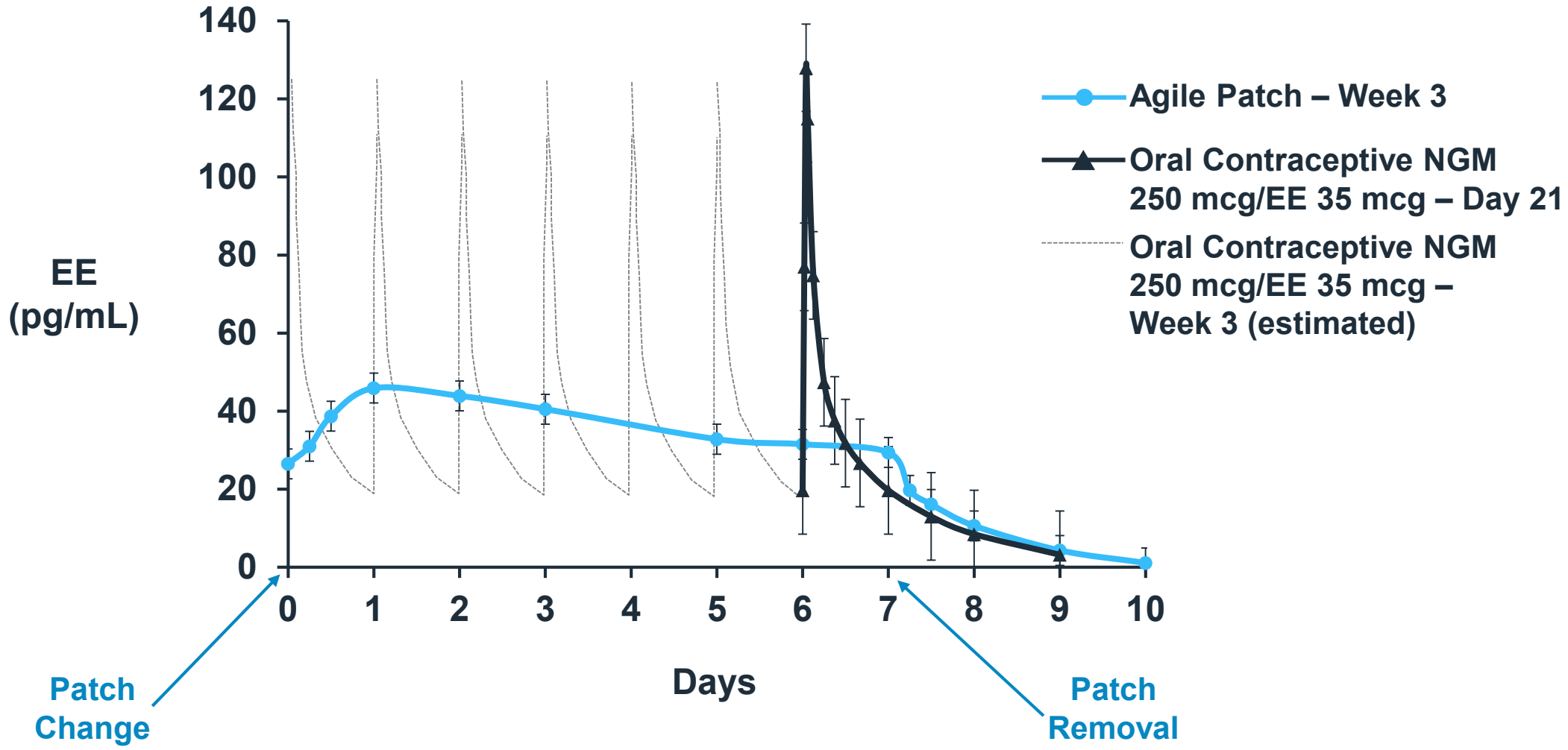
- Support filling need in available options
- Provide women and prescribers data to make informed contraceptive decisions

Study 14: Agile Patch Delivers Contraceptive Levels of Levonorgestrel

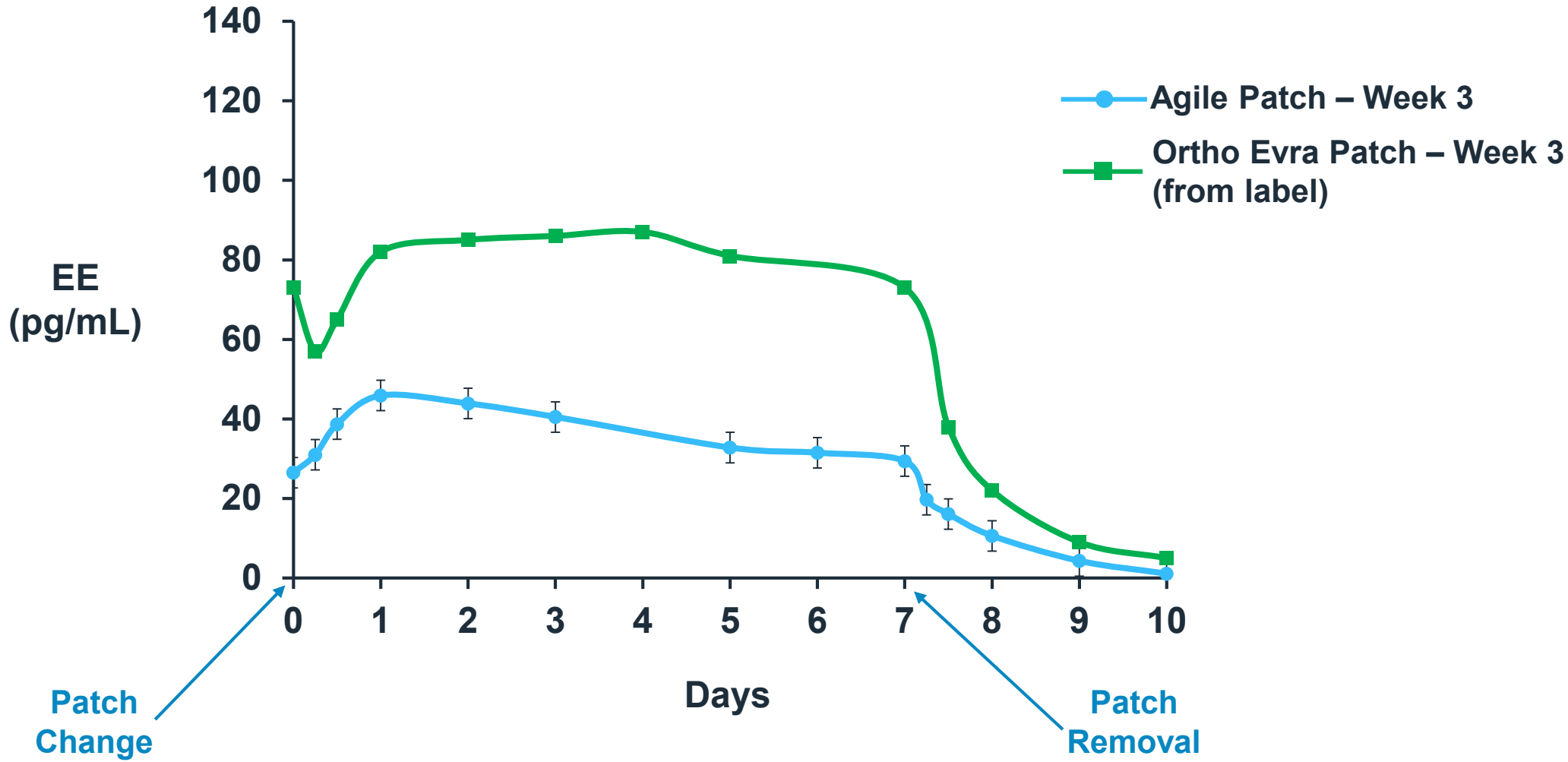


*Published threshold estimation

Study 14: EE Delivery of Agile Patch



EE Delivery of Agile Patch Compared to Ortho Evra Patch



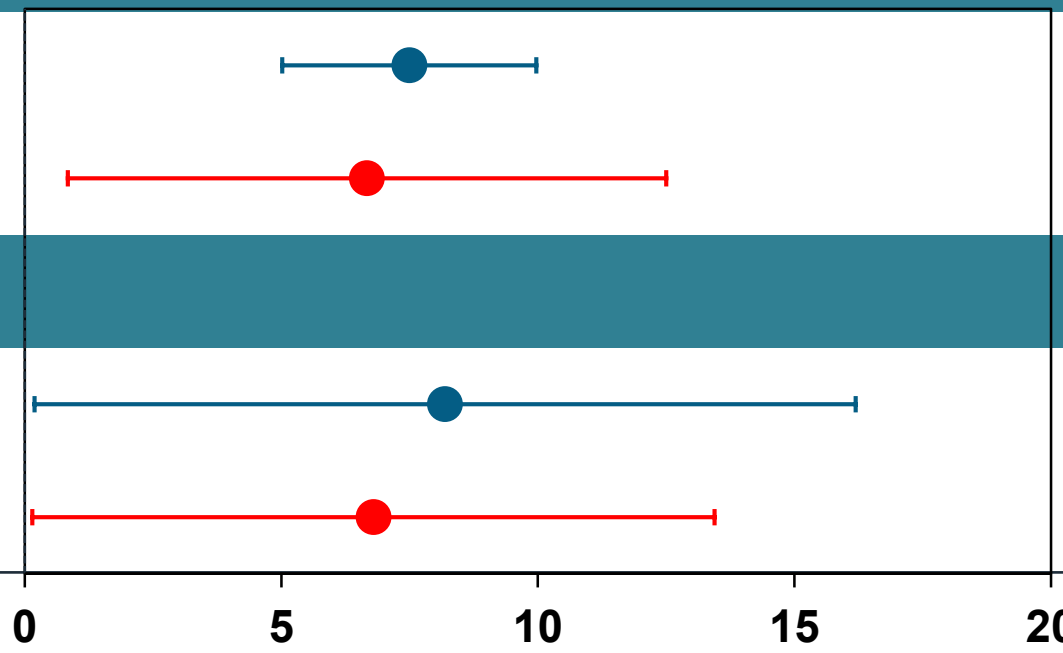
Ortho Evra patch data not from head-to-head study against Agile Patch
AUC and average concentration at steady state for EE ~60% higher in women using Ortho Evra patch

Acceptable *In Vivo* Adhesion of Agile Patch

Study	Outcome
Phase 1 Adhesion Studies	
Study 16	▪ ≥ 91% of women experienced excellent patch adhesion under a range of external conditions
Study 25	▪ *In vivo* adhesion demonstrated as non-inferior to Xulane patch
Phase 3 Study	
Study 23	▪ Learning curve observed in first 3 to 4 months of use ▪ Rate of detachments decreased from cycle 1 to 13

Studies 12/13: Agile Patch Shows Similar Efficacy to Oral Contraceptive Comparators

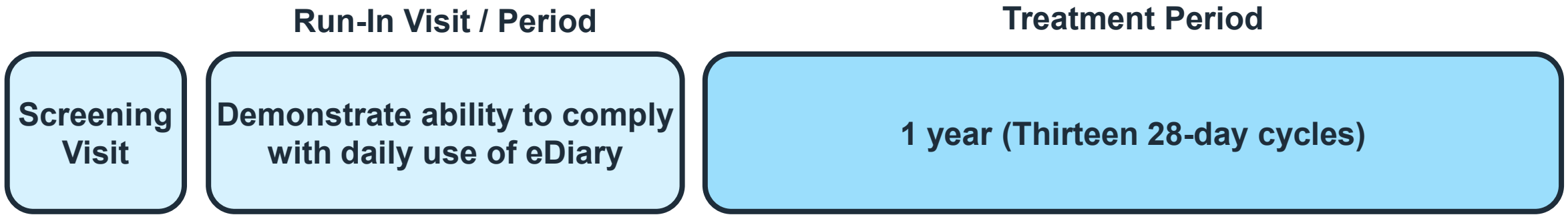
	Cycles	Pearl Index	(95% CI)
Study 12 (Efficacy and Safety Study)			
Agile Patch*	6070	7.50	(5.02, 9.97)
Lessina (Levlite)	975	6.67	(0.84, 12.50)
Study 13 (Safety Study)			
Agile Patch*	635	8.19	(0.19, 16.19)
Levora (Nordette)	765	6.80	(0.15, 13.44)



*Agile Patch Pearl Index based on FDA calculation
Agile Patch: 13-cycle estimate; OC: 6-cycle estimate

Study 23: Design

Single-Arm, Open-Label, 13-Cycle, Multicenter, Efficacy, Safety, and Tolerability Study



- Visits: 8 in-person at clinic, 6 telephone
- Rigorous pregnancy testing: urine hCG at each clinic visit; home pregnancy test kits; urine and serum hCG at study completion or discontinuation
- Assessment for AEs, including bleeding
- eDiaries used to enter information
  - Daily: adhesion, application site irritation, vaginal bleeding/spotting
  - Weekly: patch change/removal day, patch application site, sexual activity, use of back-up contraception

Study 23: Handling of Loss to Follow-Up and Discontinuations

- Loss to follow-up
  - If missed appointment, contact within 24 hours to reschedule
  - If no contact after multiple attempts, then considered lost to follow-up
- Discontinuations for reasons other than loss to follow-up
  - End of study visit
    - Confirmation of pregnancy status
    - Complete physical, gynecological exams
    - Routine lab evaluations

Primary Efficacy Endpoint: Pearl Index for Women ≤ 35 Years of Age

$$\text{Pearl Index} = \frac{\text{Number of on-treatment pregnancies} \times 13 \text{ cycles}}{\text{Number of on-treatment cycles}} \times 100$$

→ Number of pregnancies per 100 woman-years of product use

- Sample size based on projected Pearl Index of 3.5 and upper bound of 95% CI ≤ 5
- Sample size assumptions
  - Not prespecified success criterion or tested as hypotheses
  - No pass / fail for primary endpoint
  - Provide an estimate of efficacy

Study 23: Integrated More Elements of FDA Guidance Than Prior Historical CHC Trials

Study	FDA Guidance				
	Enroll Representative Population Pertinent to US	No Restrictions on BMI or Weight	Enroll Sexually Active Patients (≥ once per month)	Exclude all Sexually Inactive Cycles	Active Comparator
Agile Patch (Study 23)	✓	✓	✓	✓	
Annovera		*	*		
Quartette	✓	✓			
Generess	✓				
Lo Loestrin Fe	✓				
Natazia					✓
Lo Seasonique	✓	✓			
Lybrel		✓		✓	✓
Ortho Evra patch			✓		✓

NDA reviews

*Annovera began excluding participants with BMI > 29 kg/m^2 six months into the study; only 10.6% of the study population were women with BMI > 29 kg/m^2

Per cycle sexual activity was collected but not confirmed at clinic visits, and not analyzed in the calculation of the Pearl Index

Study 23: Results

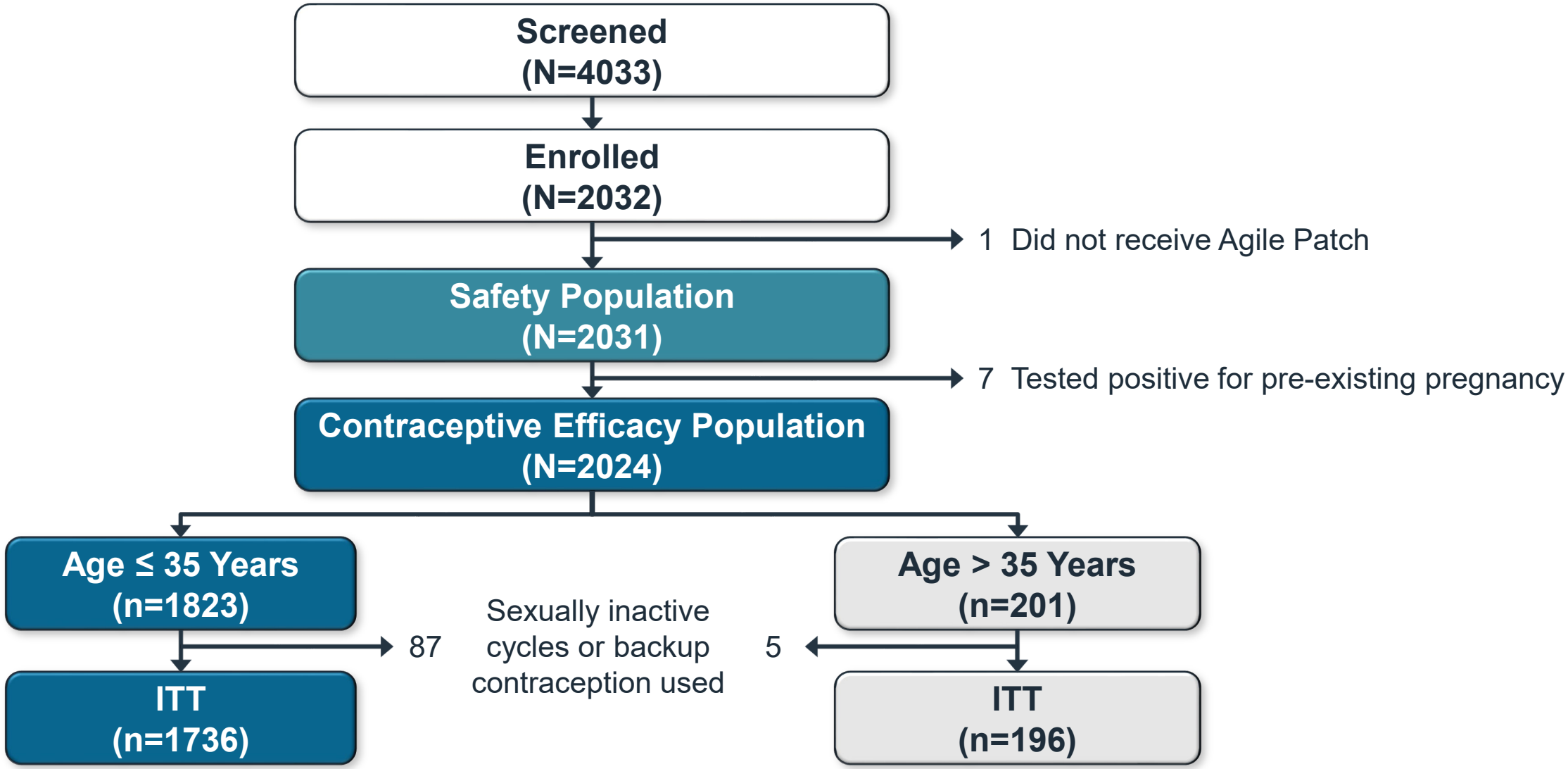
Demographics Representative of US Women Seeking Combined Hormonal Contraceptive

Study 23: Safety Population	Overall N=2031
Age, mean (years)	27.5
≤ 35	90%
Race	
White	67%
Black or African American	24%
Asian and Other	9%
Ethnicity	
Hispanic or Latina	20%

Weight and BMI Reflective of Women in US

Study 23: Safety Population	Overall N=2031
Weight; mean (lbs)	167.7
BMI; mean (kg/m^2)	28.3
Non-obese (< 30)	65%
Obese	35%
Obese (≥ 30 to < 35)	18%
Very obese (≥ 35 to < 40)	10%
Extremely obese (≥ 40)	8%

Study 23: Disposition



Study Discontinuation Rates Typical for Marketed CHCs

CHC	1-Year Discontinuation Rate
Agile Patch (Study 23)	**51%**
Annovera	**48%**
Quartette	**40%**
Lo Loestrin Fe	**42%**
Natazia	**48%**
Lo Seasonique	**43%**
Lybrel	**57%**
Ortho Evra Patch (6-month and 1-year data)	**30%**

Studies with other products are not head-to-head; data from product Package Insert

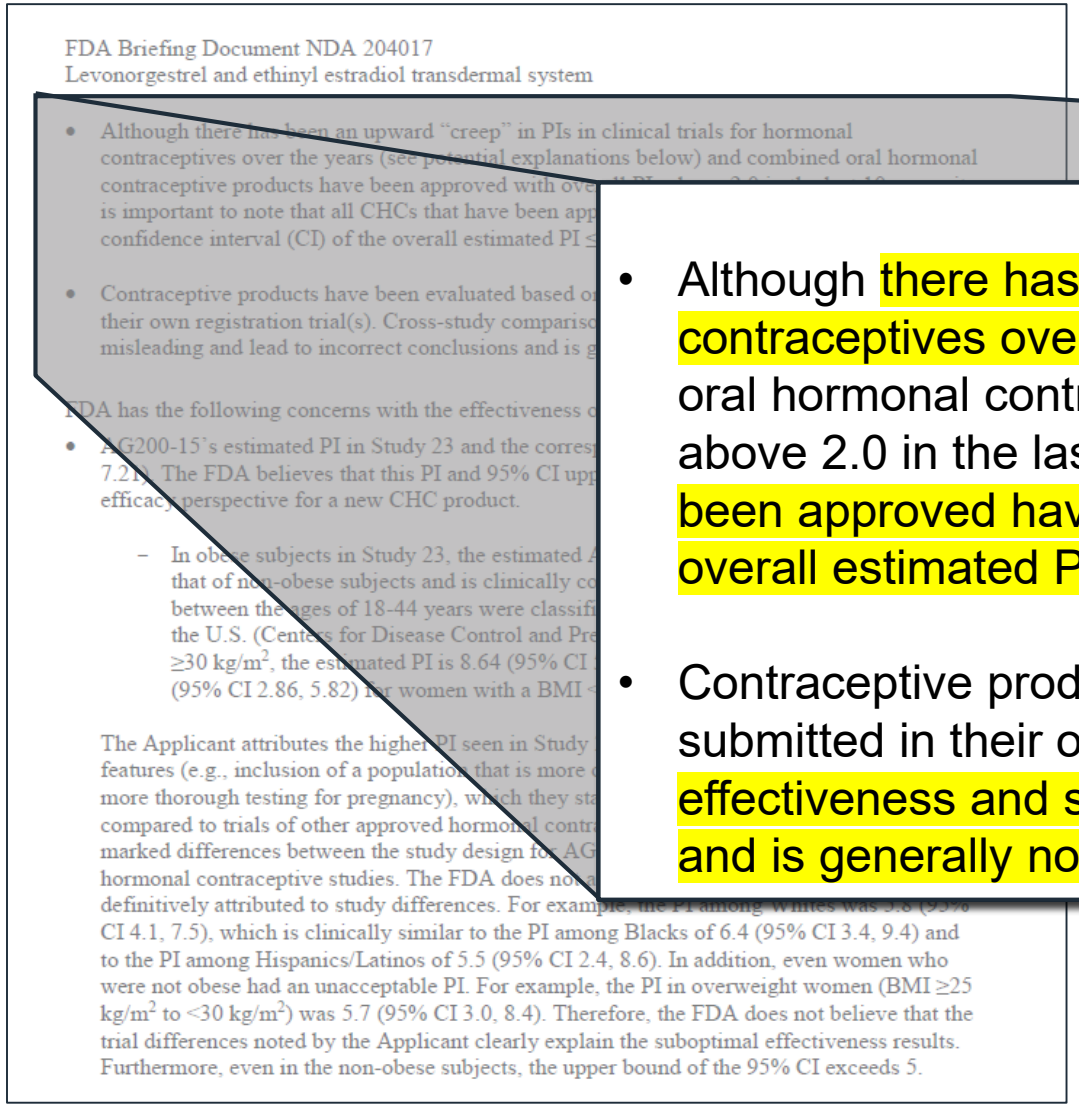
Reasons for Study Discontinuation

Study 23: Safety Population	Overall N=2031
Any Reason	51%
Subject decision	15%
Loss to follow-up	11%
Adverse event	11%
Non-compliance	6%
Pregnancy	4%
Other	5%

Study 23 Primary Endpoint: Agile Patch Efficacious in Prevention of Pregnancy

Women ≤ 35 Years of Age (ITT)	ITT N=1736	Non-Obese Population N=1123
Number of pregnancies	68	33
Number of cycles	15,165	9888
Pearl Index (95% CI)	5.83 (4.45, 7.21)	4.34 (2.86 to 5.82)

Interpreting Pearl Indices is Challenging



FDA Briefing Document NDA 204017
Levonorgestrel and ethinyl estradiol transdermal system

- Although there has been an upward "creep" in PIs in clinical trials for hormonal contraceptives over the years (see potential explanations below) and combined oral hormonal contraceptive products have been approved with ove
is important to note that all CHCs that have been app
confidence interval (CI) of the overall estimated PI ≤

- Contraceptive products have been evaluated based o
their own registration trial(s). Cross-study comparisc
misleading and lead to incorrect conclusions and is g

FDA has the following concerns with the effectiveness c

- AG200-15's estimated PI in Study 23 and the corres
7.21). The FDA believes that this PI and 95% CI upp
efficacy perspective for a new CHC product.
  - In obese subjects in Study 23, the estimated A
that of non-obese subjects and is clinically co
between the ages of 18-44 years were classifi
the U.S. (Centers for Disease Control and Pre
≥30 kg/m^2, the estimated PI is 8.64 (95% CI
(95% CI 2.86, 5.82) for women with a BMI <

The Applicant attributes the higher PI seen in Study
features (e.g., inclusion of a population that is more
more thorough testing for pregnancy), which they sta
compared to trials of other approved hormonal contr
marked differences between the study design for AG
hormonal contraceptive studies. The FDA does not
definitively attributed to study differences. For example, the PI among Whites was 5.8 (95%
CI 4.1, 7.5), which is clinically similar to the PI among Blacks of 6.4 (95% CI 3.4, 9.4) and
to the PI among Hispanics/Latinos of 5.5 (95% CI 2.4, 8.6). In addition, even women who
were not obese had an unacceptable PI. For example, the PI in overweight women (BMI ≥25
kg/m^2 to <30 kg/m^2) was 5.7 (95% CI 3.0, 8.4). Therefore, the FDA does not believe that the
trial differences noted by the Applicant clearly explain the suboptimal effectiveness results.
Furthermore, even in the non-obese subjects, the upper bound of the 95% CI exceeds 5.

- Although there has been an upward "creep" in PIs in clinical trials for hormonal contraceptives over the years (see potential explanations below) and combined oral hormonal contraceptive products have been approved with overall PIs above 2.0 in the last 10 years, it is important to note that all CHCs that have been approved have an upper bound of the 95% confidence interval (CI) of the overall estimated PI ≤5.0.

- Contraceptive products have been evaluated based on the clinical data that was submitted in their own registration trial(s). Cross-study comparisons of effectiveness and safety can be misleading and lead to incorrect conclusions and is generally not recommended by FDA.

FDA Briefing Book

Consistent Efficacy Across Studies

	Cycles	Pearl Index	(95% CI)
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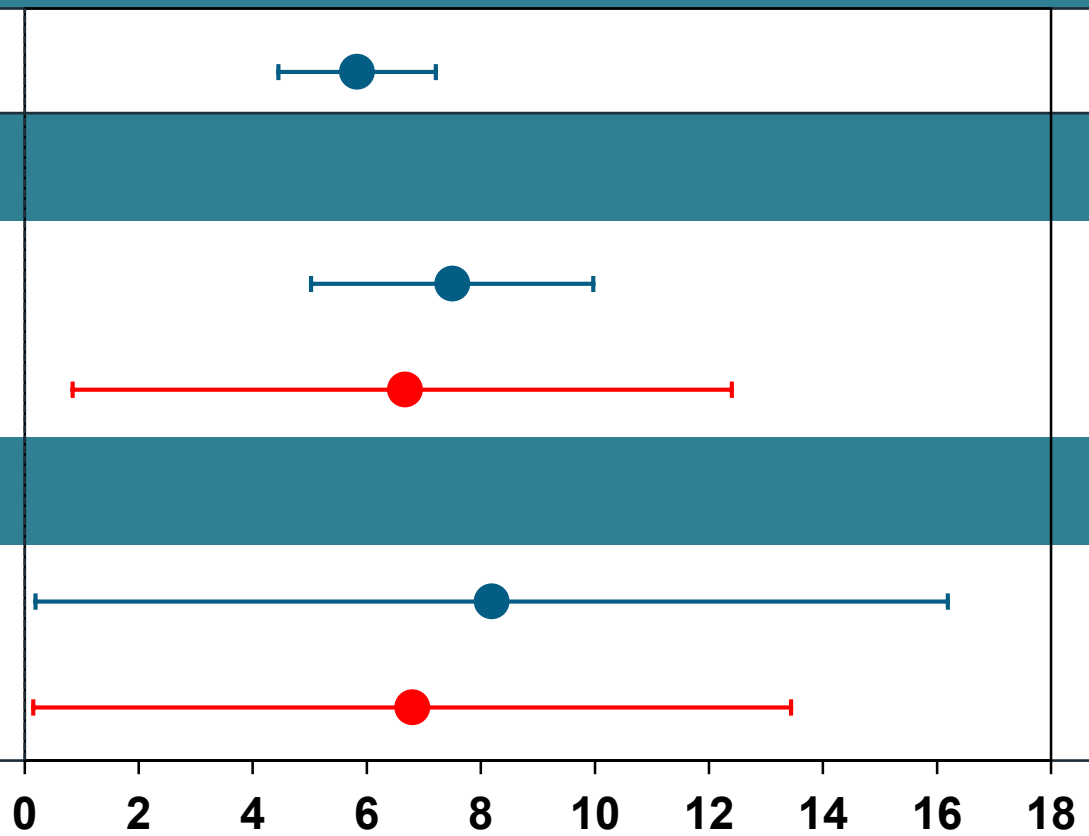
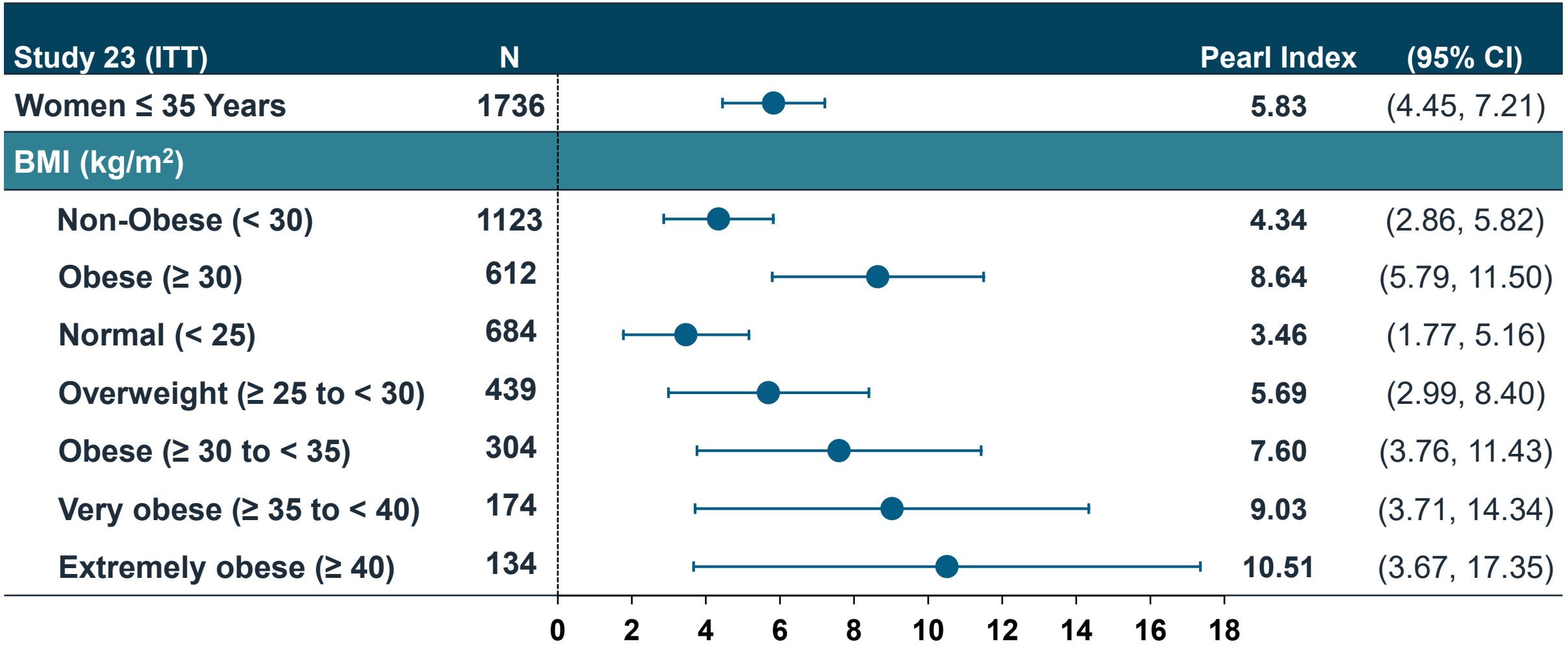
Study 13 (Safety Study)			
Agile Patch*	635	8.19	(0.19, 16.19)
Levora (Nordette)	765	6.80	(0.15, 13.44)



*Agile Patch Pearl Index based on FDA calculation
Agile Patch: 13-cycle estimate; OC: 6-cycle estimate

Pearl Index Trends with Increasing BMI



BMI could not be calculated for 1 woman

Proposed Indication

- *For use by females of reproductive potential to prevent pregnancy*
  - Limitation of Use: Agile Patch has demonstrated reduced effectiveness in women who weigh 202 lbs (92 kg) or more and/or have a BMI of 30 kg/m^2 or more

Importance of Labeling by Weight and BMI

Quartette Population	Pearl Index (Upper Bound of 95% CI)
Overall	3.19 (4.03)
Weight < 70 kg	2.59 (3.67)
Weight ≥ 70 kg to < 90 kg	3.38 (5.17)
Weight ≥ 90 kg	4.82 (7.60)

- Quartette label: no BMI information in indication, no information about Pearl Index trends by weight

Quartette: Special Protocol Assessment

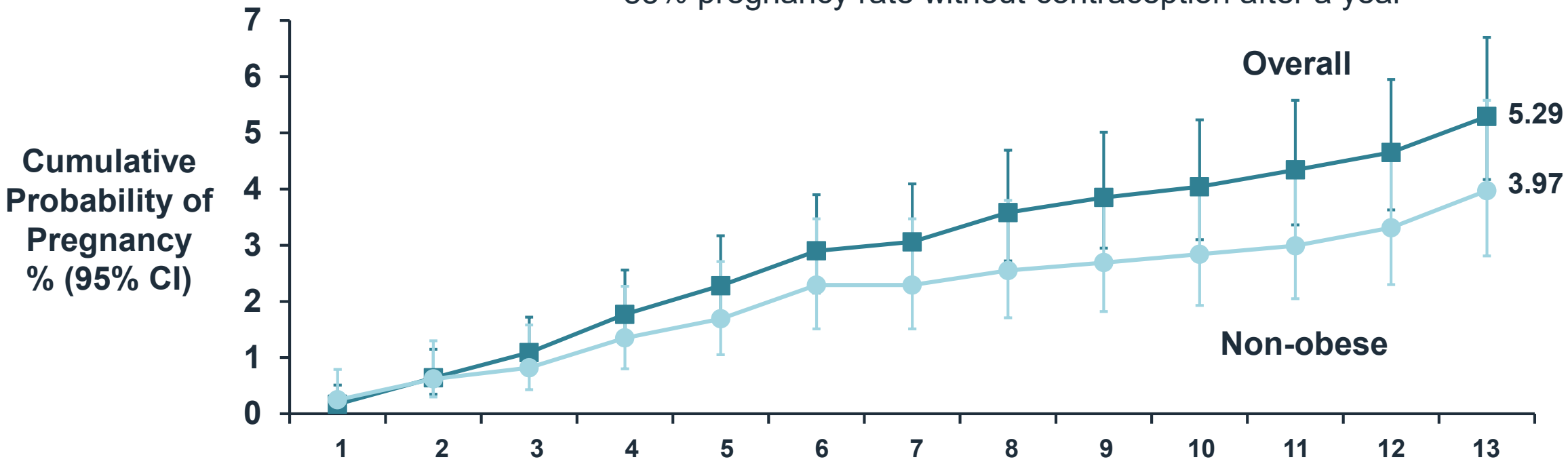
Sensitivity Analysis for Agile Patch

Cycles in Denominator Adjustment	BMI Adjustment	Pearl Index (95% CI) with 2 Adjustments*
5.4% of cycles without sexual activity added back into Agile Patch Pearl Index	Removed all women with BMI ≥ 30 from Agile Patch Pearl Index	4.08 (3.02, 5.15)

*Assumes same sample size
Agile Patch Pearl Index (95% CI): 5.83 (4.45, 7.21)

Study 23: Pregnancy Rates Based on Life Table Analysis Support Tier 2 Effectiveness

- 85% pregnancy rate without contraception after a year



Overall Women	1816	1681	1556	1448	1348	1262	1192	1130	1068	1003	966	929	891
Cumulative Pregnancies	3	11	18	28	35	43	45	51	54	56	59	62	68
Non-obese Women	1177	1082	1001	939	872	820	776	740	701	659	633	613	586
Cumulative Pregnancies	3	7	9	14	17	22	22	24	25	26	27	29	33

Agile Patch Efficacious in Prevention of Pregnancy

- Phase 3 study populations broadly representative of US
  - 35% of women with obesity, 7% in highest BMI category
- Study 23 enrolled sexually active women
- Efficacy in non-obese women consistent with historical controls
  - 65% of women were non-obese
- Efficacy results reflect contemporary, inclusive contraceptive trial conducted in manner recommended by BRUDAC in 2007 and in new FDA Draft Guidance

Safety

Agile Patch Safety In-Line with Well-Understood Profile of CHCs

- Most commonly reported AEs in CHC trials are similar
- CHCs associated with certain hormone-related AEs, many derive from exposure to estrogen
  - Breast tenderness
  - Headache
  - Nausea
- Higher doses of estrogen generally correlate with higher rates of hormone-related AEs

Phase 3 Exposures (Studies 12, 13, 23)

Study	Agile Patch	
	Number of Patients	Number of Cycles
Total (Integrated Database)	**3481**	**29,900**
Study 12	**1220**	**9843**
Study 13	**230**	**1216**
Study 23	**2031**	**18,841**

Study 23: Overall Safety Profile

Treatment-Emergent Adverse Events	Safety Population N=2031	Non-Obese Population N=1313
Any AE	53%	54%
Study drug-related AE	27%	28%
Severe AE	5%	4%
SAE	2%	1%
Study drug-related SAE	1%	0.3%
AE leading to discontinuation	11%	12%
Deaths	0	0

Study 23: Incidence of Hormone-Related AEs

Agile Patch Hormone-Related AE	Safety Population N=2031	Non-Obese Population N=1313	Ortho Evra Patch	Lo Loestrin Fe	Quartette	Annovera
Nausea	4.1%	4.7%	16.8%	4.8%	6.7%	20.1%
Headache	3.6%	3.7%	21.1%	7.0%	12.2%	35.7%
Breast tenderness	1.5%	2.0%	22.4%	3.5%	2.0%	6.1%

Ortho Evra: contraceptive patch; Lo Loestrin Fe: lowest dose EE CHC; Quartette and Annovera: most recently approved low-dose EE
Studies with other products are not head-to-head; data from product Package Insert

Study 23: Application Site AEs

Agile Patch Preferred Term	Safety Population N=2031	Non-Obese Population N=1313	Ortho Evra Patch
Any application site disorder	6.2%	5.7%	17.1%* (bundled term for application site disorders)
Irritation	1.5%	1.5%	
Discoloration	1.4%	1.5%	
Pruritus	0.9%	0.8%	
Rash	0.8%	0.7%	
Erythema	0.7%	0.4%	
Dermatitis	0.6%	0.5%	
Dryness	0.5%	0.4%	

*Ortho Evra patch data not head-to-head; data from Package Insert
Application site reactions not collected in Ortho Evra patch trials in same way as in Agile trial

Rates of AEs Leading to Discontinuation Typical for CHCs

	AEs Leading to Discontinuation
Agile Patch (Study 23 safety population)	**11.0%**
Study 23 non-obese population	**11.8%**
Ortho Evra Patch (6-month and 1-year data)	**12.0%**
Annovera	**11.5%**
Quartette	**13.0%**
Lo Loestrin Fe	**10.7%**

Studies with other products are not head-to-head; data from product Package Insert

Study 23: Low Rates of AEs Leading to Discontinuation

Agile Patch Preferred Term	Safety Population N=2031	Non-Obese Population N=1313
Any AE leading to discontinuation	11.0%	11.8%
Application site irritation	1.1%	1.2%
Nausea	0.9%	1.0%
Application site pruritus	0.8%	0.6%
Metrorrhagia	0.7%	1.0%
Application site rash	0.7%	0.5%
Vaginal hemorrhage	0.6%	0.9%
Mood swings	0.5%	0.5%
Menorrhagia	0.5%	0.6%
Application site dermatitis	0.5%	0.5%
Application site erythema	0.4%	0.2%

10 most frequent AEs leading to discontinuation

Study 23: Acceptable Bleeding Profile

- Instances of unscheduled bleeding/spotting common
- Typically lessens over time, with bleeding episodes becoming less frequent and intense
  - Reduction in incidence of breakthrough bleeding and/or spotting observed with Agile Patch

Agile Patch	Safety Population N=2031	Non-Obese Population N=1313	Ortho Evra Patch	Lo Loestrin Fe	Quartette	Annovera
Any bleeding or spotting AE leading to discontinuation	**2.2%**	**3.0%**	**1.1%**	**3.8%**	**4.9%**	**1.7%**

Studies with other products are not head-to-head; data from product Package Insert

Study 23: SAEs Occurring in ≥ 2 Women

Agile Patch Preferred Term	Safety Population N=2031	Non-Obese Population N=1313
Any SAE	40 (2.0%)	18 (1.4%)
Cholelithiasis	4 (0.2%)	0
Deep vein thrombosis*	3 (0.2%)	0
Pulmonary embolism*	3 (0.2%)	0
Major depression	3 (0.2%)	1 (0.08%)
Gastroenteritis	2 (0.1%)	2 (0.2%)
Cholecystitis	2 (0.1%)	0
Ectopic pregnancy	2 (0.1%)	0

*1 woman had concomitant DVT and PE

Number of Women with VTE by BMI

BMI Category (kg/m^2)	Agile Patch Study 23*
Non-Obese (< 30)	0
Normal (< 25)	0
Overweight (≥ 25 to < 30)	0
Obese (≥ 30)	4

*FDA and Agile excluded 1 VTE as unrelated to study drug

Agile Patch Safety Profile Acceptable

- Most commonly observed AEs
  - Expected
  - Occurred at low rates
  - Led to discontinuations at rates similar to approved CHCs
- Local patch site reactions generally infrequent, led to few discontinuations
- Serious risks with Agile Patch in-line with known CHC risks

Going Beyond Labeling to Advance Understanding

- If Agile Patch approved in **overall population,** propose class-wide study of transdermal, vaginal, and oral CHCs to answer questions about class effects in women with obesity
- If Agile Patch approved in **non-obese** population, then prospective head-to-head trial vs OC in women with obesity
  - Advance understanding of efficacy and safety
  - Inform whether indicated population should include women with obesity or not

Clinical Perspective

David Portman, MD

CEO and CMO, Sermonix Pharmaceuticals
Founder, Director Emeritus, Columbus Center for Women's Health Research and Adjunct Instructor, Department of OBGYN, Wexner Medical Center, The Ohio State University

Agile Patch: Important Addition to Available Hormonal Methods

- Cannot assume all women who use contraception are satisfied with available options
- Provide independence, reversibility, efficacy as other CHCs
  - 5.3% cumulative pregnancy rate at 1 year
  - 4.0% cumulative pregnancy rate in non-obese women
- Only non-daily, non-invasive, < 56 mcg estrogen option
- Most effective option for any individual woman is one that satisfies her preferences and needs

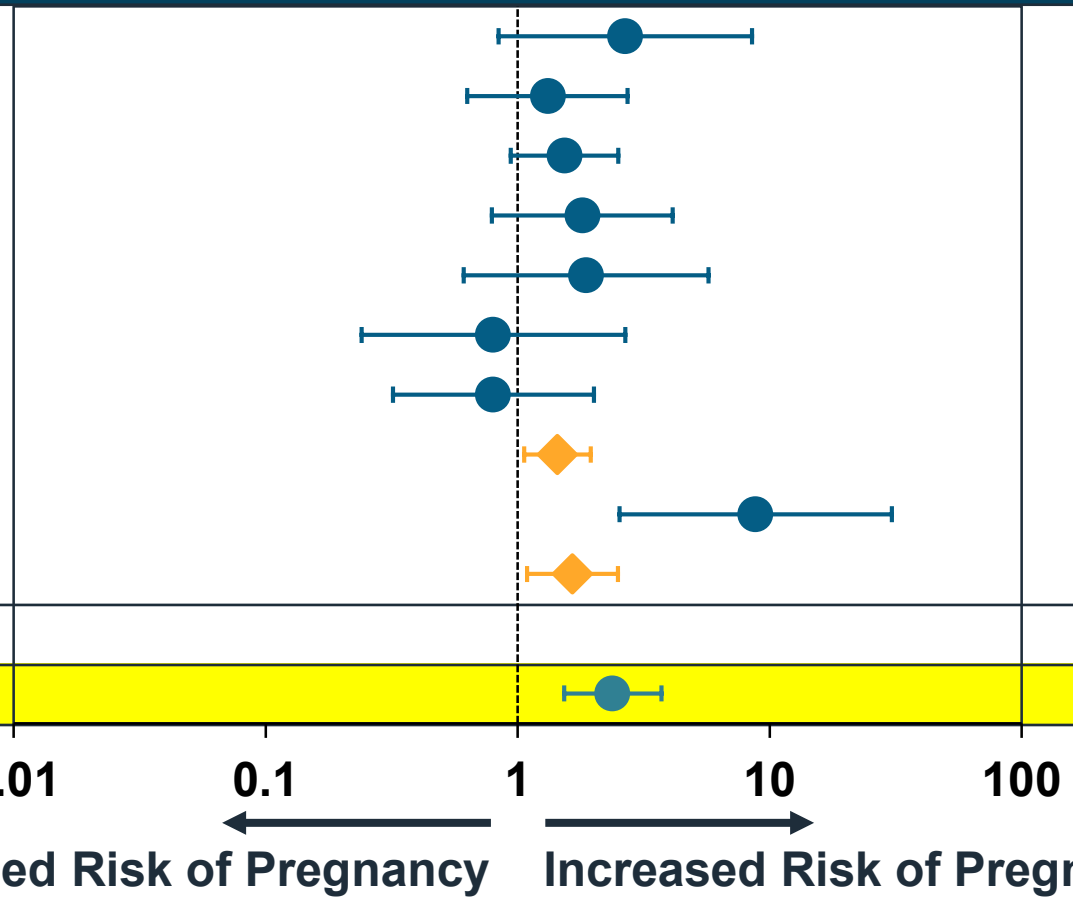
Study 23 Provided Substantial Evidence of Efficacy of Agile Patch

- Acceptable efficacy
  - Overall Pearl Index of 5.83
  - Pearl Index of 4.34 in non-obese population
- Combined effect of study design, population factors into single trial had greater impact on Pearl Index than anticipated
- Women in Study 23 used Agile Patch as only method
  - Expected annual rate for unprotected intercourse = 85%
  - Agile Patch Life Table risk for pregnancy = ~5%

FDA Meta-Analysis: Relationship Between Obesity and Contraceptive Effectiveness

Effect of Obesity (BMI ≥ 30 kg/m^2) on Risk of Pregnancy

COC / Patch Trials	Adjusted* Hazard Ratio	(95% CI)
1. Desogestrel/EE	2.67	(0.84, 8.51)
2. Levonorgestrel/EE (1)	1.32	(0.63, 2.73)
3. Levonorgestrel/EE (2)	1.54	(0.94, 2.51)
4. Levonorgestrel/EE (3)	1.81	(0.79, 4.12)
5. Norethindrone/EE	1.87	(0.61, 5.72)
6. Norethindrone Acetate/EE	0.80	(0.24, 2.67)
7. Norgestimate/EE	0.80	(0.32, 2.01)
Overall oral	1.44	(1.06, 1.95)
8. Ortho Evra Patch	8.80	(2.54, 30.5)
Overall oral + Ortho Evra Patch	1.65	(1.09, 2.50)
Agile Patch (Study 23)**	**2.38**	(1.53, 3.72)



Adapted from Yamazaki, 2015
*Age and race adjusted
**Not part of meta-analysis

Prospective Data for Traditionally Understudied Obese Population

- Proposed Limitation of Use for women with BMI ≥ 30
- First CHC to include efficacy by BMI in label
- Physicians would have specific data about CHC efficacy with heavier patients, rather than speculate from absence of data
- Indication limiting population to women with < 30 BMI supported by Agile Patch data

Safety Similar to Well-Understood CHC Profile with Known Risks in Class Label

- Estrogen-related AEs consistent with other CHCs
- No significant progestin-related side effects
- Risk of VTEs increases with CHC use
  - Rate with Agile Patch consistent with number of women with obesity in trials
  - No VTE events occurred in non-obese women
- Safe option for women without obesity
- Would consider other options as first line for women with obesity

Pearl Indices Trending Higher Over Time

Why

- Studies conducted in populations more representative of likely users in US
- Contemporary, inclusive trials
  - Broad enrollment criteria
  - No restrictions on weight or BMI
  - Documenting sexual activity
  - Removing sexually inactive cycles
  - More frequent, sensitive pregnancy testing

Impact

- Closing gap between
  - “Perfect use” in historical trials
  - “Typical use” effectiveness in diverse, US population
- Don’t return to narrow study populations and arbitrary upper bounds
- As more trials conducted this way, upper bounds > 5 will become more common
- FDA Guidance underscores importance
- Agile program step in right direction

Time to Make Agile Patch An Option for Women Deciding Among Contraceptive Methods

Pose Series of Questions

- *Is a hormone-containing product right for you?*
- *Is a low-dose appealing?*
- *Preference for daily or less frequent administration options?*
- *Comfort with methods that require a procedure or insertion?*

Share Label

- *BMI by category chart*

Discuss Compliance

- *What to do in event of missed, displaced patch*

Best, most effective choice is one a woman determines is right for her

Agile Patch could be right option for many women

Agile Patch (AG200-15)

October 30, 2019

Agile Therapeutics, Inc.

Bone, Reproductive, and Urologic Drugs Advisory Committee

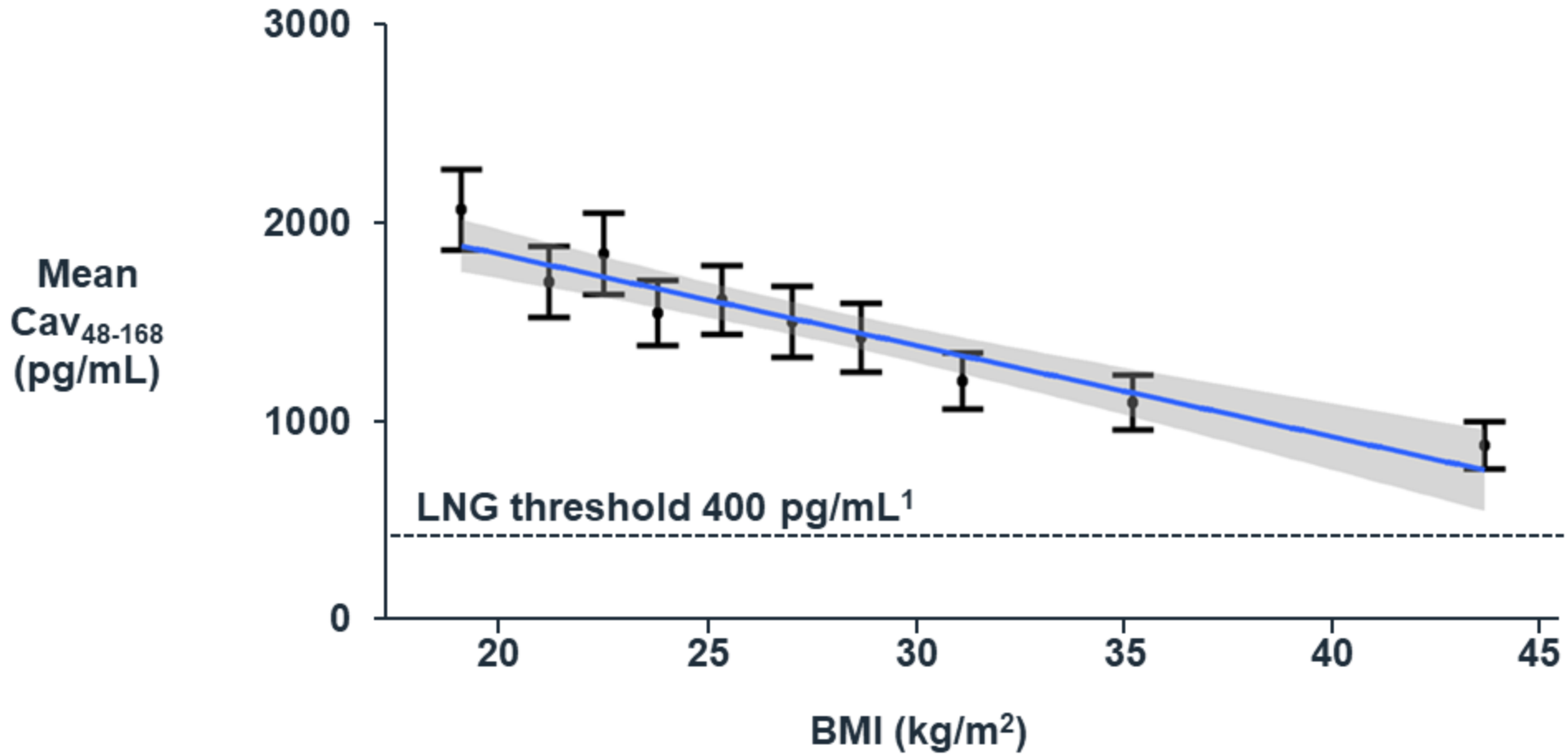
Study 14: PK Parameters for EE: The Agile Patch vs Ortho-Cyclen Pill

Parameter	Arithmetic Mean ± SD		Treatments Comparison			
	Agile Patch (N=32)	Ortho-Cyclen® Pill (N=32)	p-value	Ratio PE	90% CI	
Week 3						
C_{max} (pg/mL)	51.3 ± 17.3	131 ± 45.4	< 0.0001	39.01	35.26	43.15
$AUC_{0\text{-}168h}$ (ng.h/mL)	6.26 ± 2.46	6.97 ± 2.25	0.0532	85.96	75.67	97.66
C_{ss} (1) (pg/mL)*	35.7 ± 14.5	41.5 ± 13.4	0.0167	81.78	71.48	93.57

Calculated dose = (35.7/41.5) X 35 mcg = 30.1 mcg

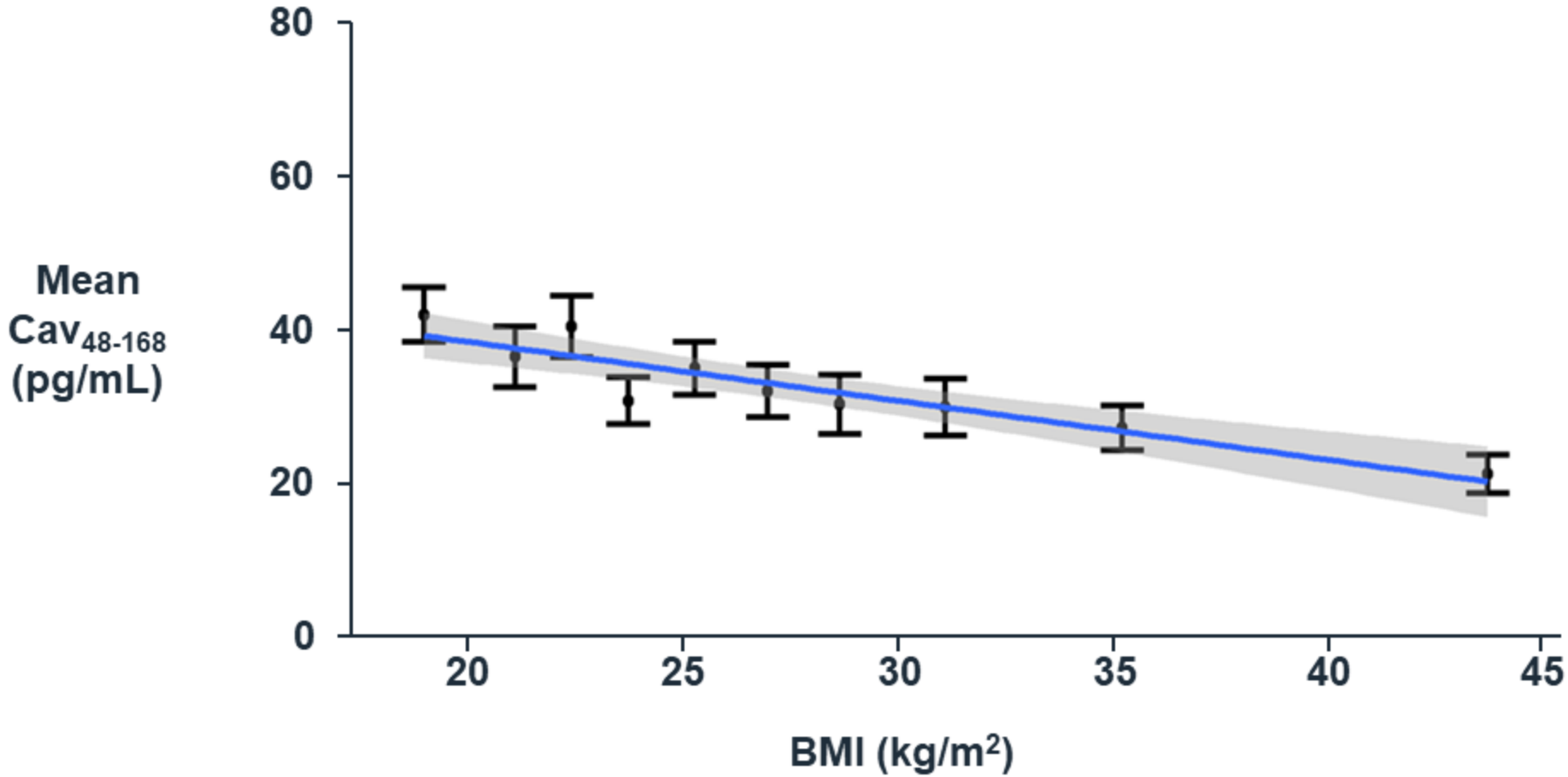
* C_{ss} (1): Average concentration within 48h-168h time interval

Study 12: Regardless of BMI, LNG Concentration Remains Above Contraceptive Threshold



1. Edelman 2016

Study 12: Consistent with EE Delivery from Agile Patch, BMI has Modest Affect on EE PK

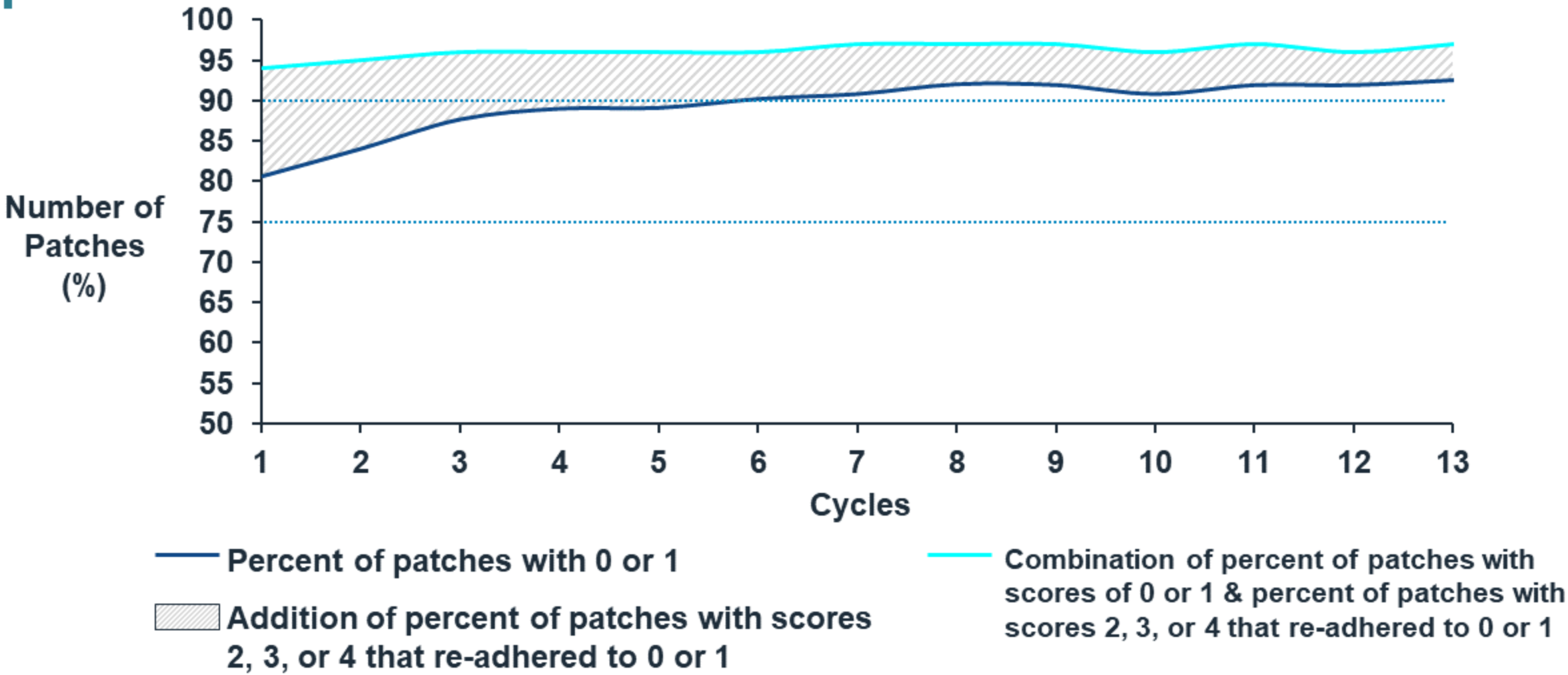


Study 23: No Difference in Adhesion by Cycles Between Women with and without Obesity

Patch Adhesion Scores	BMI < 30 kg/m^2 N=252,665	BMI ≥ 30 kg/m^2 N=138,320
0	82%	80%
1	11%	11%
2	2%	3%
3	1%	2%
4	3%	4%

N=number of reported patch adhesion scores
0: ≥ 90% adhered (no lift); 1: ≥ 75% adhered but < 90% (some edges showing lift); 2: ≥ 50% adhered but < 75% (half of patch lifts off);
3: < 50% (> half of patch lifts off, but undetached); 4 = patch completely detached

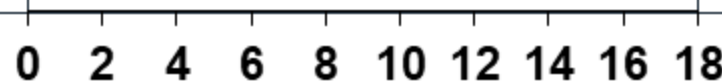
Study 23: Study Demonstrates Adequate Adhesion



All scores are reported as worst score carried forward in a cycle.
The horizontal line represents 90% and 75% of patches with worst scores of 0 or 1 (≥ 75% adhesion) indicating no worse than 25% lift at any time during wear.

Studies 12 and 13 Pooled Pearl Indices

	Cycles	Pearl Index	(95% CI)
Studies 12 and 13 Pooled (Cycles 1-6)			
Agile Patch*	4274	6.64	(3.86, 9.42)
Oral contraceptive	2041	5.62	(1.92, 9.32)
Study 23			
Agile Patch	15,165	5.83	(4.45, 7.21)



*Agile Patch pooled Pearl Index based on FDA calculation of pregnancies.

Robust Data Set Supports Favorable Benefit-Risk Profile in Non-Obese Women

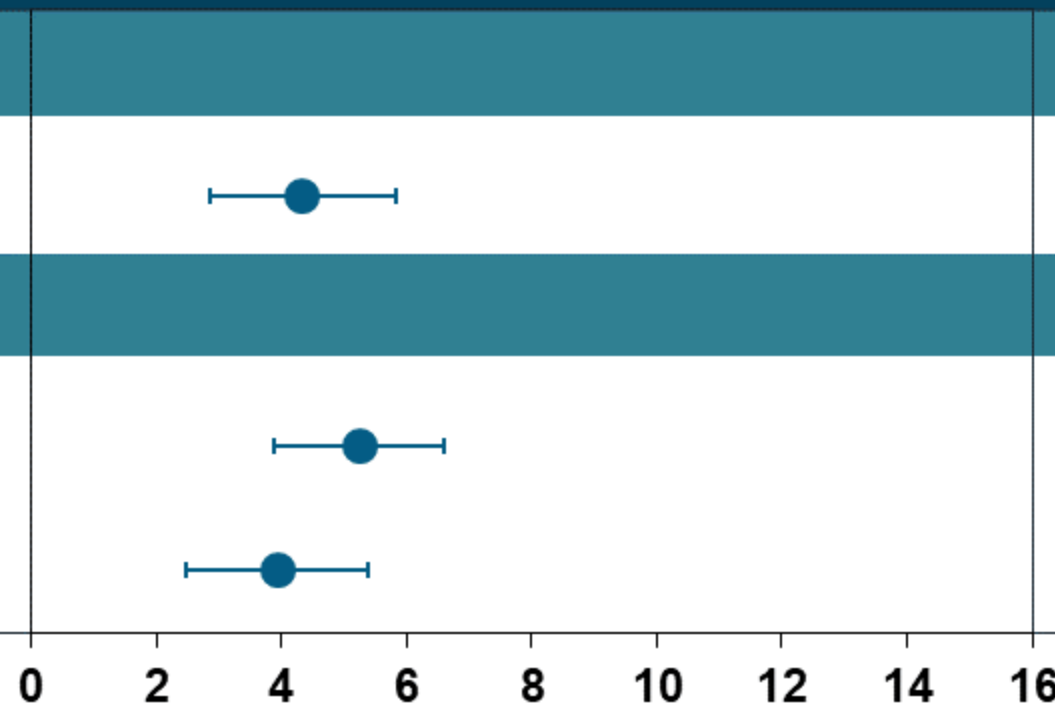
	Benefits	Risks
Overall (15,165 cycles)	**Pearl Index** (95% CI) **5.83** (4.45, 7.21)	**4 VTEs** **Low rate of hormone-related AEs**
Non-Obese (9,888 cycles)	**Pearl Index** (95% CI) **4.34** (2.86, 5.82)	**0 VTEs** **Low rate of hormone-related AEs**

Proposed Label: Section 14 to Include Table with Pearl Index by BMI Categories

BMI Category	BMI (kg/m^2)	Study Population	Pearl Index	Upper Bound 95% CI
Normal	< 25	39%	3.46	5.16
Non-Obese	< 30	65%	4.34	5.82
Obese	≥ 30	35%	8.64	11.50
Overall	15.1 – 63.0	100%	5.83	7.21

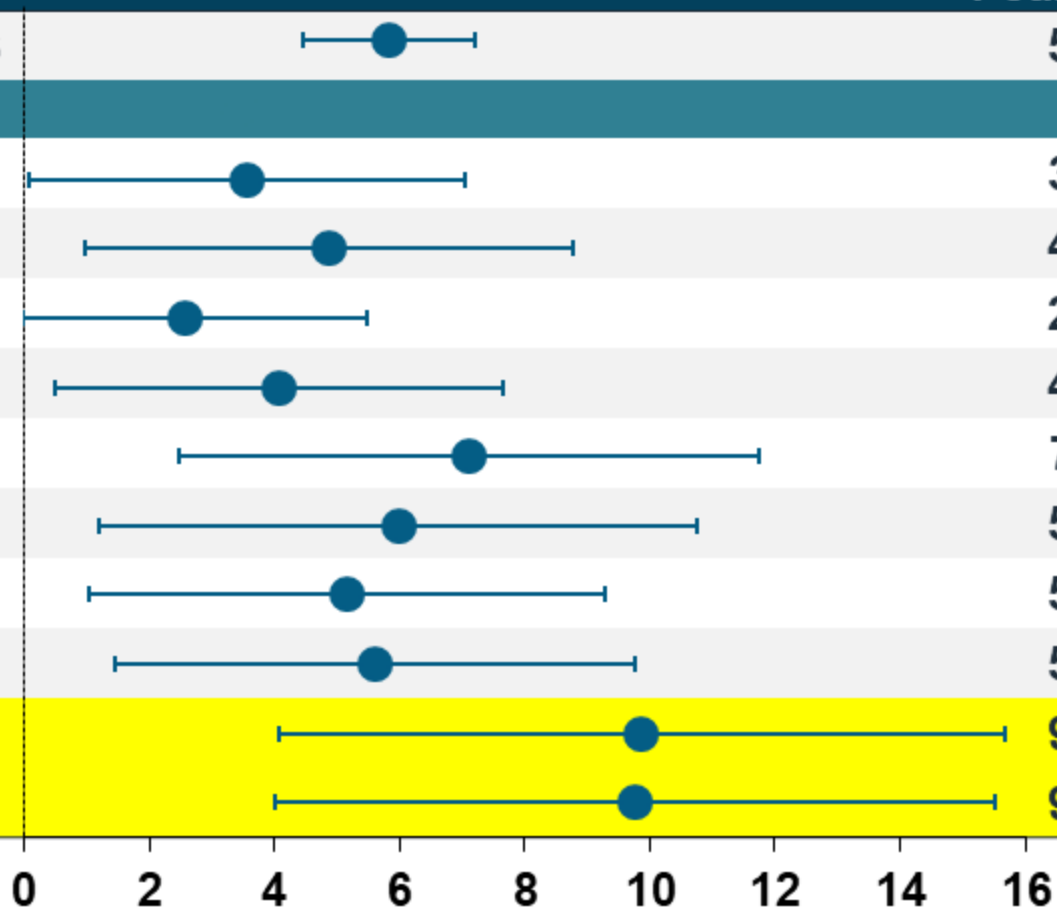
Study 23: Secondary Efficacy Endpoint Results

	N	Pearl Index	95% CI
ITT			
Women ≤ 35 years, Non-obese < 30 kg/m^2	1123	4.34	(2.86, 5.82)
PPI			
Women ≤ 35 years	1714	5.25	(3.89, 6.61)
Women ≤ 35 years, Non-obese < 30 kg/m^2	1109	3.94	(2.48, 5.40)



Study 23: Reduced Efficacy Seen in Women ≥ 202 lbs / 91 kg

	N	Pearl Index	(95% CI)
Women ≤ 35 Years	1736	5.83	(4.45, 7.21)
Weight Decile (lbs)			
Decile 1 (< 119)	171	3.56	(0.08, 7.05)
Decile 2 (≥ 119 to < 130)	180	4.88	(0.98, 8.78)
Decile 3 (≥ 130 to < 138)	172	2.58	(0.00, 5.49)
Decile 4 (≥ 138 to < 148)	175	4.09	(0.51, 7.67)
Decile 5 (≥ 148 to < 159)	179	7.11	(2.48, 11.75)
Decile 6 (≥ 159 to < 171)	167	5.99	(1.21, 10.77)
Decile 7 (≥ 171 to < 185)	172	5.16	(1.04, 9.28)
Decile 8 (≥ 185 to < 202)	179	5.61	(1.46, 9.76)
Decile 9 (≥ 202 to < 232)	165	9.87	(4.06, 15.68)
Decile 10 (≥ 232)	174	9.77	(4.02, 15.53)



Limitation of Use Weight Cutoff for Agile Patch and Ortho Evra

Agile Patch Weight Decile (lbs)	Number of Pregnancies
Decile 1 (< 119)	4
Decile 2 (≥ 119 to < 130)	6
Decile 3 (≥ 130 to < 138)	3
Decile 4 (≥ 138 to < 148)	5
Decile 5 (≥ 148 to < 159)	9
Decile 6 (≥ 159 to < 171)	6
Decile 7 (≥ 171 to < 185)	6
Decile 8 (≥ 185 to < 202)	7
Decile 9 (≥ *202* to < 232)	11
Decile 10 (≥ 232)	11

Ortho Evra Weight Decile (lbs)	Number of Pregnancies
Decile 1 (< 115)	1
Decile 2 (≥ 115 to < 121)	2
Decile 3 (≥ 121 to < 128)	0
Decile 4 (≥ 128 to < 132)	0
Decile 5 (≥ 132 to < 139)	2
Decile 6 (≥ 139 to < 146)	0
Decile 7 (≥ 146 to < 152)	1
Decile 8 (≥ 152 to < 163)	0
Decile 9 (≥ 163 to < 176)	2
Decile 10 (≥ 176)	7
(≥ 176 to < 187)	1
(≥ 187 to < 198)	1
(≥ *198*)	5

Women ≤ 35 years of age

Proposed Label Includes Extensive Information about BMI and Weight

Label Section	BMI and Weight Information
Indications and Use	• Limitation of Use – Reduced efficacy in BMI ≥ 30 kg/m^2 or ≥ 202 pounds
Warnings & Precautions	• Obesity is a risk factor for VTE
Adverse Reactions	• 5/6 VTEs and all gallbladder SAEs in safety population occurred in women with obesity and >200 pounds
Use in Specific Populations	• Reduced efficacy in BMI ≥ 30 kg/m^2 or ≥ 202 pounds • 5/6 VTEs occurred in women with obesity and >200 pounds
Clinical Studies	• Table with Pearl Index by BMI category and Pearl Index by weight decile in text
Patient Counseling	• HCPs should discuss other methods if BMI ≥ 30 kg/m^2 or ≥ 202 pounds

Treatment Options Based on Effectiveness

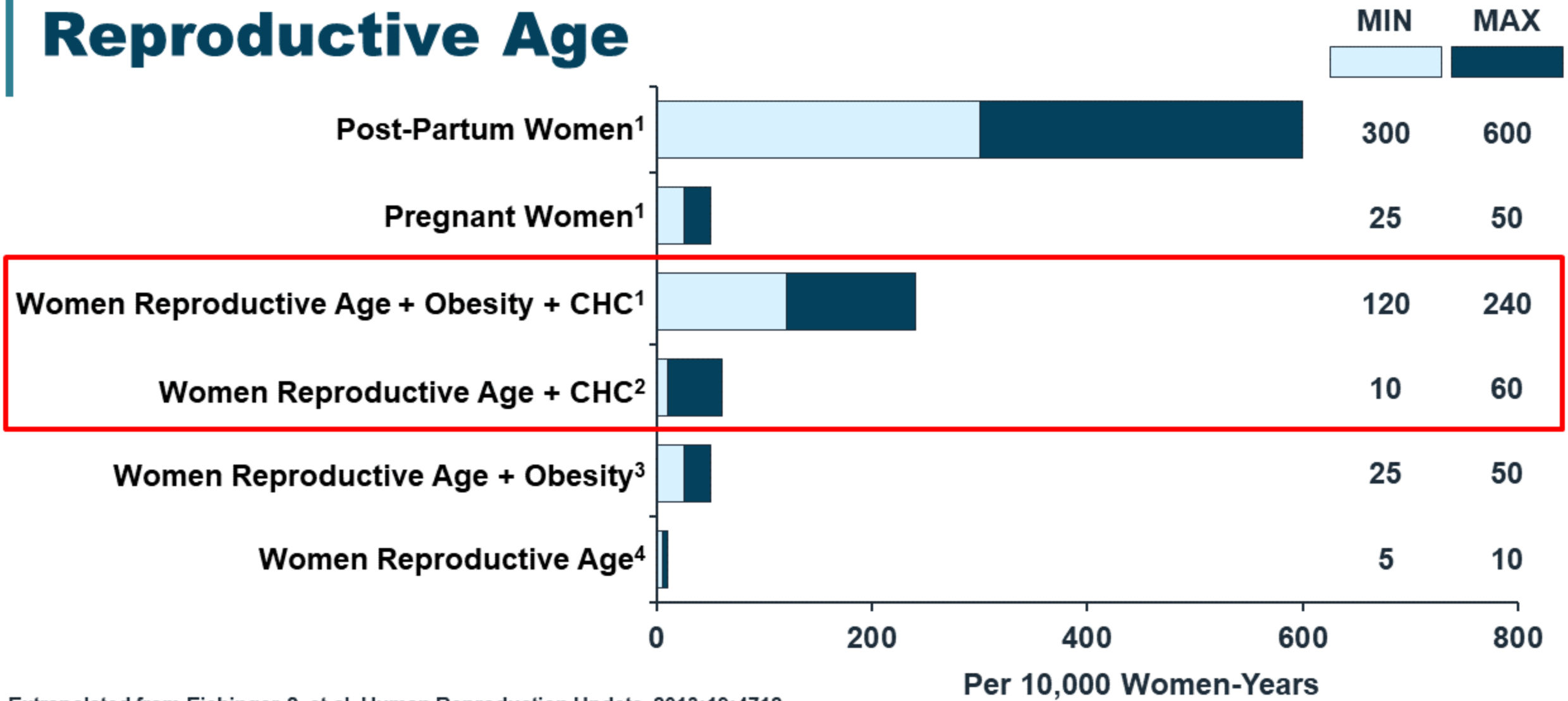
< 1 pregnancy per 100 women in 1 year	Fewer Pregnancies	• Implants • Injections • Intrauterine devices • Sterilization
		• Birth control pills • Skin patch • Vaginal ring with hormones • Vaginal system with hormones
10 to 20 pregnancies per 100 women in 1 year		• Condoms • Diaphragm
		• No sex during the most fertile days of the monthly cycle • Spermicide • Withdrawal
≥ 85 pregnancies per 100 women in 1 year	More Pregnancies	• No birth control

Bleeding Profile Consistent with Approved CHCs

	Incidence of Unscheduled Bleeding at 1 Year of Use	Mean Days of Unscheduled Bleeding / Spotting	
		Cycle 2	After 1 Year
Agile Patch	41%	2.3	1.6
Lo Loestrin Fe	36%	3.2	1.8
Quartette*	70%	17.8	6.6
Natazia	78%	1.5	0.7
Ortho Evra	8%	NR	NR
Annovera	22%	0.6	0.9

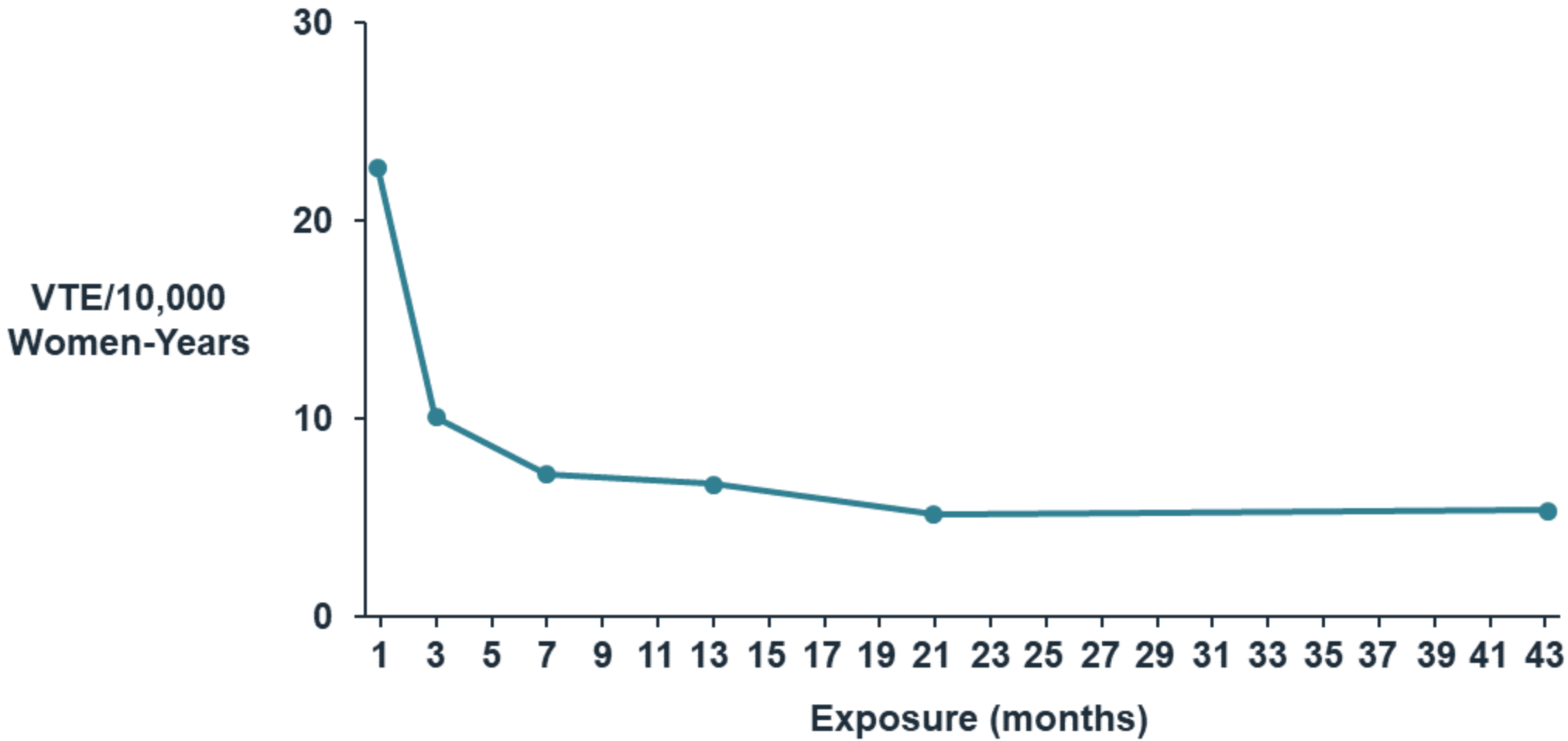
Not head to head data. NR = Not Reported
*Quartette rates of unscheduled bleeding based on four, 91-day cycles.

Incidence of VTE in Women of Reproductive Age



1. Extrapolated from Eichinger S, et al. Human Reproduction Update. 2013;19:4712.
2. Extrapolated from Lidegaard Ø, et al. BMJ. 2009;339:b2921 and BMJ. 2009;339:b2890
3. Extrapolated from Stein PD, et al. Am J Med. 2005;118:978
4. Heineman LAJ, et al. Contraception. 2007;75:328

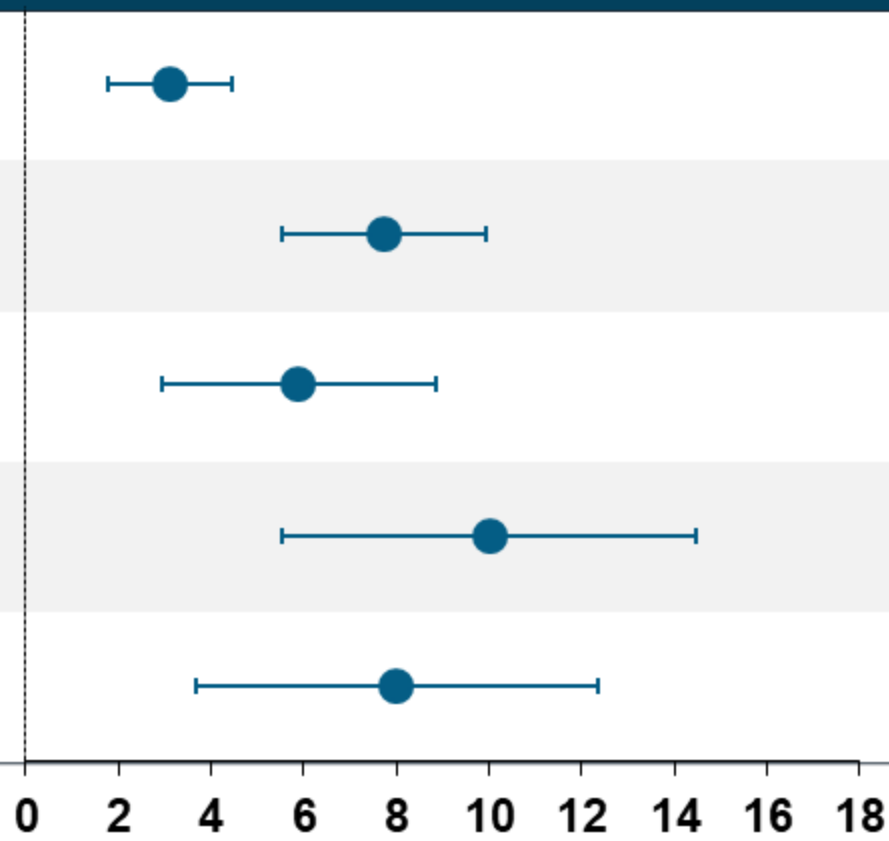
Clinical Trials Can Overestimate VTE Risk



Rabe T, et al. J Reproduktionsmed Endokrinol. 2011.

Study 23: On-Treatment Pregnancy Rates by Number of Prior Pregnancies for Women ≤ 35 Years Old

Number of Prior Pregnancies	N	Pearl Index	(95% CI)
0	937	3.10	(1.78, 4.43)
≥ 1	879	7.75	(5.54, 9.95)
1	378	5.89	(2.92, 8.87)
2	265	10.00	(5.52, 14.48)
≥ 3	236	8.01	(3.67, 12.36)



Regulatory Advice

"The Division agrees that the safety information in the updated Clinical Overview can be based on the Safety Update, which will contain data from the three phase 3 studies."

Pre-NDA Meeting 4/10/2017

"The serious risks with your product, including thromboembolic events, appear to be similar to those seen with other combined hormonal contraceptives."

Complete Response 12/21/2017

Alternative Indication

- *For use by females of reproductive potential* ***with a BMI < 30 kg/m^2*** *to prevent pregnancy*
  - Limitation of Use: Agile Patch has demonstrated reduced effectiveness in women who weigh 202 lbs (92 kg) or more and/or have a BMI of 30 kg/m^2 or more

Contraindication v. Limitation of Use

Contraindication	• Warranted when risk of use clearly outweighs any possible therapeutic benefit
Limitation of Use	• Used to identify population where drug should not be used • Situations may exist where use is appropriate based on clinical judgement

No Clinically Meaningful Differences in Exposure of LNG vs Application Site