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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

BONE, REPRODUCTIVE, AND UROLOGIC DRUGS
ADVISORY COMMITTEE
(BRUDAC)

Wednesday, October 30, 2019
8:15 a.m. to 3:55 p.m.

FDA White Oak Campus
White Oak Conference Center
Building 31, The Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland

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4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

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12 Biostatistics

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17 Associate Professor of Medicine

18 Chair, Metabolic Bone Disease Core Group

19 Division of Endocrinology

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2 *(Chairperson)*

3 Vice Provost for Faculty Development & Diversity

4 Professor, Obstetrics and Gynecology

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6 Rochester, New York

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19 Professor, Epidemiology

20 University of Pennsylvania

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1 **Sabrina Miller**

2 *(Patient Representative)*

3 Charlestown, Indiana

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5 **Thomas Ortel, MD, PhD**

6 Chief, Division of Hematology

7 Professor of Medicine and Pathology

8 Duke University

9 Durham, North Carolina

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11 ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

12 (Non-Voting)

13 **Venkateswar Jarugula, PhD**

14 *(Acting Industry Representative)*

15 Executive Director

16 Translation Medicine

17 Novartis Institutes for Biomedical Research

18 East Hanover, New Jersey

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1 **FDA PARTICIPANTS (Non-Voting)**

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3 Deputy Director

4 Division of Bone, Reproductive and Urologic

5 Products (DBRUP)

6 Office of Drug Evaluation III (ODE III)

7 Office of New Drugs (OND), CDER, FDA

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9 **Jerry Willett, MD**

10 Clinical Reproductive Team Lead

11 DBRUP, ODE III, OND, CDER, FDA

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13 **Nneka McNeal Jackson, MD**

14 Clinical Reviewer

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18 Director, Division of Biometrics III

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Rita Ouellet-Hellstrom, PhD, MPH
Associate Director of Epidemiology
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1 P R O C E E D I N G S

2 (8:15 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. LEWIS: Good morning, everyone. I would
6 like to first remind everyone to please silence
7 your cell phones, smartphones, or other devices if
8 you haven't already done so. I would also like to
9 identify the FDA press contact. She's standing
10 right there, Amanda Turney.

11 My name is Vivian Lewis, and I'm the chair
12 of the Bone, Reproductive, and Urologic Drugs
13 Advisory Committee. I will be chairing this
14 meeting. I will now call today's Bone,
15 Reproductive, and Urologic Drugs Advisory Committee
16 meeting to order. We'll start by going around the
17 table and asking everyone to please introduce
18 themselves and their affiliation. We'll start with
19 the FDA to my left and go around the table.

20 DR. GASSMAN: Good morning. My name is
21 Audrey Gassman. I'm the deputy director for the
22 Division of Bone, Reproductive, and Urologic

1 Products in the Center for Drug Evaluation and
2 Research.

3 DR. OUELLET-HELLSTROM: My name is Rita
4 Ouellet-Hellstrom. I'm associate director of the
5 Office of Epidemiology in OSE.

6 DR. WILLETT: I'm Jerry Willett. I'm a
7 clinical team leader in the Division of Bone,
8 Reproductive, and Urologic Products. I will be
9 presenting some background material. Thank you.

10 DR. McNEAL-JACKSON: Good morning. My name
11 is Nneka McNeal-Jackson, clinical reviewer in the
12 Division of Bone, Reproductive, and Urologic
13 Products.

14 DR. JOHNSON: Good morning. I'm Dr. Laura
15 Lee Johnson, director at the Division of
16 Biostatistics in the Office of Biostatistics III.

17 DR. BERENSON: Good morning. My name is
18 Abbey Berenson. I am professor of OB/GYN and
19 pediatrics and director of the Center for Women's
20 Health Research at the University of Texas at
21 Galveston.

22 DR. CHRISTMAS: Monica Christmas from the

1 University of Chicago, assistant professor and
2 director of the menopause program.

3 DR. LESLIE: Dr. Virginia Leslie, OB/GYN in
4 Portland, Oregon, at the Oregon Health and Science
5 University and at Virginia Garcia Memorial Health
6 Center.

7 DR. CURTIS: Good morning. I'm Kate Curtis.
8 I'm an epidemiologist in the Division of
9 Reproductive Health at CDC.

10 DR. E. EISENBERG: I'm Esther Eisenberg.
11 I'm the director of reproductive medicine and
12 fertility in the fertility and infertility branch
13 of NICHD.

14 DR. DRAKE: Hell. My name is Matthew Drake.
15 I'm an endocrinologist at the Mayo Clinic in
16 Rochester, Minnesota.

17 MS. BHATT: Good morning. I'm Kalyani
18 Bhatt. I'm the designated federal officer for the
19 advisory committee.

20 DR. BAUER: Good morning. Doug Bauer. I'm
21 professor of medicine, epidemiology, and
22 biostatistics from University of California, San

1 Francisco.

2 DR. SHAW: Hello. I'm Pamela Shaw. I'm
3 associate professor of biostatistics at University
4 of Pennsylvania.

5 MS. MILLER: Good morning. I'm Sabrina
6 Miller. I'm the patient representative out of the
7 Louisville, Kentucky area. Thank you.

8 DR. HUNSBERGER: I'm Sally Hunsberger. I'm
9 from the biostatistics research branch at NIAD,
10 NIH.

11 DR. MARGOLIS: Good morning. I'm David
12 Margolis. I'm a professor of epidemiology and a
13 professor of dermatology at the University of
14 Pennsylvania.

15 DR. D. EISENBERG: Good morning. I'm David
16 Eisenberg. I'm an associate professor in the
17 Department of Obstetrics and Gynecology at
18 Washington University in St. Louis.

19 DR. GAGLIARDI: Good morning. I'm Carol
20 Gagliardi. I'm a GYN consultant at the Veterans
21 Administration in New Jersey.

22 DR. HAIDER: Good morning. I'm Sadia

1 Haider. I'm an associate professor of obstetrics
2 and gynecology at the University of Chicago and the
3 division director of family planning.

4 DR. ORTEL: Good morning. I'm Tom Ortel.
5 I'm professor of medicine and pathology at Duke.
6 I'm chief of hematology and have a special interest
7 in thrombosis.

8 DR. JARUGULA: Good morning. I'm Venkat
9 Jarugula. I'm the industry representative on the
10 committee, and I'm from Novartis Pharmaceuticals.
11 I'm a clinical pharmacologist. Thank you.

12 DR. LEWIS: Thank you.

13 For topics such as those being discussed
14 today, there are often a variety of opinions, some
15 of which are quite strongly held. Our goal is that
16 today's meeting will be a fair and open forum for
17 discussion of these issues and that individuals can
18 express their views without interruption. Thus, as
19 a gentle reminder, individuals will be allowed to
20 speak into the record only if recognized by the
21 chair. We look forward to a productive meeting.

22 In the spirit of the Federal Advisory

1 Committee Act and the Government in the Sunshine
2 Act, we ask that the advisory committee members
3 take care that their conversations about the topic
4 at hand take place only in the open forum of the
5 meeting. We're aware that members of the media are
6 anxious to speak with FDA about these proceedings,
7 however, FDA will refrain from discussing the
8 details of the meeting with the media until its
9 conclusion. Also, the committee is reminded to
10 please refrain from discussing the meeting topic
11 during the break or lunch. Thank you.

12 I'll now ask Kalyani Bhatt to read the
13 Conflict of Interest Statement.

14 **Conflict of Interest Statement**

15 MS. BHATT: The Food and Drug Administration
16 is convening today's meeting of the Bone,
17 Reproductive, and Urologic Drugs Advisory Committee
18 under the authority of the Federal Advisory
19 Committee Act, FACA, of 1972. With the exception
20 of the industry representative, all members and
21 temporary voting members of the committee are
22 special government employees or regular federal

1 employees from other agencies and our subject to
2 federal conflict of interest laws and regulations.

3 The following information on the status of
4 this committee's compliance with federal ethics and
5 conflict of interest laws, covered by but not
6 limited to those found at 18 U.S.C.

7 Section 208, is being provided to participants in
8 today's meeting and to the public. FDA has
9 determined that members and temporary voting
10 members of this committee are in compliance with
11 federal ethics and conflict of interest laws.

12 Under 18 U.S.C. Section 208, Congress has
13 authorized FDA to grant waivers to special
14 government employees and regular federal employees
15 who have potential financial conflict when it is
16 determined that the agency's need for a special
17 government employee's services outweighs his or her
18 potential financial conflict of interest, or when
19 the interest of a regular federal employee is not
20 so substantial as to be deemed likely to affect the
21 integrity of the services which the government may
22 expect from the employee.

1 Related to the discussion of today's
2 meeting, members and temporary voting members of
3 this committee have been screened for potential
4 financial conflict of interest of their own as well
5 as those imputed to them, including those of their
6 spouses or minor children, and, for purposes of
7 18 U.S.C. Section 208, their employers. These
8 interests may include investments; consulting;
9 expert witness testimony; contracts, grants,
10 CRADAs; teaching, speaking, writing; patents and
11 royalties; and primary employment.

12 Today's agenda involves discussion of new
13 drug application NDA 204017, transdermal systems,
14 submitted by Agile Therapeutics, for the prevention
15 of pregnancy in women of reproductive potential.
16 This is a particular matters meeting during which
17 specific matters related to Agile Therapeutics' NDA
18 will be discussed.

19 Based on the agenda for today's meeting and
20 all financial interests reported by the committee
21 members and temporary voting members, a conflict of
22 interest waiver has been issued in accordance with

1 18 U.S.C. Section 208 (b) (3) to Dr. David
2 Eisenberg. Dr. Eisenberg's waiver addresses his
3 consulting with the competing firm. He receives \$0
4 to \$2,000 annually for this agreement.

5 The waiver also addresses his employer's
6 contract for a study with a competing firm for
7 which the employer receives between \$100,000 and
8 150,000 annually in funding. The waiver allows
9 Dr. Eisenberg to participate fully in today's
10 deliberations.

11 FDA's reasons for issuing the waivers are
12 described in the waiver documents, which are posted
13 on the FDA website. Copies of the waivers may also
14 be obtained by submitting a written request to the
15 agency's Freedom of Information division, 5630
16 Fishers Lane, Room 1035, Rockville, Maryland,
17 20857, or requests can be sent via fax to
18 301-827-9267.

19 To ensure transparency, we encourage all
20 standing committee members and temporary voting
21 members to disclose any public statements that they
22 have made concerning the product at issue. With

1 respect to FDA's invited industry representative,
2 we'd like to disclose that Dr. Jarugula is
3 participating in this meeting as a nonvoting
4 industry representative, acting on behalf of
5 regulated industry.

6 Dr. Jarugula's role at this meeting is to
7 represent industry in general and not any
8 particular company. Dr. Jarugula's employed by
9 Novartis Institutes for Biomedical Research.

10 We'd like to remind members and temporary
11 voting members that if the discussion involves any
12 other products or firms not already on the agenda
13 for which an FDA participant has a personal or
14 imputed financial interest, the participants need
15 to exclude themselves from such involvement, and
16 their exclusion will be noted for the record. FDA
17 encourages all participants to advise the committee
18 of any financial relationship that they may have
19 with the firm at issue. Thank you.

20 DR. LEWIS: Thank you.

21 I'd now like to proceed with the FDA opening
22 remarks from Dr. Gassman.

1 **FDA Opening Remarks - Audrey Gassman**

2 DR. GASSMAN: Good morning. I'd like to
3 welcome everyone to our FDA advisory committee
4 meeting on AG200-15. The purpose of today's
5 meeting is the division is seeking advisory
6 committee input on the acceptability of the
7 effectiveness and safety profile of AG200-15 and
8 their assessment of the benefit-risk.

9 Briefly, AG200-15 is a matrix transdermal
10 system containing levonorgestrel and ethinyl
11 estradiol. It delivers 120 micrograms of
12 levonorgestrel and 30 micrograms of ethinyl
13 estradiol daily. The dosing regimen is one
14 transdermal system to be worn for 7 days 3 three
15 consecutive weeks, followed by one transdermal free
16 week, and the transdermal system may be applied to
17 the abdomen, buttock, or upper torso. The proposed
18 indication is prevention of pregnancy in females of
19 reproductive potential, and the indication includes
20 a limitation of use statement related to body mass
21 index and weight.

22 Since the first combined hormonal

1 contraceptive was approved in 1960, the priority
2 has been to develop lower hormonal dose
3 formulations and more convenient dosing regimens
4 and dosage forms. However, effectiveness of the
5 combined hormonal contraceptive to prevent
6 pregnancy must outweigh the safety risks for
7 approval.

8 In January of 2007, we held an advisory
9 committee to discuss topics on development,
10 including study design and methods for hormonal
11 contraceptive trials and assessment of the
12 benefit-risk for hormonal contraceptives. We
13 received extensive recommendations during the 2007
14 advisory committee on the benefit-risks. I'm just
15 going to cover a few.

16 The committee recommended to allow
17 flexibility in Pearl indices, point estimates, and
18 upper bound of the confidence intervals for new
19 applications. However, during that time, I will
20 mention that they were talking about mean Pearl
21 indices in the 1 to 2 range. They also recommended
22 that we allow a variety of effective and safe

1 products, and that we consider active-controlled
2 trial designs.

3 At the 2007 meeting, there were also some
4 concerns raised related to active-controlled
5 trials, including permitting comparison to another
6 hormonal contraceptive product could lead to a
7 progressive widening of acceptable efficacy values,
8 otherwise known as "creep" unless decipherable
9 results. Also, there was some concern raised about
10 the feasibility of conducting active-controlled
11 trials, as this could be a barrier to the
12 introduction of new agents.

13 Now we're 12 years later, and I'm going to
14 mention some of the recommendations that we provide
15 for combined hormonal contraceptive trials. We
16 evaluate the benefit and risk of each combined
17 hormonal contraceptive product. We encourage
18 inclusion of adolescents, women of higher body mass
19 indices, underrepresented minorities, and other
20 subpopulations.

21 We changed our recommendation on
22 on-treatment pregnancy to limit it to those in

1 which the conception occurred during the treatment
2 cycle. We recommend standardized data collection
3 of bleeding and spotting data, and we continue to
4 recommend open-label, single-arm trials of at least
5 a year in duration as the basis of our
6 effectiveness and safety determination.

7 More broadly, for combined hormonal
8 contraceptives as a class, the division reviews
9 information, including but not limited to,
10 pregnancy rates using different methodologies,
11 adverse events, including those of special interest
12 for combined hormonal contraceptive, and
13 tolerability and usability data.

14 The division assesses combined hormonal
15 contraceptive effectiveness using the Pearl
16 indices. This is our primary efficacy endpoint,
17 and it's defined as the number of pregnancies per
18 100 women-years of use. Combined hormonal
19 contraceptive effectiveness is also defined by the
20 upper bound of the 95 percent confidence interval
21 of the Pearl indices.

22 The division selected a criteria of 5, and

1 this is based on pooled national survey data,
2 historic combined hormonal contraceptive trial
3 data, and also the need to find a favorable
4 benefit-risk for these products. I also briefly
5 want to mention unmet medical need. The FDA
6 defines unmet medical need as a condition whose
7 treatment or diagnosis is not addressed by
8 adequately available therapy.

9 Now, I want to turn to the division's
10 thinking on AG200-15. We do see benefits in
11 reducing unintended pregnancy, as that presents a
12 significant public health problem. From a
13 pharmacokinetic standpoint, AG200 delivers a lower
14 dose of ethinyl estradiol as compared to the
15 currently approved transdermal contraceptive
16 product. Another transdermal contraceptive product
17 could provide an additional alternative to women
18 seeking a noninvasive method of contraception.
19 AG200-15 reduces the risk of pregnancy compared to
20 women who do not use contraception.

21 I want to point out some of the division's
22 considerations regarding AG200-15. It does not

1 meet the FDA's regulatory definition of an unmet
2 need. It does not represent a low-dose product,
3 given the availability of products that are in the
4 10 to 20 microgram ethinyl estradiol range or
5 currently on the market.

6 AG200-15 does not convey safety advantage
7 over other types of combined hormonal
8 contraceptives. We believe that the Pearl indices
9 raise effectiveness concerns. We believe that the
10 VTE incidence rate, derived from the clinical
11 trial, raises a safety concern, and we also have
12 concerns that the tolerability, the cycle control,
13 raises clinical use concerns. We are seeking input
14 from this advisory committee before reaching a
15 final decision on the approvability of this
16 product.

17 Now, I'd like to briefly review the
18 discussion and voting questions. Discussion
19 question 1 is to discuss the effectiveness of
20 AG200-15, including your interpretation of the
21 efficacy results from Study 23 as they relate to
22 study design and enrolled patient population, and

1 your interpretation of the subgroup analyses by
2 body mass index, weight, race, and ethnicity.

3 The second discussion question is to discuss
4 the safety profile of AG200-15, including the
5 interpretation of the venous thromboembolism safety
6 signal and your interpretation of the product
7 tolerability data.

8 Finally, the voting question; we'd like you
9 to vote on whether the benefits of AG200-15
10 outweigh its risks and support approval for the
11 prevention of pregnancy. If you vote yes on this
12 question, we'd like panel members to explain the
13 rationale for their vote and address the following:
14 whether this product should be approved for use in
15 the general population or a narrower patient
16 population, and how this product should be used
17 within the context of available contraceptive
18 therapies. If you vote no on this question, we'd
19 like you to explain the rationale for your vote and
20 provide any recommendations you have. Thank you,
21 and I'd like to turn this back to Dr. Lewis.

22 DR. LEWIS: Thank you, Dr. Gassman.

1 Before we get started with sponsor's
2 presentation, I would like to announce that we have
3 one panel member who had to cancel due to an
4 emergency. That is Dr. Michele Orza, our acting
5 consumer representative. She's not able to attend
6 today's meeting.

7 At this point, we'll be proceeding with
8 Agile Therapeutics' presentation. Both the Food
9 and Drug Administration and the public believe in a
10 transparent process for information gathering and
11 decision making. To ensure such transparency at
12 the advisory committee meeting, FDA believes it is
13 important to understand the context of any
14 individual's presentation.

15 For this reason, FDA encourages all
16 participants, including the sponsor's non-employee
17 presenters, to advise the committee of any
18 financial relationships they may have with the firm
19 at issue, including consulting fees, travel
20 expenses, honoraria, and interest in the sponsor,
21 such as equity interest and those based upon the
22 outcome of the meeting.

1 Likewise, FDA encourages you at the
2 beginning of your presentation to advise the
3 committee if you do not have any such financial
4 relationships. If you choose not to address this
5 issue of financial relationships at the beginning
6 of the presentation, it will not preclude you from
7 speaking.

8 We will now proceed with presentations from
9 Agile Therapeutics. Thank you.

10 **Applicant Presentation - Geoffrey Gilmore**

11 MR. GILMORE: Good morning. My name is Jeff
12 Gilmore, and I'm a senior vice president at Agile
13 Therapeutics. We are pleased to be here today to
14 present the data supporting a positive benefit-risk
15 profile for AG200-15, an important new
16 contraceptive option for women. We will refer to
17 AG200-15 as the Agile Patch for the remainder of
18 this presentation.

19 Despite the many contraceptives available
20 today, women need more options to fit their
21 individual lifestyles and evolving needs. We agree
22 with FDA that unintended pregnancy is a significant

1 public health concern and that another transdermal
2 patch could provide women with a new noninvasive
3 contraceptive option.

4 Data show that many women want a
5 contraceptive patch, but the only choice available
6 today is Xulane, the generic of Ortho Evra, a
7 transdermal method that delivers approximately
8 56 micrograms of ethinyl estradiol, a high dose of
9 estrogen. Having a contraceptive patch that
10 delivers a significantly lower dose would be a
11 benefit to women who are seeking this option.
12 Today's advisory committee meeting will focus on
13 the approvability of the Agile Patch as that new
14 option.

15 Agile and FDA have discussed many topics in
16 our respective briefing books. Before we begin, I
17 would like to review four key issues. One, there
18 are varying definitions of low-dose estrogen with
19 respect to CHCs. The Agile Patch delivers
20 approximately 30 micrograms of ethinyl estradiol
21 daily, significantly less than the 56 micrograms
22 delivered daily by Xulane.

1 Two, the FDA considers an unmet need in
2 terms of serious conditions. In contraception,
3 however, needs are defined by gaps in and
4 satisfaction with available options such as an
5 alternative to a patch delivering a high dose of
6 estrogen.

7 Three, FDA suggests that Study 23 had a
8 prespecified success criterion based on the Pearl
9 index, the regulatory standard for evaluating
10 efficacy. As is typical in contraceptive trials,
11 Study 23 was not designed to meet a specific
12 criterion; it was a descriptive study designed to
13 estimate the Pearl index for the Agile Patch, with
14 a tight confidence interval. We achieved that
15 goal.

16 Four, significantly, FDA concludes that the
17 upper bound of the 95 percent confidence interval
18 of the Pearl index should be less than or equal to
19 5. This limit is based on historical contraceptive
20 studies with populations and designs known to yield
21 low Pearl indices, and thus have limited utility as
22 a basis for evaluating more contemporary trials

1 like Study 23. We will provide more detail on
2 these topics in our presentation today.

3 Now, I will provide an overview of the Agile
4 Patch in our clinical development program. The
5 Agile Patch is a combination hormonal
6 contraceptive, or CHC, that delivers
7 levonorgestrel, or LNG, and ethinyl estradiol, or
8 EE, through a multilayered, transdermal system.

9 The active ingredients LNG and EE, are
10 contained in a small active matrix that is located
11 at the center of the patch and covered by a
12 peripheral adhesive system. These active
13 ingredients are well known contraceptive hormones
14 with decades of widespread use and
15 well-characterized safety profiles. The Agile
16 Patch is designed to deliver approximately
17 30 micrograms of EE and 120 micrograms of LNG
18 daily. The patch is applied and changed weekly for
19 3 consecutive weeks, followed by a fourth week of
20 no patch.

21 The Agile Patch has been extensively studied
22 in a robust clinical program. The phase 1 and 2 PK

1 studies included our definitive PK trial, an
2 anatomic site study, an external condition study,
3 and a PK/PD study. We conducted a head-to-head
4 adhesion study against the Xulane patch.

5 Our phase 3 program consisted of three
6 clinical trials, Studies 12, 13, and 23. In
7 Studies 12 and 13, which were included in our
8 original NDA submission, the Agile Patch showed
9 similar efficacy and safety to two approved oral
10 contraceptive comparators. FDA questioned the
11 efficacy results because of study execution issues
12 that limited conclusions and confidence in the
13 results. The data, however, showed that the
14 efficacy of the Agile Patch was similar to an oral
15 CHC comparator.

16 Study 23 was designed with extensive FDA
17 input and was intended to provide a more precise
18 Pearl index estimate, with a tighter confidence
19 interval from which firm conclusions could be
20 drawn. We will present full safety and efficacy
21 data from Study 23 this morning, but it's important
22 to point out, Study 23 showed differential efficacy

1 in non-obese women and women with obesity.

2 Non-obese women had a Pearl index of 4.34,
3 while women with obesity had a Pearl index of 8.64,
4 with the Perl index increasing along with BMI.

5 Consistent with known risk factors, the VTEs in
6 Study 23 occurred only in women with obesity. No
7 VTEs occurred in non-obese women.

8 Based on these data, we propose the standard
9 indication to prevent pregnancy. Unlike other
10 contraceptive labels, we also propose the
11 limitation of use that reflects reduced efficacy in
12 women with obesity. Labeling would further clarify
13 efficacy in a table showing Pearl indices by BMI.

14 The question before you today raises a
15 possibility that the product could be approved in
16 the general population of women or in a narrower
17 population. For instance, an indication
18 restricting use to non-obese women, as shown with
19 this additional language, could also reflect our
20 data. We look forward to the committee's input on
21 this today.

22 Turning now to today's agenda, Dr. David

1 Portman, an OB/GYN who has extensively studied the
2 design of contraceptive trials and is a thought
3 leader on the evolution of Pearl indices, will
4 provide an overview of the clinical trial
5 environment and the need women have for additional
6 contraceptive options.

7 Dr. Elizabeth Garner will present the Agile
8 Patch trial design and the efficacy and safety
9 results. Dr. Portman will then return to offer his
10 clinical perspective on the data, as well as
11 provide a benefit-risk assessment on the Agile
12 Patch. We have additional experts with us today to
13 answer any questions that may arise. All external
14 experts have been reimbursed for their time and
15 expenses.

16 I will now turn the presentation over to
17 Dr. Portman. Thank you.

18 **Applicant Presentation - David Portman**

19 DR. PORTMAN: Good morning. My name is
20 David Portman, and I'm a board certified
21 obstetrician/gynecologist. Over the course of my
22 career, I've been a practicing physician, clinical

1 researcher, and an adjunct instructor of OB/GYN at
2 the Ohio State University. Today I'm a CEO of a
3 company investigating therapies to treat women's
4 advanced breast cancer.

5 Previously, I was a principal investigator
6 for the Agile Patch development program, as well as
7 for many other contraceptive trials over the last
8 two decades, informing my experience as a
9 reproductive health professional and contraceptive
10 researcher.

11 In fact, along with my fellow researcher,
12 the late Dr. James Trussell of Princeton
13 University, I co-authored a paper on a trend we
14 described as the "Creeping Pearl." The paper
15 explored why the rate of contraceptive failure,
16 known as the Pearl Index, has increased in clinical
17 trials of combined hormonal contraceptive pills
18 over the last several decades.

19 I'm here today to reflect on that assessment
20 and help set the stage for the discussion you'll be
21 having on the Agile Patch. First, I'll discuss
22 needs women and their healthcare providers have

1 when exploring contraceptive options. As you'll
2 see, options that avoid a daily pill without
3 requiring a long-acting method are limited; and
4 second, I'll review the evolving environment for
5 the contraceptive clinical trials.

6 Nearly all U.S. women will use contraception
7 at some point in their lifetime, and the selection
8 of a method is a preference-sensitive decision.
9 Each woman will weigh various factors that are
10 important to her when making an individual choice.
11 These factors include effectiveness, dose, desire
12 or not for hormonal methods, delivery route and
13 level of invasiveness, and frequency of
14 administration.

15 Certainly, no single method is right for all
16 women. Varying preferences and tolerability issues
17 lead to different contraceptive choices. This is
18 true not only from one person to another, but even
19 within an individual woman's reproductive years. A
20 woman may stay with a method for longer and is more
21 likely to be consistent with it if it's a method of
22 her choosing and fits her lifestyle.

1 Let's take a look now at the current
2 contraceptive options, which align along a spectrum
3 and are tiered based on effectiveness. The most
4 effective options, tier 1, include permanent and
5 semi-permanent methods requiring invasive
6 procedures and products such as sterilization and
7 IUDs.

8 Tier 2 include hormonal methods that mostly
9 rely heavily on user compliance, and tier 3 include
10 barrier and non-hormonal methods that require use
11 during each episode of sexual activity, and are,
12 thus, very prone to user failure. Without any
13 contraception, the annual rate of pregnancy is
14 85 percent.

15 Let's focus in on the combination hormonal
16 contraceptive options since that's the topic for
17 today's discussion. Combined hormonal
18 contraception contains both a progestin and an
19 estrogen component. A commonly used combination is
20 levonorgestrel and ethinyl estradiol, each of which
21 has been extensively utilized for decades.

22 It's the progestin component that prevents

1 pregnancy primarily by preventing ovulation, and
2 the progestins used in CHCs have differing
3 pharmacologic characteristics and tolerability
4 issues, such as mood changes, weight gain, and
5 acne. Estrogen is largely added for cycle control
6 and to optimize the bleeding profile.

7 Today, most pills have 35 micrograms or less
8 of estrogen. This dose attempts to minimize side
9 effects such as breast tenderness, headache, and
10 nausea, and improve the overall safety profile.

11 Doctors seldom prescribe contraceptives containing
12 50 micrograms of estrogen per day, and consistent
13 with this trend, here are some of the available
14 daily oral CHCs containing 35 micrograms or less of
15 estrogens that have been approved since 2001.

16 Having this selection of OCs with various estrogen
17 and progestin doses affords women the opportunity
18 to switch between a variety of combinations and
19 find the one that ultimately works best for her.

20 Here are the three, non-daily combined
21 hormonal options, the once weekly high-dose patch,
22 delivering approximately 56 micrograms of estrogen

1 per day; a monthly single-use vaginal ring; and a
2 monthly reusable vaginal ring with a year of use.
3 As you can see, lower dose options that avoid a
4 daily pill without requiring a long-acting method
5 are limited. Even with the wide variety of oral
6 contraceptives available, as you'll see here, women
7 are interested in non-oral and non-daily methods.

8 In 2002, when the Ortho Evra patch came on
9 the market, new prescriptions were initially
10 strong, accounting for more than 1 out of every 10
11 CHC prescriptions in the U.S. at its peak. In
12 2005, after reports of serious venous
13 thromboembolic events and data confirming that the
14 Ortho Evra patch's exposure level of estrogen was
15 approximately 60 percent higher than a 35-microgram
16 pill, use fell dramatically. My use and my
17 patient's interest dropped off significantly in
18 light of this news as well.

19 As the drop in Ortho Evra prescribing was
20 taking place, the intravaginal monthly
21 contraceptive NuvaRing became more popular, but use
22 of this intravaginal method never reached the peak

1 of the patch, confirming a gap in available
2 non-daily methods. The high-dose Ortho Evra patch
3 remains available as the generic Xulane, and yet
4 only 2 percent of women using contraception still
5 choose it.

6 However, there are advantages to transdermal
7 delivery. This method provides a controlled
8 release over time that offers the potential to
9 reduce the incidence or severity of side effects.
10 Transdermal delivery also avoids reduced
11 bioavailability seen with oral drug administration.
12 It may help women who have difficulty or avoid
13 taking oral medications, and a transdermal method
14 has the potential to reduce the daily pill-taking
15 burden some women associate with OCs. In fact, in
16 a multinational questionnaire, 49 percent of
17 contraception users reported preference of a
18 non-daily method and 52 percent were frustrated
19 with taking a pill daily.

20 Moving now to the evolving clinical trial
21 landscape, in clinical trials, the Pearl index is
22 the most common regulatory endpoint for

1 contraceptive efficacy. The Pearl index, defined
2 as the number of on-treatment pregnancies,
3 multiplied times 13 cycles, divided by the number
4 of on-therapy cycles times 100, provides an
5 estimate of the number of pregnancies per 100
6 women-years of product use; and the number of
7 cycles in the denominator directly impacts the
8 Pearl index, resulting with the 95 percent
9 confidence interval. Adding more patients or more
10 cycles may not affect the point estimate but would
11 drive down the upper bound.

12 As such, the Pearl index calculation is
13 highly sensitive to study design, duration, and
14 population factors, and certain factors used in
15 historical CHC trials are ones known to yield low
16 Pearl indices, including enrolling women in
17 European trial sites, restricting enrollment based
18 on BMI or weight, recruiting more affluent educated
19 women, not requiring women to anticipate or record
20 sexual activity, nor accounting for cycles without
21 sexual activity and efficacy analyses. These
22 studies produced results that were not

1 generalizable to U.S. women using contraception,
2 and as a result, there's been historically a wide
3 gap between clinical trial efficacy and actual use
4 effectiveness.

5 As drug developers have begun to update
6 enrollment criteria and analysis methods, the Pearl
7 indices from contemporary CHC trials have been
8 rising, which was the concept Dr. Trussell and I
9 termed as the "Creeping Pearl." Contemporary CHC
10 trials include multiple factors known to increase
11 Pearl indices that include limiting enrollment to
12 women living in the U.S., fewer to no restrictions
13 on body weight or BMI; documenting and removing
14 sexually inactive cycles; and more frequent
15 pregnancy testing with more sensitive tests.

16 The result has been more inclusive and
17 representative study populations, and a Creeping
18 Pearl more reflective of actual use effectiveness.
19 In fact, the identical contraceptives initial Pearl
20 index from its own registration trial often
21 increases when it's used as a comparator arm in
22 trials conducted more recently.

1 Here are three examples of this phenomenon
2 with Loestrin, Levlite, and Nordette. Just looking
3 at Levlite, for example, it had an initial Pearl
4 index upon its approval in 1998 of 0.29 based on a
5 European study, and then demonstrated a Pearl index
6 of 3.75 when it was used as a comparator in a later
7 U.S. more inclusive study.

8 Clearly, this pill is not 13 times less
9 effective now than it was in the late '90s. The
10 increase simply reflects a different population and
11 study design factors. Of note, this increase
12 occurred along with a backdrop of rapidly rising
13 rates of obesity in America that, unfortunately,
14 continues today, which is why women with obesity
15 are such an important population to consider and
16 include in CHC trials, and FDA has encouraged
17 sponsors to study women with obesity prospectively.

18 A meta analysis performed by the FDA looking
19 at individual patient data from 7 combination oral
20 contraceptive trials demonstrated that, overall,
21 there was a 44 percent increased risk of pregnancy
22 for women with obesity compared to non-obese women.

1 Keep in mind that the numbers in the third column
2 are hazard ratios and not Pearl indices.

3 Let me point you to the desogestrel/EE study
4 because it is one of the few that included no
5 restriction on BMI and had the highest percentage
6 of obese women in this analysis. The risk of
7 pregnancy was more than 2 and a half times greater
8 for women with obesity compared to women without,
9 and in the Ortho Evra patch, a nearly 9-fold
10 greater risk of pregnancy was observed.

11 When combining oral contraception and Ortho
12 Evra patch data, the overall hazard ratio for
13 pregnancy on CHCs and obese women is 65 percent
14 higher than a normal weight cohort. When including
15 a higher proportion of these women in a prospective
16 trial, the Pearl index will certainly increase.

17 In 2007, the BRUDAC provided FDA with its
18 recommendations on clinical trial design, assessing
19 the acceptability of risk and benefits and the role
20 and impact of labeling. The panel delivered clear
21 recommendations, including to change entry criteria
22 to reflect real-world prescribing, even if it

1 results in rising Pearl indices; conduct studies
2 with an active comparator; modify trial designs to
3 provide results that reflect effectiveness in the
4 real world; and avoid arbitrary limits for upper
5 bound of the 95 percent confidence interval in
6 order to bring the widest range of new
7 contraceptive options to market and ensure that all
8 relevant information be provided to the prescriber,
9 including data on particular subgroups.

10 The FDA's 2019 draft guidance on
11 contraceptive trials accepts most of these
12 recommendations listed here, but note, single-arm
13 studies are sufficient. You'll remember that in
14 2007, the BRUDAC also recommends that the FDA avoid
15 arbitrary limits for the upper bound of the
16 95 percent confidence interval be Pearl index. The
17 FDA guidance doesn't specifically set a limit but
18 expresses discomfort with upper bounds above 5 for
19 CHCs based on historic trials falling below that
20 upper bound.

21 On the one hand, FDA acknowledges that these
22 updated population and design factors, particularly

1 the inclusion of obese women, may yield higher
2 Pearl indices. On the other hand, FDA notes that
3 it's never approved a CHC with an upper bound of
4 the confidence interval greater than 5.

5 These two competing forces are across
6 purposes. We can either have narrow historical
7 studies that generate artificially low pearls, or
8 we can have inclusive, contemporary trials
9 reflective of and generalizable to the current U.S.
10 population. We can't have both. The diverse
11 population of U.S. women need a range of
12 contraceptive options as diverse as they are.
13 Women and their physicians also need accurate,
14 generalizable information generated from
15 prospective data and labels that fully inform them
16 of risks and benefits.

17 Keep in mind that the most effective
18 contraception ultimately is the one that best fits
19 with a woman's lifestyle and with an acceptable
20 side effect and risk profile, the right dose in
21 combination for her, and preferred route of
22 administration. What is currently needed is a

1 non-daily, transdermal option that does not deliver
2 a high dose of estrogen and contains a suitable and
3 different progestin component than what is
4 currently available.

5 Dr. Beth Garner will now present the Agile
6 Patch study results. Thank you.

7 **Applicant Presentation - Elizabeth Garner**

8 DR. GARNER: Good morning. My name is
9 Elizabeth Onyemelukwe Garner. I served as Agile's
10 chief medical officer from January 2014 through
11 July of this year, and continue to consult
12 on the clinical development and regulatory review
13 of the Agile Patch.

14 I'm an obstetrician gynecologist and began
15 my career practicing at Brigham and Women's
16 Hospital and Dana-Farber Cancer, and as an
17 assistant professor at Harvard Medical School.
18 I've devoted my entire career to women's health,
19 and I'm excited at the possibility of bringing the
20 new option to women who are interested in
21 transdermal contraception.

22 Today, I'll present the PK and adhesion

1 profiles for the Agile Patch, a brief overview of
2 the initial phase 3 Studies 12 and 13, and the
3 design and results of Study 23, which forms the
4 basis of the efficacy and safety of the Agile
5 Patch. I will also provide a high-level outline of
6 our postmarketing plans.

7 The data we generated support that the Agile
8 Patch feels a need and available contraceptive
9 options, and that its labeling can provide women
10 and prescribers with generalizable data to make
11 informed decisions. Let's talk about the hormone
12 delivery of the Agile Patch.

13 We evaluated the hormone delivery of the
14 Agile Patch in Study 14, confirming the Agile Patch
15 profile with regard to daily hormone delivery.
16 First, we found that the Agile Patch delivers
17 contraceptive levels of LNG. According to the
18 literature, the estimated threshold level of LNG
19 for contraceptive efficacy is in the range of 300
20 to 400 picograms per mL.

21 This shows mean cycle 2 and 3 LNG
22 concentration in 33 subjects. Mean levels of LNG

1 were above the estimated threshold for
2 contraceptive effectiveness throughout the week of
3 patch wear. Study 14 also confirmed that the Agile
4 Patch delivers daily exposure of approximately
5 30 micrograms of ethanol estradiol consistent with
6 lower dose CHCs. In CHC products, estrogen helps
7 to reduce breakthrough bleeding and support cycle
8 regularity.

9 This figure demonstrates the delivery of EE
10 over the 7-day wear period for the Agile Patch
11 compared to an oral CHC, Ortho-Cyclen. As
12 expected, based on the delivery route and dosing
13 schedule, the pharmacokinetic profiles of the Agile
14 Patch and the oral CHC follow distinctly different
15 patterns.

16 Using these same data for the Agile Patch,
17 we've now plotted the delivery of EE over one week
18 with the Ortho Evra patch. Though not a direct
19 head-to-head comparison, mean levels of EE with the
20 Agile Patch are approximately half of those of the
21 mean EE levels with the Ortho Evra patch, which
22 delivers approximately 56 micrograms per day.

1 In order to deliver adequate hormone levels,
2 it is imperative that a contraceptive patch adhere
3 to the user for the entire 7-day dosing period, so
4 we evaluated the in vivo adhesion of the Agile
5 Patch in two phase 1 studies and in Study 23, all
6 of which supported acceptable in vivo adhesion.

7 Study 16 was part of the original NDA and
8 showed at least 91 percent of women experienced
9 excellent adhesion under a range of external
10 conditions, including hot tub, cold pool,
11 treadmill, and sauna. In Study 25, conducted
12 earlier this year, the in Vivo adhesion of the
13 Agile Patch was shown to be noninferior to that of
14 the Xulane patch.

15 In Study 23, we measured at-home patch use
16 over 13 cycles. Adhesion improved over the first 3
17 to 4 months of use, and rates of detachments
18 decreased over time. This, of course, is not
19 surprising, as a learning curve is common when
20 individuals are using new products, including CHCs.

21 Now, let's turn to our phase 3 trials.
22 Studies 12 and 13 were the first two phase 3 trials

1 of the Agile Patch. Both included a comparator arm
2 of an approved LNG EE oral contraceptive and showed
3 that the Agile Patch performed similarly to two
4 approved CHCs. Importantly, the Pearl index in
5 each trial of the OC arm is well above 5, showing
6 that any study of an OC in this type of population
7 is likely to have a Pearl index above 5.

8 Study 12 was designed as a 13-cycle efficacy
9 study and yielded comparable Pearl indices at
10 6 months of 7.5 for the Agile Patch versus 6.67 for
11 the approved oral contraceptive Lessina. Study 13
12 was designed as a 6-month safety study and yielded
13 comparable Pearl indices of 8.19 for the Agile
14 Patch versus 6.8 for the approved oral
15 contraceptive, Levora.

16 Due to concerns regarding Studies 12 and 13,
17 FDA required a new phase 3 study to generate a more
18 precise estimate for the Pearl index of the Agile
19 Patch, and this brings us to Study 23, a first of
20 its kind phase 3 trial that forms the basis for the
21 efficacy assessment of the Agile Patch. We worked
22 very closely with FDA on the design of Study 23,

1 and this study was a single-arm, open-label,
2 13-cycle, multicenter study of the efficacy,
3 safety, and tolerability of the Agile Patch.

4 The study consisted of an initial screening
5 visit, followed by a run-in visit, and subsequent
6 run-in period during which women were required to
7 comply with daily use of an electronic diary.

8 Women who successfully completed the run-in were
9 enrolled for a treatment period of one year or 13
10 28-day cycles. Each participant was scheduled for
11 8 in-person clinic visits and 6 telephone visits.

12 Study 23 also featured rigorous pregnancy
13 testing. Urine pregnancy testing was performed
14 during each clinic visit, and we also provided
15 women with home pregnancy tests. Serum pregnancy
16 testing was done for all women at study completion
17 or at early discontinuation. Clinic visits also
18 included assessments for adverse events including
19 bleeding AEs.

20 Participants use e-diaries to enter daily
21 information on patch adhesion, patch application
22 site irritation or itching, and any vaginal

1 bleeding or spotting. E-diaries also captured
2 weekly information on patch change and removal day,
3 patch application site, sexual activity, and use of
4 backup contraception.

5 With the focus on study execution, we
6 incorporated
7 methods to maximize retention and to decrease the
8 discontinuation of women in the study. If a woman
9 missed a scheduled appointment or a study phone
10 call, she was to be contacted within 24 hours to
11 reschedule as soon as possible. If there was no
12 response after repeated attempts, she was
13 considered lost to follow-up.

14 When women discontinued for reasons other
15 than lost to follow-up, we arranged an end-of-study
16 visit where we confirmed pregnancy status with
17 urine and serum hCG testing, performed physical and
18 gynecological examinations, and conducted routine
19 laboratory evaluations.

20 I would like to now discuss the efficacy
21 assessment of the Agile Patch. As is the standard
22 for all contraceptive trials, the primary efficacy

1 endpoint was the Pearl index in women who were 35
2 years of age or younger. The sample size was
3 calculated based on a projected Pearl index of 3.5
4 and an upper bound of the 95 percent confidence
5 interval no greater than 5.

6 The agency's briefing books suggests that
7 this was a prespecified success criteria and that
8 is incorrect. Contraceptive trial protocols
9 include assumptions about efficacy for purposes of
10 sample size calculations, but those assumptions are
11 not intended to be tested as hypotheses. There's
12 no pass/fail for the primary endpoint. Rather,
13 contraceptive studies provide estimates of
14 efficacy.

15 Setting a sample size based on 3.5 and 5
16 seemed reasonable in 2014, based on recent
17 approvals, and it also seemed necessary based on
18 FDA stated discomfort with upper bounds greater
19 than 5. And as you'll see when I present the study
20 results, we did not accurately predict the
21 magnitude of impact the differences in the enrolled
22 population and design elements would have on

1 Agile's results compared to historical trials.

2 Based on FDA's feedback, Study 23 was a
3 contemporary inclusive trial designed to provide
4 efficacy data that are generalizable to the
5 population of women in the U.S. who use
6 contraception. The FDA's recommendations to us are
7 now included in the agency's 2019 draft guidance.

8 In particular, Study 23 enrolled only U.S.
9 patients with broad demographic diversity, had no
10 restrictions for BMI or weight, enrolled Women
11 required to anticipate sexual activity at least
12 once per month, creating an enriched population at
13 high risk for pregnancy. Study 23 excluded
14 sexually inactive cycles from the efficacy
15 analysis, and these are some of the critical
16 factors that can affect the Pearl index. Study 23
17 did not include a comparator, as Studies 12 and 13
18 had already been completed and showed similar
19 efficacy to oral contraceptives.

20 To help place the contemporary design of
21 Study 23 in context with historical CHCs, here's a
22 display with trial design factors for Annovera, a

1 vaginal ring, a representative sampling of recently
2 approved oral CHCs, and Ortho Evra, the only
3 approved patch. What is clear from this analysis
4 is that Study 23 is the only study that integrated
5 the key study design factors that can affect the
6 Pearl index, creating a unique trial.

7 In addition, it's important to go beyond
8 inclusion and exclusion criteria to see who really
9 enrolled. For example, if we look at Quartette,
10 the most recently approved oral CHC, even though
11 the enrollment criteria didn't restrict BMI,
12 28.6 percent of women were obese compared to 35.3
13 percent in the Agile Patch study. In addition, the
14 Quartette trial enrolled patients without
15 confirming anticipated sexual activity and did not
16 track sexual activity, and these differences can be
17 expected to have an impact on the data.

18 Let's move on to the Study 23 results
19 starting with demographics. Study 23's
20 demographics were representative of U.S. women
21 seeking a combined hormonal contraceptive.
22 Overall, a substantial proportion, 24 percent of

1 women were black or African American and about two
2 thirds were white. Twenty percent were Hispanic or
3 Latina, and these racial and ethnic demographics
4 are generally representative of the U.S.
5 population.

6 Without any restrictions on weight or BMI,
7 the distribution of these factors was reflective of
8 women in the U.S.. The mean weight was 167.7
9 pounds and the mean BMI was 28.3. Sixty-five
10 percent of the population studied was non-obese and
11 approximately 35 percent were women with obesity.
12 Ten percent were in a category of very obese and 8
13 percent were in a category of extremely obese.

14 Based on publicly available information and
15 FDA reviews, this population represents the highest
16 proportions of women in the categories of obese,
17 very obese, and extremely obese, and the highest
18 mean BMIs of any CHC registrational trial.

19 Now, the study disposition; 4,033 women
20 were screened and 2,032 were enrolled in Study 23.
21 Most of the screen failures were because of failure
22 to comply with the daily e-diary entries required

1 during the run-in period. One woman enrolled but
2 did not receive the Agile Patch, and so was not
3 included in the safety population.

4 Seven women in the safety population tested
5 positive for preexisting pregnancy; thus, 2024 were
6 eligible to be included in the overall
7 contraceptive efficacy population. 1,823 were
8 women age 35 or younger, and of these, 87 did not
9 contribute cycles to the analysis. Thus 1,736
10 women comprised the primary efficacy population.

11 With regard to discontinuation, overall,
12 including women over 35 years of age, 51 percent
13 withdrew prior to completion of 13 cycles.
14 Discontinuations were evenly distributed across the
15 13 cycles of the trial. The discontinuation rate
16 of 51 percent was similar to the rates observed in
17 phase 3 studies of many currently available CHCs,
18 and as a reminder, these are the same CHCs that I
19 presented earlier for comparisons of the study
20 designs.

21 The reasons for study discontinuation were
22 as follows: 15 percent decided to discontinue

1 mostly due to e-diary, fatigue, or scheduling
2 challenges; 11 percent were lost to follow-up.
3 Adverse events led to study discontinuation in
4 about 11 percent of women.

5 Now, I'd like to move on to the efficacy
6 results. The results of the primary efficacy
7 analysis in Study 23 demonstrate that the Agile
8 Patch was efficacious in the prevention of
9 pregnancy. Based on a total of 68 on-treatment
10 pregnancies across 15,165 cycles, the Agile Patch
11 effectively prevented pregnancy with a Pearl index
12 of 5.83 and a 95 percent confidence interval of
13 4.45 to 7.21.

14 Importantly, the results in the non-obese
15 population, which comprised 9,888 cycles, shows a
16 Pearl index of 4.34 and an upper bound of 5.82,
17 also a tight estimate. And because study 23
18 included other new study design factors that go
19 beyond BMI, we find this efficacy finding both
20 reassuring and acceptable.

21 Interpreting Agile's results in a time of
22 rising Pearl indices is challenging. FDA

1 acknowledges the Pearl indices have been rising
2 over time and notes the cross-trial comparisons can
3 lead to incorrect conclusions and are generally not
4 recommended. The agency then relies on historical
5 comparisons when it finds the Agile Patch efficacy
6 is unacceptable in light of other approved
7 products, which showed an upper bound of less than
8 5 at approval. This analysis relies on Pearl
9 indices that come from different studies with
10 different designs, with different populations.

11 Study 23 is also supported by Studies 12 and
12 13 in which the Agile Patch demonstrated similar
13 efficacy to oral contraceptive comparators. We
14 conducted Study 23 to refine the point estimate for
15 the Pearl index and achieved this goal as
16 demonstrated by the substantial reduction in the
17 width of the confidence interval.

18 Now, let's take a closer look at our BMI
19 data. Keeping in mind that 35 percent of our
20 population had obesity and that this is an
21 important emerging factor affecting Pearl pro
22 indices, we prespecified an analysis to look at

1 this. Overall, these findings show that BMI had a
2 substantial impact on efficacy most notably in
3 women with BMI at or above 30.

4 As a reminder, our proposed labeling
5 includes a full description of these results by
6 BMI, as well as the limitation of use based on
7 reduced efficacy for women with obesity. In an
8 alternate label, as you can see on the screen, the
9 Agile Patch could be approved in a restricted
10 population of non-obese women and further studied
11 in women with obesity, and we very much look
12 forward to the panel's discussion on this issue.

13 Many CHC labels are silent on BMI and
14 weight. Quartette is one of these products. In
15 the Quartette pivotal study, while the upper bound
16 of the 95 confidence interval was 4.03 overall, the
17 Pearl index increased with weight, reaching an
18 upper bound of 7.6 in women with a weight of 90
19 kilograms or higher. Quartette's label, however,
20 has no BMI information in the indication and has no
21 information about Pearl index trends by weight.

22 We've talked a lot about BMI, but I don't

1 want to lose sight of the fact that there are other
2 study factors that affect the overall Pearl index
3 and the Pearl index in non-obese women. We
4 conducted a sensitivity analysis in the overall
5 population to illustrate the effects of study
6 design and population on efficacy results. For
7 this analysis, we assessed the impact of just two
8 key study design factors: sexual activity and BMI.

9 First, regarding sexual activity, to model a
10 study that did not monitor sexual activity or
11 remove sexually inactive cycles from the Pearl
12 index denominator, we added back in the 5.4 percent
13 of cycles with no sexual activity that had been
14 excluded from the Agile Patch Pearl Index
15 denominator. To model a study in which women with
16 obesity were excluded, we then removed cycles from
17 women with a BMI over 30, while assuming a similar
18 overall sample size of Study 23

19 With just these two adjustments, the Pearl
20 index for the Agile Patch was calculated to be 4.08
21 with an upper bound of 5.15, showing a substantial
22 effect of just two of the study design factors on

1 the efficacy results.

2 Finally, I'd like to briefly present the
3 life table efficacy analysis, which provides the
4 cumulative probability of pregnancy or failure rate
5 observed across the 13 cycles of a study.

6 Statisticians generally prefer life table analyses
7 because they're much less dependent on
8 unsupportable assumptions in the PI. Prescribers
9 rely on life table analyses to communicate
10 clinically relevant information when counseling
11 their patients.

12 In Study 23, the cumulative probability of
13 pregnancy for the overall population was 5.29
14 percent, which is within the failure rate that is
15 currently observed from actual use data in women
16 using tier 2 methods. When we look at the
17 non-obese population, the cumulative probability of
18 pregnancy drops to 3.97 percent; and as a reminder
19 for context, the one year pregnancy rate without
20 contraception is 85 percent.

21 In summary, the clinical data demonstrate
22 that the Agile Patch is efficacious in the

1 prevention of pregnancy. The phase 3 study
2 populations were broadly representative of U.S.
3 women, 35 percent of whom are women with obesity;
4 7 percent of whom are women in the highest BMI
5 category.

6 Study 23 in particular enrolled a population
7 of sexually active women. In non-obese women, who
8 comprised 65 percent of the population, the Agile
9 Patch demonstrated acceptable efficacy, and these
10 results reflect a contemporary inclusive
11 contraceptive trial conducted in the manner that
12 the BRUDAC in 2007 and the FDA have recommended in
13 its new draft guidance.

14 Next, I'll review the safety results from
15 study 23. Study 23 showed that the safety of the
16 Agile Patch is in line with the well understood
17 profile of combination hormonal contraceptives.
18 Overall, the most common adverse events among CHC
19 trials are similar. All CHCs are associated with
20 certain hormone-related adverse events, many
21 derived from exposure to estrogen, most commonly
22 breast tenderness, headache, and nausea. Higher

1 doses of estrogen, such as in the Ortho Evra patch,
2 generally correlate with higher rates of
3 hormone-related adverse events.

4 The phase 3 safety database included
5 integrated data from Studies 12, 13, and 23, and
6 was composed of a population of 3,481 women with
7 29,900 cycles of exposure. Our NDA safety
8 assessment is based on integrated data from
9 Studies 12, 13, and 23, as requested by FDA.
10 Today, though, I'll be focused on safety from
11 Study 23 to align with FDA's briefing book.

12 This table reflects treatment- emergent
13 adverse events occurring in women who used the
14 Agile Patch in both the overall safety population
15 and the non-obese population in Study 23. In the
16 overall population, 53 percent of women experienced
17 an adverse event and 27 percent experienced a study
18 drug related adverse event. Five percent
19 experienced a severe AE; 2 percent experienced a
20 serious AE; and 1 percent had a study drug related
21 AE; 11 percent of women discontinued due to an AE,
22 and there were no deaths in women using the Agile

1 Patch. These numbers are similar for non-obese
2 women.

3 Looking at these AE categories more closely,
4 for a CHC, hormone-related adverse events are the
5 most relevant. In Study 23, the most common events
6 were nausea and headache in both the overall and
7 the non-obese populations. Although there are
8 limitations of cross-trial comparisons, showing
9 data from other relevant CHC trials can provide
10 some helpful context for safety.

11 We selected these comparators to provide a
12 spectrum of recently approved estrogen CHCs, as
13 well as Ortho Evra, the only approved contraceptive
14 patch, and as shown, adverse events reported by
15 patients in the Agile Patch trial were generally in
16 line with those observed in the phase 3 trials of
17 Lo Loestrin, the lowest dose CHC, and Quartette,
18 the most recently approved oral CHC.

19 Percentages of hormone-related AEs observed
20 in the Agile Patch trials were generally lower than
21 those observed in the Ortho Evra trials. For
22 example, 4.1 percent for nausea for the Agile Patch

1 and 16.8 percent for Ortho Evra. These differences
2 are possibly related to the higher delivery of
3 estrogen with the Ortho Evra patch compared to the
4 Agile Patch.

5 For the topical delivery system, rates of
6 patch application site adverse events were
7 important to evaluate. Overall, 6.2 percent of
8 women in Study 23 reported any application site
9 disorder. The most common application site adverse
10 events reported in 1 percent or more included
11 irritation, skin discoloration, and pruritis.
12 Overall, few women discontinued from the trial due
13 to application site disorders; and again, the
14 results in the non-obese population were similar.

15 Although not a head-to-head comparison, the
16 overall percentage of women reporting application
17 site disorders with the Agile Patch was lower than
18 the 17.1 percent observed with the Ortho Evra patch
19 trials, which reported a bundled term for
20 application site disorders.

21 With regard to AEs leading to study
22 discontinuations, rates for the Agile Patch were

1 generally in line with other registrational trials.
2 With respect to the types of these AEs, overall,
3 the rates were low for any specific type. The most
4 frequently reported were patch site irritation,
5 nausea, and patch site pruritis for both the safety
6 population and the non-obese population.

7 When women begin a CHC, instances of
8 unscheduled bleeding and spotting of varying
9 duration and intensity are common. For most women,
10 episodes of bleeding become less frequent and less
11 intense over time. The bleeding profile for women
12 who used the Agile Patch in Study 23 was consistent
13 with this profile. Over time, we observed a
14 reduction in the incidence of breakthrough bleeding
15 and/or spotting.

16 While FDA raised concerns about
17 discontinuation due to bleeding, rates of adverse
18 events of bleeding or spotting that led to a
19 discontinuation were low for both the overall and
20 the non-obese populations and generally in line
21 with those for other approved CHCs.

22 Moving on to serious adverse events, 2

1 percent of women experienced an SAE. The most
2 common were cholelithiasis, deep vein thrombosis,
3 pulmonary embolism, major depression, and
4 gastroenteritis. Focusing on the most important
5 SAE related to hormonal contraception, a total of
6 5 individuals experienced 6 events of a deep vein
7 thrombosis and/or pulmonary embolism, together
8 referred to as VTEs or venous thromboembolism.

9 The FDA excluded one of these as not related
10 to the Agile Patch, resulting in 4 women
11 experiencing a hormone-related VTE event. In the
12 non-obese population, including normal and
13 overweight subjects, no woman experienced a VTE.
14 All VTE events occurred in women with obesity who
15 are known to be at a higher baseline risk for
16 clotting events.

17 In summary, the Agile Patch has a safety
18 profile that is acceptable. The most commonly
19 observed adverse events were expected and occurred
20 at low rates, and led to discontinuations at rates
21 consistent with other CHC products. Further, local
22 patch site reactions were generally infrequent and

1 also led to few discontinuations. The serious
2 risks with the Agile Patch, including
3 thromboembolic events, are in line with known CHC
4 risks.

5 I'd like to end with a review of our
6 post-approval plans should the Agile Patch be
7 approved. Agile proposed to participate in a
8 class-wide study of transdermal, vaginal, and oral
9 CHCs to answer remaining questions about the class
10 effects of these products in women with obesity.

11 We recognize that there are practical
12 limitations for a multisponsor study. If
13 discussion today leads to approval of the Agile
14 Patch in the non-obese population, we would propose
15 to conduct a prospective, head-to-head trial,
16 comparing the Agile Patch versus an oral
17 contraceptive in a population of obese women. The
18 outcome of such a study would certainly advance our
19 understanding and also inform a decision regarding
20 whether the indicated population should include
21 women with obesity or not, and we welcome the
22 committee's thoughts on what such a study might

1 look like.

2 Thank you very much. I'd like to ask
3 Dr. Portman to return to offer his clinical
4 perspective.

5 **Applicant Presentation - David Portman**

6 DR. PORTMAN: Thank you, Dr. Garner.

7 I believe the Agile Patch provides women
8 with a lower dose contraceptive patch option with
9 an acceptable benefit-risk profile. Thinking about
10 the unmet need, the Agile Patch would be an
11 important addition to the available hormonal
12 methods and at last offer a choice among
13 transdermal options.

14 We cannot assume that all women who use
15 contraception are necessarily satisfied with
16 currently available options. The assortment of CHC
17 pills with a variety of doses, estrogens, and
18 progestins allows women to switch to one that will
19 ultimately meet her needs. Like the current CHC
20 options, the Agile Patch would provide women with
21 independence, reversibility, and efficacy, and with
22 a cumulative annual pregnancy rate of 5.3 percent,

1 it fits nicely among the other CHC methods.

2 In non-obese women, the cumulative annual
3 pregnancy rate drops to 4 percent. Uniquely, the
4 Agile Patch would be the only non-daily,
5 noninvasive option that delivers less than 56
6 micrograms of estrogen. Importantly, the most
7 effective option for an individual woman is the one
8 that she feels the most comfortable using that
9 satisfies her own preferences and needs.

10 Turning to efficacy, Study 23 provided
11 substantial evidence of efficacy of the Agile
12 Patch. The observed Pearl index point estimate was
13 5.83 in the overall population and 4.34 in the
14 non-obese population, demonstrating acceptable
15 efficacy. Importantly, results show that the
16 combined effect of all study design and population
17 factors into a single trial, particularly
18 significant numbers of women with obesity, had a
19 substantially greater impact on the Pearl index and
20 upper bound results than anticipated.

21 Remember, these sexually active women in
22 Study 23 used the Agile Patch as their only method

1 of contraception at an expected rate of pregnancy
2 with unprotected intercourse as 85 percent after
3 one year. In Study 23 the life table risk for
4 pregnancy was 5 percent, demonstrating robust
5 contraceptive efficacy. We did observe reduced
6 efficacy in women with BMI greater than or equal to
7 30, which represented 35 percent of the study
8 population.

9 Let's place the Agile Patch data on obesity
10 in the context of FDA's individual patient
11 meta-analysis, and remember that we're looking at
12 hazard ratios and not Pearl indices. The findings
13 are consistent with results from other trials, with
14 a calculated hazard ratio for the Agile Patch of
15 2.38 for pregnancy risk in women with obesity
16 compared with non-obese women and a tight
17 confidence interval because of the number of obese
18 women included in the trial. You'll also note that
19 this is similar to the effect seen in the approved
20 oral contraceptive, desogestrel/EE study, which had
21 no restriction on BMI in its study and had an
22 adjusted hazard ratio of 2.67.

1 The impact on the Pearl index from the obese
2 populations is evident, and this type of
3 prospective data in a traditionally understudied
4 population is useful and very welcomed. The Agile
5 Patch proposed label includes a limitation of use
6 based on its prospective results in women with a
7 BMI greater than or equal to 30, and would be the
8 first CHC to break down effectiveness by BMI in its
9 label.

10 For the first time, physicians have specific
11 data to share with heavier patients about CHC
12 efficacy rather than an absence of data from which
13 to speculate. Alternatively, if the panel only
14 recommends approval in the population of women with
15 a BMI of less than 30, I'd still like sufficient
16 information to discuss the effect of BMI on
17 efficacy and safety with my patients.

18 Turning to safety, the safety profile of the
19 Agile Patch is acceptable and similar to the well
20 understood profile of other CHCs, which carry known
21 risks disclosed through class labeling. The low
22 incidence of estrogen-related side effects such as

1 nausea, breast tenderness, and headache, and a
2 favorable bleeding profile were consistent with
3 that of approved CHCs.

4 The well-characterized levonorgestrel
5 component did not lead to significant
6 progestin-related side effects and offers women
7 seeking a patch, not only a lower dose of estrogen
8 in the currently available Xulane, but a different
9 progestin, which may be preferred by many women.

10 As for venous thromboembolic events, it's
11 well known that the risk increases with CHC use in
12 all women, and even more so in women with obesity.
13 The observed rate with the Agile Patch is
14 consistent with what would be expected in the women
15 enrolled. The VTE events occurred in women with
16 obesity, and no VTEs occurred in non-obese women.
17 So for my non-obese patients, the Agile Patch would
18 be a safe, effective option, and for my patients
19 with obesity, the data generated in this study
20 would encourage me to strongly discuss alternative
21 contraceptive strategies as a first line of
22 therapy.

1 Returning to the Pearl index, we are seeing
2 Pearl indices rising. To summarize why, more
3 recently studies like Agile's have been conducted
4 in populations of women who are increasingly
5 representative of likely users in the U.S.. These
6 contemporary trials include, among other things,
7 the factors listed here, which are known to yield
8 higher Pearl indices.

9 This is a positive development since results
10 from studies like 23 help us in closing the gap
11 between perfect use efficacy results observed in
12 historical clinical trials and typical use
13 effectiveness seen in a diverse U.S. population.
14 It does pose a challenge to all of us who have
15 become accustomed to lower Pearl indices. We
16 should not, however, return to the days of narrow
17 study populations rigged to succeed and hit an
18 arbitrary upper bound, and instead embrace the
19 challenges that inclusive studies present.

20 As more trials are conducted in this way,
21 upper bounds higher than 5 will likely become much
22 more common. The FDA's 2019 draft guidance

1 underscores the importance of making these changes,
2 and the Agile program is a significant step in the
3 right direction.

4 As I conclude, I wanted to share my thoughts
5 on how I would counsel a woman who is considering
6 the Agile Patch among a variety of options. I'd
7 pose a series of questions that clarify what would
8 work best for her and her individual needs, such as
9 is a hormone-containing product right for you? Is
10 a lower dose of estrogen appealing to you? Do you
11 have a preference for a daily or less frequently
12 administered option? And are you comfortable with
13 a method that requires a procedure or insertion?

14 I'd assess her health status and share the
15 Agile Patch label, specifically the BMI chart so
16 she could see her own risk category. With a BMI
17 over 30, I would seriously consider other
18 alternatives and would certainly not recommend an
19 even higher dose patch. And should she ultimately
20 choose the Agile Patch, we'd discuss the importance
21 of weekly compliance and what to do in the event of
22 a missed or displaced patch.

1 It's all of these factors she and I would
2 weigh with shared decision making to be able to
3 consider and help her make an informed decision.

4 As we've discussed, ultimately the best,
5 most effective contraception for an individual
6 woman is the one she determines is right for her.
7 I believe the Agile Patch could be that right
8 decision for many women, and hope you'll support
9 making it available to them. Thank you.

10 Dr. Garner will now return to moderate the
11 Q&A session.

12 **Clarifying Questions to Applicant**

13 DR. LEWIS: Thank you.

14 Are there any clarifying questions for Agile
15 Therapeutics? Please remember to state your name
16 for the record before you speak and please identify
17 which presenter your question is directed to, or if
18 it's a general question, to all the presenters.

19 I'm going to ask Dr. Shaw to ask the first
20 question.

21 DR. SHAW: Hi. Thank you. I just have two
22 clarifying questions, and this is for Dr. Garner.

1 The first question relates to slide 33. I just
2 wanted to clarify that I think I heard a statement
3 about the exposure for the Agile Patch was 30
4 micrograms of the ethinyl estradiol. In the
5 package I received, looking at the PK, I saw a
6 number that was closer to 35.7, and that was in
7 Table 7, page 43. That was the steady-state
8 concentration between 2 to 7 days.

9 So I just was wondering is it 36 or is it
10 30? Why are those numbers different?

11 DR. GARNER: Right. First of all, you're
12 correct in the table that you saw. There is an
13 additional calculation that takes place to
14 generate, to get to the 30. We can provide more
15 detail on that analysis for you.

16 Actually, Dr. Furmanski, would you like to
17 describe the specific calculation that gets the 30
18 micrograms?

19 DR. FURMANSKI: Sure. Good morning. I'm
20 Brian Furmanski. I'm the senior director of
21 clinical pharmacology and pharmacokinetics at
22 Nuventra. As for the calculation and dose, there

1 are very minor differences. The difference is due
2 to the parameter chosen.

3 FDA utilized AUC 0/168. The sponsor used a
4 C average, which is the concentration over time
5 divided by the dosing interval. That ultimately
6 yields a very small change in dose, about a
7 microgram? The biggest change is the inclusion of
8 the groups. So if you group 1 and 2 together, as
9 the sponsor did, you get 30 micrograms. If you
10 choose only one group, you get 36, as FDA.

11 DR. GARNER: Dr. Furmanski, could you also
12 just specify in the table, the 35.7 and how you get
13 to the 30 one?

14 DR. FURMANSKI: Right. Thank you. To
15 calculate the sponsor's dose, you use the first
16 CS-1 concentration, the 35.7, divided by the
17 Ortho-Cyclen exposure, 41.5, times the Ortho-Cyclen
18 dose, which is 35 micrograms, and that's how you'll
19 get 30.

20 DR. GARNER: And just to point out, FDA used
21 the same methodology to reach the 35 micrograms,
22 really not a significant clinical difference, at

1 least, between 30 to 35. We really have no
2 disagreement there.

3 DR. SHAW: Yes, I appreciate that. I just
4 wanted to understand that, so I appreciate the
5 detail. Then one other quick question, I think.
6 It's on slide 54, and it's the sensitivity analysis
7 for Dr. Garner as well.

8 I just want to make sure, because I was
9 really interested in the sensitivity analysis for
10 the Pearl index in the materials you provided. I
11 thought I saw a similar statistic that when you
12 remove these two factors, the 5.4 percent of the
13 cycle, so that's sexual activity, and you remove
14 the women with a greater BMI, that the upper limit,
15 the Pearl index was 5.5 -- and it was on page 70 of
16 the packet -- and not the 5.15. I was just
17 wondering.

18 DR. GARNER: I suspect that may have been a
19 typographical error. It should be 5.15.

20 DR. SHAW: So in the presentation or in the
21 materials?

22 DR. GARNER: In the materials.

1 DR. SHAW: Because all the numbers are
2 different. It was 4.10, and then 2.7, and 5.5.

3 DR. GARNER: Okay. My apologies for that.
4 These are the correct numbers.

5 DR. SHAW: Alright. Thank you.

6 DR. LEWIS: Thank you. Dr. Margolis?

7 DR. MARGOLIS: Great. Thank you. I also
8 have two questions for Dr. Garner. The first one
9 is slide 41. I just want to make sure I understand
10 this slide.

11 To me, what seems to be incredibly important
12 for these studies is including women who are
13 sexually active. Is it true, based on this slide,
14 and the vast majority of other studies, women
15 weren't prescreened that shows that they were
16 sexually active or even asked, before they were
17 enrolled?

18 DR. GARNER: Just to clarify on that,
19 generally what is asked for a contraceptive trial
20 is a yes/no question. Are you sexually active; yes
21 or no? In order to ensure that our subjects were
22 having regular sexual activity, we added an extra

1 question. And this was actually at the
2 recommendation of FDA, and we discussed it with
3 them. We really wanted to make sure we had a
4 population that was truly at exposure for
5 pregnancy.

6 So what we added to the question was not
7 only just a yes/no answer, but do you anticipate
8 that you will have sexual activity at least once a
9 cycle during this study? And if the answer was no
10 to that question, the subject was not eligible for
11 the study, and that is very different. We could
12 only find one other trial -- I believe the most
13 recent, I believe Slynd approval, or it may be the
14 Annovera, one of those two -- that included that
15 question.

16 Just one other point to that. I think FDA
17 was careful to point out that they have recommended
18 over the years that during the study, sexual
19 activity be tracked, so that one other thing, and
20 that at the end of the study, that you exclude any
21 cycles from the denominator of the Pearl index in
22 women who didn't have sexual activity, and they

1 have consistently recommended that.

2 We could only find our trial. Our prior
3 phase 3 studies, and the Lybrel study is the only
4 ones that have actually followed that
5 recommendation. So it has been a consistent
6 recommendation, but it hasn't been followed by
7 sponsors. I think Quartette is a particularly
8 excellent example. They had the yes/no question,
9 so obviously patients answered yes to be enrolled
10 in the trial. But then during the trial, no sexual
11 activity was tracked.

12 So we have no idea, actually, in the
13 Quartette trial what the sexual activity was of the
14 patients who are enrolled, and, of course,
15 therefore they couldn't exclude those cycles
16 either.

17 DR. MARGOLIS: And do you know how often
18 people were screened out?

19 DR. GARNER: From our trial? We had a
20 number of prescreeners that were done. Those
21 patients didn't make it into our actual screening.
22 Once we prescreened people, sites had various

1 questionnaires that were available. Once we
2 actually prescreened people, there was a fairly
3 small number of people who actually screened out
4 for lack of regular sexual activity.

5 DR. MARGOLIS: Then the other question has
6 to do with your use of the word "substantial."

7 DR. GARNER: Yes.

8 DR. MARGOLIS: You use it quite frequently
9 when you're comparing parameters. By using the
10 word substantially, were you saying that things
11 were statistically significantly different or that
12 the numbers just appeared different to you, and
13 you're using substantial as an intensifier?

14 DR. GARNER: Yes, that's a great point. We
15 are not necessarily claiming we are showing
16 statistical difference.

17 DR. MARGOLIS: Thank you.

18 DR. LEWIS: Dr. Jarugula?

19 DR. JARUGULA: This is I think for
20 Dr. Garner. I have a couple of questions regarding
21 the performance of the patch, the transdermal patch
22 in Study 23. You have monitored the adhesion

1 performance in the study. I'd like to see the
2 adhesion data and also the effect of the body
3 weight on the blood levels, the PK of both LNG and
4 also EE. We just would like to issue ourselves
5 that the performance in obesity is not because of
6 the exposure issues and adhesion issues.

7 DR. GARNER: Why don't we have Dr. Furmanski
8 speak first to the PK profile and obesity. And
9 while he's walking up there, I will say we've seen
10 slight differences, but overall, obese women in all
11 of our studies have been above that threshold for
12 efficacy, but Dr. Furmanski can provide more
13 detail.

14 DR. FURMANSKI: Great. As Dr. Garner said,
15 we do see a slight trend in decreasing exposure
16 with increasing BMI. The first example is with EE.
17 As you see, the mean concentration or the average
18 concentration with increasing BMI, you see a slight
19 trend in exposure in this decile plot.

20 We see the same effect with LNG, which is
21 here. It's important to note, though, with LNG,
22 that it's above this critical threshold previously

1 identified of 400 picograms per mL. So even in the
2 morbidly obese population, above 40 kilograms per
3 metered per meter squared, you still see adequate
4 exposure of LNG.

5 DR. GARNER: Thank you. And then to answer
6 your question around adhesion in Study 23, first
7 I'll point out that we didn't see any differences
8 in adhesion in women with and without obesity, so I
9 think that's a very important point. But
10 overall -- can you just bring up the slide showing
11 the re-adhesion data?

12 As we're waiting for that slide, the graph
13 showing re-adhesion, this is the overall results
14 from Study 23. What we see very clearly is that we
15 showed adequate adhesion. I would also point out
16 that during Study 23, subjects were using an
17 electronic diary to enter daily scores. So we have
18 far more adhesion data in
19 Study 23 than any other trial of a patch, and
20 particularly the Ortho Evra trial.

21 What we see here is that -- sorry, the
22 scores are a little bit confusing. But the bottom

1 line here is we saw a substantial -- careful using
2 that word. But we saw an increase in patch
3 adhesion, both with regard to partial adhesions and
4 detachments. We saw an improvement as the study
5 went on.

6 I would add also it's important to note that
7 patients were instructed in the actual trial of
8 Study 23, that if they saw the patch may be
9 partially coming off, to re-adhere it. What we
10 show in this slide in particular is that once
11 subjects followed those instructions to re-adhere
12 the patch, you can see that by, 3-4 months into the
13 trial, we were showing very, very high adhesion
14 rates.

15 DR. JARUGULA: Just a quick follow-up
16 question on this slide. Also, you have another
17 slide, which states that there is a learning curve
18 of 3 to 4 months to apply this patch properly.

19 DR. GARNER: Yes.

20 DR. JARUGULA: I was wondering if you have
21 any data on the time course of the pregnancies that
22 occurred in the study.

1 DR. GARNER: So we did look at whether there
2 was any evidence of relationship between adhesion
3 and pregnancy. We looked at this in a number of
4 different ways and found no relationship. It's
5 also very common in contraceptive trials in
6 general. I would say the OB/GYNs here are familiar
7 with this, that the failures tend to occur a little
8 bit earlier in the trial. But we saw no evidence
9 that that was related in any way to adhesion.

10 DR. JARUGULA: Just one quick follow-up on
11 this. So then the patient reapplied the patch, did
12 you also monitor the timeline about when they
13 reapplied as opposed to when the previous patch
14 fell off?

15 DR. GARNER: When I say reapplied, I mean
16 they're reapplying the same patch. And edge might
17 have come up slightly, and then they reapply the
18 same patch. Generally speaking, we did look at
19 those adhesion scores very carefully, and, in
20 general, the patch did not seem to be partially
21 adhered for generally any more than a 24-hour
22 period. Patients seemed to follow it quite closely

1 and made sure they re-adhered the patch quickly.

2 DR. JARUGULA: Okay. Thank you.

3 DR. LEWIS: Dr. Curtis?

4 DR. CURTIS: Kate Curtis. First, I wanted
5 to say that I'm really glad to see the study design
6 of Study 23. I agree that that's really getting us
7 closer to more of a real-world effectiveness. It's
8 not typical use effectiveness. But I was wondering
9 if you could tell us more about your decision not
10 to use an active comparator.

11 You had seen higher PIs in the earlier
12 studies, and even though you did have an active
13 comparator, that wasn't convincing to FDA. I think
14 we're essentially moving to a new standard for
15 effectiveness, and when you do that, you generally
16 use some kind of active comparator to be able to
17 make that transition.

18 DR. GARNER: Yes, we certainly considered
19 it. Ultimately, our belief in what we have seen in
20 Studies 12 and 13, we believe was very informative.
21 I'm going to ask Dr. Wittes to describe some of
22 that thinking.

1 DR. WITTES: I'm Janet Wittes. What we saw
2 in 12 and 13, as you saw before, what to me was
3 really interesting was actually the high pearls in
4 the oral contraceptives. They were much higher
5 than had been projected.

6 What we did at the time was to do a little
7 meta-analysis, taking all the data from 12 and
8 13 -- I'm trying to get it to come up, and it
9 doesn't want to come up -- and asking what is the
10 Pearl index in the oral contraceptives in 12 and
11 13. So this is a meta-analysis weighted by the
12 inverses of the variances, and you see a Pearl
13 index of 5.62 with pretty narrow confidence
14 intervals, pretty close to the Agile patches.

15 So the thinking was, although some people
16 would have preferred a control, was that this told
17 us that if there had been a control in 23, the oral
18 contraceptive would have been pretty similar to the
19 Agile Patch.

20 DR. CURTIS: Can I just follow up real
21 quick on that? Can you tell us a little bit about
22 the differences between 12 and 13 and 23? I mean,

1 if it were just numbers, then maybe you could make
2 that assumption, but from the briefing book, I'm
3 getting there were several differences between 12
4 and 13 and the design of 23. So I think that would
5 help us think through whether that assumption is
6 correct, whether if you had an active comparator in
7 23, would it still have given you a similar point
8 estimate but just a narrow confidence interval. I
9 guess I'm not convinced that you can make that
10 assumption.

11 DR. GARNER: I can speak to that.
12 Certainly, the study populations were very, very
13 similar, and we think that was obviously important.
14 What we didn't see in Studies 12 and 13 was the
15 obesity issue. I think that had to do, to a large
16 degree, with mostly approaches of the study
17 execution, not so much the design of the trial.

18 So, really, the only substantial difference,
19 I would say that study 12 had a crossover arm where
20 the patients on OCs switched over. Obviously, we
21 didn't have the comparator, so that's not an
22 important difference. Then in study 23, we added

1 that question about sexual activity, which we had
2 not had before. So in the prior studies, all we
3 asked was the typical, are you sexually active; yes
4 or no?

5 So we think we might've had a more sexually
6 active population potentially in study 23. But
7 again, we were heavily focused on compliance,
8 avoiding loss to follow up as best we could. So we
9 do believe a lot of this is numbers and getting
10 more precision.

11 One thing Dr. Wittes I think has described
12 to us is if the results from 23 were truly just
13 unexpected, what we should not have seen was,
14 really, just a narrowing of that confidence
15 interval, coming to just bring down what we saw in
16 Studies 12 and 13 and to narrow it. So we believe,
17 essentially, what we got out of Study 23 was more
18 precision around the Pearl index.

19 DR. LEWIS: Thank you. Dr. Bauer?

20 DR. BAUER: Hi. Doug Bauer. So a couple of
21 questions. I'm sure it's in the book, but were 12
22 and 13 open-label studies or were they --

1 DR. GARNER: Yes.

2 DR. BAUER: They were. Then going to slide,
3 the first slide I wanted to ask you about was just
4 the run-in, so that's slide 45. I think you said
5 that between screened and enrolled, that was during
6 the run-in. And I'm sorry. How long was the
7 run-in?

8 DR. GARNER: Two weeks.

9 DR. BAUER: Two weeks. Just two weeks.
10 Okay. And was a dummy patch applied then or was
11 that only for a diary?

12 DR. GARNER: No. Yes.

13 DR. BAUER: Okay. Thank you. Then my last
14 question actually has to go to slide 51, please.
15 You spent a lot of time talking about obesity, but
16 as you can see, there are a lot of overweight women
17 in your studies as well. In fact, the point
18 estimate is between the normal and the obese, which
19 I guess suggests that it's a continuous
20 relationship.

21 DR. GARNER: Right.

22 DR. BAUER: So I was just wondering if we're

1 going to discuss that at some point or how you feel
2 that the risk-to-benefit ratio differs for the
3 obese women, but you haven't really talked much
4 about overweight women.

5 DR. GARNER: We believe that the
6 benefit-risk profile of this product supports that
7 it should be made available to all women. I think
8 we've talked about our Pearl index and the reasons
9 we saw this Pearl index, and the safety profile
10 with VTE rates that we believe are expected for
11 this population and consistent with other trials.

12 We have focused on the non-obese women here,
13 as you see on the slide, because I think their
14 profile is a little bit different from the obese
15 women. So we focused on non-obese mainly because,
16 from a robustness standpoint, we have a substantial
17 number of cycles in that group of women. We have
18 9,888 cycles, so we believe they can essentially
19 stand on their own.

20 In terms of overweight women, as you ask
21 about, we agree with you completely this is, I
22 believe, a continuum, and of course overweight

1 women are included in that non-obese populations,
2 so we're putting them into that same category. If
3 we believe they saw no VTEs in that category, a
4 lower rate of hormone-related AEs.

5 I'd like Dr. Portman, though, to provide
6 some of his clinical perspective on these
7 particular groups.

8 DR. PORTLAND: As Dr. Garner mentioned,
9 based on the group that we looked at as non-obese,
10 that's really where we see that the safety and the
11 benefit-risk are clearly in favor of that. This
12 being a continuum, I think that's really why the
13 informative label will really help with shared
14 decision making. The patient can see where she
15 falls in that range. She can think of the various
16 options that she has.

17 So if we go ahead and look at the Pearl
18 indices, as you see, for the normal weight
19 patients, 3.46, non-obese, 4.3, these are virtually
20 identical pregnancy rates. So I think that when
21 we're talking about a continuum of effectiveness,
22 these are all clearly in the tier 2 category,

1 highly effective, reversible methods. They're not
2 tier 1, they're not IUDs, they're not implants, but
3 they're far superior to barrier, and acts, and the
4 types of methods that require activity for each
5 sexual act.

6 So I think that's what we have to weigh and
7 then put into context, is highly effective,
8 reversible versus those that they might choose as
9 an alternative, which would be far less helpful in
10 preventing unintended pregnancy.

11 DR. BAUER: I specifically was asking
12 whether you plan to address the overweight women as
13 a subgroup separate from the non-obese women, as
14 related to both safety and efficacy.

15 DR. PORTLAND: As I said, I think that a
16 label that breaks it down by BMI category, um,
17 would be in the clinical efficacy section of the
18 label would be very informative, and then patients
19 and physicians can make that choice. There may be
20 some women who are overweight but not technically
21 in that category that may choose the method, and
22 the benefit-risk balance for that patient may be

1 adequate. There may be others that would say that
2 would sway them to use a different method.

3 DR. LEWIS: Thank you. Dr. Leslie?

4 DR. LESLIE: I'm curious to hear more detail
5 on how you incorporated, or did not incorporate,
6 cohort 1 and 2 into your primary and secondary
7 outcome data. We haven't talked about that much
8 yet. You mentioned it on page 18 of your
9 monograph.

10 DR. GARNER: Can you clarify?

11 DR. LESLIE: You mentioned on page 18 of
12 your monograph discussion of a cohort 1 and a
13 cohort 2. Cohort 1 involved patients who did not
14 comply, I believe, with your backup method. When
15 they missed a patch, there were certain
16 requirements about whether they were using backup
17 methods or not.

18 I'm afraid the detail was not as clear as I
19 wanted it to be, but it looks like you talked about
20 those cohorts based on your primary outcomes and
21 your secondary outcomes a bit.

22 DR. GARNER: Yes. I believe what you're

1 referring to is the ITT versus what we call the per
2 protocol population. By doing this, we were
3 essentially trying to get at some of the deeper
4 compliance issues around whether they used backup
5 or not, because, obviously, if you are late to
6 applying a patch and you don't use backup, you have
7 a higher risk of pregnancy.

8 So that's what essentially we were looking
9 for. These are the results from that analysis.
10 Again, what we see is that particularly for women
11 in the non-obese category, when we actually looked
12 at this particular population and excluded women
13 who didn't use that backup method, then we see an
14 even lower Pearl index. So it's a little bit like
15 following the instructions versus not, and if they
16 did, they had a lower Pearl index.

17 DR. LEWIS: Dr. David Eisenberg?

18 DR. D. EISENBERG: Dr. Eisenberg from St.
19 Louis. I agree with Dr. Curtis that I think we're
20 approaching the kind of trials we want to see that
21 are more typical-use trials. I applaud the
22 communication between the FDA and the company to do

1 this study, but I have some questions about the
2 submission packet -- I guess it's
3 Section 11.4 -- regarding how the e-diary works.

4 Having been a PI on contraceptive trials and
5 knowing that diaries are, at best, not perfect, the
6 e-diary seems like it has opposing forces as well.
7 Am I correct in that the subject was prompted every
8 day to fill it out? It's not the kind of thing
9 where they were sitting in the parking lot outside
10 the research center filling in the last month worth
11 of data?

12 DR. GARNER: That's correct. She was given
13 a reminder to enter the diary data.

14 DR. D. EISENBERG: So while that is a more
15 accurate assessment of the actual prospective
16 experience of the subject user, it is also not
17 typical use to be prompted to deal with your patch
18 on a daily basis. So how do we account for those
19 competing interests?

20 DR. GARNER: Yes. That's an interesting
21 conversation that we've had also. We were very,
22 very careful in the design of our diary. We

1 thought very carefully about that. We knew it was
2 important, of course, to gather the information we
3 needed, so understanding when the patient was
4 applying her patch and removing it was critical, of
5 course, to getting accurate results around the
6 dates to be able to assess pregnancy.

7 It was also really important to get -- I
8 think the FDA in particular was extremely
9 interested in subject-reported adhesion, so that
10 was a big reason why we had those reminders. We
11 were very careful not to over-remind, though, about
12 applying patches. So it was a reminder to just put
13 your diary data, but it wasn't necessarily a
14 reminder to apply patches.

15 So we felt we achieved that right balance of
16 getting the data, having a much better collection
17 system than the paper diaries that you described
18 that we needed to do, but also achieving a balance.

19 Dr. Portman, do you have any thoughts on
20 that for real world?

21 DR. PORTMAN: I appreciate Dr. Eisenberg's
22 comment that we are approaching where efficacy

1 meets effectiveness, which is what I think all of
2 us want to know, is how to inform our patients what
3 they might experience in the real world.

4 Interestingly, Pearl creep seems to be in
5 clinical trials, but if you look at the national
6 survey for family growth, patients in the general
7 population have had a relatively stable pregnancy
8 rate. I think this might be due to the new use of
9 apps. Even though they're using these diaries to
10 record bleeding and sexual activity, I think in the
11 real world, they'll be able to use similar methods
12 for reminders to mimic what we're kind of seeing
13 here.

14 So I don't think that this is such an
15 idealized group that we're enriching for
16 compliance, and I think there's also still a social
17 desirability bias. Patients want to come in and
18 please the investigators and the site personnel, so
19 they're going to really tell us about perfect
20 compliance in the trial setting, and it probably
21 isn't. So we probably are seeing something that's
22 very reflective of what's going on in the general

1 population.

2 DR. D. EISENBERG: So just to clarify, this
3 was basically an app that they could use on their
4 own mobile device or you gave them a device?

5 DR. GARNER: They had a hand-held device.

6 DR. D. EISENBERG: So it was a separate
7 device that wasn't their own device?

8 DR. GARNER: Correct.

9 DR. D. EISENBERG: Okay.

10 DR. LEWIS: Thank you. Dr. Esther
11 Eisenberg.

12 DR. E. EISENBERG: Thank you, and we're
13 unrelated.

14 (Laughter.)

15 DR. E. EISENBERG: My question has to do
16 with breakthrough bleeding. You talked a little
17 bit about it, but in use with patients, that tends
18 to be a real issue. Did you look at breakthrough
19 bleeding by BMI, and was there a difference?

20 DR. GARNER: We did, and we did not see any
21 significant differences around BMI. We can show
22 you those data if you'd like.

1 DR. LEWIS: Dr. Berenson.

2 DR. BERENSON: My question is about slide
3 number 52, the proposed indication where 202 pounds
4 is mentioned in addition to the BMI of 30. Why is
5 it necessary to have the 202 pounds and not just
6 the BMI as the indication? I'm concerned that
7 patients or providers could fixate on that number,
8 and that is certainly a very high number for women
9 of average height.

10 DR. GARNER: As we figured out sort of what
11 this limitation of use should be in terms of BMI
12 and weight, we considered a couple of things. One,
13 the Ortho Evra label is actually based just on
14 weight, so they don't have a BMI that's mentioned
15 in that labeling. We were really trying to be
16 pretty much consistent with what providers and
17 patients have been used to seeing.

18 As well, just to mention, we also used the
19 same methodology in terms of the deciles, and
20 that's how we reached the 202. But the other issue
21 is that I think most patients, probably if you
22 asked them, would not know their body mass index.

1 They'll mostly know where they are more or less in
2 terms of pounds. So we felt that that was just
3 more clearer for patients to see a number that they
4 could relate to in terms of weight.

5 DR. BERENSON: Can I ask a follow-up
6 question? Because I didn't see any data presented
7 in your presentation examining 202 pounds. Did I
8 miss that?

9 DR. GARNER: We didn't show it, but I can
10 show you now. We actually prespecified a decile
11 analysis also by weight, and that's what you see
12 here. In addition to BMI, we also did a number of
13 analyses related to weight, showed the very same
14 effects on Pearl index that we saw for BMI.

15 Where the 202 comes from is that -- and this
16 is the same methodology that was used, I would just
17 point out, for coming up with the cutoff for the
18 Ortho Evra patch; and these aren't firm statistics
19 I would point out, but we followed the same
20 approach. They saw in the highest decile of
21 weight, over on the right for Ortho Evra, a
22 breaking point, essentially, at 198 pounds. We saw

1 what we thought was a fairly similar breaking point
2 for the highest two deciles, and that ninth decile
3 starts with the 202, which is why we selected that
4 number.

5 DR. LEWIS: Thank you. Dr. Hunsberger.

6 DR. HUNSBERGER: I just have two quick
7 clarifying
8 questions. I'm trying to understand the
9 denominator for the number of cycles, and I think I
10 read that you excluded cycles where there was a
11 backup method.

12 DR. GARNER: Correct.

13 DR. HUNSBERGER: Did the other studies do
14 the same?

15 DR. GARNER: Yes. That has been very
16 consistent across studies.

17 DR. HUNSBERGER: Okay, so across studies.
18 Okay. Great.

19 The other thing, it's a clinical question.
20 Is there a higher number of VTEs for obese people
21 just in general?

22 DR. GARNER: Yes. I would like Dr. Piazza

1 just to speak a little bit to what is observed in
2 the general population for VTEs.

3 DR. PIAZZA: I'm Greg Piazza. I'm one of
4 the vascular medicine cardiologists at Brigham and
5 Women's Hospital and a thrombosis researcher.
6 Depending on the analysis, there's a 2- to 8-fold
7 increased risk of venous thromboembolism in the
8 obese population. When you combine that with
9 hormonal contraception, it gets magnified.

10 DR. LEWIS: Thank you. Dr. Ortel?

11 DR. ORTEL: On slide 52, and to follow up on
12 the last comment, we've had a lot of discussion
13 about the safety component, but in this, both you
14 and Dr. Portman don't have anything about the
15 potential concern for safety in the obese
16 population. Should there be something in there
17 that also says there is the potential concern for
18 increased risk of venous thromboembolism in the
19 obese population? Otherwise, it just gets dropped.

20 DR. GARNER: We have a number of places in
21 the proposed labeling where we talk about safety.
22 The reason that's not mentioned in the limitation

1 of use is that typically a limitation of use is
2 based on efficacy, and that's what providers expect
3 to see. So they wouldn't be looking there for any
4 safety issues.

5 There are typical places in the labeling
6 where they would be looking for it, and we spent a
7 lot of time thinking about how best to label this
8 product for those women. The indication, as I
9 mentioned, the limitation is based on efficacy.
10 But in the warnings and precautions, we've
11 mentioned specifically that obesity is a risk
12 factor for VTE.

13 In the adverse events section, we specify
14 the VTEs that were observed in women with obesity.
15 We've specifically mentioned that all of the
16 women -- actually, we included the
17 additional -- the fifth patient that we talked
18 about that was excluded in our labeling, and also
19 mentioned specifically that all of those patients
20 were women with obesity just to advise prescribers
21 and patients.

22 In the specific populations section, again,

1 we mentioned a reduced efficacy. We talk again
2 about the VTEs. Then in the patient counseling
3 section, we take care to mention that people who
4 would potentially be prescribing this should think
5 about other methods, specifically if a woman has a
6 higher BMI.

7 So there are a number of places where it's
8 mentioned and the places where providers I think
9 would be looking for that information, so we feel
10 it's obviously very important to communicate.

11 DR. LEWIS: Dr. Shaw, did you have another
12 question?

13 DR. SHAW: Dr. Berenson asked my question
14 about that 202 pounds. Thanks.

15 DR. LEWIS: Dr. Curtis, did you have another
16 question?

17 DR. CURTIS: I do. So you've given us a lot
18 of good information about the proposed labeling
19 with regard to BMI, but I was wondering if you
20 could talk a little bit about the proposed labeling
21 for effectiveness overall, given that we do have
22 higher Pearl indices, and we're not sure how much

1 that relates to actual method effectiveness versus
2 the creeping Pearl issues, and women and their
3 providers are going to be making decisions and
4 comparing effectiveness across methods.

5 Can you talk a little bit about how you will
6 present just general effectiveness in the label and
7 communicate that?

8 DR. GARNER: Of course, we've not had a
9 chance to discuss this with FDA at all, but that, I
10 recall from the labeling, we haven't necessarily
11 mentioned specifics around, the reasons why it
12 potentially -- you know, the population reasons and
13 so on, the reasons why our Pearl index might be
14 higher but not indicate lower effectiveness in the
15 overall population.

16 I think your thinking is actually very
17 interesting, and that gives us some thoughts about
18 how we might do this to communicate to providers.
19 What we plan to do so far is to provide, obviously,
20 this information around BMI, specifically in a
21 table. There's also a weight -- in the text of the
22 labeling, we also mention the same findings in

1 weight, but only have the table for BMI. Then, of
2 course, the study population section does describe
3 in great detail the study population in terms of
4 all of the various factors that we've mentioned.

5 Anything to add, Dr. Portman?

6 DR. PORTMAN: As you know, the Pearl index
7 will be included in the prescribing information.
8 Clinicians will be able to look, and hopefully
9 marketers won't come in and compare label to label
10 and say, "Oh, look. This product has a Pearl of 5,
11 and a pill that was approved 20 years ago has a
12 Pearl of 0.5. Look how much better that is."

13 So I think it's very important that this
14 educational piece get out there and put it into the
15 context of modern trial design. But they will have
16 that information, so if a clinician feels that this
17 Pearl is informative and that they would choose a
18 product with perhaps a slightly better one, they
19 would have that ability to do so. I hope they put
20 it in the context of when those trials are
21 conducted and the differences between trial design.

22 DR. GARNER: Another item that's in the

1 labeling also is the failure rates as well, along
2 with that, showing the continuum of effectiveness,
3 as well, that we think might be helpful. But we
4 would appreciate any recommendations.

5 DR. CURTIS: So if I could quickly follow up
6 on that. I'm actually not sure if this is a
7 question for you or for the FDA, but in that tiered
8 figure that is included in the label, it's slightly
9 different than the Trussell tier table on
10 contraceptive technology. But that is based on
11 typical effectiveness, and you really don't have
12 any typical effectiveness rates for the Agile
13 Patch.

14 So I guess I'm wondering if you use that
15 figure, how you will put it in there. I'm not sure
16 that you could just slot it right into tier 2, but
17 am a little concerned that as people are thinking
18 about that, that may be what happens, without
19 understanding the data behind the methods that are
20 there now and the Agile Patch.

21 DR. GARNER: Yes. I believe in -- and,
22 again, I think this particular question might be

1 also for FDA. But I believe that what they've
2 moved to is using more of this type of
3 illustration, I think possibly for that reason, but
4 they could also comment; that there is a continuum.

5 I think what we show certainly in our study
6 is -- and we do believe strongly that just by the
7 design of our trial and the population, that we
8 actually are approaching those actual use rates in
9 the trial as well. But I think this also
10 illustrates that continuum, and that we would fall
11 somewhere in that birth control pills, skin patch
12 range as well with our efficacy. But I totally
13 understand what you're saying about providing more
14 information on the impact of the population in the
15 design. I think that would be very helpful.

16 DR. LEWIS: And you'll have an opportunity
17 to get more information from the FDA later, unless
18 you wanted to comment now FDA?

19 (Dr. Gassman gestures no.)

20 DR. LEWIS: No. So later, it might be a
21 good question.

22 Dr. David Eisenberg.

1 DR. D. EISENBERG: Thank you. I just wanted
2 to clarify the weight discussion that we're having,
3 both with regards to efficacy and thromboembolic
4 risk. Was that the weight at entry? That's the
5 first question?

6 DR. GARNER: Yes.

7 DR. D. EISENBERG: So the weight at
8 enrollment in the study. Then, can you comment on
9 the change in weight that occurred during the 13
10 months of follow up amongst the 50-ish percent of
11 women who actually completed the 13 months of
12 follow up?

13 DR. GARNER: Yes. We did see some weight
14 changes. They went in both directions. We didn't
15 see any particular trend. People gained anywhere
16 from around 10 to 15 pounds, but also we saw
17 patients who lost weight during the trial. So we
18 saw no particular trend.

19 DR. D. EISENBERG: And I might have missed
20 this. Was there discontinuation because of weight
21 change as one of the discontinuations that was
22 listed?

1 DR. GARNER: We did an analysis that's not
2 included in -- it's in the NDA but not included in
3 your books, where we went back and looked into the
4 reasons -- in the reasons for discontinuation table
5 that you saw, there's that subject decision. We
6 went back because we wanted to explore a little
7 more, really, what was that subject decision? We
8 actually didn't see any evidence that patients were
9 discontinuing for weight changes.

10 DR. LEWIS: Dr. Ortel?

11 [No audible response.]

12 DR. LEWIS: Then Dr. Haider.

13 DR. HAIDER: Yes. This is a question about
14 the bleeding profile. On slide 65, there's a
15 discussion. You discussed some of the unscheduled
16 bleeding and spotting, typically lessening over
17 time. Can you talk a little bit more specifically
18 about what that looked like over the cycles and in
19 relation to -- you compare it to Ortho Evra and
20 some of the other methods, mostly because that's
21 something that's really important to women in terms
22 of counseling, and preference, and shared decision

1 making.

2 DR. GARNER: For sure. We absolutely agree
3 that this is really, really important. We did look
4 at our product alongside a number of other
5 products. I think one thing that's very important
6 to mention is -- and I think we mentioned it during
7 the talk.

8 Women, as I'm sure you understand, they will
9 tolerate varying levels of bleeding in products in
10 order to get other benefits. So if it's a low-dose
11 method, or, for instance, a continuous method,
12 they'll tolerate, generally speaking, a little more
13 bleeding or a little less.

14 Our bleeding profile looks pretty consistent
15 with low-dose methods, and I would add it's also
16 quite difficult to compare because the collection
17 and evaluation of bleeding has been very variable
18 over time. But what we do see here is the
19 incidence of unscheduled bleeding, breakthrough
20 bleeding, that is at one year of use.

21 Our rate was 41 percent, Quartette was at 70
22 percent by the end of the year, and the Natazia

1 product was at 78 percent; those are continuous
2 regimens. Ortho Evra, not surprisingly, had a much
3 lower rate, but that, of course, is probably
4 related to the higher dose of estrogen.

5 So it's a trade off in terms of bleeding. I
6 think what's most important for us is getting an
7 indication of how many patients were discontinuing
8 from the trial because of bleeding, and for that,
9 we saw an extremely low rate, as we had shown.

10 DR. LEWIS: If I could just ask, is that
11 mean days of unscheduled bleeding or spotting per
12 month?

13 DR. GARNER: Yes. We saw a decrease in the
14 mean days of bleeding per cycle, as patients
15 continued on.

16 DR. LEWIS: Dr. Berenson?

17 DR. BERENSON: Yes. This question is about
18 the 202 pound again. You presented that there are
19 4 patients that had a deep venous thrombosis event.
20 Do you have data on the weight on those patients?
21 It was presented by BMI.

22 DR. GARNER: Yes. They were all over 200

1 pounds as well.

2 DR. LEWIS: Okay. Thank you. If you think
3 of other questions, we'll have an opportunity for a
4 few more this afternoon, but at this point, I would
5 like to take a break.

6 We'll now take a 15-minute break. Panel
7 members, please remember, no discussion of the
8 meeting topic during the break amongst yourselves
9 or with any member of the audience. We will resume
10 at 10:25.

11 (Whereupon, at 10:10 a.m., a recess was
12 taken.)

13 DR. LEWIS: I would like to call the meeting
14 back to order for the FDA presentations.

15 **FDA Presentation - Jerry Willett**

16 DR. WILLETT: Good morning. My name is
17 Jerry Willett. I'm a clinical team leader in the
18 Division of Bone, Reproductive, and Urologic
19 Products at the FDA, and I'll be adding some
20 additional background material to augment
21 Dr. Gassman's initial presentation. My
22 presentation will cover unintended pregnancy,

1 combined hormonal contraceptive development in the
2 United States, the regulatory history of AG200-15,
3 and certain trial considerations of the applicant's
4 Study 23 for this product.

5 The CDC defines unintended pregnancy as a
6 pregnancy that is unwanted or mistimed. In 2011,
7 45 percent of the 6.1 million pregnancies in the
8 U.S. were unintended. Public health consequences,
9 including adverse maternal and child health
10 outcomes, as well as social and economic costs,
11 result from unintended pregnancies.

12 The delicate balance that needs to be
13 addressed in CHC development includes the
14 following: prevent unintended pregnancies with
15 highly effective products; reduce serious adverse
16 reactions, including death, venous thromboembolism,
17 myocardial infarction, and stroke; reduce
18 tolerability issues such as unscheduled bleeding
19 that may discourage use or result in
20 discontinuation.

21 Through the years, there have been a number
22 of CHCs study design changes. These include more

1 accurate and frequent pregnancy testing during
2 trials; better imaging to estimate conception date;
3 a focus on overall pregnancy rate rather than
4 method and user failure analyses; exclusion from
5 effectiveness evaluations of treatment cycles in
6 which concurrent contraception was used or no
7 sexual activity was reported; and finally,
8 electronic diaries to record study drug use and
9 cycle control.

10 None of these design changes could be
11 described as recent ones that have just been
12 incorporated over the last few years. Improvements
13 in pregnancy testing, imaging, and electronic
14 diaries have been an ongoing process. The
15 recommendation for exclusion of cycles for lack of
16 sexual activity became more consistent for the
17 division approximately 9 to 10 years ago.

18 In the applicant's briefing document, the
19 applicant points out a number of other products,
20 where lack of sexual activity per cycle was not
21 included in the efficacy analysis. The clinical
22 trials, however, for these products all started

1 before the year 2009.

2 Next, I will discuss some of the key issues
3 related to study population. The division, for the
4 most part, focuses on U.S./Canadian effectiveness
5 data. We often receive European data in our NDA
6 submissions, but this is primarily looked at in
7 terms of safety. We encourage sponsors to enroll
8 study participants that reflect current
9 demographics.

10 The subjects need to be sexually active with
11 regular menstrual cycles and have no known
12 fertility problems for the partners. Effectiveness
13 is characterized in a study subset up to age 35.
14 Subjects enrolled over the age of 35 contribute
15 additional safety data for the product. We expect
16 that the subjects selected will have adequate
17 washout of prior hormonal contraceptives, and will
18 be avoiding concurrent contraceptives during the
19 trial. Although the division has encouraged
20 sponsors for a number of years to include
21 adolescents and subjects with no restrictions
22 related to BMI, we have faced a reluctance to do so

1 by some sponsors based on certain safety and
2 regulatory reasons.

3 The National Center for Health Statistics
4 Information notes that the obesity prevalence in
5 the U.S. for adults as a whole increased to 40
6 percent in the 2015-26 [sic - 2016] time period.
7 This represents a 10 percent increase in
8 approximately 15 years. The prevalence of obesity
9 in reproductive age women of 20 to 39 years in this
10 same time period was 37 percent.

11 In regard to obesity and CHC development,
12 it's been noted already today that obese subjects
13 have been largely excluded from some of our
14 previous clinical trials for CHCs. Some applicants
15 have allowed BMIs greater than 30, but then
16 oftentimes capped it at 35 in their particular
17 studies. When we've looked at our own products and
18 we've looked at the literature, there's been mixed
19 results when comparing BMI and effectiveness over
20 the past years.

21 An FDA meta-analysis evaluating the impact
22 on obesity on contraceptive effectiveness was

1 published in 2015. Data from seven clinical
2 studies of oral CHCs were analyzed. Of note, only
3 two of the products had a large number of cycles
4 greater than 4,000 in obese subjects. Although the
5 Pearl index was higher in this pooled data for the
6 obese subjects compared to non-obese, there were
7 questions, still, whether this was clinically
8 significant.

9 In regard to study limitations, the authors
10 noted that a selection bias in regard to the
11 enrolled obese patients could not be ruled out and
12 that the study lacked adequate information based on
13 compliance. The authors concluded in this paper
14 that obese women using combined hormonal
15 contraceptives may have a higher pregnancy rate,
16 but more data was necessary to obtain further
17 evaluation of this topic.

18 I'll next turn to the regulatory history
19 with AG200-15. The application was originally
20 submitted to the division in April of 2012.
21 Efficacy and safety focused on two phase 3 studies,
22 Studies 12 and 13. The division's non-approval in

1 February of 2013 stated that Studies 12 and 13 had
2 unacceptable on-treatment pregnancy rates and
3 significant problems with study conduct and product
4 quality.

5 I'd like to emphasize this to a greater
6 degree. We had significant problems with data on
7 on-treatment pregnancies, and we had a lot of other
8 problems in terms of the information coming in
9 those studies. That's why the FDA is focusing
10 primarily on Study 23 and not on Studies 12 and 13.
11 At the October 2013 end of review meeting, the
12 division informed the applicant that no combination
13 hormonal contraceptive had been approved with an
14 upper bound of the 95 percent confidence interval
15 around the Pearl index that exceeded 5.

16 Next, turning to the second review cycle,
17 the applicant's NDA for AG200-15 was resubmitted in
18 June of 2017 with clinical data from a new phase 3
19 study-that of Study 23. The division did not
20 approve this submission in 2017. There were
21 continuing problems about an unacceptable high
22 pregnancy rate, product adhesion, high subject

1 withdrawal rates, and manufacturing quality issues.
2 And as I said before, we'll focus our presentation
3 today on Study 23.

4 The third review cycle, which is the current
5 one, the resubmission was submitted in May of 2019
6 with additional product quality data from an
7 in-house comparative adhesion study. No new
8 efficacy data was submitted.

9 I'll turn next to some trial considerations
10 for AG200-15. In looking at the factors that may
11 have increased pregnancy rates in our clinical
12 trials, there are a number of things that we
13 consider. One is the possibility that decreasing
14 hormone doses present less of a margin for missing
15 the product, and thereby allowing ovulation.

16 We've also had more sensitive and more
17 frequent pregnancy testing as mentioned before.
18 Also, the inclusion of obese subjects may play a
19 role, then we also look at the possibility of
20 higher noncompliance in the subjects in the U.S.
21 trials, and we've seen that to a large degree when
22 we compare studies in Europe,

1 I'll next turn to dosing considerations. In
2 1996, 2.5 percent of all oral CHC prescriptions in
3 the U.S. were for formulations with 50 micrograms
4 of estrogen. There is now an approved oral CHC
5 that contains just 10 micrograms of ethinyl
6 estradiol.

7 This was discussed earlier this morning in
8 terms of the difference between FDA's analysis and
9 the applicant's. Applicant's Study 14 compared
10 ethinyl estradiol and AG200-15 versus that in an
11 oral CHC containing 35 micrograms of EE. The
12 division's analysis of pharmacokinetic data found
13 similar EE, steady-state, systemic exposure, or the
14 area under the curve, for both products.

15 Therefore, based on this particular data and also
16 the consideration of the 10 and 20 microgram
17 products on the market, we do not consider this a
18 low-dose EE CHC product.

19 Next, turning to some more conduct
20 considerations, pregnancy testing requirements have
21 generally been consistent over the last 10 years.
22 The division has been consistent in its

1 recommendation to exclude cycles without at least
2 one episode of vaginal intercourse for other
3 products in development in the last 10 years.

4 I'd like to also mention briefly that the
5 FDA biostatisticians do a separate confirmation of
6 all the numbers that get presented in an NDA
7 submission, and in discussing this with them this
8 morning, we didn't find that when you add back the
9 cycles with no sexual activity, that the upper
10 bound goes down to as low as 5.5. So that still
11 needs to be reconciled a bit; so we had a higher
12 number with that.

13 We do acknowledge that Study 23 did have a
14 greater proportion of obese subjects, but we feel
15 that, in general, the rest of all the
16 considerations, that its overall design and conduct
17 were similar to other recent phase 3 contraceptive
18 trials.

19 Study 23 strongly encouraged compliance.
20 Subjects were required to have 90 percent
21 compliance with an electronic diary during the run-
22 in period. Compliance was reviewed at all office

1 visits and phone contacts. Table 36 in the
2 applicant's briefing document states that the
3 noncompliance with the e-diary during the run-in
4 period accounted for 625 screen failures.

5 A run-in period that is used to test for
6 compliance is very unusual in a contraceptive
7 trial. The division has concerns that this
8 product's high pregnancy rate, even after this sort
9 of enrichment -- so we're still concerned that the
10 high pregnancy rate, even with this enrichment, was
11 done to obtain a more compliant study population.

12 There are uncertainties for any given
13 product in regard to post-approval effectiveness.
14 Post-approval pregnancy rates have typically been
15 higher than the rates in clinical trials,
16 especially for products requiring user compliance.
17 It's possible that the following aspects of a
18 clinical trial could further contribute to higher
19 post-approval pregnancy rates, and that includes
20 strict compliance subjects, subjects lost to
21 follow-up, and subjects who prematurely discontinue
22 a study without an exit pregnancy test.

1 Lastly, I'd like to address one of the
2 figures with a bar graph that was presented by the
3 applicant this morning. I'd like to explain in a
4 little bit more detail some of the numbers that we
5 see in this particular bar graph.

6 Turning first to the yellow areas, this is
7 the Nordette product. Nordette was originally
8 approved in 1982, based on approximately 8,000
9 cycles. The Nordette study, in comparison to
10 studies that we do today, had no scheduled
11 pregnancy tests, evaluated subjects up to age 38
12 for efficacy, and had subject data past 13 cycles,
13 all of which would keep the Pearl index low.

14 Later trials, shown in yellow here, that
15 included Nordette were based on much smaller
16 numbers of cycles, 1758 cycles in 2003 and only 591
17 cycles in 2006. Smaller studies that utilize
18 active comparators may sometimes record
19 pregnancies, but are really more focused on cycle
20 control than on efficacy itself.

21 Levlite, the gray bars, was approved in the
22 U.S. in 1998. The pregnancy rate of 0.9, in the

1 left grouping that you see on this slide, is
2 derived from a European study, and the pregnancy
3 rate of 1.08 in the middle grouping is derived from
4 the U.S. study. So these studies were done and
5 approved at the same time period, so this does not
6 represent a change over time; this just represents
7 what happened in the European study versus the U.S.
8 study. It's noteworthy that all the results in the
9 far-right grouping, where it shows fairly high
10 Pearl indices, were based on a low number of
11 cycles.

12 Of note, also, let me briefly discuss the
13 problems that we sometimes have with active
14 comparator trials. In the middle grouping where
15 you see the blue bar, this was actually an approval
16 for Ortho Tri-Cyclen low, and the active comparator
17 that was selected was Loestrin 1/20. Here we have
18 a tricyclic product being compared to a monocyclic
19 product. We have two different progestins, so
20 norgestimate with the Ortho Tri-Cyclen, and we have
21 a norethindrone acetate with 1/20, and we also have
22 different estrogen levels. So we had 25 micrograms

1 in the Ortho Tri-Cyclen low and 20 in the 1/20
2 product.

3 This gives you an idea, sometimes, of how
4 difficult active comparators can be to establish a
5 comparable product, to develop a good
6 noninferiority trial with a reasonable margin to
7 evaluate the two products. None of these
8 comparative trials, which you see in the second two
9 groupings, were in that particular category. None
10 of them were a well-designed, noninferiority trial.
11 They would come out with some pregnancy results and
12 just generally say that they were comparable. I
13 just wanted to give some clarification to this
14 particular slide.

15 Next, I'll turn to the efficacy discussion
16 by Dr. Tang.

17 **FDA Presentation - Yun Tang**

18 DR. TANG: Thank you, Dr. Willett.

19 Good morning. I'm Yun Tang, the statistical
20 reviewer for this submission. Today, I will be
21 presenting the evaluation of the effectiveness of
22 AG200-15. In my presentation, I will first begin

1 with the division's current recommendations on key
2 aspects of study design for combined hormonal
3 contraceptives.

4 This will provide a context for our
5 evaluation of the effectiveness for AG200-15, then
6 I will present our efficacy evaluation of AG200-15
7 using data from Study 23. Specifically, I will go
8 over the design elements of Study 23, and then
9 present results for the primary and the secondary
10 efficacy endpoints. I will end my presentation
11 with a summary of our findings.

12 In general, open-label, single-arm, phase 3
13 trials of at least one year duration are sufficient
14 to establish efficacy of CHCs. For typical CHC
15 trials, the primary efficacy endpoint is the
16 pregnancy rate measured by the Pearl index in women
17 35 years old or younger. Pearl index is defined as
18 the number of pregnancies per 100 woman-years of
19 product use.

20 To calculate the primary Pearl index, the
21 division recommends that on-treatment pregnancies
22 are limited to those that occur during use of the

1 product or within a specific time frame after last
2 use of the product, for example, 7 days. Evaluable
3 cycles are on-treatment cycles where vaginal
4 intercourse occurs and no backup or emergency
5 contraception is used.

6 In terms of the study size in CHC trials,
7 for new molecular entity products, the division
8 recommends that the total drug exposure in a trial
9 should include at least 20,000 cycles for safety
10 reasons, and at least the 400 subjects should
11 complete the study. For non-NME products like
12 AG200-15, the recommendation is at least 10,000
13 cycles and 200 completers.

14 The division also recommends the evaluation
15 of the Pearl index by BMI, race, ethnicity, and the
16 region for multinational studies. But of note,
17 studies are not designed to meet specific efficacy
18 criteria within these subgroups.

19 The primary efficacy evaluation of CHCs is
20 based on the upper bound of the two-sided 95
21 percent confidence interval for the Pearl index not
22 exceeding 5. In other words, to demonstrate

1 efficacy, a CHC would be expected to result in no
2 more than 5 pregnancies per 100 woman-years of
3 product use.

4 Essentially, there are three main reasons
5 for why the division decided to set the acceptable
6 upper bound at 5 for CHC products. First,
7 according to national survey data, over the past 30
8 years, the estimated percentage of women having
9 unintended pregnancies during their first year of
10 typical use of hormonal pills is 5 to 7 percent,
11 and such postmarketing estimates tend to exceed
12 estimates seen in premarketing clinical trials.

13 Second, the upper bound of the Pearl index
14 estimate for approved CHCs have never exceeded 5 in
15 clinical trials used as the basis for approval for
16 U.S. marketing. Third, given the known ATE and VTE
17 risks associated with CHC use, the division
18 believes that CHC products must demonstrate a high
19 level of efficacy in preventing unintended
20 pregnancies in order to justify the risks.

21 The division acknowledges that there are
22 limitations in setting 5 as acceptable upper bound,

1 as it is proposed partly based on survey results
2 and partly based on low Pearl index estimates we
3 have seen in historical CHC trials. On the other
4 hand, it is difficult to directly compare
5 premarketing clinical trial results with
6 postmarketing survey results.

7 On the other hand, directly comparing Pearl
8 index estimates from a later trial with those from
9 historical trials is susceptible to the limitations
10 of cross-study comparisons; that is, each study
11 varies with regards to populations, design,
12 conduct, or other aspects of studies.

13 Therefore, other than drug effects, many
14 factors that might differ between the studies could
15 explain differences in Pearl indices. However,
16 despite these limitations, 5 is the criteria that
17 the division has used to date to establish a CHC's
18 effectiveness.

19 As Dr. Willett noted previously, before the
20 applicant designed Study 23, they were informed
21 that the division had never approved a CHC for
22 which the upper bound exceeded 5.

1 Now, I will present our review of the
2 efficacy data from Study 23. Study 23 was a
3 single-arm, open-label, multicenter, one-year
4 phase 3 study. The study was conducted in 102
5 clinical sites in the United States. In total,
6 2,032 women, age 18 to 40 years, were enrolled in
7 Study 23 without BMI or weight restrictions.

8 Here, I want to point out one key enrollment
9 criteria for Study 23. As Dr. Willett noted
10 previously, in order to be eligible for enrollment,
11 subjects had to demonstrate at least 90 percent
12 compliance with the electronic diary entry; that
13 is, the subject may miss no more than 1 day of
14 diary entry during the 2-week run-in period. In
15 addition, subjects had to return 2 phone calls
16 during the run-in period. This is not a typical
17 enrollment criteria in CHC trials. By doing this,
18 the population was enriched to be a more compliant
19 population.

20 As stated previously, the applicant was
21 informed that the division had never approved a CHC
22 for which the upper bound of its Pearl index

1 exceeded 5. With this recommendation, the
2 applicant designed the study with the adequate
3 number of subjects to meet the requirements for
4 Study 23, as you can see on this slide, and the
5 evaluable cycles in Study 23 exceeded the number of
6 recommended cycles for the primary assessment. The
7 primary analysis population for Study 23 consisted
8 of 1,736 subjects. This slide lists the criteria
9 that defines the inclusion of subjects in the
10 primary analysis population.

11 The primary efficacy endpoint for Study 23
12 was the pregnancy rate measured by Pearl index in
13 women 35 years old or younger. The definitions
14 about treatment pregnancies and the evaluable
15 cycles used in the calculation of this Pearl index
16 are in line with the agency's recommendations in
17 the division's draft guidance on hormonal
18 contraceptives.

19 As for the secondary endpoints, the
20 applicant prespecified the evaluation of Pearl
21 index by BMI, race, and ethnicity. As Dr. Gassman
22 noted earlier, the applicant is seeking the

1 standard indication for prevention of pregnancy
2 with a limitation of use statement related to BMI
3 and weight. However, the statistical analysis plan
4 did not include a planned subgroup analysis by
5 baseline weight of 92 kilograms.

6 It was not clear what methodology the
7 applicant used to propose the cutoff of 92
8 kilograms, but since it was proposed, we conducted
9 this subgroup analysis to evaluate the basis of the
10 applicant's proposal. You will hear more about the
11 discussions on the applicant's limitation of use
12 proposal in the next FDA presentation.

13 Now, we are going to look at the efficacy
14 results. These results are based on analysis
15 performed by the agency's statistical review team.
16 This table shows the efficacy results for the
17 primary endpoint. Among women 35 years old or
18 younger, the estimated Pearl index was 5.8 with an
19 upper bound of 7.2. These results suggest that the
20 data are consistent with pregnancy rates on AG200-
21 15 as high as 7.2 unintended pregnancies per 100
22 woman-years of product use. Recall that our advice

1 to the applicant for demonstrating efficacy is the
2 upper bound of Pearl index not exceeding 5. For
3 the overall population, both the point estimate and
4 the upper bound were greater than 5.

5 Now, we move on to the subgroup analysis.
6 This table shows the subgroup results by BMI and
7 weight. The estimated Pearl index for non-obese
8 women was 4.3 with an upper bound of 5.8. The
9 estimated Pearl index for obese women was higher,
10 at 8.6 with an upper bound of 11.5. These results
11 suggest that the estimated AG200-15 pregnancy rate
12 was almost doubled in the obese subgroup compared
13 to the non-obese subgroup.

14 The estimated Pearl index in women with
15 weight less than 92 kilograms was 4.9 with an upper
16 bound of 6.3. The estimated Pearl index in women
17 with weight equal to or greater than 92 kilograms
18 was higher at 9.9 without an upper bound of 14.0
19 Therefore, there were trends toward lower pregnancy
20 rates in women of lower BMI and weight. However,
21 despite these trends, we want to point out that the
22 upper bounds of the Pearl index estimate in each

1 BMI and weight subgroup were greater than 5, even
2 in the subgroup of non-obese women and women with
3 weight less than 92 kilograms.

4 This table shows the subgroup results by
5 race and ethnicity. There were some slight
6 numerical differences in Pearl index point
7 estimates among the racial and ethnic subgroups.
8 Nevertheless, we want to reiterate that the upper
9 bounds of the Pearl index estimate in all racial
10 and ethnic subgroups exceeded 5, ranging from 7.5
11 to 9.4.

12 This figure shows the overall and subgroup
13 efficacy results I just presented. Again, for both
14 overall populations and subgroups you can see that
15 all the upper bounds of the 95 percent confidence
16 intervals for the Pearl index estimates exceeded 5,
17 and all the point estimates of the Pearl indices
18 were above 5, except for 3 subgroups. But even for
19 these 3 subgroups, there estimated Pearl indices
20 were still close to 5, ranging from 4.3 to 4.9.

21 In summary, the primary analyses results
22 suggest that the effectiveness of AG200-15 in the

1 general population does not meet the division's
2 previously communicated criteria. The subgroup
3 analysis results suggest that regardless of which
4 subgroup we are looking at, the effectiveness of
5 AG200-15 does not meet the criteria, even in the
6 non-obese subjects.

7 Thank you for your time. Now, I'll hand it
8 to Dr. McNeal-Jackson for her to present the review
9 of safety under discussed benefit-risk
10 considerations.

11 **FDA Presentation - Nneka McNeal-Jackson**

12 DR. McNEAL-JACKSON: Good morning. I am
13 Dr. Nneka McNeal-Jackson. I'm an
14 obstetrician/gynecologist, clinical reviewer in the
15 Division of Bone, Reproductive, and Urologic
16 Products. I will be discussing the safety profile
17 and benefit-risk considerations for AG200-15
18 transdermal system.

19 For the outline of my talk, the discussion
20 will proceed as follows. I will be discussing the
21 populations that were used for the safety analysis
22 of AG200-15, discussing specific safety information

1 that suggests a VTE safety signal associated with
2 AG200-15 use, the applicant's proposed labeling
3 that includes a limitation of use, and will
4 conclude with the division's concerns with the
5 AG200-15 benefit-risk assessment.

6 Let's start with the discussion of the
7 populations used. In this slide, this represents
8 the safety populations that were used from
9 Study 23. Due to the division's concerns with the
10 study conduct and data quality issues that were
11 noted in Studies 12 and 13, we limited the scope of
12 this review cycle to Study 23 only.

13 The safety population represents those
14 subjects that used at least one TDS for any length
15 of time during the clinical trial. The safety
16 cycle data is a subset of the safety population
17 that was used to calculate the number of treatment
18 cycles that the subjects completed. A treatment
19 cycle, as discussed earlier, was a 28-day period
20 consisting of 21 days with the consecutive
21 administration of three 7-day-wear TDS's, followed
22 by 7 days where no TDS was applied.

1 The total number of treatment cycles that
2 was used to calculate the incidence rates of
3 certain AEs for Study 23 in 2,023 subjects
4 completed 18,841 treatment cycles. The last
5 population, the cycle control population, was used
6 to assess tolerability and usability of the product
7 based on the subject's e-diary data.

8 This slide shows the subject demographics
9 for Study 23. Based on the safety population of
10 2,031 subjects, 35 percent, as noted here, were
11 obese, having a BMI equal to or greater than 30.
12 This is in line with the 2017 CDC statistics of 37
13 percent of the U.S. female population of
14 reproductive age referenced earlier in
15 Dr. Willett's presentation. Regarding race and
16 ethnicity, the demographic information is roughly
17 in line with the 2010 U.S. census data.

18 This slide represents the subject's
19 disposition for Study 23. I want to note that 51
20 percent of the subjects prematurely discontinued
21 the trial. For Study 12 that was reviewed in the
22 first review cycle of this NDA, the discontinuation

1 rate was even higher at 57 percent. I want to note
2 that despite the applicant's efforts to reduce the
3 number of dropouts that occurred during their
4 trial, the discontinuation rate for Study 23 was
5 still high. The top three reasons for trial
6 discontinuation are noted here. Subject decision
7 was the highest, at 15 percent; lost to follow-up,
8 11 percent; and adverse events at 11 percent.

9 The class labeling for CHCs includes risks
10 of certain adverse events. Adverse events of
11 interest include but are not limited to VTEs such
12 as pulmonary embolism and deep vein thrombosis;
13 ATEs such as myocardial infarctions and strokes;
14 liver disease; hypertension; gallbladder disease;
15 and depression. But it is the VTE incidence rate
16 that occurs during contraceptive trials, while
17 rare, that are of particular interest to the
18 division, given the significant risk of mortality
19 and morbidity to subjects when they occur.

20 I'd now like to discuss the VTE safety
21 signal that's been associated with AG200-15's use.
22 This slide represents both the applicant's and the

1 division's calculations for VTE incidence rates.
2 The division's calculations of VTE incidence rates,
3 just for background, is based on the number of
4 subjects that experienced a VTE. The applicant
5 included the safety information from all three of
6 their phase 3 clinical trials.

7 I want to reiterate that the division
8 reviewed all the safety data, but for this review
9 cycle, given the data quality discussions that we
10 talked about for 12 and 13 referenced earlier in
11 mine and Dr. Willett's presentation, again, we are
12 limiting it to Study 23 only.

13 Now, I will discuss the calculation of the
14 VTE incidence rate. For this calculation, one
15 subject from Study 23 was excluded by both the
16 division and the applicant, based on the timing
17 that the VTE occurred, which is almost 2 months
18 after the last TDS was removed. I also want to
19 note that one subject from Study 12 with a normal
20 BMI experienced a DVT.

21 Note in this slide that the denominator that
22 is used by the applicant and by the division

1 differ. It is greater in the case of the applicant
2 because they include the treatment cycles from all
3 three of their phase 3 trials.

4 The VTE incidence rates can be seen here.
5 The applicant suggests in their background document
6 that the observed VTE rate is driven almost
7 entirely by the events in obese women. They note,
8 with the exception of one subject, all the other
9 VTEs occurred in obese women. We acknowledge that
10 there is a significant uncertainty around this
11 estimate due to the small number of subjects that
12 experienced VTEs, however, based on the division's
13 experience, 4 subjects in one trial with a VTE,
14 regardless of BMI, is concerning to the division
15 and represents a safety signal.

16 In this slide, the applicant attempts to
17 conclude that their VTE incidence rates for
18 AG200-15 is generally in line with -- and
19 correction; this is general rates, not U.S.
20 background rates -- and is between 15.4 to 18.9 per
21 10,000 women-years for a population with similar
22 mean BMI and age. However, clinical trials, again,

1 are not sufficiently sized to evaluate the rate of
2 these rare events. The VTE clinical data cannot be
3 extrapolated to inform VTE risks in the
4 postmarketing setting, which is based on approved
5 products.

6 I'd now like to go into a discussion of the
7 proposed labeling. The applicant's proposed
8 labeling can be seen here. I just want to note
9 that the indication is consistent with previously
10 approved CHCs. Note that the AG200-15 is intended
11 for use in all women regardless of BMI.

12 We have concerns about the inclusion of an
13 LOU in labeling. The LOU statement is typically
14 reserved for when there is reasonable concern or
15 uncertainty about a drug's risk-benefit. The
16 division does not believe that the applicant's
17 proposed LOU mitigates the division's concern about
18 the overall benefit-risk of AG200-15 for the
19 intended patient population. Further, we are
20 uncertain that the proposed limitation of use would
21 limit prescriptions to -- and this is a
22 correction -- non-obese women.

1 I'd like to go into a discussion of the
2 benefit-risk assessment. The outline of this part
3 of my discussion will proceed as follows. I will
4 discuss the general benefit-risk considerations,
5 followed by a brief discussion of considerations
6 regarding dosing tolerability and usability of
7 AG200-15, and conclude with the division's current
8 thinking on the benefit-risk of AG200-15.

9 In general, the basis for approval of CHCs
10 is the benefit-risk assessment. Each
11 investigational CHC for the prevention of pregnancy
12 is assessed in the context of available therapies.
13 In this slide, we're seeing the benefit-risk of the
14 AG200-15. The division has approved products using
15 the PI and upper bound of the 95th percentile of
16 the confidence interval for no greater than 5.

17 I want to note here that what's noted here
18 with the upper bound in obese women of 11.4, it is
19 concerning to the division in the non-obese
20 population that the upper bound is 5.8, and this in
21 the context of a known VTE safety signal for this
22 product is concerning.

1 There are other factors that we use when
2 we're considering the benefit-risk for this
3 product. The first is the dosing considerations.
4 In this slide, the applicant's benefit-risk
5 assessment asserts that the AG200-15 delivers
6 approximately 30 micrograms of EE per day, which is
7 similar to what they consider a low-dose oral CHC.

8 This calculation was based on the pooling of
9 pharmacokinetic data from two groups, both that
10 received 2 treatments of AG200-15. Some of the
11 information, however, was collected when the EE
12 concentrations for AG200-15 was not allowed to
13 reach steady state. Based on the division's
14 calculations, this was collected when the EE
15 concentration was allowed to reach steady state,
16 and for that reason, our calculations put this
17 closer to a 35, not 30, as proposed by the
18 applicant, micrograms.

19 We acknowledge, however, that the AG200-15
20 does have less EE exposure than the approved TDS.
21 However, given the availability of CHCs, where the
22 EE now less than 20 micrograms, the division does

1 not consider the product to be a low-dose product.

2 The next thing that I would like to discuss
3 is levonorgestrel in the context of VTE risk. The
4 applicant presents levonorgestrel as a safer
5 progestin, which may decrease the VTE risk as
6 compared to other progestins. Epidemiological
7 studies evaluated whether newer progestins, such as
8 drospirenone-containing CHCs are associated with
9 higher VTE risk than levonorgestrel-containing
10 CHCs.

11 The observational study results, however,
12 are inconsistent, with some studies reporting up to
13 a 3-fold increase in VTE risk, while other studies
14 reported no differences in VTE risk between
15 products. There is significant heterogeneity in
16 these published studies, and the limitation of
17 these studies include the following.

18 Some studies compared prevalent users to new
19 users of CHCs, who might be at different baseline
20 risk for VTEs. Some key confounders were not
21 measured and controlled certain studies.
22 Physicians may prescribe a certain CHC product to

1 women with higher baseline risk for VTEs, based on
2 the safety data available at the specific time of
3 the prescriptions.

4 Self-reported exposure data or prescription
5 data may sometimes lead to misclassification of
6 exposures. The division concludes that slightly
7 different risks in VTEs observed by progestin types
8 could be explained in part by study design issues
9 and an uncontrolled bias. In conclusion, the
10 division feels that the AG200-15 is not a low-dose
11 EE, CHC product based on available therapies, and
12 the AG200-15 levonorgestrel component may not
13 convey a safety advantage over other progestins.

14 Tolerability in usability. The applicant
15 claims that AG200-15 offers an advantage over other
16 CHCs, and that it is not invasive, unlike an
17 intrauterine device, or injectable, or implant, and
18 a more convenient dosing regimen, unlike oral CHCs
19 that have to be taken on a daily basis. However,
20 other factors such as tolerability and usability of
21 the product could undermine such conveniences over
22 time and could affect the patient's compliance and

1 sustained use of the product.

2 Let's start with our discussion of
3 tolerability. One of the most bothersome symptoms
4 to women is lack of predictability of their cycles.
5 Tolerability is the division's assessment of the
6 product's ability to address this issue. In
7 Study 23, subjects captured the bleeding and
8 spotting information in e-diaries on a daily basis.

9 The definitions was that the bleeding was
10 defined as blood loss that was significant enough
11 to require the use of a sanitary napkin or a
12 tampon. Spotting was defined as blood loss
13 requiring no more than a panty liner. For the
14 unscheduled bleeding and spotting data, based on
15 the division's analysis, after the first cycle, 60
16 percent of the subjects were experiencing
17 unscheduled bleeding and spotting; 41 percent of
18 subjects after 13 cycles were experiencing this
19 symptom. So after one year of treatment, that 41
20 percent are still experiencing this event is
21 concerning to the division in the context of
22 benefit-risk.

1 Now let's go into the discussion of the
2 usability for AG200-15. The usability in the
3 proposed dosing regimen, AG200-15 is one TDS for
4 7-day wear for 3 consecutive weeks, followed by
5 1 TDS-free week. The carton contains only 3 TDS's,
6 however, based on our analysis, almost 15 percent
7 of all the completed treatment cycles, which was
8 18,841, had to use 4 or more TDS's in order to
9 complete the treatment. The challenge of obtaining
10 replacement TDS's could prove problematic for
11 subjects.

12 In summary, regarding the tolerability and
13 usability of the product, these two issues could
14 outweigh the products offered convenience and
15 affect the compliance and sustained use of the
16 product.

17 I would now like to go into the discussion
18 of the division's assessment of benefit-risk for
19 AG200-15. The division's current thinking is that
20 another transdermal CHC could provide another
21 alternative for women seeking a non-invasive method
22 of contraceptive. However, AG200-15 does not meet

1 the FDA's regulatory definition of an unmet need,
2 given the multitude of approved therapies for the
3 prevention of pregnancy.

4 Further, AG200-15 is not a low-dose product,
5 given the availability of CHCs with less than 20
6 micrograms of EE in the United States. The
7 levonorgestrel component in AG200-15 may not convey
8 an additional safety advantage. The AG200-15's
9 effectiveness, as discussed in Dr. Tang's
10 presentation, in addition to the identification of
11 the VTE signal, is not acceptable in the general or
12 non-obese population in the context of other
13 available therapies. Product tolerability and
14 usability issues could outweigh AG200-15's
15 convenience.

16 Finally, the inclusion of an LOU in the
17 labeling does not sufficiently address the
18 division's overall concern regarding the
19 benefit-risk of AG200-15.

20 In summary, the division has concerns about
21 the benefit-risk assessment for AG200-15 in the
22 context of other available contraceptive therapy.

1 This concludes my presentation on the safety
2 profile and benefit-risk considerations for AG200-
3 15. Thank you for your time. I'd now like to turn
4 the discussion back over to Dr. Lewis.

5 **Clarifying Questions to FDA**

6 DR. LEWIS: Thank you.

7 Are there any clarifying questions for the
8 FDA? Please remember to state your name for the
9 record before you speak. We'll start with
10 Dr. Margolis.

11 DR. MARGOLIS: I have another question that
12 has to do with definitions. To clinical trialists,
13 the words "efficacy" and "effectiveness" have deep
14 meanings that are very different. It appears to me
15 today that all four of the FDA people used the
16 words almost interchangeably, sometimes in the same
17 sentences. Sometimes the slide would say
18 "effectiveness," you would use the word "efficacy."
19 One of the questions that we have proposed to us
20 begins with "effectiveness" and then ends with a
21 discussion of efficacy.

22 Could someone explain to me how you're using

1 those two words and what they mean in the context
2 of this medication?

3 DR. GASSMAN: In general, when we talk about
4 effectiveness, we're talking about it from the
5 effectiveness and safety profile of the product.
6 Efficacy usually refers to endpoints. They are
7 sometimes used interchangeably, but from a
8 regulatory standpoint, effectiveness is a
9 determination, whereas efficacy refers to efficacy
10 endpoints, efficacy calculations.

11 Laura, did you want to add to that?

12 DR. JOHNSON: There are specific ways that
13 are defined for us in this CDER style guide.

14 DR. MARGOLIS: The other question has to do
15 with the gold standard statement that's been made
16 several times now, about the upper bound of 5. It
17 seems to me that most of the evidence for the upper
18 bound of 5 that's been presented today is because
19 what we've always done.

20 Has anybody actually done a risk-benefit
21 study or talked to patients using the drugs, looked
22 at whether the benefits changed based on the upper

1 bound changing, or is this just what we've always
2 done? We meaning the agency.

3 DR. JOHNSON: Unfortunately, to date, CDER
4 has not done a formal patient preference study such
5 as what you would have seen at a CDRH for weight
6 maintenance and weight reduction therapies for
7 obese patients.

8 DR. GASSMAN: I'd just like to add that just
9 from a historical perspective, we started with
10 Pearl indices of 1. So we have changed over time,
11 but --

12 DR. MARGOLIS: But that was just a change
13 because it's a change. It wasn't based on study
14 designs, preference studies, utility studies.

15 DR. GASSMAN: No. It was based on national
16 survey data and what we could get from our
17 experience.

18 DR. JOHNSON: And I would also add, it was
19 based on the 2007 discussion that happened at the
20 advisory committee. And as Dr. Gassman mentioned,
21 really, most of the discussion was about Pearls of
22 1 and 2, and then also thinking about what would

1 happen if you were looking at formal noninferiority
2 studies and active controlled trials.

3 So there is some information in those
4 summary notes, some of which were saying actually 3
5 and some of which were saying if you had a
6 significant safety change of 5 and 6.

7 MS. BHATT: If I can please remind everybody
8 to state their name for the record, please.

9 DR. WILLETT: Jerry Willett. One additional
10 factor is that we have not always used Pearl
11 indices in the label itself. At one time we had an
12 estimate of what the pregnancy rate should be. For
13 the longest period of time, at least in
14 Contraceptive Technology, that typical use for
15 those particular products has stuck around
16 5 percent.

17 Now, in the past few years, it jumped up to
18 9, and then in the last edition, it went back down
19 to 7. So obviously, you have problems with survey
20 data as to establishing what the typical use was.
21 James Trussell also tried to adapt the figures for
22 abortion in terms of coming up with those

1 particular numbers.

2 But when we were looking at labels, perhaps
3 12 to 15 years ago, we always kept in mind these
4 technology factors of about a 5 percent
5 effectiveness in the real world, and we knew if we
6 approved products with clinical trials, that we
7 would expect the numbers of 2 to 3, or even less
8 than that, then would go to 5. So it was sort of a
9 perspective in terms of what the National Growth
10 Survey was finding and then what we were doing in
11 our clinical trials. But again, we've never had
12 any formal trials looking at the specifics.

13 DR. LEWIS: Thank you. Dr. Shaw, and then
14 Dr. Curtis.

15 DR. SHAW: Hi. I have two clarifying
16 questions. Is that alright? Okay. Thank you.
17 This first question is for Dr. Willett, with
18 reference to slide 34. I just wanted to clarify,
19 it was more something that you said while you were
20 on that slide, where you were talking about the
21 calculation about excluding some cycles when you
22 compute the Pearl index, and how that remained

1 relatively consistent.

2 I thought I heard you say something like you
3 weren't able to reproduce all of the upper limits
4 that the applicant had provided. There were some
5 discrepancies. Did I understand that correctly or
6 can I have more information about that?

7 DR. WILLETT: Jerry Willett. When I
8 originally prepared my talk, I was basically using
9 the applicant's numbers on page 70, where they did
10 the sensitivity analysis. Now, they did a
11 sensitivity analysis for adding back these 5.4
12 percent of cycles where there was no sexual
13 activity. They analyzed it for the entire
14 population under age 35, with no relationship to
15 obesity or non-obesity. Then they added
16 non-obesity in, and they also came up with a
17 number. And then they also even added back that
18 population that had used backup contraception.

19 In all cases, in the applicant's briefing
20 document, they indicated that all of those numbers
21 still had an upper bound of 5 or above. So when I
22 talked to our statisticians this morning, right

1 after the talk by Agile, and then heard that that
2 number had actually gone to 5.15, when they
3 mentioned to me that they thought it was higher
4 than that, that's why I brought up the fact that I
5 think these two numbers need to be reconciled.

6 Whether you're going from a 5.82 down to
7 5.5, or 5.6, or down to 5.15, I don't know at what
8 point in time you call that a substantial change or
9 the fact that this particular analysis, or thing
10 that's incorporated into a study cycle, how
11 significant that is.

12 I will comment, though, that the first time
13 that the FDA did anything at all related to sexual
14 activity, and then changing the cycles that were
15 calculated for efficacy occurred in 2004, we had
16 one patient that was indicated in a study, who had
17 no sexual activity at all in 13 cycles, and the
18 sponsor wanted to add those into the efficacy
19 analysis.

20 We've always thought that perhaps one
21 episode per cycle is a reasonable way to go, but we
22 will admit that for years and years and years, all

1 that happened was asking for are you sexually
2 active or not? So there has been a change. This
3 has happened over the last 9 to 10 years, and we've
4 been consistent with other sponsors with that
5 particular recommendation.

6 DR. SHAW: Thank you very much. And I just
7 want to say I agree with the discomfort that you're
8 unable to reproduce the numbers on page 70. Those
9 are the exact numbers I had concerns about. I
10 agree that these aren't huge swings, but what there
11 seems to be is a lack of clarity in which women and
12 how cycles are being included in those
13 calculations, and they migrated. The data changed.
14 So that just needs to be cleared up just to make
15 sure nothing else changed, I think.

16 My second question is in Dr. Tang's
17 presentation on page 53. This is a presentation of
18 the subgroup analysis. Thank you. The number 5 I
19 think, in some ways, is related to this idea of 5
20 percent unexpected pregnancies. The upper limit
21 being connected to that is -- so the estimates that
22 are consistent with the data are starting to

1 include numbers that people are uncomfortable with.

2 But that upper limit is very connected to
3 sample size, and we're not doing a good job with
4 tracking that. As we talk, there's a lot of
5 concern being expressed about numbers like 11.5 for
6 the obese upper limit for this Pearl index. I
7 think that we have a hard time interpreting the
8 number because there are only 600 women that are in
9 there.

10 So some suggestions or further discussion on
11 how we can look at these analyses. I believe there
12 are requirements in terms of the minimum number of
13 completers and the minimum number of cycles that
14 help standardize the precision of these confidence
15 intervals across trials. Some discussion I think
16 when we talk about the upper limits, I think we
17 need to do a better job of clarifying that,
18 particularly for these subgroups we may have more
19 comfort in because they have an adequate number of
20 women for the width to be informative.

21 I think certainly for all of them for which
22 the point estimate is above 5, we can be fairly

1 confident that the right end is above 5, and for
2 the obese women, we can see the lower end is
3 excluding 5, and that might be more informative.

4 So I guess my bottom line is -- my question
5 is which of these intervals do we think that upper
6 limit of 5 has enough women? Has there been a
7 formal analysis of that? Maybe I might stop there.

8 DR. JOHNSON: This is Laura Lee Johnson.
9 Typically -- and you'll notice that this is in your
10 FDA backgrounder -- when we give the tables
11 associated with this, we do give the number of
12 cycles. Typically, we are looking for at least
13 5,000 cycles.

14 DR. SHAW: That's the kind of thing that
15 might be helpful, to put little stars, which are
16 these intervals had more than 5, or more than 5,000
17 cycles.

18 DR. WILLETT: This is Jerry Willett. If you
19 get a new product in Europe, they oftentimes are
20 looking for the study to be powered to have just
21 one on either side of the point estimate. So
22 that's oftentimes requires at least 20,000 cycles

1 to get that particular level of confidence.

2 The FDA through the years -- I certainly
3 agree with Laura in the sense that 5,000 to us
4 seems like the minimum number that we should have
5 when we're making any sort of decisions, but
6 through the years, we've had issues where a product
7 comes in, where we know -- that comes in with a
8 dosage level that's in between 2, that we already
9 know about and know about the safety for.

10 So in a circumstance like that, we might
11 allow them to only have a duration of 6 months and
12 have less cycles to analyze. In general, that's
13 worked out fairly well in terms of what we found
14 with the pregnancy rates.

15 As I said before, there's a number of
16 factors now that seem to be increasing these rates.
17 We don't always know what's giving us the most
18 change here, whether obesity is a huge one at the
19 moment or not. Once we start climbing above what
20 we've been used to before -- I mean, you're right
21 in terms of did we have enough cycles to really
22 analyze that and are we getting that upper bound

1 just because of the number that was evaluated.

2 DR. LEWIS: Thank you. Dr. Curtis?

3 DR. CURTIS: Kate Curtis. I had a
4 clarifying question on slide 64 about the VTE
5 safety signal. Clearly, these numbers are small,
6 and I'm sure their variability is large, but there
7 does seem to be a safety signal. In reading the
8 briefing materials, though, I had got the sense
9 that that safety signal was in line with what we
10 would expect from other combined hormonal
11 contraceptives. But in the remarks on your slide,
12 you seem to be saying that maybe there was even a
13 higher risk.

14 If you could just clarify FDA's
15 interpretation about this safety signal, is it in
16 line with CHCs or is there something more
17 concerning; and if so, could you talk a little bit
18 more about that?

19 DR. GASSMAN: Audrey Gassman. I'll start
20 with that. I can't remember a clinical trial where
21 we've had 4 VTEs, 4 subjects with VTEs, not 4 ever.
22 Now, these subjects are all 200 pounds in Study 23.

1 We also had one subject -- I believe it was
2 Study 13 that also had a VTE and a normal weight
3 subject. But if you look at the totality of the
4 data, we have seen VTEs, but -- and again, we
5 totally understand, the confidence intervals are
6 very wide around this, but it's something that we
7 can't just say, well, this is what we expect with
8 combined hormonal contraceptives.

9 Obviously, to do this signal probably will
10 take a very good study of maybe 8 to 10 years to
11 actually get the actual risk around it.

12 DR. GARNER: Dr. Lewis, may I --

13 DR. GASSMAN: Does the applicant want to say
14 anything?

15 DR. GARNER: Please, with the chairwoman's
16 permission. I believe, if I'm correct, the
17 recently approved Annovera study had 4 VTEs, 2 in
18 non-obese women and 2 in obese women. That's the
19 recently approved product.

20 DR. CURTIS: Sorry. Was the study size
21 about the same size?

22 DR. GARNER: Slightly larger than our phase

1 3 alone, but smaller than our combined programs.

2 DR. LEWIS: And the VTE incidence was what
3 in that one? Sorry.

4 DR. GASSMAN: In Annovera, the VTE incidence
5 rate was 24 per 10,000, and we required a large
6 postmarketing trial. But again, we're talking
7 about risk-benefit, so we were looking at a
8 different Pearl indices, a different bleeding
9 profile, a different product, a delivery rate of 17
10 micrograms of EE, a different progesterone.

11 One of the things that we're faced with is
12 we don't believe that you can -- it's very
13 difficult when you start to do cross-study
14 comparison, so we try to evaluate each product on
15 its own benefits and risks rather than saying what
16 were all the characteristics of the last product.

17 DR. LEWIS: Thank you. Dr. David Eisenberg,
18 and then Dr. Bauer.

19 DR. D. EISENBERG: I actually have two
20 questions. The first one is for
21 Dr. McNeal-Jackson. When you were on slide 74, you
22 mentioned that the way in which the FDA has

1 calculated the dose profile for estrogen exposure
2 is different than the way the applicant has done,
3 and therefore, something about the time in the
4 cycle and sampling of the pharmacokinetic
5 parameters, and that you feel like the exposure
6 parameter is 35 micrograms, whereas the applicant
7 says about 30. And somewhere there's a difference
8 between what is or isn't low dose.

9 Can you just speak a little more about what
10 your methodology is that you came to a different
11 conclusion and where you're coming up with that?

12 DR. McNEAL-JACKSON: So I will defer the
13 calculations to my clinical pharmacology colleague
14 for the discussion of how that was calculated, and
15 then I'll conclude with your question.

16 DR. ZOU: This is Peng Zou, clinical
17 pharmacology reviewer. Can we go to the backup
18 slides, the last backup slide, FDA slides? No, the
19 last one, that shows a table of the PK data.

20 I want to emphasize the transdermal CHC, how
21 different the PK characteristics are compared with
22 oral CHC. For 80 to 115, I want to emphasize it

1 takes 2 cycles, 2 consecutive cycles, to achieve
2 steady state of pharmacokinetics. In Study 14, the
3 applicant conducted a study with two groups, group
4 1 and group 2.

5 In group 1, the study sequence is patch,
6 TDS, and oral. In group 1, there are 17 subjects.
7 The sequence is 80 to 115 in OC. In group 2, it's
8 80 to 113 OC and 80 to 115. So in group 2, there
9 are 15 subjects, and we don't think the
10 steady-state PK was achieved in group 2 because
11 there is one cycle OC, 4 weeks washout. So we only
12 rely on the PK data from group 1 from 17 subjects.

13 If you compare the steady-state AUC for 80
14 to 115, it's 7.2. For OC, the steady state is
15 between 7.0 and 7.5. I will say they have similar
16 exposure to EE, so I assume the 80 to 115 is
17 equivalent to 35-microgram EE oral CHC. Also, the
18 applicant approved data from 32 subjects from group
19 1 and group 2, and then exposure from 80 to 115 for
20 EE is 10 percent lower than the OC, but we don't
21 agree with their calculation.

22 DR. LEWIS: Would the sponsor like to chime

1 in?

2 DR. FURMANSKI: Thank you. This is Brian
3 Furmanski from Nuventra. As you stated, there are
4 differences between the sequence here. I would
5 argue that it's not necessarily a steady state. I
6 think this could be chance variability as well.
7 You're suggesting a sequence or period effect, but
8 the change in exposure is quite minor, 15-20
9 percent between the periods.

10 Typically, regardless of therapeutic
11 indication, FDA considers 15 to 20 percent
12 increases in exposure to be not clinically
13 meaningful. And you can see that in the dose.
14 It's a 30 versus 35. So I'm not disagreeing in
15 that it's a similar profile. It's hard to exactly
16 put what exactly this dose is. It could be closer
17 to 30 or closer to 35, as you're suggesting, so I
18 don't disagree with you there.

19 I'm not exactly sure if it's a steady-state
20 phenomenon because for EE, if you look at the
21 pre-dose calculation -- if the woman completed one
22 cycle, then got a blood draw just prior to putting

1 on the next patch, EE concentrations our zero. So
2 there is no detectable pre-dose concentrations,
3 which again speaks to is it a really steady-state
4 phenomena or not.

5 DR. D. EISENBERG: Could I just ask if the
6 two pharmacokinetic experts agree -- while I
7 recognize cross-product comparison is challenging,
8 can both the applicant and the FDA pharmacokinetic
9 experts agree that the cumulative dose and exposure
10 to estrogen is lower than the currently FDA
11 approved patch that's on the market, or we can't
12 agree that?

13 DR. ZOU: I think FDA's conclusion is 80 to
14 115 has a similar exposure to EE compared with
15 FDA-approved 35-microgram EE oral CHC.

16 DR. D. EISENBERG: What about the currently
17 approved transdermal system, Xulane?

18 DR. ZOU: We acknowledge the 80 to 115 has a
19 lower exposure to EE compared with the FDA-approved
20 TDS.

21 DR. FURMANSKI: Right, and it's about 50
22 percent lower.

1 DR. D. EISENBERG: I want to move on to
2 another totally unrelated question, but if there
3 are other panelists that want to stick on this
4 maybe we should stay here.

5 DR. LEWIS: We do have other questions, so
6 maybe we'll come back to you. How about that?

7 DR. D. EISENBERG: That's fine.

8 DR. LEWIS: Great. Dr. Bauer?

9 DR. BAUER: Thank you. Doug Bauer. I think
10 I have a question for Dr. Tang, where it relates to
11 her slide 51. It's shown here that the Pearl index
12 values -- and I'm referring to the right column
13 now -- differed from those that were provided by
14 the sponsor in our group. I'm just wondering did
15 you also do similar analyses for women that were in
16 the not obese but overweight group? Were there any
17 data about that?

18 While you're coming to the microphone, I'll
19 just tell you what my comment is. My comment is,
20 by doing these dichotomous things, it looks like
21 there's something magical about suddenly becoming
22 obese. In fact, these are clearly, at least to my

1 mind, continuous relationships. And I might
2 suggest some complementary analyses, where you look
3 at the increase in Pearl index per, for example,
4 1 BMI unit increase might be more useful, and
5 actually, it might get at some of the issues about
6 sample size as well because I think it might be
7 relevant to understand what is the risk and what is
8 the Pearl index in someone whose BMI is 27 or 28,
9 for example, and not just above 30 and below 30.

10 DR. TANG: Thank you for your comment. this
11 is Yun Tang. We have those numbers. For example,
12 for the overweight women, I'd like to defer this
13 question to Dr. Laura Lee Johnson.

14 DR. JOHNSON: This is Laura Lee Johnson, and
15 let me pull up those numbers for you. I think also
16 the applicant had a very fine gradation of
17 breakdown by BMI and by weight in their package, so
18 you may want to refer to that. But looking at
19 their general information, the overweight
20 population alone -- and this is broken out of the
21 primary analysis population -- we have 439 women
22 with 3,881 evaluable cycles, a Pearl index of 5.69

1 that was estimated with an upper bound 8.4.

2 DR. LEWIS: Okay. Dr. Margolis, and then
3 Dr. Haider.

4 DR. MARGOLIS: I have another question about
5 the Pearl index, which has been bothering me since
6 I first learned about it the other day. I've also
7 talked to some of my statistical colleagues here,
8 and they can't seem to give me a good answer
9 either. But historically, I have a feeling that
10 you all have a good answer.

11 You keep talking about cycles as if they're
12 independent events, and statistically they're
13 probably not. They're probably very dependent on
14 both the person -- these people's fertility rates
15 are different, probably sexual activity;
16 seasonality we know is important.

17 So why aren't we using more modern
18 statistical models that allow for fixed effects and
19 random effects as opposed to calling these
20 independent events, or am I completely confused
21 because I'm a dermatologist?

22 (Laughter.)

1 DR. GASSMAN: The history of contraceptive
2 trials plays into this. We have discussed
3 active-controlled trials. We have discussed other
4 methodologies. Because of some of the limitations
5 of active-controlled trials up to now, we have used
6 the single arm. We also do calculate life table
7 analysis.

8 It would be difficult to do, I think, and
9 Laura can comment on this, some sort of a
10 randomized trial. Obviously, that's one of the
11 reasons why we're asking for recommendations.
12 You're not going to put a woman on a contraceptive
13 for just a month and then randomize her to
14 something else.

15 Maybe if you could kind of elaborate on
16 that.

17 DR. MARGOLIS: In a randomized trial, it
18 wouldn't be as much of an issue because
19 theoretically, you would have randomized people
20 with similar risks, and similar cycle differences,
21 and fertility differences, and sexual frequency
22 differences to both arms. But in these one-arm

1 studies, or really cohort studies, you would worry
2 about the fact that you're measuring something that
3 you're claiming as an independent event, each
4 cycle, when they're really not.

5 DR. GASSMAN: But that would be whether you
6 did active-controlled trials or any type of
7 long-term trial; correct?

8 DR. JOHNSON: This is Laura Lee Johnson.
9 Let me try to address this question. It's one
10 that, again, in that 2007 discussion also came up.
11 We do life table analysis, and the convention has
12 been to stick with the Pearl index because of the
13 discussions with other obstetricians and
14 gynecologists.

15 That said, especially for a year-long trial
16 of these 13-cycle trials, when we run the other
17 methods, the life table methods, again, as long as
18 we have the information available, we tend to come
19 up with very similar results, which is why you'll
20 notice both we and the applicant have those life
21 table measures there.

22 Are there more modern ways to try to do

1 these analyses? That's there, but that's not what
2 has been proposed. And in particular, when you
3 have single-arm trials, and only a single,
4 single-arm trial, it is very difficult to have the
5 information that you may need in order to
6 understand that you have a solid model in some of
7 those other methods. But we do the life table
8 methods. If you look, those answers are fairly
9 similar for the Pearl.

10 DR. WILLETT: Jerry Willett. I would say in
11 the 20 years that I've been looking at these
12 trials, I've never seen any life table evaluation
13 that was dramatically different, which encouraged
14 us to do something different.

15 DR. HUNSBERGER: Have you done any analysis
16 of time to discontinuation? That would help us
17 understand if there's a few people that are giving
18 the bulk of the cycles, and then not many that are
19 really in the analysis. So have we done anything
20 like that?

21 DR. TANG: Yun Tang again; no, we don't.

22 DR. LEWIS: Dr. Haider?

1 DR. HAIDER: This is Sadia Haider. I want
2 to go back to the safety signal with the VTE risk
3 again. Based on the fact that the ethinyl
4 estradiol level is now either 30 to 35 micrograms,
5 we're saying it's lower than the other trans dermal
6 product, and that only the 4 VTEs are the most
7 you've seen in clinical trials, how does this
8 compare in this trial to the other transdermal
9 product? Can we compare in terms of safety risk?

10 I think it's going back to Dr. Curtis'
11 question and Dr. Eisenberg's question. I think
12 this is the thing that we're trying to wrap our
13 mind around as far as risk. How do we make that
14 comparison if we can?

15 DR. GASSMAN: That's one of the issues we
16 face, is because we have small numbers of serious
17 rare events in clinical trials. One of the slides
18 that we had specifically went that we can
19 extrapolate from postmarketing studies. We know
20 that we have these events. We know we have seen
21 them with other trials.

22 We look at the VTE incidence rate just to

1 give us a baseline for some sort of a risk, but
2 it's something that we consider when we're doing
3 the benefit-risk because, obviously, we're not
4 going to be able to do very long postmarketing
5 studies to compare products to see how this
6 compares to a 10 microgram, or a continuous use, or
7 Ortho Evra.

8 The other problem is I don't think you could
9 do a comparison to Ortho Evra in postmarketing
10 because, obviously, also if the product is not
11 being used that much, it makes it very difficult to
12 get an estimate of how this might compare to a
13 product that is not used very much in current
14 studies.

15 DR. HAIDER: Do we have any data from the
16 clinical trial itself for Ortho Evra? I guess
17 that's my question, from the actual premarketing.

18 DR. OUELLET-HELLSTROM: This is Rita
19 Ouellet-Hellstrom. Postmarketing studies are very
20 heterogeneous. They capture women at different
21 ages, and different exposures, and at different
22 time periods following approval. So the risk

1 estimates will vary very, very much. Based on
2 whether exposure is determined as idiopathic or not
3 will also make a big difference in the risk
4 estimates and in the incidence.

5 DR. GASSMAN: One of the other things I'd
6 like to point out is your clinical trial population
7 is a overall healthy population. That is something
8 to consider when we look at these rates. When it
9 goes into the general population, obviously, you
10 may have more smoking, more other risk factors.

11 It becomes very difficult to try and
12 extrapolate, other to say we've got the safety
13 signal from our perspective, but I understand your
14 frustration. I wish we could be able to look at a
15 VTE number and say we expect this incidence, but I
16 don't think we can.

17 I think the sponsor may want to say
18 something.

19 DR. LEWIS: Yes, I was going to let the
20 sponsor say something.

21 Dr. Hellstrom, did you have something else
22 to add there?

1 DR. OUELLET-HELLSTROM: I just wanted to add
2 that in the U.S., in particular, VTE or pulmonary
3 embolism is captured very well, and confirmed and
4 validated when the patient is hospitalized. But if
5 it's just a DVT, it's treated outpatient and much
6 more difficult to capture in the U.S.. Other
7 countries do it differently, but in the U.S., we
8 don't.

9 DR. PORTMAN: David Portman, consultant.
10 It's critical to remember that only 3 percent in
11 the Ortho Evra clinical program were obese, yet
12 they accounted for 33 percent of the pregnancies.
13 Also, with that small denominator of obese women,
14 it would be very hard to replicate the kind of
15 signal that we have with 35 percent of obese
16 patients in that.

17 There have been chart reviews that showed a
18 2-fold increased risk, although there are data
19 postmarketing [inaudible - mic malfunction.] We do
20 know that 50-microgram products have [inaudible -
21 mic malfunction] microgram products.

22 DR. LEWIS: Another comment?

1 DR. PIAZZA: Yes, if I may.

2 DR. LEWIS: Go ahead.

3 DR. PIAZZA: Gregory Piazza from Brigham and
4 Women's Hospital, cardiologist in thrombosis. I
5 think it is very important when we think about
6 these trials, about the difference between absolute
7 risk. And talking about the safety signal, all
8 hormonal contraceptives have a safety signal when
9 it comes to venous thromboembolism. The failure to
10 recognize differences in study populations can lead
11 to misinterpretation of the magnitude of the safety
12 signal.

13 I'd like to draw the attention to this graph
14 here, which uses epidemiological data to show that
15 in women of reproductive age, if you look at the
16 two middle bars, exposure to hormonal contraception
17 increases the risk of venous thromboembolism, and
18 when obesity is added to that, it further increases
19 the risk. The failure to mention that the
20 population in Study 23 was substantially -- and
21 that's a significant meaning there -- more obese
22 than other studies is critical. Thank you.

1 DR. OUELLET-HELLSTROM: Granted that obesity
2 does increase the risk of VTE, but we have to
3 remember that VTE risk occurs within the first 3 or
4 6 months of exposure. And if we compare it to oral
5 contraceptives, there's a difference, and it's
6 still controversial as to what obesity --

7 DR. PIAZZA: If I may, Madam Chairwoman, I
8 would contend that although the risk of venous
9 thromboembolism is highest in the first 6 months
10 after starting contraception of a hormonal
11 modality, the risk continues and extends for the
12 duration of their use of hormones.

13 We can see here, if you actually look at the
14 area under the curve, there's much more cumulative
15 risk distributed over month 6 onward than there is
16 under the curve for months 1 through 6. So we
17 should be careful about attributing the risk to
18 hormones just within the first 6 months. Thank
19 you.

20 DR. LEWIS: Dr. Jarugula, and Dr. David
21 Eisenberg.

22 DR. JARUGULA: I have a quick clarification

1 question, actually, to Dr. Jackson, slide 79. It's
2 interesting that 15 percent of completed treatment
3 cycles use 4 or more patches; 15 percent of all
4 completed treatment cycles use 4 or more patches.

5 We heard from applicant that there is a
6 learning curve in using these patches. I was
7 wondering if you have looked at the time course of
8 the usage of more patches than required. Is there
9 any information on that?

10 DR. McNEAL-JACKSON: Yes, we have looked at
11 that information, and I would like to defer the
12 answer of this question to my OPQ colleague,
13 Dr. Strasinger.

14 DR. STRASINGER: Hi. I'm Caroline
15 Strasinger from the Office of Pharmaceutical
16 Quality. We do have time profiles. I believe it
17 was 20 percent of all patients in cycle 0, moving
18 down to 10 percent in cycle 13. The 15 comes from
19 all cycles.

20 DR. LEWIS: Dr. David Eisenberg, you had a
21 follow-up, I think.

22 DR. D. EISENBERG: Thank you. The

1 discussion about both effectiveness and efficacy,
2 as well as the risk of putting a product on the
3 market that I would disagree with the physician
4 from the Brigham regarding the risk exposure for
5 thromboembolic risk because as a provider of
6 contraceptive services for women and a researcher
7 in this world, what I know is that women switch,
8 and they switch often.

9 As it was evidenced in this trial, 50
10 percent of women discontinued within the 13 months,
11 and they switched to something else, potentially
12 estrogen containing. There may be a cumulative
13 risk issue here, but I want to go back to something
14 that was brought up by Dr. Laura Lee Johnson at the
15 beginning.

16 You mentioned that CDER has not surveyed
17 women regarding their desires for effectiveness of
18 their contraceptive products in light of their risk
19 tolerances for adverse events; and we all know that
20 the average woman in the United States who wants to
21 have two children is going to use a contraceptive
22 method for over three decades. And while it might

1 not always be a combination or hormonal
2 contraceptive, we are talking about a prolonged
3 lifetime risk in order to avoid pregnancy.

4 So I would like to know whether the FDA has
5 any plans to try to understand what do women and
6 people who use contraception in this country want
7 from their contraceptives, and how can that inform
8 this panel on whether to approve what might be a
9 slightly higher risk product than we realize, but
10 might be also desirable by many women, as they
11 won't desire other contraceptive methods. And we
12 know that pregnancy in the postpartum period has a
13 higher risk of thromboembolic event.

14 So when we're talking about risk tolerance,
15 we need to have that in mind. Does CDER have any
16 intent to assess that, and how do we use that to
17 inform this decision that this panel has to make?

18 DR. JOHNSON: This is Laura Lee Johnson.
19 Unfortunately, I can't create the trial and have
20 all the results immediately in the next several
21 hours. However, we will take this to our senior
22 management for discussion.

1 DR. D. EISENBERG: Is that something that
2 the panel can make a recommendation to the FDA
3 that's not on the list of questions that's in front
4 of us today?

5 DR. LEWIS: I think you just did.

6 (Laughter.)

7 DR. JOHNSON: Yes. The answer is yes. We
8 are looking for recommendations, and we will take
9 everything back with us.

10 DR. D. EISENBERG: Do we have to vote on
11 that? Because I'm happy to make a motion or
12 whatever.

13 (Laughter.)

14 DR. JOHNSON: No. We hear you.

15 DR. LEWIS: Dr. Berenson, last question.

16 DR. BERENSON: Returning to the issue of the
17 15 percent of all completed treatment cycles used 4
18 or more of the patches, there's only 3 patches in a
19 box, so I'm assuming that they are falling off and
20 cannot be reapplied. They disposed of them. They
21 lost them. Because if people don't have another
22 patch to put on, they will probably just use

1 nothing for the rest of the cycle.

2 DR. LEWIS: I'll let sponsor address that.

3 DR. PORTMAN: I just wanted to clarify about
4 replacement patches. When the division mentioned
5 there were either 20 percent or 10 percent, it's
6 important to realize that in the clinical trial, we
7 gave the patients numerous additional patches,
8 oftentimes 8 to 10. We accounted for those, but
9 like anyone knows, if you've got something, you're
10 going to use it. If you had 3 patches and you knew
11 those were the ones you had to try to reapply,
12 women were much more likely to use spare patches,
13 even with partial detachments.

14 So I think that the number of extra patches
15 in the clinical trial setting was different than
16 will be in the marketed setting where they will
17 have 3 patches with a replacement patch program.

18 DR. STRASINGER: I would also like to say
19 one thing. This is Caroline Strasinger again. The
20 proposed labeling does state that if a patch does
21 not stick completely, she should remove it and
22 apply a replacement patch. In the trial, they were

1 instructed to try to press the product back on.
2 They were given extra products in their trial. And
3 as you mentioned, there will only be 3 in the
4 carton itself that a user would receive, and the
5 label stills currently says if the patch does not
6 stick completely, she should remove it and apply a
7 replacement patch, which there may not be one
8 currently.

9 DR. LEWIS: Thank you. Dr. Hunsberger?

10 DR. HUNSBERGER: I just wanted to clarify.
11 So if you put on a new patch, that changes the
12 dose? Is that true? I don't know. I'm just
13 asking.

14 DR. FURMANSKI: It's time dependent, so
15 there is an absorption profile with this. If they
16 truly removed it and then applied a new one, there
17 might be a slight more accumulation, but not a
18 large change in dose, no.

19 DR. LEWIS: No comment, FDA? That's fine.

20 We will now break for lunch. We will
21 reconvene in this room in one hour at 1:05, at
22 which time we will begin the open public hearing.

1 Please take any personal belongings you may want
2 with you at this time. Panel members, please
3 remember no discussion of the meeting during lunch
4 amongst yourselves, with the press, or any member
5 of the audience. Thank you. Panel members, there
6 is a conference room for lunch.

7 (Whereupon, at 12:05 p.m., a lunch recess
8 was taken.)

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A F T E R N O O N S E S S I O N

(1:05 p.m.)

Open Public Hearing

DR. LEWIS: I'd like everyone to please take their seats so that we can get started with the afternoon portion of our meeting.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, such financial information may include sponsor's payment for your travel, lodging, or other expenses in connection with attending this meeting. Likewise, FDA encourages you at the

1 beginning of your statement to advise the committee
2 if you have no such financial relationships.
3 However, if you choose not to address this
4 information about financial relationships at the
5 beginning of your statement, it will not preclude
6 you from speaking.

7 The FDA and this committee place great
8 importance in the open public hearing process. The
9 insights and comments provided can help the agency
10 and this committee with its decision making in
11 their consideration of the issues before them.

12 That said, in many instances and for many topics,
13 there will be a variety of opinions, and one of our
14 goals today is for the open public hearing to be
15 conducted in a fair and open way such that every
16 participant is listened to carefully and treated
17 with dignity, courtesy, and respect. Therefore,
18 please speak only when recognized by the chair.

19 Thank you for your cooperation.

20 Would speaker number 1 please step up to the
21 podium and introduce yourself? State your name and
22 any organization that you are representing for the

1 record.

2 MS. CHRISTOPHERSON: My name is Sarah
3 Christopherson, and I am the policy advocacy
4 director at the National Women's Health network. I
5 do not have any financial ties to any of the
6 entities here today. In fact, we are a nonprofit
7 advocacy organization that does not accept any
8 financial support from drug companies or device
9 manufacturers. We work to improve the health of
10 all women, and we appreciate the agency's interest
11 in fostering the development of a wide range of
12 innovative, safe, and effective methods.

13 My purpose here today is to encourage the
14 panel to consider the questions here a little
15 differently than they have been presented by the
16 division in several key ways; first, filling an
17 unmet need. We know from speaking to women that
18 there is a demand for safe user-controlled methods
19 that don't have to be taken daily, don't have to be
20 taken orally, or don't have to be inserted into the
21 vagina.

22 The briefing document sort of sidesteps the

1 question of whether this is an unmet need in the
2 plain meaning of that phrase by grouping all
3 combined hormonal contraceptives together,
4 regardless of their route of administration, and by
5 narrowly defining unmet need. But we know that a
6 daily pill isn't the same user experience as a
7 weekly patch and the contraceptive user's benefit
8 from having access to a full range of methods. In
9 fact, the data presented in the briefing document
10 actually make that clear.

11 In arguing against the applicant's claims
12 about dosing convenience, the briefing document
13 relies on a study of contraceptive users that
14 extrapolates compliance from data about refill
15 timeliness. Based on this study, the briefing
16 document concludes that switching to a transdermal
17 system did not improve refill behavior, and thus
18 may not improve compliance.

19 But a deeper dive into that study finds that
20 among women who were using an OC and were delayed
21 refillers, switching to the patch increased timely
22 refills from less than 48 percent while on OCs to

1 more than 72 percent while on the patch. That
2 suggests that while the patch is not the right
3 option for everyone, there is a subset of consumers
4 who want and would benefit from access to a lower
5 dose patch.

6 Furthermore, in the appendix, the briefing
7 document makes a strong, albeit unintentional,
8 argument for considering the Agile Patch as filling
9 an unmet need. The document notes that
10 drospirenone containing COCs and the transdermal
11 system had the largest decrease in utilization
12 between 2006 and 2018.

13 That's a period that we know corresponds to
14 increased public safety concerns about those
15 methods' safety. In fact, it's been talked about
16 today that not that many women are on the patch,
17 but that represents a decrease in usage, as women
18 have gained that fear of the patch.

19 As an aside, just for background, the
20 National Women's Health Network has called for
21 drospirenone containing OCs to be removed from the
22 market because we do believe they pose a

1 potentially higher safety concern, at the same time
2 that they don't provide a unique route of
3 administration. That balance is really important.

4 The combined effect of those two datasets
5 that are included in the briefing document, suggest
6 that safety concerns, not a lack of interest, are
7 driving consumers away from the patch, and that
8 there is a subset of consumers that wants a safe
9 patch and could have improved compliance on one.

10 Thus, the central question for the committee
11 shouldn't be whether the new patch is safer than
12 all other approved estrogen-containing CHCs, but
13 whether it's safer for the only other patch that's
14 currently on the market. We've heard a lot of
15 discussion about 10 microgram pills today.

16 Ten microgram pills are a great advancement
17 for women's health, but they aren't a replacement
18 for a patch. And if, in fact, AG200-15 is as safe
19 as other approved non-patch the CHCs, which the
20 briefing document did seem to suggest, although I
21 know we've had debate about that this morning, that
22 represents a significant improvement over what's

1 currently available to women.

2 We agree with Dr. Gassman's comments this
3 morning that Annovera's higher rate of VTEs in
4 clinical trial was appropriately balanced against
5 its unique benefit to women. We argue that the
6 lower dose patch also provides a unique benefit.
7 And while I don't know that we have gotten a clear
8 answer, I'm not a safety expert, about the safety
9 signal, the division has acknowledged, albeit
10 somewhat belatedly, that the Agile Patch dose is
11 significantly lower than the only other patch
12 available to women, and I think that really is a
13 critical comparison.

14 The second point I want to raise is that
15 efficacy matters, but it's not the only
16 consideration. We know pregnancy intention is
17 complicated, but a nominally less effective method
18 that you like and stick with is ultimately much
19 more effective than a nominally more effective
20 method you don't like and discontinue.

21 I think I'm done. Thank you so much.

22 DR. LEWIS: Thank you. Speaker number 2,

1 please.

2 MS. NUNEZ-EDDY: Thank you for the
3 opportunity to speak today on behalf of the
4 National Center for Health Research. My name is
5 Claudia Nunez-Eddy. Our center analyzes scientific
6 and medical data to provide objective health
7 information to patients, health professionals, and
8 policy makers. We do not accept funding from drug
9 and medical device companies, so I have no
10 conflicts of interest.

11 When choosing a birth control method,
12 patients weigh many factors, including safety,
13 efficacy, convenience, and personal preference.
14 Patients use contraceptives more consistently when
15 they are satisfied with their chosen method. A
16 variety of safe, effective, and convenient
17 contraceptive methods are needed to meet the needs
18 of patients.

19 We would like to commend Agile for
20 conducting several studies with racial and BMI
21 diversity that reflects the U.S. population seeking
22 contraception. Women with obesity are often

1 excluded from clinical trials even though they
2 comprise a substantial percentage of the U.S.
3 population.

4 We understand FDA's concerns about the
5 efficacy of this product. The Pearl index of 5.8
6 reported in Study 23 is higher than other combined
7 hormonal contraceptives approved by the FDA.
8 However, we agree that cross-study comparisons of
9 effectiveness can be misleading, especially when
10 study populations and designs are different.

11 There are several factors, aside from
12 product efficacy, that could explain an increase in
13 Pearl indices between the sponsor's product and
14 previously approved contraceptives. When looking
15 at Study 23 Pearl index for women with normal BMI,
16 the Pearl index of 3.4, with a 95 percent
17 confidence interval upper bound of 5.1, does not
18 seem to be substantially higher than other recently
19 approved contraceptives that were tested in
20 primarily thin, white women.

21 In addition, the sponsors initially
22 conducted active-controlled trials that

1 demonstrated a similar Pearl index between AG200-15
2 and a combined hormonal oral contraceptive. Though
3 the confidence interval was wide and FDA noted
4 concerns about data collection and quality, this
5 adds to the evidence that the real-world failure
6 rates of previously approved contraceptives may be
7 higher than the rates provided in original clinical
8 trials.

9 Unfortunately, because Study 23, which FDA
10 focused on to determine efficacy, was a single-arm
11 trial, it is impossible to tell whether the study's
12 Pearl indices are substantially different from
13 other historical contraceptive studies had those
14 studies also included a similar demographic
15 population and similar study design.

16 There are major problems with directly
17 comparing the results from Study 23 to previous
18 contraceptive clinical trials submitted to the FDA.
19 Differences in how the clinical trials determine
20 the Pearl index, such as excluding cycles where no
21 sexual activity occurred, as well as improved
22 accuracy of pregnancy testing, may make these

1 comparisons inaccurate.

2 A particularly important point is that
3 increases in women's BMI also make using historical
4 controls inadequate because most contraceptive
5 clinical trials have included only limited number
6 of overweight and obese women. As a result, there
7 may be a wide gap between clinical trial efficacy
8 and real-world effectiveness. Without comparative
9 effectiveness trials, it is impossible to evaluate
10 whether a new hormonal contraceptive is as safe and
11 effective as one or more other hormonal
12 contraceptives already on the market.

13 We are concerned that 51 percent of subjects
14 dropped out of the study. While only 11 percent
15 discontinued due to an adverse event, this raises
16 questions about compliance, high user failure, and
17 patient accessibility of the product. The FDA and
18 sponsor state that this is comparable to rates of
19 discontinuation in other recently approved combined
20 hormonal contraceptives. However, that raises
21 concerns about the data on which regulatory and
22 clinical decisions are based for all hormonal

1 contraceptives.

2 Lastly, we would like to address the safety
3 and efficacy of AG200-15 for patients with obesity.
4 For these women, the serious risks of
5 thromboembolic events outweigh the benefits, given
6 the reduced efficacy. We support FDA's conclusion
7 that the data presented warrants a contraindication
8 for patients with BMI greater than or equal to 30.
9 We also strongly recommend that FDA require all
10 previously approved combined hormonal
11 contraceptives be tested in patients with obesity,
12 and a contraindication included on the label for
13 those that also find limited efficacy in those
14 patients.

15 In summary, it is crucial that clinical
16 trials include participants who are representative
17 of the patients that would consider using the
18 product. Such studies provide more comprehensive,
19 generalizable data that can better inform patients
20 and providers as they make decisions about
21 contraceptives.

22 The FDA has acknowledged that it is unclear

1 whether the higher Pearl index reflects differences
2 in study population and design or truly indicates
3 suboptimal effectiveness of AG200-15. The FDA
4 should always require that manufacturers conduct
5 comparative effectiveness trials or
6 active-controlled trials when differences between
7 previous studies make it difficult to directly
8 compare efficacy and safety of new products with
9 previously approved hormonal contraceptives. Thank
10 you.

11 DR. LEWIS: Thank you. Speaker 3, please.

12 MS. LUKAS: Good afternoon. My name is
13 Vanessa Lukas. During the course of the secure
14 Agile 23 trial, I worked as a clinical research
15 coordinator at Women's Health and Research
16 Consultants in Washington, D.C., under Dr. James A.
17 Simon. I have consulted with Agile Pharmaceuticals
18 in the past, who supported my travel, but I'm not
19 being compensated for my time to be here today.

20 My testimony is accurate to my experiences
21 during the Agile secure trial and has not been
22 influenced by Agile Therapeutics. After four years

1 with Women's Health and Research Consultants, I
2 enrolled at the Wake Forest University School of
3 Medicine. In fact, as I speak with you now, my
4 classmates are just finishing their second-year
5 renal block exam.

6 When approached to provide comment regarding
7 my experiences with the patch, I made special
8 accommodations with my institution to be available
9 to be here today. I did so because as an advocate
10 for women's health and as a future physician, I
11 feel strongly that contraceptive options like the
12 Agile Patch should be available as an option for
13 women.

14 At our site in D.C., I guided 25 women
15 through the process of study participation without
16 any pregnancies. Over the course of their
17 enrollment, I got to know these women very well,
18 from university students and young professionals,
19 to a bike messenger and a prison guard. Our
20 subject pool represented a diverse population in
21 the D.C. metro area. Each was seeking a simple and
22 effective contraceptive method.

1 The once-weekly placement appealed to
2 patients, as it was one less thing they had to work
3 into their busy lives. One of my patients was a
4 single mother and a prior oral contraceptive pill
5 user. Between morning and bedtime routines with
6 her active toddler, the pill did not fit well in
7 her day-to-day life. She was excited to try
8 something different that did not require strict
9 daily compliance to protect fully against
10 pregnancy.

11 Similar sentiments were made by others with
12 unpredictable schedules, like the young
13 professionals who were happy they didn't have to
14 remember their pill packs when they traveled for
15 work or stayed over at their partners' apartments.

16 In addition to occupational and lifestyle
17 diversity, our site enrolled women of all sizes and
18 shapes, spanning from petite to plus size, or in
19 the committee's words, obese. At clinic, we worked
20 with women to find the patch sites within the
21 prescribed locations that worked well for their
22 unique contours and would be easy for them to apply

1 and remove on their own without assistance.

2 At our site, we observed a learning curve
3 for what would be the best patch sites for each
4 woman. This was due to factors that women are not
5 mindful of until they're wearing the patch. For
6 example, there was the waistband of their jeans and
7 where it sits on their abdomen when they're seated,
8 or where a sports bar moves during exercise on
9 their shoulder.

10 Preparing women for these factors so they
11 could find their best spot made wearing the patch
12 obtrusive and allowed them to set it and forget it
13 for the week. As I mentioned earlier, we had a
14 bike messenger participating in the trial, but we
15 also had a patient who swam for exercise multiple
16 times a week; many patients who went to the beach
17 on vacations, and all of our patients were
18 subjected to the humid D.C. summer.

19 Initially, patients were unsure that the
20 patch's adhesive qualities would be robust enough
21 to meet the challenges of all these environments,
22 but ultimately each was impressed with the patch's

1 long-lasting adhesion and ability to re-adhere if
2 necessary. Each of the 25 women who I worked with
3 during the SECURE trial initially joined because
4 they already were interested in using a birth
5 control and were committed to preventing pregnancy.
6 That continued commitment throughout the trial was
7 the motivating factor that ensured compliance with
8 the patch.

9 At the end of the trial, a few participants
10 were even interested in continuing with the patch
11 for their primary form of contraception. In
12 particular, one participant who was a prior Ortho
13 Evra and Xulane patch user wanted to continue with
14 the Agile Patch if she could because she preferred
15 its round shapes, adhesive qualities, and it's
16 lower dose.

17 Lastly, in regards to patients leaving the
18 trial, people move; people's relationships end, so
19 they're not meeting that one sexual activity per
20 week; and people's reproductive needs change. I
21 came here in support of the Twirla patch because as
22 evidenced in this statement, every woman has

1 different needs, different opinions, and different
2 preferences when it comes to birth control. Based
3 on my experiences in women's health and with
4 patients in the SECURE trial, the Agile Patch fits
5 a unique space in the current contraceptive market.
6 Thank you.

7 DR. LEWIS: Thank you. Speaker 4, please.

8 DR. WALDBAUM: Good afternoon. My name is
9 Arthur Waldbaum. First, I'd like to disclose that
10 Agile did pay for my travel here but is not
11 compensating me for my time today, and I have no
12 other financial arrangements with them. I felt it
13 was important for me to be here today to be an
14 advocate for women, to support a better option in
15 birth control if the Agile Patch is approved.

16 Just some background on myself, I'm an
17 OB/GYN physician, board certified. I've been
18 involved in patient care for over 40 years. I've
19 also been a clinical investigator in women's health
20 care for the past 30 years, and have been a
21 principal investigator in over 170 different
22 studies, 35 of which have been birth control

1 studies, and a number of the Agile studies, which
2 I'll mention in a few minutes.

3 My goal as an OB/GYN physician has been to
4 provide the best care for my patients. In
5 reproductive age women, the most important thing to
6 them is pregnancy prevention. Many of them are in
7 school. Many of them are starting work, starting a
8 new profession, and they are not prepared for
9 pregnancy. Most of them do want to be responsible
10 and they want to use something that's going to give
11 them protection.

12 Besides the emotional and financial effects
13 of the unwanted pregnancy, I should point out, too,
14 that the risks related to pregnancy greatly
15 outweigh the risks of any use of any means of birth
16 control. It is my desire to use a very effective,
17 safe means of birth control for them, but it's easy
18 to just prescribe something to a patient. You need
19 to give them something that they're going to
20 actually use.

21 As we've heard, there are many options in
22 birth control, including permanent sterilization,

1 invasive IUDs, vaginal rings, hormonal injections,
2 and so forth. Everything is not right for every
3 patient. Some are not appealing to them, and you
4 need to use something that they will actually use.

5 The birth control pill is the most commonly
6 used means of birth control currently in the United
7 States, but the major problem that I've seen with
8 patient care is patient compliance; that is, there
9 has been a lack of compliance with the birth
10 control pill because of the difficulty of
11 remembering to have to take a pill every day. If
12 they're not taking it every day, then that of
13 course increases the pregnancy rate and increases
14 the rate of irregular bleeding.

15 There are also many times that women may
16 have GI illnesses, have nausea and vomiting, and of
17 course during their illness, they're not going to
18 be able to absorb any means of oral protection, so
19 they're more at risk at that time as well.

20 I feel that a transdermal contraceptive
21 patch is a very vital option to improve compliance
22 in women. In my experience with the trials that

1 I've done with contraceptive patches -- and I was
2 involved in the original Ortho Evra studies and in
3 many of the Agile studies -- there has been
4 immensely better patient compliance to remember to
5 use the patch weekly rather than take a daily birth
6 control pill.

7 The current patch that is approved on the
8 market, Xulane, a generic for Ortho Evra, has too
9 high of an estrogen content to have widespread
10 usage because of the increased risk of side
11 effects. Prior to these risks being recognized, I
12 should mention that Ortho Evra had a very large
13 percentage usage in the birth control marketplace,
14 indicating how popular the patch is to women and
15 will be in the future if we do have a patch like
16 the Agile Patch that has a lower estrogen rate and
17 can be used more safely and effectively.

18 I've been involved in five different Agile
19 studies going back to 2001. Personally, I've
20 supervised over 100 subjects in these trials. I've
21 seen significant improvement in the adhesion
22 properties of the patch through the years, so that

1 in the most recent studies, that has not been a
2 problem at all. In the most recent study three
3 years ago, I supervised 42 patients, and there was
4 excellent patient compliance and excellent patient
5 satisfaction.

6 Finally, in my opinion, women should not be
7 deprived of the critical and important option of a
8 new contraceptive patch as a safe, effective means
9 of birth control, where they can be more compliant
10 than with the pill. Thank you.

11 DR. LEWIS: Thank you. Would speaker 6
12 please approach the podium?

13 MS. GRAY: Five?

14 DR. LEWIS: Five; sorry.

15 MS. ERICKSON: Thank you. My name is Jan
16 Erickson, and I am director of programs for the
17 National Organization for Women Foundation. We
18 represent our own interests here today and not of
19 any other organization or company.

20 I want to thank you, especially, for this
21 opportunity to share our concerns because it is
22 something that we talk about daily. Our parent

1 organization, NOW, Inc., has 300 chapters in all
2 the states and the District of Columbia, and
3 women's access to reproductive health care and
4 bodily autonomy is one of our major, major
5 concerns, and we hear that from so many of our
6 activists and our supporters.

7 So we are really concerned about the slow
8 pace of the development of contraceptives in this
9 countries. But we are pleased to see that this
10 lower dose, combined hormonal contraceptive patch
11 AG200-15 is finally being considered by the
12 advisory committee, though we were a little
13 discouraged to hear from some of the division about
14 some of the division findings this morning.

15 Agile Therapeutics began efforts to seek FDA
16 approval more than 10 years ago. That's an awfully
17 long period to have to go through the review
18 process, though we know that certain guidances were
19 issued during that period and different requests
20 were made of Agile in supplying more information of
21 their clinical trials. But if we look, history
22 shows that women's contraceptive drugs and devices

1 review process is long an often tortured.

2 I was very distressed to learn, counting up
3 all the years it took, that Plan B emergency
4 contraception to be sold over the counter with no
5 age restrictions took more than 50 years. That's a
6 sad comment on the world's wealthiest and most
7 technologically advanced country, I think. There's
8 far too much political pressure being brought on
9 the development of these drugs and on the agencies
10 that deal with them. We regret that, and we work
11 very hard to try to limit that.

12 We are concerned that there may be a coming
13 reproductive healthcare access crisis in this
14 country with the closing of many women's clinics
15 across the country and the defunding of our many
16 decades-old family planning network. Then we are
17 also waiting for the Supreme Court to take up the
18 constitutionality challenge of the Affordable Care
19 Act and the consequences of that if there is a
20 decision against the ACA, maybe. Women's
21 reproductive health care remains to be determined.
22 We certainly hope that doesn't happen, but it is a

1 matter of concern.

2 In preparing for this event, we looked at a
3 wonderful issue of May '19 Scientific American,
4 which focused on the development or lack of
5 development of women's healthcare products, and
6 services, and so forth. There weren't many good
7 pieces of information.

8 One study in 2015 was conducted by Diana
9 Foster, director of research at Advancing New
10 Standards in Reproductive Health at the University
11 of California, San Francisco. She found that the
12 three features of birth control, deemed extremely
13 important by the largest proportions of women, were
14 effectiveness, lack of side effects, and
15 affordability.

16 For 91 percent of women, no contraceptive
17 has all those features that they believe are
18 important. Despite the fact that the first birth
19 control pill was made available to the public
20 nearly 60 years ago, a birth control product with
21 all these features does not exist in 2019.

22 Dr. Foster concluded that it is time to

1 invest in women and ensure that they have access to
2 options for multiple forms of birth control. I
3 must say that we did just a very informal survey of
4 our interns at the office and found that they had
5 quite varied needs and concerns about their birth
6 control; and all agreed that having a patch seemed
7 like a tremendous advance for them in their busy
8 lives.

9 Foster said that the solution to better
10 birth control is reliant on making the effort to
11 collect and respect women's preferences when it
12 comes to contraception, and then using science to
13 develop methods that meet their needs. We couldn't
14 agree more.

15 The National Organization for Women does not
16 endorse any specific drug or device, but we broadly
17 support innovation and expansion of access of all
18 types of safe and effective contraceptions. AG200-
19 15 stands out as the only lower dose transdermal
20 contraceptive patch to potentially become approved
21 and available, and we really hope that happens.
22 The time is now to stand up for reproductive health

1 and the opportunity for women to make well-informed
2 decisions among an array of contraceptive options.
3 Thank you.

4 DR. LEWIS: Thank you. Speaker 6, please.

5 MS. GRAY: Good afternoon. My name is Marta
6 Hill Gray, and I'm the founder of Gray Matter
7 Group. I have no financial relationship with
8 Agile, and I'm here at my own expense. My company
9 is dedicated to improving women's health. I work
10 with women's healthcare professionals and
11 organizations focused on and dedicated to improving
12 the health and wellbeing of women.

13 I'm here today because Agile Therapeutics
14 has invested heavily in a low-dose birth control
15 patch for women. The Agile Patch study was a
16 real-world trial that included populations of women
17 who have often been ignored and discounted. The
18 one particular population of women included, that
19 has never been part of a birth control trial such
20 as this, were women who were considered obese.
21 Agile has worked closely with the FDA and invested
22 heavily to make sure that all measures taken would

1 lead to all women having another low-dose birth
2 control option not currently available.

3 Obese women need options, too, and they need
4 to know the risks. Not having this patch hurts all
5 women. Over the past few decades, obesity rates
6 have nearly doubled. According to the data from
7 the National Center for Health Statistics, the
8 prevalence of obesity among women age 22 and older
9 increased from 25.5 percent to 40.7 percent over
10 this time period.

11 A few questions and points I'd like to raise
12 today. The FDA in a published report I read today,
13 in this report, it was allowed as how the current
14 generic patch went through clinical trials 20 years
15 ago, and it did not dispute the fact that there was
16 not a real-world measured sampling of women. The
17 Agile Patch study has included a highly
18 representative obese population, and the label
19 could provide clarity on efficacy and safety for
20 this very important group of consumers.

21 The vague and unhelpful limitation of use
22 statement on some current birth control pills and

1 products states, "not adequately evaluated in women
2 with obesity" might lead some to think that 35
3 percent of the female population are not worthy of
4 evaluation. Surely that cannot be the case. It
5 might lead one to think that had the birth control
6 products on the market today, with this language in
7 the packaging, had been held to real-world clinical
8 trial standards, they may have never come to
9 market.

10 I'm concerned about an apples-to-apples
11 comparison here. Agile has invested in women
12 completed with real-world clinical trial structures
13 to reflect more of the real lives of women than
14 ever before. As a result, women of all BMI
15 categories can now see for themselves their risk
16 factors, based on their weight for this low-dose
17 patch.

18 What message are we sending about investing
19 in women's reproductive health? What are women to
20 think when there is an option that may not be
21 perfect for all, but it may work well for many? Is
22 it not true that, FDA, a birth control on the

1 market today is not in fact perfect for all?

2 I speak here today on behalf of women who
3 have no voice, no opportunity to address you face
4 to face. These women are not invisible. They are
5 real and at risk without options and choices. How
6 much protection is no protection? For some, it may
7 be the difference between using birth control or
8 not. Birth control is not a luxury. It needs to
9 be as diverse as the women who use it and
10 accessible to those who need it.

11 Today, we have a company who is invested in
12 women and done the heavy lifting to ensure the
13 regulatory requirements have been met and worked
14 closely with FDA. They are now prepared to take
15 the next financial step to bring this birth control
16 patch to market. Women carry the great load and
17 responsibility of family planning. It is our
18 obligation to lighten that load by giving them more
19 choices to make the best decisions for themselves
20 and their families.

21 Do not let women be the losers here. Do not
22 punish a company that has followed the rules and

1 invested in women with a product that fills an
2 unmet need. Let's remember, when it comes to risk,
3 the greatest risk is pregnancy. To deny us of a
4 solid, well-developed, and studied option that will
5 benefit so many women would be an affront to women,
6 to women's healthcare companies who invest in birth
7 control options, and certainly does not bode well
8 for FDA and its commitment to women's reproductive
9 health. Thank you.

10 DR. LEWIS: Thank you. Could we hear from
11 speaker 7, please?

12 MS. THIMMESCH: Good afternoon. My name is
13 Rebecca Thimmesch, and I have no financial ties to
14 any entities represented here today. I'm here with
15 Advocates for Youth, which is a 501(3)(c)
16 organization that champions efforts to help young
17 people make informed and responsible decisions
18 about their reproductive and sexual health. We
19 believe that we can best serve the field by boldly
20 advocating for a more positive and realistic
21 approach to adolescent sexual health.

22 We focus our work on young people aged 14 to

1 25 in the U.S. and around the globe. In my role at
2 Advocates, I work to make sure that all young
3 people, regardless of their circumstances, can
4 access comprehensive, youth-friendly, sexual health
5 services, including the contraception of their
6 choice.

7 I'm here today because I remain unsatisfied
8 with the current range of contraceptive options
9 available, and I believe I can speak for many young
10 people who feel the same. I'm here today because I
11 am inspired by the work presented this morning to
12 continue to innovate the field of contraceptive
13 care, and I wish to testify on behalf of the Agile
14 Patch.

15 The Agile Patch, a lower dose combined
16 hormonal and transdermal patch, represents an
17 exciting development in the contraceptive field.
18 Not only does the Agile Patch suit a tier of young
19 people looking for non-daily methods outside of
20 LARC, but the information gleaned from these
21 clinical trials indicates tremendous advancement in
22 our ability to adequately counsel young people of

1 all backgrounds and sizes on their contraceptive
2 options.

3 Young people deserve more and better
4 contraceptive options in order to help them take
5 control of their lives and their futures.
6 Contraceptive patches in particular help fill a
7 need for methods that suit young people who don't
8 want to take a daily pill, but who aren't
9 interested in a LARC.

10 This is a group who cannot be served by
11 rings alone, and currently young people seeking a
12 non-daily contraceptive methods outside of LARC
13 have the choice between a vaginal ring, which may
14 be uncomfortable, invasive, cause gender dysphoria
15 in trans and nonbinary young people, or
16 traumatizing for survivors of sexual assault, and a
17 transdermal patch with significantly higher levels
18 of hormones than the average available combined
19 oral contraceptive, a choice which is unacceptable.

20 Many young people choose low-dose combined
21 hormonal contraceptive methods to help treat
22 painful periods, acne, and other conditions.

1 However, there is no one size fits all CHC, and
2 young people deserve an ever expanding range of
3 options in order to make the best choice for them.

4 In addition to working with young people
5 nationwide, I am also a young person myself. Is
6 anyone 23 here or is it just me?

7 (Laughter.)

8 MS. THIMMESCH: When I was in school, I had
9 a story like many others. I worked and interned,
10 in addition to taking a full-course load, a hectic
11 schedule which often led to miss pills and
12 unnecessary stress. My sophomore year, I became
13 pregnant during finals week. My junior year, I
14 began using a hormonal IUD. My senior year, after
15 almost two years of severe discomfort, I had my IUD
16 removed and began using the shot, which I also
17 later discontinued. Now, just over a year and a
18 half out of school, my schedule is just as hectic,
19 and I am still struggling to find a non-daily
20 method outside of LARC that works for me, and I
21 know I'm not alone.

22 We need more and better contraceptive

1 options so that, hopefully, young people like
2 myself can focus on our careers, our education, and
3 our lives, not our contraception. For myself and
4 for the young people I represent, the methods used
5 to conduct clinical trials for the Agile Patch are
6 particularly exciting.

7 As someone who is quite happily living in a
8 body that has been described this morning as
9 overweight, I continue to be frustrated by the
10 reality that the contraceptive options currently
11 available were not designed with me in mind. And I
12 am not alone. We deserve to be included. We
13 deserve to know how exactly a method will work with
14 our bodies regardless of our BMI or our weight.

15 We know that a higher Pearl index is not
16 necessarily unique to this method, but what is
17 unique is that this would be the first method
18 available, accompanied by transparent and accurate
19 information, for young people of all backgrounds,
20 giving them the tools to work with their providers
21 to make the best contraceptive choice for them.

22 As an organizer, a public health

1 professional, and a young person myself, I'm
2 heartened by the efforts that Agile has taken to
3 ensure that their trials reflect my relived reality
4 and encouraged that we may look forward to a future
5 in which our contraceptive choices reflect all of
6 our bodies and all of our lives. Thank you.

7 DR. LEWIS: Thank you. Could we please hear
8 from speaker 8?

9 DR. OSIER: Hello. My name is Nicole Osier,
10 and I'm currently living in Austin, Texas. I was
11 living in Pittsburgh, Pennsylvania when I was a
12 patient in the Agile trial, and I would like to
13 disclose that while Agile has supported my travel
14 to be here today, they are not compensating me for
15 my time.

16 When I was in the Agile trial, I was in
17 graduate school, and I was currently taking a
18 hormonal contraceptive that was high dose, and I
19 had previously been recommended by my nurse
20 practitioner to find another alternative due to my
21 family history of blood clots and migraines. When
22 I was asked what those options were, I was told

1 that as a woman who had not had any children, there
2 really weren't any.

3 So even though I had access to a few
4 different options that put me at risk, and they
5 were being paid for by my insurance, I decided to
6 be part of this trial because I felt we needed more
7 better options for people who are not able to
8 safely take these drugs or who have other
9 limitations or barriers.

10 I'm currently an assistant professor at the
11 University of Texas at Austin, and I am taking time
12 out of my incredibly busy schedule to be here. I
13 moved around several classes and meetings because I
14 think that it's important that women have new
15 options for birth control that are not currently
16 available.

17 I'm here today to share my perspective in
18 the trial, which was overwhelmingly positive. In
19 addition to having a high risk for blood clots that
20 made me not a good candidate for a high-dose oral
21 contraceptive pill, I have a really hard time
22 swallowing pills, and having an option that was

1 easy to apply myself was a great asset to me.

2 I found the patch extremely easy to use on
3 my own and discreet so that nobody had to know my
4 personal business about my sexual health. I found
5 it less stressful than something I had to take
6 daily, and it was very easy to work into my busy
7 schedule. As a registered nurse, I work long
8 hours, and if I don't bring my pills with me to
9 work, I can very easily find myself outside of the
10 window where I need to be taking the medicine for
11 it to be effective.

12 I liked that I got to change the patch
13 weekly, and I found that it was very easy to
14 maintain that schedule. Also as a nurse and an
15 academic, I represent two very large groups of
16 Americans. There are over 3 million registered
17 nurses, and I promise you, all of their schedules
18 are incredibly hectic. We are doing our best to
19 serve the patients of the community, and certainly
20 needing to go on maternity leave could put a
21 significant damper on our efforts.

22 I chose to be a part of this trial because

1 we need better options to prevent pregnancy, and I
2 think that there's an overreliance on daily oral
3 options or long-term options like IUDs.
4 Fortunately, physicians are now being more open to
5 giving longer term options to people who've not had
6 children or who are young, but when I was in grad
7 school, it was extremely difficult to find anybody
8 to give me something that wasn't a daily pill.

9 Overall, my experience with this patch was
10 very good. It did not irritate my skin. I had no
11 problems with patch adherence, and the few times
12 when it did sort of slip up, I found it very easy
13 to put back down. I also found that the people who
14 trained me to use the patch were very thorough, and
15 the instructions provided to me were clear and easy
16 to follow.

17 I felt empowered to take control of my own
18 health, and it was nice to not have to use
19 something that was invasive or required an
20 unpleasant stimulus like a shot. On a personal
21 note, I'm also a trans individual, and the thought
22 of using an insertable ring weekly is really quite

1 traumatizing and dysphoric to me. And something
2 like a patch that's way more discreet and easy to
3 hide is just a much better alternative in my
4 opinion.

5 I would like the advisory committee to
6 remember that myself and many other women and trans
7 individuals want a patch as an option because it is
8 way less labor intensive for us to use on our end,
9 and it is less permanent than the IUD in case our
10 reproductive needs or decisions change over time.

11 I would also like to echo what had been
12 previously stated about the dropout in the study
13 and how relationships do change. And the
14 requirement that people be sexually active during
15 the trial I think was an important one, but I
16 suspect that a lot of people who dropped out of the
17 trial probably did so because they were no longer
18 having regular sexual encounters with a partner.

19 I think, overall, we've waited too long for
20 new birth control options, and we just need a
21 better system, and I think that the patch offers a
22 lot of alternatives to a lot of people, whether

1 they don't like taking pills, have trouble taking
2 pills, are afraid of needles, or don't want a
3 longer term, more permanent solution. Thank you
4 for your time.

5 DR. LEWIS: Thank you. Would speaker 9
6 please come forward?

7 MS. ARRINDELL: Thank you. As speaker 9,
8 I'm tempted to drop the microphone and say what
9 they said. I'm Deborah Arrindell. I'm vice
10 president of health policy for the American Sexual
11 Health Association, and I have no conflicts to
12 report. I really appreciate the opportunity to
13 talk to you.

14 Our organization was founded in 1914, just
15 two years before Margaret Sanger established the
16 first birth control clinic in New York city in
17 1916. I should say those were very long years if
18 you consider how many women are constantly looking
19 for contraception options and how many fewer they
20 had then compared to what we are still in need of
21 today.

22 On average, more than 99 percent of women,

1 15 to 24, who've ever had sexual intercourse, have
2 used contraception. I wish I were a statistician
3 so that I could just tell them more than 99 is like
4 almost everybody. That's probably not a good
5 statistical way to frame it, but it's really almost
6 everybody. As one of the committee members
7 mentioned earlier, on average, a woman who wants to
8 have two children will spend 30 years avoiding
9 getting pregnant, and that is no joke as a woman
10 who only wanted one kid can say.

11 Across this 30-year lifespan, women are
12 going to have lots of different ways that they want
13 to use contraceptives, and there are going to be a
14 lot of different things that happen, and lots of
15 decisions are going to be made that are sometimes
16 emotional, sometimes personal, sometimes practical;
17 it's just kind of a complex set of factors that go
18 into determining this.

19 So we still don't have enough options to
20 meet all those needs, as we've been hearing this
21 afternoon and again this morning. So the patch
22 that's being considered today might be the option

1 for some women. It might be the option for
2 hundreds of women who can't take a pill easily,
3 don't want to take a pill, don't want a shot, and
4 don't want something that's invasive.

5 There really isn't time for us to fully
6 address it today, but some women of color in
7 particular have a complex relationship with
8 contraception and have a legitimate mistrust of
9 healthcare systems. If you consider the fact that
10 as recently as the late 1970s, 32 states permitted
11 involuntary sterilization. So having an option
12 that you can completely control, you can put it on,
13 you can take it off, is the kind of option that
14 could be perfect for many women.

15 So is it perfect? I think this morning it
16 was clearly established that it's not perfect, and
17 it's not for all women. But it seems reasonable to
18 expect that women with their providers can make the
19 decisions about what's right for them. What's
20 shocking to me is that according to the -- well,
21 not really shocking. But according to the
22 Department of Labor, women make 80 percent of the

1 healthcare decisions in this country.

2 It's women who decide who the doctors are
3 going to be, who the nurse practitioner will be, if
4 we should get a second opinion, where the second
5 opinion should come from, and take the children to
6 healthcare providers. And we are perfectly
7 comfortable with women making those decisions, so
8 we have to believe, at some level, that women are
9 able to make those decisions intelligently with
10 their healthcare providers.

11 Then there's obesity. I'm not going to get
12 into that because there's been so much discussion
13 about that already. I don't have anything new to
14 add. I will only say that, because no one has said
15 it today anyway, there are more adults living with
16 obesity in America than in any other country in the
17 world, so that alone should help us to fully
18 understand that this isn't something that we can
19 deal with next year. This is something we need to
20 be dealing with immediately.

21 Finally ASHA, our organization, was really
22 honored to join a letter to this committee from 11

1 respected, diverse women's health organizations.
2 Together, we believe that adding a low-dose patch
3 to the available FDA-approved birth control methods
4 is absolutely essential, and I hope you've all been
5 given copies of that letter.

6 We need all the options we can get. The
7 ability to avoid, delay, and space child bearing is
8 crucial to women's social and economic wellbeing.
9 It's a basic human right and essential to a woman's
10 constitutional right to simply pursue happiness.
11 Thank you.

12 **Clarifying Questions to FDA and Applicant**

13 DR. LEWIS: Thank you.

14 The open public hearing portion of this
15 meeting has now concluded, and we will no longer
16 take comments from the audience. We're going to
17 move into a segment of the afternoon where we take
18 clarifying questions. Before we do, I think the
19 FDA has one more slide they want to show.

20 DR. GASSMAN: Yes. We'd actually like to go
21 back to the sponsor's slide 73, please. We'd like
22 to discuss the meta-analysis and the Agile Patch

1 hazard ratio. One thing I'd like to point out is
2 that when we did the meta-analysis, we actually
3 received the comment from Dr. Trussell.

4 It's a very short comment, but in the paper
5 that he sent us, he mentioned that the difference
6 between a pearl of 2.53 in the non-obese and a
7 pearl of 3.15 was probably not clinically
8 significant. Although we do talk about percentage
9 difference between obese and non-obese, at least
10 for the purpose of this paper, we were not talking
11 about a pearl between 2 and eight or 2 and 11. So
12 I think although we do see differences between the
13 obese and the non-obese population, I think there's
14 still a lot of work to be done in trying to get
15 estimates around this.

16 Now I'd like to ask Dr. Johnson to comment
17 on this slide please.

18 DR. JOHNSON: One question that we had for
19 the applicant is here you're looking at the hazard
20 ratios, but did you also do a similar analysis with
21 the incidence rate ratios that were also reported
22 in the manuscript?

1 DR. GARNER: No, we didn't do that specific
2 analysis for today.

3 DR. JOHNSON: Okay, because that's where you
4 start to see that while the incidence rates were
5 maybe 34 to 44 percent for some of these and those
6 ratios, for the product under discussion today, it
7 would be about 100 hundred percent because most of
8 these Pearl indices that we're looking at are
9 doubling.

10 I think this is an important element. As
11 we're trying to understand and dissect the
12 information today, we have to focus on the product
13 that is in front of us for our discussion today.
14 But when we're thinking about the broader
15 picture -- and I think we have an additional backup
16 slide that ties to some of this other work.

17 So thinking about the Quartette slide that
18 was shown, you broke things down by weight for less
19 than 70 kilograms, 70 to 90, and then 90 and
20 over -- and if you have the similar data for the
21 transdermal system broken down by that.

22 Yes. So we have this slide, and you said

1 this is for Quartette, but with the AG200-15 data
2 up against it, we do have --

3 DR. GARNER: I don't believe we have that
4 slide. Do you have that side as a backup?

5 DR. JOHNSON: Yes. Can you go to our backup
6 slide please? Now, bearing in mind that we've had
7 a lot of discussion today about how cross-study
8 comparisons, there are a lot of different issues.
9 Also bear in mind, our statistician very quickly
10 put this together while looking at this. So if we
11 are going to try to think about these types of
12 comparisons, I do want us to really consider what
13 we're looking at.

14 There is a lot of uncertainty, and there
15 have been a lot of different ways that we're
16 slicing the pie, and a lot of different pies, as
17 Dr. Shaw brought up as well. But when you look at
18 the basic primary analysis population, the data
19 don't rule out pregnancy rates as high as 7.2,
20 unintended pregnancies per 100 woman-years of
21 product use.

22 When we look at a slide like this, we can

1 also see, whether you're looking at that analysis
2 population, which would be your first column, or
3 whether you put back in those sexually inactive
4 cycles, we still have some pretty high values here.
5 Now, some of them are lower, some of them are
6 higher, but in none of these analyses are we ruling
7 out, even with enough data to do so, a number of
8 unintended pregnancies that is unusually high in
9 trials for approved products and also with a
10 concerning safety signal.

11 So this is, as we're talking about different
12 groups, something that we wanted to make sure was
13 really clear.

14 DR. GARNER: Thank you. So I'll try to
15 respond as best I can to the various points you've
16 made. I think, for one, the intention of showing
17 the Quartette a description of effects by weight
18 was not to suggest and do any cross-study
19 comparisons at all. The only point we were making
20 there is I think one of the points that was made
21 during the open public hearing, that there are
22 other products which have seen some effects of

1 weight and BMI. The single point was there's not
2 been any information in labeling so far that
3 indicates that just for informational purposes. So
4 it was not to do a cross-study comparison across
5 our Pearl indices versus the Quartette trial.

6 I think what we're saying overall from our
7 presentation today is the Pearl indices are
8 changing, and we believe the Pearl indices are
9 changing and rising because study population and
10 design factors have played a role. Essentially,
11 what we're raising questions for discussion about
12 is really this 5 number, which we believe has
13 generally been based on historical studies with
14 more limited populations, and that our study
15 results don't actually indicate lower efficacy of
16 the patch overall, but rather as a reflection of
17 our study design and the population.

18 Would you like to add any more clinical
19 perspective on to that, Dr. Portman?

20 DR. PORTMAN: I'm always happy to talk about
21 the Pearl. I think what's so critical, and I think
22 it was said here today, is that we're evaluating

1 these products on their own merit, and yet we keep
2 coming back to this 5, which is really based on
3 this body's historic experience with older studies.

4 We've made a lot of analogies. There are
5 European studies that have pearls of 0.5, and the
6 same product and the same approval time have a
7 pearl of 2.5 here. There was a gestodene patch
8 studied in different populations in Europe that had
9 a Pearl of, I believe, 1, and it was 6 here.

10 So we clearly see that there's a huge, huge
11 impact on the demographic makeup of the population
12 that you recruit in the clinical trial. I commend
13 the public forum speakers for validating what I've
14 done as a researcher, is really tried to move and
15 advance the science by including a demographically
16 diverse population.

17 I think this population mirrors the United
18 States more than any other trial. If you look at
19 the ethnicity, if you look at the weight, it is a
20 mirror image of where we're at now, and I think
21 that's so critical that patients will have that
22 information about what happens now in the real

1 world and not what happens with an arbitrary cutoff
2 of 5.

3 Just a few other things that we really
4 haven't addressed when it comes to the Pearl. The
5 OB/GYNs in the audience will recognize that the
6 three P's vary how a pregnancy outcome is going to
7 happen. It's the patient, it's the passenger, and
8 it's the provider. You don't know how labor is
9 going to go if you don't take all three.

10 Dr. Trussell identified three P's that occur
11 in contraceptive research that are also variables:
12 poverty, so socioeconomic status; partner status,
13 whether you're cohabitating or whether you were
14 married; and parody. Let's just take the example
15 of parody, for one, and this is something that we
16 looked at, but we didn't put into modeling. I
17 think we could try to parse out all these factors,
18 but there are just too many, and I don't think it's
19 necessary to try to add them in, and then subtract
20 and try to get down below 5 because I think that's
21 an exercise that's in vain.

22 But here you see if you have never had a

1 child, if you are nulliparous, your Pearl index in
2 Study 23 was 3.1. It does come under the upper
3 bound of 5. You'll note that in the clinical
4 development program for Annovera, they had twice as
5 many nulliparous patients. So if you want me to
6 design a trial that gets you under 5, we could do
7 that, but that does no service to the diverse
8 population. We don't need to recruit a
9 tri-population that's then Caucasian and
10 nulliparous just to hit an arbitrary endpoint.

11 So I think we have to think about all these
12 variables, judge this patch in the context of the
13 study that was done recently, and I think that's
14 really the most important issue that this committee
15 could discuss today.

16 DR. GARNER: I just wanted to add one more
17 thing to the point that was made also about the
18 safety signal, which we strongly disagree with. We
19 don't believe that our data suggest that there is a
20 safety signal for VTE. We believe that our data
21 reflects the population, once again, with 35
22 percent of obese women.

1 One thing I just wanted to point out that we
2 have noted in all of our discussions with the FDA,
3 is that at the time of our presubmission meeting in
4 2017, before we submitted these Study 23 data, we
5 did have a discussion with the FDA as to how we
6 were going to submit our safety data, and we agreed
7 with the FDA at that time -- these are from the
8 minutes of that meeting -- that the safety
9 information should be combined from all three
10 phase 3 studies. That was agreed to by the FDA,
11 and that's what we did in our submission. This was
12 the integrated data that we submitted.

13 We then, in the CRL that resulted several
14 months later after the review, received the
15 following language from the FDA and their complete
16 response. Specifically based on the integrated
17 data across the three phase 3 trials, the FDA
18 concluded that the serious risks with our product,
19 including thromboembolic events, appear to be
20 similar to those seen with other combined hormonal
21 contraceptives.

22 I think FDA suggested today that during this

1 next cycle, they decided they would only focus on
2 Study 23, and it's appears that by, of course,
3 reducing the overall denominator and by selecting
4 the trial in which we had, of course, the 4 VTE
5 events in the obese women, that that would, of
6 course, dramatically increase the calculated rate,
7 which of course to me just strongly illustrates
8 that you really can't get -- and I think the FDA
9 has acknowledged -- accurate rates in rare events
10 like VTEs from clinical trials.

11 Overall, as we've shown today, I think what
12 we've seen in the safety is that non=obese women
13 had 0 to 1, if you want to count Study 12 and 13,
14 and that all of our VTE events occurred in women
15 who had underlying baseline risks.

16 DR. LEWIS: Thank you. I'd like to give the
17 panel time to ask questions. Are there any
18 additional clarifying questions for either sponsor
19 or the FDA? Please remember to state your name for
20 the record before you speak and identify which
21 presenter your question is for or if it is a
22 general question for all presenters.

1 Dr. Shaw?

2 DR. SHAW: Hi. Thank you. I have a
3 question for the FDA, and I'm sure you guys can
4 figure out who's best able to answer this. We're
5 going to be asked to discuss the effectiveness of
6 AG200-15, and I'd just like clarity on the
7 definition of effectiveness and whether you want us
8 to define effectiveness as the upper limit needs to
9 be below 5, or whether we are to look at the point
10 estimate, which is hovering maybe around 6, maybe
11 around 7; it sort of depends on the population; and
12 whether we're asked to debate whether a Pearl index
13 of 7 is acceptable.

14 DR. GASSMAN: I'll take this on. We're
15 asking for your opinion, as clinicians and experts
16 in the field, as to what your opinion is on the
17 effectiveness. Now, we recognize that using 5 is
18 based on national surveys, but we recognize that we
19 need input from you as to whether you think there
20 is a point, whether it be mean or upper bound.
21 What is your consideration?

22 We look at this and wonder, when we start to

1 get into non-obese patients of upper bounds of 5,
2 6, 7, that's 5 per 100, if you don't think that the
3 5 is where the cutoff is and you think we should
4 use a different cutoff, do you have any thoughts on
5 what the cutoff is.

6 It's an open question. We have
7 traditionally used 5 as an upper bound, and that's
8 what we have been consistent at telling them --

9 DR. PORTMAN: Madam Chair, can I clarify?

10 DR. GASSMAN: -- but that's why we're coming
11 to the committee.

12 DR. SHAW: Basically, we'll be robustly
13 discussing that.

14 DR. GASSMAN: I hope so.

15 DR. SHAW: Okay. Thanks.

16 DR. PORTMAN: You keep mentioning survey of
17 5. I looked at the most recent publication from
18 the National Family Growth. In 1995, they quote a
19 typical use rate failure of 9 percent. In 2002, it
20 was 9 percent. In 2010, it was 7 percent. They've
21 never used a figure of 5, so there's no place where
22 they've said a 5 is the survey's number. They may

1 have used a range from 5 to 7, but they've never
2 used the number 5 in their survey as the definitive
3 number for typical rates of failure.

4 DR. GASSMAN: That's correct, but, again,
5 when we're looking at a clinical trial population,
6 which is compliant, and we expect -- although I
7 don't know that in post-approval, the numbers might
8 be very different. So we have used a 5, assuming
9 that these are the most compliant, best patients.
10 But I'd like to hear from the committee on their
11 thoughts.

12 DR. LEWIS: Thank you. Dr. David Eisenberg?

13 DR. D. EISENBERG: I have a question both
14 for the applicant and for our representative for
15 industry, from Novartis, Dr. Jarugula, as well as
16 the FDA, and anyone else can chime in, which is, if
17 a non-approval was the decision of this board,
18 would it cause a chilling effect on the development
19 of new contraceptive methods and new contraceptive
20 technologies in this country, given the effort that
21 the applicant has gone to, to prove not only
22 effectiveness or efficacy -- I guess I should say

1 efficacy; that seems like the right term in my
2 world -- the efficacy of this method is acceptable;
3 and the efforts they've gone to, to prove safety in
4 a population that reflects the population of
5 American users.

6 The concerns that the FDA has put out
7 regarding this historical upper bound, what would
8 be the impact on industry in terms of bringing new
9 contraceptive methods and new contraceptive
10 technologies to the market? I don't know that.
11 I'm an academic. I'm a clinician. I'm an
12 advocate, but I don't work in industry.

13 DR. LEWIS: Dr. Gassman?

14 DR. GASSMAN: I was just going to say that
15 we can't comment on other products under
16 development. We can't.

17 DR. D. EISENBERG: I'm not asking you about
18 other products in the pipeline. I'm asking about
19 what might be the predictable effect on some of the
20 folks in the audience, some of the folks behind me,
21 the gentleman at the end of the row here who
22 represent the pipeline.

1 DR. GARNER: We do have one comment. I'll
2 say something very briefly, and then it looks like
3 Dr. Wittes also has something to say. I believe
4 that this already has had an impact. We've
5 certainly talked to many colleagues in industry who
6 expressed frustration about wanting to do the right
7 trials, wanting to include representative
8 populations, but having concerns about these
9 limitations.

10 So I believe there's already been an impact,
11 and certainly the decision today we believe would
12 have a very profound impact.

13 Dr. Wittes, do you have anything else to
14 add?

15 DR. WITTES: Yes, I can say something. I'm
16 a statistician, and I give companies a lot of
17 advice, and I know exactly the advice I'd give.
18 I'd say go to thin women, upper middle class, and
19 do your study to make sure you get an upper bound
20 below 5, and I think that would be a chilling
21 effect on what we really need.

22 DR. LEWIS: Thank you. Dr. Jarugula?

1 DR. JARUGULA: I can comment on my
2 perspective from the industry. Whenever you have
3 uncertainty regarding the criteria, yes, that plays
4 into the decision for the companies. Having said
5 that, the company wants to develop another patch,
6 looking to this development patch, the history and
7 how this has taken place, and might learn some
8 lessons and better design the trials. That is
9 possible, if there is really a business case for
10 this.

11 So my answer is yes and no. Yes is that if
12 you see uncertainty in the criteria that agencies
13 have been applying and improving these products,
14 that gives industry some pause, but at the same
15 time if they see the path in the business case,
16 their company can certainly develop another patch.

17 DR. LEWIS: Thank you. Dr. Haider?

18 DR. HAIDER: This is a question for
19 Dr. Johnson. Do you mind going back to that slide
20 that you were discussing, just the comparisons
21 between the patch and Quartette, an explaining one
22 more time, the point you were trying to address? I

1 apologize. I didn't really get it.

2 DR. JOHNSON: This is Laura Lee Johnson. So
3 bearing in mind again, we don't necessarily like
4 making cross-study comparisons. The way you do
5 that is you do a randomized head-to-head trial.
6 But with that, when you just look at Quartette, and
7 you look at the weight breakdown, it looks like,
8 hey, as we have people who are getting heavier,
9 there are already products available, and they have
10 high pearls, and they have high on both the
11 estimated and the estimated upper bound. So that's
12 that far-right column.

13 But what wasn't compared was the product
14 that we're actually talking about today. So while
15 some different breakdowns by weight and by BMI or
16 on other slides and other presentations, I think
17 it's important to point out that especially as
18 you're getting to those higher weights, that upper
19 bound is significantly higher and the point
20 estimate is significantly higher.

21 So as Dr. Tang pointed out during her
22 presentation, when you get to that bottom row,

1 we're not ruling out, perhaps, close to
2 14 pregnancies per 100 women-years. This is
3 something that as you all are having these robust
4 discussions is what we wanted to point out. And a
5 lot of times, I feel like the data was a lot of
6 different places and to try to focus us at that
7 point.

8 But again, I want to caution, these aren't
9 head-to-head trials, but we can break down the data
10 by race, by low BMI, by normal -- you can slice
11 this stuff up a lot of different ways, but this is
12 to try to illustrate our concern here.

13 DR. GARNER: I would also add that -- sorry.
14 Dr. Lewis, you were pointing to --

15 DR. LEWIS: I don't think the question was
16 directed to sponsor.

17 DR. GARNER: Okay.

18 DR. PORTMAN: If I could pile on to this
19 cross-trial comparison fest, which I agree is not
20 the best way to look at this. But if we're going
21 to compare apples to apples, let's talk about Ortho
22 Evra, where 3 percent of the patients who were

1 obese accounted for 33 percent of the pregnancies.
2 If we start putting those numbers up there, they
3 might even look worse than the Agile Patch.

4 So I think we're looking at a lower dose of
5 estrogen, which is what we've heard patients want.
6 And the FDA reviewers had said with Evra, that it
7 was clear that patients greater than 90 kilograms
8 had decreased effectiveness. The label reads, "may
9 be less effective because of the limitation of the
10 number of patients."

11 So I think it's quite obvious that the two
12 transdermals that we have do have some signals for
13 an increased pregnancy rate with obesity, but we
14 have real numbers with this product that can be in
15 the label and can inform patients, whereas Evra
16 doesn't.

17 DR. LEWIS: Thank you. Dr. Eisenberg, and,
18 please, if you have a question, say who it's for.

19 DR. E. EISENBERG: This is Esther Eisenberg.
20 I just want to make a comment about the comment
21 from the FDA. We're comparing apples and oranges,
22 pills versus patches, and the Quartette, from what

1 I understand, is a continuous pill without any
2 break, which would change its efficacy because
3 there's no window where you could get a
4 breakthrough ovulation.

5 So I think that to say that the obese women
6 with a BMI greater than 90 could -- the data speaks
7 for itself. On the other hand, I don't think it's
8 a fair comparison, and I think that it seems like
9 it biases it in a direction. That's all.

10 DR. LEWIS: Thank you. Dr. Berenson?

11 DR. BERENSON: This question is for the FDA.
12 On slide number 68, it says, "Further, we are
13 uncertain that the proposed limitation of use would
14 limit prescriptions to obese women." Could you
15 please clarify that for those of us that are not as
16 familiar with a LOU?

17 DR. GASSMAN: That should have said
18 non-obese women.

19 (Crosstalk.)

20 DR. GASSMAN: She said the correction.

21 (Crosstalk.)

22 DR. BERENSON: Even if you said non-obese,

1 the question is the same.

2 DR. GASSMAN: Yes. It should have said
3 non-obese. If the committee decides that this
4 should be used in non-obese women or in all women,
5 the LOU that was stated when we reviewed this,
6 we're uncertain that that would limit prescriptions
7 to the non-obese group. So from our perspective,
8 we're trying to look at does this belong, and
9 that's why the questions are there.

10 Is this really acceptable for all women or a
11 narrower population? If you're thinking it's a
12 narrower population of proposed LOU, it wouldn't
13 necessarily limit the prescriptions.

14 DR. BERENSON: Is there another mechanism to
15 do that, then, a contraindication for obese women?

16 DR. GASSMAN: There are. There are other
17 mechanisms we could do. I think the sponsor has
18 proposed an alternative, but we just wanted to
19 remind the committee that what we had when we were
20 reviewing the package wouldn't necessarily limit
21 prescription use to non-obese. We need your input.
22 That's why we're here.

1 DR. LEWIS: Did you have a comment?

2 DR. GARNER: Sure. We'd like to put up the
3 alternative indication that we talked about, if
4 that's okay. This would be one potential approach
5 that we had thought about. Again, I want to
6 emphasize, we've not discussed any of this with the
7 FDA, so we obviously want to learn also from their
8 experience and from the input of the panel today.

9 So a possible approach would be to actually
10 include, in the indication itself, that this is for
11 use by women with a BMI less than 30. What that
12 would lead to is that, of course, the company could
13 not market this product. In their giving providers
14 and patients information, they could not talk about
15 marketing this product in women with obesity.

16 We would also propose, of course, still
17 having that limitation of use in this situation,
18 and all of the other things that we had already
19 described that would go in our labeling around
20 putting the table in with the Pearl indices, BMI by
21 weight, all of the other things around safety as
22 well. So this would be one mechanism.

1 I also just wanted to comment -- can you put
2 up the contraindication LOU slide that compares the
3 scenarios? I'm going to ask Dr. Portman to comment
4 shortly, so if you'd like to head up to the mic if
5 we have time, just really quickly.

6 A contraindication, just to be clear, from a
7 regulatory standpoint, this is warranted when the
8 risk of use clearly outweighs any possible benefit.
9 And we're talking, when we say this, this is for
10 every single person. There is never a possible
11 situation where there is a potential benefit that
12 may outweigh risks.

13 A limitation is used, rather -- and this is
14 why we thought it was appropriate. It's used to
15 identify a population where the drug probably
16 shouldn't be used, as Dr. Portman described, and
17 probably shouldn't be the first choice, but there
18 may be situations where the use is appropriate,
19 based on the clinical judgment, and that's where
20 I'd like Dr. Portman to give a couple of examples.

21 DR. PORTMAN: As the clinicians in the room
22 know, we use a lot of things off label. Certainly

1 birth control pills don't have all the indications
2 that we use them for. I can give you an example of
3 a patient who may be obese, that I wouldn't want to
4 have a contraindication. A woman who has bariatric
5 surgery who wants to lose weight in a year and have
6 a child, this would be the preferred method to
7 avoid the poor bioavailability of oral medications.
8 I wouldn't want to have my hands tied and not be
9 able to use my clinical judgment.

10 I think also using a contraindication would
11 make it difficult to study this further because
12 enrolling women in a clinical trial, should the
13 sponsor want to do that, that would put some
14 significant barriers to do that. So I think a
15 limitation of use makes a lot more sense. The
16 indication statement, one could work with, but as
17 clinicians we do need to have some liberty. And I
18 think our patients are smart enough to work with us
19 and have shared decision making so that we can
20 follow the label and deviate from it when it's
21 clinically necessary.

22 DR. GARNER: I think the one point that

1 Dr. Portman made that's critically important is we
2 have proposed today a potential postmarketing study
3 in which we would very much like to do some
4 additional work in obese women on this patch, to
5 look at the various things that I think FDA has
6 pointed out. What's the role of compliance?
7 What's the role of potential delivery mechanisms,
8 PK -- a number of things. I think that would be
9 very important to study for our patch in obese
10 women, and, of course, a contraindication wouldn't
11 allow us to do that.

12 DR. LEWIS: Thank you. Dr. Gagliardi?

13 DR. GAGLIARDI: I'd like to ask Agile A
14 question about the usability. One of the things
15 that was mentioned was that almost 15 percent of
16 completed treatment cycles used 4 or more of the
17 transdermal devices, and in order to maintain
18 efficacy and in order to make this a user friendly
19 method of contraception, there has to be a method
20 in place that makes it really easy to get that
21 extra patch.

22 If that extra patch is not really easily

1 available, then we're going to see a decrease in
2 efficacy. We're going to see people getting
3 pregnant because their patches aren't available. I
4 know how hard it is for patients to sometime get
5 in, so I'm really interested in what you're
6 planning to do to make this user friendly. Thank
7 you.

8 DR. GARNER: We agree with you completely on
9 that. I would also point the reminder that during
10 the trial, patients had extra patches. So we think
11 that was some of what we saw, was that they had an
12 extra one and one pulled off slightly. They'd just
13 apply a new one, which they wouldn't do in the real
14 world.

15 But to your point, in actual use, we agree
16 we've spent a lot of time thinking about this and
17 thought of various approaches to be able to provide
18 a replacement patch immediately.

19 Can you just show me the replacement patch
20 program again? We've thought of a few mechanisms
21 to provide replacement patches. This isn't the
22 slide we're going to show, but just to inform you.

1 We have plans already for single-system replacement
2 patches that would be available in pharmacies
3 through a separate prescription for women who need
4 an additional patch prior to the start of their
5 next cycle.

6 Remember, most women are going to get
7 3 cycles worth at a time, so for the first 2-plus
8 cycles, they're always going to have extras. So
9 this really is the most important in that third
10 cycle. We will be sure that we have at least
11 single replacement patches. The same approach was
12 in place for Ortho Evra when they were approved.

13 The other thing we're exploring and have
14 been spending quite a bit of time on is the ability
15 to direct ship to a patient an extra patch within
16 24 hours of her needing it. So we've been
17 exploring that extensively because we agree with
18 you.

19 DR. LEWIS: Thank you. Dr. Ortel?

20 DR. ORTEL: This is for you. I just had a
21 question or clarification. On that proposed
22 indication slide, if you had in there the text,

1 "for use by females of reproductive potential with
2 a BMI less than 30 kilogram per metered squared to
3 prevent pregnancy," and then you have the
4 limitation of use statement, doesn't that open the
5 door for confusion among providers?

6 If you've already given a
7 contraindication -- don't use it in this group, and
8 then you put a limitation of use that explains
9 something about what --

10 DR. GARNER: Yes. To be clear, having an
11 indication that's worded this way is not a
12 contraindication.

13 DR. ORTEL: Correct.

14 DR. GARNER: A contraindication is
15 specifically wording that says, outright, this
16 product is contraindicated in women with a BMI of
17 30 or over. So really, what this limits us
18 potentially being able to do is talk about this
19 product. When we're speaking to doctors, for
20 instance, to say, hey, you can use this in women of
21 high BMI. That's all this really stops us from
22 doing, is marketing it to that group. It's not a

1 contraindication.

2 So if we were to have contraindication, what
3 this would basically say is it would be pretty much
4 the prior language, or this, and then there would
5 be specific wording added that contraindication in
6 this product is not to be used.

7 Does that makes sense?

8 DR. ORTEL: It just seems like it's opening
9 the door for confusion about -- if I read that and
10 I was told something, and then I said, but in your
11 very next sentence it just says I can -- it's just
12 got this.

13 DR. GARNER: We appreciate all of the
14 insights. We really appreciate that. As I said,
15 we haven't talked about it with the FDA, but it's
16 definitely something we'll take into consideration.
17 Thank you.

18 DR. LEWIS: Thank you. Dr. Hunsberger, and
19 then Dr. Christmas.

20 DR. CHRISTMAS: Yes, with the same slide,
21 though, if you could put it back up. I think that
22 if you're going to go with less than 30 for the

1 BMI, and then to put the 202 pounds or 92 kilograms
2 in, it's very confusing because you can
3 actually -- depending on how tall the woman is,
4 their weight could be more or less than that, and
5 you could still be around the 30.

6 So I don't know that it's beneficial to keep
7 the 202 in if it's going to be a cutoff of a BMI of
8 30. Does that make sense?

9 DR. GARNER: Absolutely, another great
10 insight. Thank you, and we'll take all of that
11 into consideration.

12 DR. LEWIS: Thank you. Dr. Hunsberger?

13 DR. HUNSBERGER: I guess this question is
14 for the FDA. I'm just trying to understand a
15 little bit more about our criteria. You've said
16 that you've never approved anything with an upper
17 limit, a PI upper limit greater than 5, but then
18 I've also heard us say that we don't have data on
19 women with BMIs, overweight or obese.

20 So for the things that you have approved
21 with the upper limit less than 5, is it true that
22 we don't have data on that? Because I think when

1 we're not doing comparative studies, you can set an
2 upper limit of less than 5, but then you have to be
3 very clear about the population you're using. I
4 think to what they're saying is we've done a
5 different population than other people.

6 So I just want to understand this absolute
7 and the population that we actually have data on
8 that had been approved.

9 DR. JOHNSON: This is Laura Lee Johnson. We
10 do have several products that are currently
11 available on the market that are combined hormonal
12 contraceptives, that have women with a large range
13 of BMI and weight, and that go well above 30 BMI.

14 DR. HUNSBERGER: And you saw the increase in
15 the PI for that or no, or they were all less than
16 than 5?

17 DR. JOHNSON: It varies, and also, many
18 times there may not be enough cycles to feel that
19 we have an adequate understanding of what that
20 point estimate and confidence interval would be.
21 However, in certain cases -- and that was part of
22 what was laid out in the publication, and there

1 have been additional approvals since then. But
2 sometimes there is no effect, and sometimes you do
3 see that there are higher estimated rates of
4 pregnancy.

5 DR. HUNSBERGER: So you didn't put any
6 limitations on those where there were -- if you
7 looked at the higher body mass index and you saw a
8 higher PI, you didn't put any limitations on those
9 products?

10 DR. WILLETT: There have been some
11 differences here. I think we need to talk about
12 the fact of Agile having quite a few cycles to make
13 a determination here in terms of obesity versus
14 non-obesity. When you look back at Ortho Evra, it
15 was simply a matter of counting 15 pregnancies and
16 finding out what number of those individuals were
17 over a certain weight, and it happened to be 5. So
18 that ends up being your 33 percent.

19 Now, I would say that having a huge number
20 of cycles with a more representative population is
21 going to give me more information than that. We
22 also had LoSeasonique, where it was categorized by

1 certain deciles. And we did not see any effect in
2 terms of those particular weights, so we didn't
3 address that specifically in labels.

4 So again, it's sort of been a mixed response
5 in terms of how we address labeling with obesity in
6 the past. But as I said before, we've had so many
7 sponsors not agree to study this population, that
8 we've been dealing with a hand before where we just
9 didn't have the data.

10 DR. LEWIS: Dr. Margolis?

11 DR. MARGOLIS: I have a question
12 about -- actually I guess either group could answer
13 this -- the absorption of the products. Skin
14 thickness varies greatly between the back, and the
15 abdomen, and then the thigh, which are all areas
16 that are indicated. The epidermis can vary greatly
17 based on just common diseases like atopic
18 dermatitis, and there are certainly genetic
19 changes. Atopic dermatitis increases
20 transepidermal water loss, which increases
21 absorption through the skin.

22 Are there differences in absorption of your

1 product in different areas of the body? Is this
2 contraindicated in people who have active skin
3 disease, not just in the site, but just a history
4 of atopic dermatitis or ichthyosis vulgaris, which
5 are both associated with decreased skin barrier.

6 DR. GARNER: We can provide a response if
7 you'd like. Dr. Furmanski?

8 DR. FURMANSKI: Thank you. Brian Furmanski,
9 Nuventra. I can't address the atopic dermatitis
10 directly. You're correct. There's a history for
11 dermal disruption and potential enhancing of
12 absorption. But I can address the question
13 regarding meaningful differences in site location.

14 Here in this figure on the left, you'll see
15 the concentration over the average time, as well as
16 application site. Effectively, you see relatively
17 similar concentrations regardless. This is just a
18 simple box and whisker plot. The black line is the
19 mean, and effectively there is no clinically
20 meaningful difference in exposure, although the
21 abdomen tends to be a little bit less, which is
22 also consistent with the Ortho Evra product.

1 DR. LEWIS: And that's true of the ethinyl
2 estradiol as well. That slide just says
3 levonorgestrel.

4 DR. FURMANSKI: Yes, that's also true for
5 EE; that's correct.

6 DR. LEWIS: Dr. David Eisenberg?

7 DR. LU: Hi.

8 DR. LEWIS: I'm sorry. FDA?

9 DR. LU: This is Yanhui from FDA. I think
10 that's a great point. A lot of times you can see
11 the disease of the skin may increase the absorption
12 of the drug. In this case, I don't think we have
13 seen any data related to that, but it's a
14 possibility that disease may affect the absorption
15 or possibly increase the absorption of the drug.

16 DR. LEWIS: Dr. Gassman, did you have
17 anything to add?

18 DR. GASSMAN: No, I was just trying to get
19 your attention.

20 DR. LEWIS: Thank you. Dr. David Eisenberg?

21 DR. D. EISENBERG: One question for the
22 sponsor and one question for the FDA regarding

1 postmarketing. Dr. Garner, you mentioned there was
2 a plan for postmarketing surveillance, and I was
3 hoping you could expand upon that, what the plan
4 is, number one. And number two, for the FDA to
5 comment on what they can require of a manufacturer.
6 Is there like a probationary approval that if they
7 submit data after so many years? What does that
8 postmarketing requirements look like?

9 If you could start with what your plan is.

10 DR. GARNER: Certainly. First to say that
11 we do believe it's extremely important to go beyond
12 the labeling to continue to advance the
13 understanding. We feel that's very important.
14 What we had proposed in our NDA and mentioned to
15 the FDA is that if the Agile Patch were approved in
16 the overall population, what we would propose would
17 be a class-wide study of not only transdermal CHCs
18 but also vaginal and oral CHCs, primarily to answer
19 questions that I think have been asked quite a bit
20 today about the class effects in women with
21 obesity. We think there are still a number of
22 questions to be asked and answered there.

1 Understanding that sometimes we know the FDA
2 has done this before, I would add. This has been
3 done recently for testosterone products. So it has
4 been done and I think it can be done, but can be
5 challenging, of course, to get sponsors to all work
6 together with the FDA.

7 What we propose is -- and this could be in
8 addition to this proposed study or indeed if the
9 Agile Patch were just approved today, or at least
10 that the recommendation was made, I should say, in
11 the non-obese population, then we would discuss
12 with the FDA a prospective trial.

13 Here, We would do a head-to-head study
14 versus an OC or perhaps other methods as well;
15 again, specifically in women with obesity because
16 that's where we feel are the main questions here.
17 I think we've shown clearly that the benefit-risk
18 in non-obese, overweight women supports that this
19 should be made available. Where the questions lie
20 are still in obesity. So we've thought about a
21 number of things that we could do.

22 DR. LEWIS: FDA?

1 DR. GASSMAN: So I'll just briefly answer
2 the question. We could require a study
3 pre-approval. We could say before you get
4 approved, you have to do that. However, studies
5 for VTE risk and ATE risk usually take in the
6 10-year range. It's not usually something we have
7 thought about pre-approval. We can require a
8 post-approval study to look at the rates of ATE and
9 VTE. They can have different forms.

10 Rita, did you want to talk about -- I'm
11 going to let Dr. Ouellet-Hellstrom talk about this
12 a little.

13 DR. OUELLET-HELLSTROM: Postmarketing
14 studies depends on the data source, but you're
15 mentioning a trial. Are you considering or
16 thinking about a randomized clinical trial?

17 DR. GARNER: For the patch study that we
18 were mentioning, where we would want to compare
19 against an OC, we have considered a randomized
20 approach, but we also know that could be
21 challenging in the clinical setting. So what we
22 want to do is figure out some way to make

1 comparisons, and, of course, we're open to
2 discussing that with the panel or with the FDA
3 today, as to how specifically to address that.

4 DR. OUELLET-HELLSTROM: Frequently,
5 postmarketing studies are done using claims data,
6 and you cannot measure obesity, smoking, or alcohol
7 use in claims data. So you would need to do an
8 interview study, basically, and there, you're
9 subject to selection bias because you need informed
10 consent from the participants, and who would give
11 their informed consent is a big question that we
12 would have.

13 DR. GASSMAN: And I'd also point out that to
14 some extent when you talk about other products, it
15 can be very challenging when something like Ortho
16 Evra has very limited pool to which you could draw,
17 and not all the contraceptives have equal market
18 share. So are you really comparing -- what would
19 you pick as a comparison?

20 It's the same problem when we think about
21 active control designs, what would be the right
22 comparison for this? Would it be a 35-microgram

1 pill? Would it be a 10-microgram pill? Would it
2 be a pill with levonorgestrel or drospirenone
3 because that's, I believe, one of the more common
4 products? Or should it be Ortho Evra?

5 If so, then is there a margin beyond which
6 that we should say the risks outweigh the benefits?
7 And that's one of the things that we have struggled
8 with when we think about an active control trial.
9 I believe the sponsor chose Levlite. Am I correct?
10 Which is a levonorgestrel product, but it's not a
11 35-microgram product.

12 So if we're going to talk about this, then I
13 think we can't require the comparator that the
14 sponsor chooses. But any recommendations that you
15 have on this, or if you think there is a point
16 beyond which we need to really think about other
17 things, we appreciate. Europe usually does, as
18 Dr. Willett mentioned -- they really look at this
19 for cycle control, and their approval path is
20 different because, obviously, one of the things
21 that they talk about is cost. So they're looking
22 for a balance.

1 DR. OUELLET-HELLSTROM: There's also
2 concern, and it was mentioned earlier, that women
3 switch, and they tend to switch to newer products,
4 and newer products have a higher risk than older
5 products, and of course you pay more for the brand
6 than you do for the generic.

7 So if you don't do well on generic, you
8 switch to the brand and the newer products. But
9 what tends to happen -- and we've seen this with
10 drospirenone and the patch, in the past, is you
11 have the New York Times talking or publishing about
12 the Patch of Death. They identify the risk right
13 away, and women tend to --

14 DR. GASSMAN: Run.

15 DR. OUELLET-HELLSTROM: -- run from the
16 newer product.

17 DR. D. EISENBERG: And that goes back to the
18 point that I made earlier, the understanding of
19 attributable risk and relative risk from one method
20 to another, with different known risk factors like
21 obesity, age, smoking status, et cetera.

22 It does argue for not only the FDA to

1 understand what do women and people in this country
2 who use contraception to avoid pregnancy want in
3 their contraception, but what are they willing to
4 tolerate with regards to risk and side effects.
5 But it also argues for a large prospective cohort
6 study of multiple methods similar to like the CREST
7 data for sterilization for instance, looking at
8 reversible methods; but that is going to be long in
9 duration, large in cost, multicentered, and
10 difficult. I agree.

11 But I don't think randomization is always
12 the right way because when it comes to
13 contraceptive method preference, we tried doing
14 randomized trials in my institution and many
15 others, and women have very strong preferences. So
16 therefore --

17 DR. OUELLET-HELLSTROM: The data source
18 becomes very important.

19 DR. D. EISENBERG: Right. So therefore,
20 while randomization is one way to control for all
21 these factors that we've discussed, I'm not sure
22 it's a realistic study model for the American

1 woman.

2 DR. JOHNSON: May I just add a couple of --

3 DR. LEWIS: We will have opportunity to
4 discuss. This is really time for clarifying
5 questions. So I'm going to let Dr. Johnson weigh
6 in, and then we're going to take a break.

7 DR. JOHNSON: Thank you. Dr. Eisenberg,
8 what I needed to understand is if you were asking
9 about requirement for safety, requirement for
10 efficacy, or requirement for both, because we can
11 make postmarketing requirements with respect to
12 safety, but typically, if efficacy is what is being
13 measured, that is a postmarketing commitment. It
14 is not a requirement.

15 So I just want to make sure that we're
16 clear, and my more regulatory colleagues can
17 clarify that more. But what can be required -- of
18 course, we always rely on the good faith of the
19 sponsor, and they say they're committed, and we
20 hope that that happens. But also there are, as
21 everybody has mentioned, a lot of other factors
22 that go into that. But I do just want to make sure

1 that we aren't misstating what FDA can require.

2 DR. D. EISENBERG: And I appreciate that.
3 I'm not sure I have a preference necessarily. I'm
4 just trying to understand what the FDA can or can't
5 require, or what they can ask for in the way of a
6 commitment, number one. And number two, you're
7 asking us to answer a question based on known risk,
8 potential theoretical risk, whether the advantage
9 and the benefit of using this method, based on its
10 efficacy, justifies approval in light of those
11 known and theoretical risks, which is a hard
12 question to answer.

13 DR. WILLETT: Jerry Willett, just one
14 comment. We have seen postmarketing evaluations do
15 both safety and efficacy, both. When we saw a big
16 comparison between 21/7 and 24/4, we saw that in
17 place where they were doing both safety and
18 efficacy.

19 DR. GARNER: We also have the slide that
20 presents a couple of recent postmarketing studies
21 for recent approvals that we can present if we have
22 time.

1 DR. LEWIS: I think that's a little beyond a
2 question.

3 I'm going to call the question period to a
4 close. We're going to have a break, and then when
5 we come back we will discuss the discussion items
6 and the questions.

7 Panel members, please remember no discussion
8 of the meeting topic during the break amongst
9 yourselves or with any member of the audience. We
10 will resume at 3:00 p.m.

11 (Whereupon, at 2:46 p.m., a recess was
12 taken.)

13 **Questions to the Committee and Discussion**

14 DR. LEWIS: Okay. We're about to get
15 started with the questions and panel discussions.
16 FDA has one further point they'd like to clarify,
17 and then I'll explain the ground rules for the next
18 phase.

19 DR. GASSMAN: Before we discuss this, I just
20 want to clarify what we can and can't require. We
21 can require a safety study that was from the FDAAA
22 regulations. If there is identified a safety

1 signal, we can require a study. We can require, in
2 general, the study design that we might want, but
3 again, the protocol and the study, this would be a
4 discussion point for the sponsor.

5 For effectiveness, that would be a
6 postmarketing commitment. It would be in agreement
7 with the sponsor. We can't require effectiveness.
8 We could, again -- and this will come up in
9 discussion for comparative stuff that would be in
10 the purview of research, and that would be a
11 totally separate topic that we would probably need
12 to have a workshop on.

13 In terms of labeling, a
14 contraindication -- and this is page 28 of the
15 briefing package -- is a situation, which the drug
16 should not be used because the risks outweigh the
17 benefits. In this case, if the drug were
18 contraindicated, it would not be used. In that
19 case, if the sponsor chose, they could do a
20 postmarketing commitment to look at a different
21 population.

22 A limitation of use is generally a

1 reasonable concern about the uncertainty of the
2 benefit-risk profile, when data in a
3 subpopulation -- when there is concern. Again, we
4 can put these things in labeling, but we understand
5 that there is off-label use, and there is the
6 ability to use your clinical judgment, whichever
7 way things are labeled. So I just want to make
8 sure that that's clear. Thank you.

9 DR. LEWIS: We will now proceed with the
10 questions to the committee and panel discussions.
11 I would like to remind public observers that while
12 this meeting is open for public observation, public
13 attendees may not participate except at the
14 specific request of the panel. We have two
15 discussion questions and then one voting question.

16 First discussion question, discuss the
17 effectiveness of AG200-15, including interpretation
18 of efficacy results from Study 23 as they relate to
19 study design and enrolled patient population, and
20 B, interpretation of subgroup analyses by body mass
21 index, weight, and race/ethnicity.

22 If you have something to contribute to the

1 discussion, please, panel members, flag your name
2 cards so that we have your attention, and I will
3 call on you in turn. So let's start with
4 Dr. Miller -- or Ms. Miller. Sorry.

5 MS. MILLER: Thank you. Sabrina Miller,
6 patient representative, in regards to discussion A,
7 based on an endpoint of 5.0, it appears that AG200-
8 15 doesn't meet the efficacy standards. However,
9 my understanding of this creep may change that
10 standard in the future. I think that's making this
11 product more effective.

12 So I feel like this isn't a question of
13 effectiveness as much as recommending to the FDA to
14 consider the patient's and provider's perspective
15 of effectiveness, with as much label information as
16 FDA can offer to make an informed decision because
17 my provider isn't going to tell me this birth
18 control is less than a point over the PI standard,
19 so you should think about that, because he knows I
20 don't have any idea what that means. But my worry
21 here is if my provider will understand that to give
22 me informed choices. So I think the more

1 information that he has on the label, the better he
2 can offer to counsel his patients about the risk
3 factors.

4 B, especially for obese patients, and his
5 interpretation of those risks for subgroups, the
6 more information, the better. I think this really
7 is more, possibly, a labeling discussion. As a
8 patient, I do see this as an informed decision by
9 my provider and myself, more than that the data
10 suggests that a 5.0 endpoint is a deciding factor
11 on this. However, I want to make this clear that
12 this is my opinion based more for a non-obese
13 population more than anything. Thank you.

14 DR. LEWIS: Thank you. Dr. Shaw?

15 DR. SHAW: Yes. thank you. I guess I would
16 just like to clarify how we're all thinking about
17 effectiveness. As Ms. Miller asked some questions
18 about that upper limit of 5, I think we can think
19 about the different levels of effectiveness, being
20 the first definition, which was the definition that
21 this trial was originally designed for, which was
22 90 percent power, that the underlying Pearl index

1 is no larger than 3.5 and that the upper limit of
2 the two-sided confidence interval is no larger than
3 5.

4 I think the well-designed trial -- I did
5 rule that out. So if we're going to be very hard
6 supporters of the 5 being an upper limit, then we
7 have to be really concerned about the efficacy
8 level. What we have before us is an overall
9 efficacy confidence interval that's ranging from
10 4.5 to 7.2. We can't think about how that compares
11 to other populations or other birth control methods
12 because no one's done the study to inform that
13 discussion.

14 We've had a lot of indirect suggestions,
15 that, oh, the Pearl index is historically too low.
16 We can't use that to judge the efficacy of this
17 product from the point of view of -- we have to
18 stare at the numbers in front of us, which say that
19 the Pearl index seems to be about 6 overall,
20 ranging from 4.5 to 7, somewhere in there, and is
21 consistent with the data. There is subgroup
22 analysis that suggest it's much higher in the obese

1 subjects, and then fact 5 is ruled out by the lower
2 end of the confidence interval. So the data is not
3 consistent with something as low as 5.

4 So I guess it would be nice to hear -- I
5 don't think we've had a lot of discussion
6 about -- we've had a lot of theoretical discussions
7 about the Pearl index is in a population we haven't
8 studied, but what we really need to think about is
9 this an effective -- is this an acceptable level of
10 the Pearl index, if it is, overall, around 6, and
11 if it's actually in a subset such as BMI around 9
12 or as high as 12.

13 I don't know. I'm sort of opening it up.
14 It seems that we've talked about this as being
15 equating it to how many pregnancies per 100 women.
16 Maybe 14 pregnancies as is suggested for the upper
17 limit, greater than 92 kilograms, may put people at
18 discomfort, but the 6 out of 100 put people at
19 discomfort.

20 DR. LEWIS: That is the question.

21 Dr. Margolis?

22 DR. MARGOLIS: I'm going to talk more about

1 that same thing. As an epidemiologist, a
2 pharmacoepidemiologist clinical trialist, who's
3 designed efficacy studies, effectiveness studies,
4 postmarketing studies, some of which were
5 commitment studies from the FDA, I almost feel like
6 there needs to be a discussion about what the
7 endpoint should be.

8 The endpoint, what was just stated, was
9 initially 5, and that was a traditional endpoint.
10 Whether it's the endpoint that it should be or not
11 is really what I feel like we're now discussing. I
12 don't know that this is the forum to determine
13 that. I feel like, as maybe it was implied, that
14 there almost needs to be a meeting, and I guess one
15 was held about a decade ago, but another to
16 interpret what that should be. If one's going to
17 basically have cohort studies, they have to reach a
18 pre-described endpoint to demonstrate efficacy,
19 which is really what we're talking about here.

20 I don't quite understand how we can be asked
21 to determine whether or not a new endpoint is as
22 good as an old endpoint. And in a way, I almost

1 feel like that's, really, what we're being asked to
2 discuss, and I don't know that we have the data to
3 do that.

4 DR. LEWIS: Dr. Curtis?

5 DR. CURTIS: Yes, I think we've all been
6 struggling with all those questions, and I think
7 I'm coming at it from a slightly different
8 perspective but going to end up with the same
9 place; so we don't have the data to do it. One
10 question is, is there a cutoff? But another
11 question is -- and I think some of our public
12 commenters spoke about this very
13 articulately -- women want choices. There's no one
14 method that's going to be best for everyone, and
15 women can make the decisions and weigh the pros and
16 cons about different methods for themselves, along
17 with their providers.

18 However, to do that, women and their
19 providers need to have good information, especially
20 about effectiveness, which is only one piece of
21 information that women use. But in most studies,
22 it is the most important piece of information.

1 Given that we now have a new Pearl index of about 5
2 to 6, we can't compare that to old Pearl indices.
3 It's not typical effectiveness. I think most
4 providers generally use typical effectiveness now.
5 This study, while it's getting closer to that, we
6 can talk about that if we want, but I think it's
7 still very far from the typical effectiveness rates
8 we use that come from surveys like the National
9 Survey of Family Growth.

10 If we were to approve this, how would we
11 present that effectiveness information in a way
12 that women and their providers can make the best
13 informed decision? And I don't think we've heard
14 much about that either. Maybe one way to talk
15 about that is to specifically talk about that
16 tiered figure that I think ends up in most labels
17 right now, and I don't even know where this patch
18 would go in that figure.

19 DR. LEWIS: Thank you. Dr. Bauer?

20 DR. BAUER: First, I just want to start by
21 thanking the sponsor for being brave and doing a
22 trial that was inclusive, including a larger person

1 population. But I will say I think a lot of these
2 discussions would have been a whole lot easier had
3 there been a comparative group, both for the
4 efficacy discussion as well as for the safety.
5 From my perspective, I think a comparison to the
6 other existing and approved patch would have been
7 very, very useful, but that's not what we have in
8 front of us.

9 Given that, I have grown increasingly
10 uncomfortable with a specific cutpoint for a Pearl
11 index, be it 5, be it 6. I don't really think that
12 we, nor the FDA, is in a position to dictate what
13 that should be. The reason I say that is because I
14 really think it is, partly, because we really don't
15 have rigorous data on what patient preferences are
16 and how they weigh efficacy versus convenience,
17 versus other things.

18 I think that may not be the sponsor's
19 responsibility. I'm not sure whose it is, but it's
20 difficult for me to weigh those things. Clearly,
21 we heard from women that they do weigh those
22 things, and I'm not sure that is what's clearly

1 represented in the discussion.

2 The last thing I'll say, I want to reiterate
3 how important I think this issue about this notion
4 that the efficacy differs by weight and how that
5 really needs to be communicated clearly in the
6 label, not with a contraindication presumably with
7 limits of use, but with specific data that will
8 allow patients and providers, then, to weigh their
9 informed desires and make a decision about whether
10 it's the right choice for them.

11 DR. LEWIS: Thank you. Dr. Leslie?

12 DR. LESLIE: Thank you. I wanted to thank
13 Dr. Shaw as well for her clarity regarding a range
14 in which we can discuss Pearl indexes just so we
15 can grapple with something today rather than talk
16 about next steps, which are also wise.

17 But particularly, from a clinical
18 standpoint, when I'm in the patient's room having
19 these discussions, where the rubber hits the road,
20 really, is trying to help folks make the best
21 decision for their lives, as we've alluded to.
22 Currently, in the last five years, that discussion

1 always tends us towards Pearl indices that are
2 much, much higher.

3 LARC has set the standard, and I realize
4 that's not what we're discussing today, but in
5 terms of patients' expectations for efficacy, they
6 expect a very high efficacy. So the fact that
7 we're flirting with a Pearl index as low as 6 I
8 think really is unacceptable on today's
9 contraceptive market.

10 As I have these discussions face to face
11 with my patients, that becomes quite clear. If I'm
12 talking about a Pearl index of 6, I'm going to be
13 saying we need to use two methods because the other
14 options that are out there get me to efficacy,
15 where their failure rate's going to be less than 1
16 percent. To me, this is very significant. We're
17 pushing the Pearl index, to me, in the wrong
18 direction with this discussion.

19 DR. LEWIS: Thank you. Dr. Esther
20 Eisenberg.

21 DR. E. EISENBERG: Perfect is the enemy of
22 the good, and if we want to talk about efficacy, we

1 should consider a hundred percent effective. The
2 opposite is what is acceptable. And as a clinician
3 provider, what's acceptable to one woman might not
4 be to another. A patient might be willing to
5 accept a risk of 5 percent or 10 percent or might
6 not. And if not, then choose a different method.
7 But if this is not approved, then this is not an
8 option, and there is not an option for a different
9 type of continuous hormonal contraception.

10 So then without this option, someone might
11 not choose to do any contraception, and then their
12 risk is much greater. So I think that needs to be
13 balanced. Perfect is the enemy of the good.

14 The other point is that the life table
15 analysis is a real-world assessment rather than a
16 Pearl index. According to slide number 55, the
17 overall risk was 5.29 percent over 13 months.
18 That's very close to 5.

19 DR. LEWIS: Thank you. Dr. Christmas?

20 DR. CHRISTMAS: I guess my concern was that
21 when we're looking at these other options that have
22 a lesser Pearl index, it's not based on the same

1 criteria that this study used. I liked that they
2 included women that look like me, and those studies
3 did not. I think we really have to take -- as
4 Dr. Shaw said, what is the indication that this
5 upper limit that's been set really hold, and does
6 that mean that this is not efficacious if it's not
7 at that number?

8 DR. LEWIS: Dr. Haider?

9 DR. HAIDER: I think along the lines of what
10 Dr. Christmas said, I think, actually, my patient
11 population is a little bit different than perhaps
12 yours in Portland, where I have a number of
13 patients who had very different experiences with
14 LARC, don't necessarily want a hundred percent
15 efficacy, want autonomy, have issues with trust,
16 our youth.

17 I think the more options available, the
18 better. I do think the Pearl index discussion
19 needs to happen in a way that's much more real
20 world. I would actually say we need to push it
21 further out as opposed to closer to perfect. So
22 that's my thought.

1 DR. LEWIS: Anyone else?

2 (No response.)

3 DR. LEWIS: Oh, go ahead. Dr. Shaw?

4 DR. SHAW: We talked a lot about the
5 subgroups, particularly the weight subgroup and the
6 BMI subgroup. But we didn't talk a lot about the
7 other question, which was the race subgroup.
8 That's part of this question.

9 I just want to say, I don't think we got a
10 lot of clarity on the race subgroup, and I think,
11 in part, because I'm guessing it's probably
12 confounded with weight, or we certainly didn't see
13 whether or not that was confounded and which of
14 these may be the driving factor, because a lot of
15 times those things can be correlated in a
16 population.

17 I guess I just wanted to put that discussion
18 out there, is we don't have clarity on that.

19 DR. LEWIS: Thank you. Dr. Berenson?

20 DR. BERENSON: I actually did a large
21 NI-funded clinical trial that was published in the
22 Green Journal in 2008, on women using low-dose

1 birth control pills, versus depo, versus
2 non-hormonal methods. We were kind of alarmed to
3 find that -- we did not do Pearl index, but we had
4 a failure right due to pregnancy that was about 6
5 percent because we did use a population that was
6 more like the normal world. We did not have all of
7 these restrictions on white or race ethnicity.

8 So it's been a long time for me to wait and
9 see that it's recognized, that the
10 effectiveness -- these actual world effectiveness
11 of these methods is perhaps not as high as we
12 believed it to be --

13 DR. LEWIS: Not as high?

14 DR. BERENSON: -- and maybe that information
15 needs to get out there to the patients

16 DR. LEWIS: Effectiveness is not as high; is
17 that what you're saying, or pregnancy rate?

18 DR. BERENSON: Effectiveness is not as high.

19 DR. LEWIS: Great. Thank you. Dr. David
20 Eisenberg?

21 DR. D. EISENBERG: I think Dr. Berenson's
22 comment reminded me that I think there's something

1 I wanted to point out. Having been one of the
2 co-investigators for the Contraceptive CHOICE trial
3 in St. Louis, where it was a prospective cohort
4 study, where we let women choose any method, number
5 one, women's preference, which has been said many
6 times today, for a method that fits their lifestyle
7 that they can continue with is really important.
8 For some women, that drives their personal
9 experience with effectiveness more than the
10 perfect-use effectiveness of the method when it's
11 done in a trial like this.

12 So I think we do have to keep that in mind.
13 The fact is that the landscape of contraceptive
14 methods has been limited, and having more choices
15 may inform the next drug in development, and I
16 think we need to keep that in mind. I think that
17 an arbitrary cutoff of what is effective enough
18 concerns me. I'm not sure that we academics are
19 the right people to make that call, especially
20 those of us academics who don't have a
21 contraceptive that we can use outside of condoms.

22 (Laughter.)

1 DR. D. EISENBERG: I mean, the fact of the
2 matter is that I think if we are going to set a
3 cutoff at which the FDA decides a contraceptive
4 method is acceptable based on efficacy, we need to
5 ask the people who are going to be using that
6 method as their method of contraception.

7 So when I look at this, discuss the
8 effectiveness and interpretation of results, it's
9 good. I agreed with Dr. Esther Eisenberg that
10 sometimes the enemy of good is better, and it's
11 good.

12 DR. LEWIS: Dr. Jarugula?

13 DR. JARUGULA: I just wanted to offer one
14 comment, a real comment, about the subgroup
15 analysis on race and ethnicity. I think I've seen
16 in the briefing book that the race and ethnicity
17 analysis was done, and there was no difference. I
18 was assuming that the body weights were adjusted
19 for when the race and ethnicity analysis was done.
20 So I just wanted to offer that.

21 DR. LEWIS: Thank you. Any other comments
22 from the panel?

1 (No response.)

2 DR. LEWIS: Okay. Thank you.

3 On the first question of the effectiveness
4 of AG200-15, including efficacy results for Study
5 23 related to study design and enrolled patient
6 population, and interpretation of subgroup analyses
7 by BMI, weight, and race/ethnicity, panel members
8 agreed that certainly there were different levels
9 of efficacy with respect to the Pearl index than
10 was expected in this trial.

11 That is certainly different than much of the
12 data that are out there on currently available,
13 combined hormonal contraceptive methods. That
14 might be acceptable to a lot of patients. It
15 depends on what they are looking for in the way of
16 choice and what kinds of criteria they're using to
17 make their choice.

18 It was commented that certainly the LARC has
19 set a very high level of expectations among some
20 patients, but that's not a method that's going to
21 be desirable for every patient. Most of the panel
22 did talk about the fact that this trial has

1 reflected what might be expected of this product in
2 a population with a BMI that is what many of us are
3 seeing today.

4 It's hard to interpret how that would
5 compare to other products, except to note that when
6 we do get studies that look at what the clinical
7 pregnancy rate is in a real-world situation, it's
8 different, higher than what we see in a clinical
9 trial setting, and that may pose some challenges in
10 interpreting -- in how patient recommendations are
11 made by a provider.

12 Anything else that people want to add?

13 (No response.)

14 DR. LEWIS: Okay. Let's move to discussion
15 question 2, discuss the safety profile of AG200-15,
16 including interpretation of the venous
17 thromboembolism safety signal as it relates to
18 weight and body mass index, and interpretation of
19 the product tolerability, specifically cycle
20 control.

21 Ms. Miller?

22 MS. MILLER: Sabrina Miller, patient

1 representative. The VTE is concerning for all
2 CHCs, but for AG200-15, I'm not really convinced
3 that it has a greater risks than the other options
4 out there for non-obese patients.

5 B, the spotting during birth control is
6 expected, but based on my knowledge of the data I'm
7 seeing, 41 to 60 percent seemed a little extreme.
8 And as a patient, I'm not so sure that with that, I
9 would choose this patch over others. But I think
10 the patch method would be a deciding factor that
11 would motivate my decision to choose over others if
12 that wasn't the case.

13 In general, I do have a great concern over
14 the 30 percent BMI risk over efficacy. I would
15 recommend more labeling discussions on this if it
16 were approved in postmarket, head-to-head safety
17 studies against OC maybe.

18 DR. LEWIS: I'm sorry. Would you clarify?
19 You said recommend more efficacy decisions?

20 MS. MILLER: You had spoken about
21 head-to-head and safety studies against OCs,
22 postmarket, and I agree that that would definitely

1 be a recommendation if it were approved. Thank
2 you.

3 DR. LEWIS: Dr. Ortel?

4 DR. ORTEL: Speaking about it from my
5 perspective, which it seems like everybody I see
6 who's on oral contraceptives has had a VTE.

7 (Laughter.)

8 DR. LEWIS: Wow.

9 DR. ORTEL: I would say that we have to be
10 cautious in how we look at it because if we take
11 patients with a chronic risk factor, be it obesity,
12 be it If we know somebody has an inherited
13 thrombophilia, be it if we know they have some
14 other risk factor, and then we put something on top
15 of it, we're going to increase that risk further,
16 we have to recognize that.

17 I don't feel like the data that we've seen
18 tells us that this is way out of proportion to what
19 I would expect to see in somebody with some other
20 type of chronic risk factor that they've got
21 present, and it just mandates that you take the
22 time when you counsel a patient about the relative

1 risk, about what can potentially happen, then you
2 have to couch it with all of the other efficacy
3 data, et cetera, as you talk about this individual
4 choice. But I feel like you see what you would
5 expect to see in a patient population that has an
6 underlying risk factor for this event.

7 DR. LEWIS: Dr. Berenson?

8 DR. BERENSON: I don't think the cycle
9 control is an issue because we see issues with
10 cycle control with many methods, and that's very
11 individualistic to the patient as to whether or not
12 they can tolerate that. But when we talk about
13 VTEs, we're also talking about PEs, and we have to
14 remember that does carry a certain risk of death.
15 That is the most serious concern that you can think
16 of.

17 My comment on this is under the labeling.
18 Even with the proposed limitation of use, it does
19 not have anything about the safety in patients with
20 the BMI. It talks about reduced effectiveness, and
21 I would think that when we get to that discussion,
22 we would have to say, "and increased risk in

1 patients with a BMI over 30" if we do an LOU
2 indication.

3 DR. LEWIS: Thank you. Dr. Esther
4 Eisenberg?

5 DR. E. EISENBERG: I agree with
6 Dr. Berenson. I think that it's not clear whether
7 the 41 percent, or whatever that number was, is
8 spotting or bleeding, and many women can tolerate a
9 little bit of spotting periodically. And it could
10 be that that's the case, so I don't think that
11 that's an issue.

12 The other point is that the number of
13 headaches was much, much lower with this patch than
14 with other products, and that sometimes can be an
15 issue. But I do think that we really have to keep
16 in mind first do no harm, and VTEs are a big
17 problem. In the obese population, the addition of
18 any continuous hormonal contraception may increase
19 the risk, and I think that that's really an issue
20 of concern and needs to be addressed.

21 DR. LEWIS: Thank you. Anyone else?

22 (No response.)

1 DR. LEWIS: Okay. On the issue of the
2 safety profile, including interpretation of the VTE
3 safety signal as it relates to weight and body mass
4 index, panel members understandably are quite
5 concerned about the signal, but not necessarily to
6 the point where it seems like it's unexpected.
7 It's very important, critical, to communicate this
8 risk to the prescribing public, so labeling is
9 really crucial, especially when it comes to talking
10 about pulmonary embolus risk, as that's a fatal
11 complication, potentially fatal.

12 The importance of the product tolerability
13 in terms of spotting or bleeding, that's the common
14 also to other kinds of hormonal contraceptives.
15 For some patients, that effect will be tolerable,
16 whereas for others, it will not. Certainly, the
17 magnitude of the effect is going to be important,
18 whether it's spotting or bleeding, and that didn't
19 come through clearly when we got the data. At any
20 rate, it pales, so to speak, in terms of the
21 potential safety signal of the VTE rate.

22 Any other comments?

1 (No response.)

2 DR. LEWIS: No. Okay.

3 So now we come to the voting question. Do
4 the benefits of AG200-15 outweigh its risks to
5 support the drug's approval for the prevention of
6 pregnancy?

7 If you vote yes, explain the rationale for
8 your vote and address the following, whether this
9 product should be approved for use in the general
10 population or a more narrowly defined patient
11 population, and how this product should be used
12 within the context of available contraceptive
13 therapies. If you vote no, explain the rationale
14 for your vote and provide any recommendations.

15 Now, before we do that, I want to make sure
16 that people are clear with the question, and I'll
17 go over the electronic voting system in a moment.
18 Also, by way of process, once you vote, I'll be
19 asking each person individually to explain their
20 rationale.

21 So first, is everyone clear on the question?

22 (No response.)

1 DR. LEWIS: No questions on the question?

2 Okay.

3 We will be using an electronic voting
4 system. Please press the button on your microphone
5 that corresponds to your vote. You will have about
6 20 seconds to vote. Please press the button
7 firmly. After you've made your selection, the
8 light might continue to flash. If you're unsure of
9 your vote or you want to change your vote, please
10 press the corresponding button again before the
11 vote is closed.

12 Oh, I'm sorry. Dr. Margolis?

13 DR. MARGOLIS: What does it mean to abstain?

14 DR. LEWIS: It means you're not sure whether
15 you want to vote yes or no. You can't commit.

16 (Laughter.)

17 DR. LEWIS: Is that clear?

18 Any other clarifying questions?

19 (No response.)

20 DR. LEWIS: No? There's the question and we
21 can vote.

22 (Voting.)

1 DR. LEWIS: Are the buttons clear to
2 everybody? Okay.

3 MS. BHATT: The voting results, yes, 14; no,
4 1; abstain, 1.

5 DR. LEWIS: We're going to start on my left
6 with Dr. Berenson, and we'll have you please
7 explain the rationale for your vote.

8 DR. BERENSON: I voted yes because as a
9 gynecologist, I feel women do need more choices,
10 and the patch was very popular, and many of our
11 younger patients don't have the full range because
12 they are not willing to use some of the more
13 invasive methods. So it is important to have more
14 methods.

15 But I am concerned about the LOU because I
16 feel the prescribers need very accurate information
17 that they can convey to the patients. So I would
18 recommend that we have an alternative indication
19 that suggests that it should be used in patients
20 with a BMI under 30 and to eliminate any language
21 regarding a weight of 202, and to discuss that as
22 decreased safety with that BMI in addition to

1 decreased efficacy.

2 DR. LEWIS: Thank you. Dr. Christmas?

3 DR. CHRISTMAS: I voted yes because I do
4 think that it adds a benefit or additional
5 selection to the choices that we have presently. I
6 felt that the safety and efficacy for most patients
7 was pretty similar, if not better than what we
8 have, especially if you compare it to the Ortho
9 Evra or Xulane patch.

10 I agree that there should be language that
11 describes the potential risks for patients with a
12 BMI over 30, and I think it should be specified to
13 be BMI and not weight, but both not only includes
14 efficacy but safety concerns regarding
15 thromboembolic events.

16 DR. LEWIS: Thank you. Dr. Leslie?

17 DR. LESLIE: Dr. Leslie. I voted no because
18 of my concern about the efficacy of this
19 contraceptive option in today's landscape. I
20 absolutely agree that we need more options in our
21 communities for our patients and ones that fit the
22 patient.

1 Our question today, though, is not if we
2 need another transdermal option, we do; but it's if
3 this is it -- and I am not at all certain that this
4 is the correct one to add to our landscape, but I
5 want to be exceedingly clear that the goal is the
6 diversity of options for our patients who are
7 immensely diverse.

8 I want to commend our researchers on their
9 innovation and the goal of a safer and a set of
10 varied options. But my concerns really have to do
11 with the selection bias that I'm troubled about
12 with the study, that 51 percent of the patients did
13 not come or did not complete the study, and 90
14 percent compliance with an electronic diary was
15 required.

16 I take care of immigrants, undocumented
17 Latino ladies, and there's no way they could
18 complete an electronic diary, although I commend
19 you for including 20 percent in your study. I'm
20 also reflecting some of the FDA worries that there
21 was no new efficacy data with Study 23, and that
22 they had concerns regarding the first two studies

1 that we really didn't get to review today.

2 I'm not concerned, at this point, by the
3 safety data, but agree with the follow-up that
4 needs to happen, but that wasn't the primary reason
5 that I voted no today. My goal in medicine is to
6 first do no harm, and I have concerns regarding the
7 efficacy here and giving our patients a false sense
8 of hope, when our expectations in the country have
9 risen quite high for what we can offer them in
10 terms of adequate contraception. Thank you.

11 DR. LEWIS: Thank you. Dr. Curtis?

12 DR. CURTIS: Kate Curtis. I voted yes, but
13 it was a hard decision, and actually I had a lot of
14 the same thoughts that were just reflected. I
15 voted yes because I do think that the data we have
16 about effectiveness do you suggest that this patch
17 may be less effective than what we generally see
18 for combined hormonal contraceptives.

19 We've talked about all the reasons why we
20 may be seeing that Pearl index today, but we really
21 don't have any idea how much that Pearl index
22 reflects actual method effectiveness versus the

1 study design in this study population.

2 So I am concerned about effectiveness. I
3 think the safety data and the tolerability data
4 seem to be similar to what we would expect for
5 CHCs. I do think that women need choices and,
6 again, that women and their providers can make
7 decisions if they have good information. So I am
8 still very concerned about how the effectiveness
9 information is going to be presented for normal
10 weight women, as well as for women over normal
11 weights.

12 I would be very discouraged if it just sort
13 of got bundled as effectiveness with CHCs, or the
14 message was this is another CHC and they all have
15 the same effectiveness. I think that would be a
16 disservice to women and misinformation. So,
17 hopefully, there can be more conversations between
18 that, the applicant and the FDA, about the best way
19 to present the data that we have, which will be
20 difficult because we couldn't come to a consensus
21 about that today, but I think that's one place that
22 needs some focus.

1 DR. LEWIS: Thank you. Dr. Esther
2 Eisenberg?

3 DR. E. EISENBERG: I voted yes because this
4 fills a need. Certainly for women with a BMI less
5 than 30, the effectiveness is probably acceptable
6 to many women, and there are other options for whom
7 that effectiveness would not be acceptable. I am
8 concerned about the safety in women with a BMI over
9 30, and as well as the effectiveness in women with
10 a BMI that is above 30, probably above 35.

11 So I think that the use should be limited to
12 women that are less than 30 with language that
13 talks about both the effectiveness and safety in
14 women that have a BMI that's over 30.

15 DR. LEWIS: Thank you. Dr. Drake?

16 DR. DRAKE: My thoughts align very closely
17 with those of Dr. Berenson. Everything she said, I
18 could recapitulate. I would also say that I would
19 strongly recommend a well-done postmarketing study,
20 specifically with the venous thromboembolism risk.
21 That should be carried out, and that should be I
22 would think required.

1 DR. LEWIS: Thank you. I also voted yes,
2 largely along the same lines that Dr. Berenson
3 suggested. I do think it's important to offer this
4 choice, and hopefully additional products will come
5 to market.

6 My only other thing that I would add is that
7 the FDA has commented that this seems more like a
8 35-microgram dosage than an actual low-dose
9 contraceptive, and I don't know how important that
10 will be in the communications that go out in terms
11 of the marketing and the indications. But
12 certainly, that needs to be clarified, and I think
13 it's really important to talk about what the safety
14 profile is if the drug comes to market, and
15 certainly in terms of communicating what the
16 expected pregnancy rate is.

17 DR. BAUER: Doug Bauer. I also voted yes
18 for all the reasons that have been stated. If the
19 drug is approved, I know there will be lots of
20 discussion between the sponsor and the FDA about
21 the label. I just hope that those discussions
22 include some discussion that, in fact, from an

1 efficacy standpoint, it's not just women with BMIs
2 over 50, but rather some question about all
3 overweight women. I hope there can be some nuance
4 in the label that says something about the efficacy
5 may be reduced in all overweight women, and
6 particularly those over a BMI of 30. I would not
7 exclude this from women over 30, though.

8 DR. SHAW: Hi. Pam Shaw. I voted yes, but
9 it's a conditional yes, because if the LOU was not
10 in place, I would not vote yes because I think
11 there are more questions for the BMI over 30 group
12 in terms of whether or not there is increased risk
13 and how much. The efficacy is very underwhelming,
14 with possibly 10 or these numbers that were quite
15 large.

16 So I think that it's a conditional yes; that
17 there will be an LOU. I really strongly believe
18 that some language or a suggestion that
19 effectiveness is decreasing with increasing BMI;
20 that you're not saved if you're a BMI of 29.9. I
21 think that's very important.

22 This issue that it's confusing to have the

1 202 versus the BMI, actually I think it would be
2 great if the PK experts and those that understand
3 drug absorption, and what it is about this
4 BMI -- is it the layers of fat or is it just the
5 pure microgram per kilogram needed for efficacy, or
6 you don't know -- I think that's what determines
7 whether or not you have to put both the weight
8 limit and the BMI limit, or one of them, and which
9 one. So I think maybe that needs further
10 discussion.

11 DR. LEWIS: Dr. Miller?

12 MS. MILLER: Sabrina Miller. I did vote
13 yes. As a patient, the benefit that I can see is
14 that it's a lower dose, TDS. It appears the
15 risk-benefit is similar to other choices for
16 non-obese patients, who have a history of being
17 noncompliant or having application issues.

18 I would approve this for the non-obese
19 patients with warnings on the contraindications or
20 LOU label, however it is that you can offer that
21 information. This may not meet that unmet need for
22 a majority of Americans, but it's an option that we

1 need, I feel. My recommendation, those suggestions
2 for continued studies, I would like to see you
3 continue to move forward with that, reviews of
4 obesity and CHCs, as well as long-term VTE risks.

5 Finally, the low dose may not fit, but the
6 lower dose choice may. I would hope that the
7 barriers of terminology here wouldn't interfere
8 with giving product choices for patients who could
9 benefit from this. Thank you.

10 DR. LEWIS: Thank you. Dr. Hunsberger?

11 DR. HUNSBERGER: Sally Hunsberger. I voted
12 yes. I think this data has clearly shown that
13 there's a relationship between the Pearl index and
14 BMI and weight. This is a little heresy, but as a
15 statistician, I hate the p-value of 0.05. I hate
16 that artificial cut. So again, when I saw the 5 as
17 a criteria, I kind of rubbed up against it and
18 thought, I don't know how we make that decision.

19 I think on the label, I would like to have a
20 curve with confidence intervals, not just cutpoints
21 of obese or non-obese. I would like to see a
22 curve with confidence intervals, and I think if you

1 are a patient with a certain BMI and your
2 confidence interval went up to 20, you might think
3 differently than if it was at 10. So I think
4 that's very important. I think the choice part of
5 that, where you want to weigh out how much you want
6 to gamble is important. I would like more data on
7 safety of the VTE.

8 DR. LEWIS: Thank you. Dr. Margolis?

9 DR. MARGOLIS: Thank you. I was really
10 excited to see abstain.

11 (Laughter.)

12 DR. MARGOLIS: So depending on the moment,
13 it's dependent on whether I would have voted yes or
14 no. I do believe choice is important, and I think
15 that was all brought out by other speakers today
16 and certainly by people from the community.

17 I do think that the 5 is too rigid, as what
18 was just stated. But to be completely honest, I
19 don't know what that number should be, and I feel
20 like it's nearly impossible for us to make a
21 decision on the efficacy, which is really what this
22 is of this product.

1 Without knowing what that number should be,
2 and without having additional groups like this, or
3 studies to look at what patient preference actually
4 is, or what's an acceptable rate of failure, I
5 think it's nearly impossible to actually make a
6 decision on the efficacy. And while this study did
7 include more people and perhaps didn't game the
8 system, it's still not an effectiveness study, and
9 we really don't know how well it's going to work.
10 It could be 10 or 15 percent by the time it's in
11 the general population.

12 The original study was designed with the 5;
13 I mean, that's the way the sample size was set up,
14 and I think there's something important to say
15 about study design and having failed at that
16 outcome. Normally, in conversations, if somebody
17 fails to achieve the outcome that they designed the
18 study for, we view the study as being a failure.

19 So for all those reasons, I couldn't make a
20 decision, and I'm happy that I didn't have to.

21 (Laughter.)

22 DR. LEWIS: Dr. David Eisenberg?

1 DR. D. EISENBERG: This was a lot harder
2 than I thought it was going to be. When I read the
3 briefing materials, I really thought I knew what my
4 answer was going to be, and that is not where I
5 landed. I've been back and forth between no, yes,
6 and even when I found out abstain was an option.
7 But I ended up with yes because I take care of
8 patients who need contraceptive care, and there
9 aren't enough choices out there.

10 I take care of people who are smart enough
11 with accurate information in the counsel of their
12 clinician, and it's our job as clinicians to
13 distill these complicated concepts of confidence
14 intervals and Pearl indices, to help patients
15 understand what their personal risk is. I think we
16 can do that, and I think patients can understand
17 that, and patients are smart and capable of
18 deciding what's best for them and their family.

19 Having that choice I think is where I landed
20 on yes. And I will reiterate the things that both
21 Dr. Hunsberger and Dr. Shaw said, that the
22 dose-response curve that we see -- or that's

1 probably not the right term -- of BMI and
2 decreasing efficacy needs to be displayed in a way
3 that is more continuous than categorical.
4 Similarly, the dose-response curve and risk of
5 thromboembolic event is likewise more of a
6 continuous and categorical risk.

7 I think we need to keep that in mind when
8 that package label is put together. I think the
9 limitation of use idea is a good one, but I would
10 agree that BMI is probably where we need be and not
11 wait, and we can help patients understand what
12 their BMI is.

13 Lastly, I will take the opportunity to say
14 to the sponsor, not only how much I appreciate the
15 tenacity they've had with making sure this gets to
16 the goal line for women, but also the app that they
17 were using for their electronic diary could be an
18 easy patient support tool that many other companies
19 have used with their products to ensure compliance.

20 If that is what helps us stay at a life
21 table risk of 5 percent per year, because if it
22 isn't there, it might be twice that or higher, I

1 think we should help patients be as successful as
2 they can. And if the sponsor can help that with
3 something like an app for women who are getting
4 these prescriptions, that would be great.

5 DR. LEWIS: Thank you. Dr. Gagliardi?

6 DR. GAGLIARDI: Yes. Hi. I voted yes. I
7 voted yes because of the same reason most people
8 voted yes, is that I think the more options you
9 have for a patient for birth control, the more
10 likely you are to find something that they can use
11 and hopefully stick with. I do think that this is
12 an option that is problematic. It is an option
13 that is problematic from a safety standpoint, and
14 it's also problematic from an efficacy standpoint.

15 I do think that we need further research. I
16 am concerned, as has been mentioned by the previous
17 presenters, previous doctors, that BMI be
18 prominently displayed and preferably as a
19 continuous factor both for efficacy and for risks.

20 DR. LEWIS: Thank you. Dr. Haider?

21 DR. HAIDER: I also voted yes for many of
22 the reasons stated already, much of which was

1 stated by Dr. Eisenberg recently. I also thought
2 this was a very challenging process and landed
3 where I didn't think I would, reading the briefings
4 and coming here. But I do think that with good
5 information in the labeling, patients and providers
6 can really do an appropriate job of conveying this
7 message.

8 Many women after counseling for all methods
9 of contraception still choose condoms, and that's
10 perfectly okay; very low efficacy, but that's their
11 choice. So I do think that this is really a move
12 towards patient-centered, shared decision making
13 with really good information for counseling, and I
14 do think the obesity piece is really novel in the
15 sense that it's being included.

16 Though I do think the limitation of use
17 should be there, specifically for the safety and
18 efficacy for that group, and probably using BMI or
19 some continuum, I don't think we should restrict it
20 and not make it available to obese women because,
21 again, we have so many other methods. We don't
22 know anything about obesity, and we are prescribing

1 those methods based on CDC eligibility criteria and
2 et cetera.

3 So I don't think we should limit it, because
4 once you start limiting it, then you're like
5 closing off that population's access. Those are my
6 comments.

7 DR. LEWIS: Okay. Thank you. Dr. Ortel?

8 DR. ORTEL: Thank you. I also voted yes for
9 the reasons that have been stated around the table.
10 One thing I would say is that this meeting has made
11 me very aware of the limitations of the data that
12 we're actually working with, and whether or not new
13 metrics should be developed for the next series of
14 studies.

15 A Pearl of 5 that counts for everybody,
16 obviously, doesn't seem to work, and it needs to
17 vary by weight or some metric, something like that.
18 I think that it's important to have choices. I do
19 see a lot of patients who have chronic risk factors
20 and they want to know what is safe that they can
21 take, and they do want their options also. So
22 being able to explain that to the individual

1 patient is important.

2 I agree. I don't think I would restrict it
3 to weight, but people need to have a well-worded
4 limitation of use statement in there that explains
5 why you should think twice before doing it, for the
6 patient who fits the criteria for obesity, et
7 cetera.

8 DR. LEWIS: Thank you.

9 With that, I'm going to ask the FDA if they
10 have any last comments before we adjourn.

11 DR. GASSMAN: I would just like to thank all
12 the members of the committee for providing us with
13 their thoughts and their advice to us. We will
14 take all of this back, and we appreciate your
15 taking time out of your busy schedules to come and
16 discuss this because this is important.

17 **Adjournment**

18 DR. LEWIS: Thank you. Thank you to the FDA
19 for providing us with the information they did.
20 Thank you to the sponsor for their thorough
21 preparation and input during the meeting. And
22 thank you, panel, for taking your responsibilities

1 so seriously and being engaged throughout the whole
2 process.

3 The meeting is adjourned.

4 (Whereupon, at 3:55 p.m., the meeting was
5 adjourned.)

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