FDA Briefing Document NDA 204017
Levonorgestrel and ethinyl estradiol transdermal system

Bone, Reproductive and Urologic Drugs
Advisory Committee (BRUDAC) Meeting
October 30, 2019

Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Office of New Drugs

Division of Epidemiology II
Office of Surveillance and Epidemiology

Division of Biometrics III
Office of Biostatistics
Office of Translational Sciences

Division of Clinical Pharmacology III
Office of Clinical Pharmacology
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I. Introductory Memorandum

To: The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC)

From: Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive and Urologic Products (DBRUP)

Subject: New Drug Application (NDA) 204017
Levonorgestrel and ethinyl estradiol transdermal system
Overview of topics to be discussed at the October 30, 2019, advisory committee meeting

Introduction
Agile Therapeutics, Inc. (hereafter referred to as the Applicant), is seeking FDA approval of AG200-15, a new transdermal system (TDS) containing levonorgestrel (LNG) and ethinyl estradiol (EE) for the prevention of pregnancy in women of reproductive age. The FDA is convening this advisory committee (AC) meeting to obtain input on whether the contraceptive benefits of AG200-15 outweigh the safety risks to support approval. AG200-15 is a 28 cm² matrix type TDS designed to deliver 120 mcg of LNG and 30 mcg of EE per day. The proposed dosing regimen for one cycle of AG200-15 is one TDS to be applied to either the abdomen, buttock, or upper torso every 7 days for three consecutive weeks followed by one TDS-free week.

Unintended Pregnancy
An unintended pregnancy (as defined by the Centers for Disease Control and Prevention) is a pregnancy that is considered either unwanted or mistimed. An unwanted pregnancy is one that occurs when no children or no additional children are desired. A mistimed pregnancy is one that occurs earlier than desired (Centers for Disease Control and Prevention 2019b). Unintended pregnancy affects millions of women in the United States each year with significant public health consequences including adverse maternal and child health outcomes as well as social and economic costs at the family and state level. In 2011, nearly one-half of the pregnancies in the U.S. were unintended. The Centers for Disease Control and Prevention has named the benefits and access to contraception as one of the greatest public health achievements of the 20th century (Centers for Disease Control and Prevention 1999). Of the all the contraceptives available marketed in the U.S., oral combined hormonal contraceptives (CHCs), products containing both estrogen and progestin, are most commonly used (See Figure 1 in the Appendix).

Since CHCs were first developed, the use of lower hormonal doses with more convenient dosing regimens and dosage forms has become a priority. Epidemiologic studies have shown that the use of a CHC, regardless of the route of administration, increases the risk for rare but serious side effects such as arterial thrombotic events (e.g., myocardial infarction and stroke) and venous thromboembolism (e.g., deep vein thrombosis and pulmonary embolism). For approval, the effectiveness of the CHC to prevent pregnancy must outweigh the safety risks. Although there
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due to numerous approved CHCs, the FDA is committed to innovation that provides more
convenient dosage forms and dosing regimens for these types of products.

FDA has approved many contraceptives, both hormonal (estrogen/progestin or progestin only)
and non-hormonal, for the prevention of pregnancy. A brief overview of available contraceptives
is outlined below:

Contraceptive Products currently marketed in the U.S.:

Hormonal

- Combination oral contraceptives (COCs), progestin only
- oral contraceptives (POPs), progestin-releasing intrauterine
  systems (IUSs), implants, injectables, vaginal rings,
  transdermal system

Non-hormonal

- Copper intrauterine device (IUD), diaphragms, condoms
  (male and female), sponges, spermicides

Ortho Evra and its generic (Xulane) are the only transdermal CHC that have been approved in
the U.S. for prevention of pregnancy in reproductive aged women. Ortho Evra contains 6 mg of a
different progestin, norelgestromin (NGMN) and 750 mcg of EE. While Ortho Evra was
discontinued from marketing in the U.S. (not for reasons related to safety or effectiveness),
Xulane is still marketed. The most recent approved labeling for Xulane states there may be an
increased risk of venous thromboembolism among women who use Xulane compared to women
who use certain oral contraceptives. The EE pharmacokinetic profile of Xulane differs from that
of COC containing 35-mcg of EE in that Xulane has higher systemic and steady state EE
concentrations, but lower EE peak concentrations.

AG200-15 Development Overview

AG200-15 is undergoing its third NDA review cycle by the FDA. The Applicant has used the
same EE/LNG formulation for all three of the phase 3 clinical trials, (ATI-CL12 and ATI-CL13
from the first review cycle; ATI-CL23 from the second review cycle) and the in-vivo adhesion
trial included in the current review cycle. Our presentations for this AC meeting will focus on
data from Study ATI-CL23 (hereafter referred to as Study 23). Study 23 was a phase 3, open-
label, single arm clinical trial that evaluated the contraceptive effectiveness, safety, cycle control,
treatment compliance, and transdermal adhesion of AG200-15. The Applicant conducted this
trial after problems were identified in Study 12 and 13 that could be resolved.

FDA Considerations on Effectiveness

FDA evaluates contraceptive products with the following considerations:

- The evaluation of effectiveness for hormonal contraceptives is based on the number of on-
treatment pregnancies observed in the phase 3 trial(s). This number is used in the calculation
  of the Pearl Index (PI) which reports the pregnancy rate per 100 women-years of drug
  exposure. For efficacy analyses of contraceptives including AG200-15, the FDA focuses on
  the number of pregnancies occurring in women 35 years and younger utilizing 28-day cycles
  in which subjects report sexual intercourse and use no back-up contraception. In most
  circumstances the efficacy analysis focuses on U.S./Canadian data.

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

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

FDA has the following concerns with the effectiveness of AG200-15:

• AG200-15’s estimated PI in Study 23 and the corresponding 95% CI was 5.83 (95% CI 4.45, 7.21). The FDA believes that this PI and 95% CI upper bound is unacceptable from an efficacy perspective for a new CHC product.

  - In obese subjects in Study 23, the estimated AG200-15 pregnancy rate is almost twice that of non-obese subjects and is clinically concerning given that 28% of women between the ages of 18-44 years were classified as obese (BMI ≥30 kg/m²) in 2017 in the U.S. (Centers for Disease Control and Prevention 2019a). For women with a BMI ≥30 kg/m², the estimated PI is 8.64 (95% CI 5.79, 11.50) compared to a PI of 4.34 (95% CI 2.86, 5.82) for women with a BMI <30 kg/m².

The Applicant attributes the higher PI seen in Study 23 to its study population and design features (e.g., inclusion of a population that is more obese and racially/ethnically diverse, and more thorough testing for pregnancy), which they state better reflects “real world use” as compared to trials of other approved hormonal contraceptives. We do not find support for marked differences between the study design for AG200-15 and other recently conducted hormonal contraceptive studies. The FDA does not agree that the overall high PI can be definitively attributed to study differences. For example, the PI among Whites was 5.8 (95% CI 4.1, 7.5), which is clinically similar to the PI among Blacks of 6.4 (95% CI 3.4, 9.4) and to the PI among Hispanics/Latinos of 5.5 (95% CI 2.4, 8.6). In addition, even women who were not obese had an unacceptable PI. For example, the PI in overweight women (BMI ≥25 kg/m² to <30 kg/m²) was 5.7 (95% CI 3.0, 8.4). Therefore, the FDA does not believe that the trial differences noted by the Applicant clearly explain the suboptimal effectiveness results. Furthermore, even in the non-obese subjects, the upper bound of the 95% CI exceeds 5.

• To address the increased PI, the Applicant is proposing a Limitations of Use in the INDICATIONS AND USAGE section of product labeling stating that AG200-15 has reduced effectiveness in women who weigh 202 pounds (92 kg) or more and/or have a BMI of 30 kg/m² or more. The statement is intended to address the concerns about the higher PI reported in Study 23. The Applicant included in their statistical analysis plan a pre-specified secondary analysis in the subgroup of women with baseline BMI less than 30 kg/m². The statistical analysis plan did not include a planned subgroup analysis by baseline weight less than 202 pounds (92 kg). It is unclear what methodology the Applicant used to add the additional criterion of 202 pounds (92 kg).
The FDA is concerned that AG200-15 is not adequately effective in the general population of women in the U.S. as well as in non-obese women.

*General Comments Regarding Efficacy in Contraceptive Studies*

The FDA acknowledges that pregnancy rates in phase 3 studies submitted in support of approval for new contraceptive products has increased through the years. This apparent increase could be due to several factors including:

- Changes in the types of patients enrolled in trials over time, such as inclusion of a larger number of heavier subjects in whom the products may be less likely to work
- Lower dosages of estrogens and progestins
- Increased user failure (i.e., the subject does not completely follow the recommended dosing regimen, such as failure to take one or more doses) resulting in unintended pregnancy
- Other factors, such as improvement of pregnancy detection (e.g., more frequent and more sensitive pregnancy testing).

Although an increasing proportion of obese women in the U.S. are in their reproductive years and are at risk of unintended pregnancy, this subgroup has previously been largely excluded from clinical trials of CHCs, and the effect of obesity on the effectiveness of CHCs remains unclear. In 2015, the FDA published a meta-analysis using phase 3 clinical trial data from combined oral contraceptives. This meta-analysis assessed the effect of obesity on hormonal contraceptive effectiveness. The meta-analysis showed a PI for obese patients of 3.1 (95% CI 2.3-4.2) compared to a PI for non-obese patients of 2.5 (95% CI 1.9-3.4). The clinical relevance of these differences is unclear. In addition, as stated in the publication, there were a number of limitations to the FDA study that prevented reaching a definitive conclusion, including whether the selection of women into these previously conducted trials may have differentially affected the baseline risk of unintended pregnancy of women in the two BMI groups as well as inconsistent definitions and variables used across the trials. Also, the study was not able to evaluate compliance of these women which is one of the most important considerations when evaluating risk of unintended pregnancy.

Another unanswered question is whether the effectiveness of a transdermal system may be more greatly impacted by obesity than CHCs delivered by other routes of administration. For example, a transdermal system relies on drug absorption through the skin and it is unclear whether the additional subcutaneous fat in obese women may adversely impact absorption compared to CHCs administered by other routes (e.g., oral, intravaginal).

Given these and other potential differences between Study 23 and previous studies of other CHC products, it is difficult to directly compare the effectiveness and safety of AG200-15 with other approved hormonal contraceptive products—observed differences (or lack thereof) based on cross-study comparisons may be due to differences in drug effects or may be due to differences in populations, design, conduct, or other aspects of the studies. However, despite these limitations, as noted previously, all approved hormonal contraceptives to date have an upper bound of the 95% CI for the overall PI ≤5.0.
The Applicant asserts that AG200-15 represents an unmet need in the contraceptive arena. FDA defines an unmet need as a condition whose treatment or diagnosis is not adequately addressed by available therapy (FDA 2017a). An unmet need includes situations where there is an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer term need for society (e.g., to address the development of resistance to antibacterial drugs). The FDA does not believe that the Applicant has met this determination.

User Compliance

One of the proposed benefits of AG200-15 is dosing convenience and thereby, potentially improved compliance. Although transdermal systems may require less frequent administration than other routes of administration (e.g., weekly application to the skin vs. daily oral administration), compliance may not be improved in women using a transdermal system as compared to combined oral contraceptive products. In a recent study of nearly 18,000 women who had commercial insurance in the U.S., approximately one third did not refill their combined oral contraceptive prescriptions in a timely manner. Overall, switching to a transdermal system or ring did not improve refill patterns as greater proportions of women on these products were delayed refillers (reported as 42% [transdermal system] and 51% [ring], respectively) (Law et al. 2014). In addition, tolerability, especially unscheduled vaginal bleeding and spotting, is an important consideration with use of these products as it may contribute to reduced compliance which can lead to unintended pregnancy. There is also the need to assure that the transdermal system remains on the skin for the full week. The Applicant has not proven that there is improved compliance with its product compared to other available therapies.

Disposition, Cycle Control and Usability Issues in Study 23

Study 23 reported:

- Regarding disposition, an overall discontinuation rate of 51% of which 11% reported discontinuing for an adverse event.
- Regarding cycle control, approximately 60% and 41% of women who provided information on vaginal bleeding and TDS application in their electronic diaries (eDiaries) in cycles 1 and 13, respectively, had unscheduled vaginal bleeding or spotting.
- Regarding usability, the percent of women experiencing a complete detachment ranged from 25% of all women in Cycle 1 to 6% in Cycle 13. A total of 54% of women experienced a complete transdermal system detachment at some point during the trial. In looking at usability based on cycle data, a total of 15% of all cycles studied (N=18,841) required the use of more than three TDS.

Safety Issues

In general, the safety profile of AG200-15 appears comparable to that of other approved CHCs. One of the most significant safety concerns associated with CHC use is venous thromboembolism (VTE), which can be life-threatening. In Study 23, four women experienced 5 drug-related VTEs. Contraceptive trials cannot reliably estimate the incidence of VTE that will occur in the postmarketing setting. These trials are substantially underpowered to evaluate these rare events and typically few events are reported, yielding unstable estimates. The risk of VTE is related to the estrogen dose, and, as explained below, we do not consider AG200-15 to be a low-
dose estrogen-containing CHC and the LNG component does not convey any specific advantage over other approved CHC products. It is not possible to conclude that AG200-15 demonstrates improved safety over other combined hormonal products in terms of VTEs.

**Dose Concerns**

The Applicant states in its briefing document that AG200-15 “contains 2.60 mg LNG and 2.30 mg EE within an active drug matrix core. It delivers daily doses similar to daily oral doses of 120 mcg of LNG and 30 mcg of EE, which are within ranges reported for currently available low-dose oral CHC products.”

In FDA’s view, AG200-15 is not a “low-dose” product. The FDA believes that the term “low-dose” is typically reserved for CHC products with daily estrogen doses of 20 mcg or less. The American College of Obstetricians and Gynecologists issued a recent clinical practice bulletin entitled, “Use of Hormonal Contraception in Women with Coexisting Medical Conditions”. This bulletin defined contemporary low dose oral CHC’s as 35 mcg or less, but this definition was in the context of discussing hormonal contraceptives for women with chronic hypertension. To our knowledge, there is no standard clinical definition for low-dose hormonal contraceptives. Review of the supportive clinical pharmacology data from ATI-CL-14 (hereafter referred to as Study 14) appears to demonstrate that the steady-state EE systemic exposure following two consecutive cycles of AG200-15 is closer to a 35-microgram (mcg) oral contraceptive product rather than one that delivers between 15 to 20 mcg (refer to Clinical Pharmacology Summary for more details).

It is challenging to compare information obtained from Studies 14 (pharmacokinetics) and Study 23 (clinical data) to data obtained from other CHC products. More recent pharmacokinetic studies have used different and improved clinical hormonal assays that may confound comparisons. In addition, clinical trial data comparisons across products are limited because of differences in population and methodology.

The implication of stating that a product has a low dose from a contraceptive perspective is that the product (AG200-15) would have similar risks to the lowest dose oral contraceptive products containing EE available in the U.S., which deliver between 15 to 20 mcg of estradiol daily. There were several reports of VTE in the Applicant’s clinical trial database. We conclude that AG200-15 does not appear to demonstrate a safety advantage over other CHCs, including over the lower dose CHCs containing 15 to 20 mcg EE.

**Summary**

The FDA agrees with the Applicant that AG200-15 reduces the risk of pregnancy compared to not using contraception, but considers the PI and upper bound of the 95% CI unacceptable for a CHC product when considering alternative products available on the U.S. market. The Applicant attributes the higher PI to its study population and design features (e.g., inclusion of a population that is more obese and racially/ ethnically diverse, and more thorough testing for pregnancy), but it is unclear whether the findings reflect these differences or suboptimal effectiveness of AG200-15. Even among non-obese women, the estimated PI and the upper bound of the corresponding 95% CI is higher than that of any approved CHC, and it is possible that there may be a more dramatic effect of weight on the effectiveness of a CHC transdermal system compared to CHCs that have other routes of administration.
It is also important to consider that a high BMI may not be the sole cause of the increased overall PI and 95% CI. It is also possible that issues related to usability (in terms of number of TDS used per cycle) and tolerability also contributed to these high rates. This leads to additional questions regarding tolerance and compliance with use.

The FDA does not believe that the data show a safety advantage over available CHC products, and questions whether the observed effectiveness for a product intended to prevent pregnancy outweighs its risks in the context of available therapy.

The FDA appreciates your input on the benefits and risks of AG200-15, including the estimated PI overall and for subgroups, the risk of VTE, and the occurrence of unscheduled bleeding and spotting.
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Draft Points to Consider

The advisory committee members should consider the following while preparing for the meeting:

1. Discuss the effectiveness of AG200-15, including:
   a. Your interpretation of the efficacy results of Study ATI-C123 (Study 23), including the extent to which the efficacy findings reflect the study design and enrolled patient population
   b. Relevance of supportive efficacy analyses for Study 23, including subgroup analyses by weight, body mass index, and race/ethnicity

2. Discuss the safety profile of AG200-15, including:
   a. Your interpretation of serious risks (e.g., venous thromboembolism)
   b. Your interpretation of the tolerability profile, particularly with respect to cycle control

3. Do the benefits of AG200-15 outweigh its risks and support approval for the prevention of pregnancy?

Provide rationale for your vote.

If you vote YES, explain whether the benefits outweigh the risks in the general population or in a narrower patient population, and how this product should be used within the context of available therapy.

If you vote, NO, explain what data could be obtained to show that the benefits of AG200-15 outweigh its risks.
II. Regulatory History

First Review Cycle

The Applicant submitted the NDA for AG200-15 in April 2012, which included two phase 3 studies.

Study ATI-CL12 (hereafter referred to as Study 12) was a multicenter, open-label randomized study that was comparative for 6 cycles against a 100 mcg LNG/20 mcg EE oral product (Lessina) and then extended to 13 cycles that included both AG200-15 users and switchers from the oral product. For AG200-15, the Applicant calculated a PI based on 30 on-treatment pregnancies (Cycles 1-13 and BMI <32 kg/m^2). The FDA identified 8 additional on-treatment pregnancies of which 5 were in the primary efficacy dataset. The FDA’s calculated PI was 7.50 (95% CI 5.02, 9.97) based on 35 on-treatment pregnancies and 6,070 evaluable cycles.

Study ATI-CL13 (hereafter referred to as Study 13) was a multicenter, open-label, randomized study that compared AG200-15 to a 150 mcg LNG/30 mcg EE oral product (Levora). For Study 13 the FDA identified no additional on-treatment pregnancies beyond those identified by the Applicant and verified the PI estimate to be 8.19 (95% CI 0.19, 16.19) based on 4 on-treatment pregnancies and 635 evaluable cycles.

The FDA notified the Applicant in February 2013 that the application could not be approved based on the following deficiencies:

- The two phase 3 studies submitted in this NDA failed to demonstrate acceptable evidence of effectiveness.
- There were substantial problems with study conduct, including low completion rates and issues with subject follow-up and data collection.
- There were discrepancies in reporting of serious adverse events and lack of adequate information about diagnostic workups making it difficult to determine whether an event was drug-related.
- There were subject concerns about adequate AG200-15 adhesion and application site reactions.
- There were multiple product quality issues.

The FDA informed the Applicant that they would need to conduct a new phase 3 study and address issues related to product quality.

End-of-Review Meeting

In October 2013, FDA met with the Applicant to discuss the decision regarding the unacceptable evidence of effectiveness and the steps required before the application could be approved. The Applicant was informed that the Division had never approved a combination hormonal contraceptive product for which the upper bound of the 95% CI around the PI exceeded 5.
Second Review Cycle

The Applicant submitted a complete response in June 2017 with data from a new phase 3 study (Study 23) that is discussed in greater detail in Sections I, IV and V of this document. The FDA notified the Applicant in December 2017 that the application still could not be approved. There were product quality issues and deficiencies identified at a manufacturing facility. The FDA also had concerns related to product adhesion, high subject withdrawal rates and the high PI. It was unclear to what extent adhesion problems affected efficacy, unscheduled bleeding and high discontinuation rates.

In the 2017 Complete Response letter, the FDA conveyed to the Applicant that given that the main advantage of AG 200-15 would be a more convenient dosing schedule, we were unable to conclude that the reduced overall effectiveness (i.e., PI of 5.83 (95% CI 4.45-7.21)) outweighed the risks. Other recommendations to the Applicant focused on the adhesion issues and manufacturing.

Formal Dispute Resolution Requests

In June 2018 and again in August 2018, the Applicant submitted Formal Dispute Resolution Requests to FDA’s Office of Drug Evaluation III and the Office of New Drugs, respectively. The Applicant asked that FDA consider the existing in vivo adhesion data for AG200-15, along with planned risk management activities, to be adequate for approval.

In both cases the FDA denied these appeals.

Third Review Cycle

The Applicant submitted a second complete response in May 2019 which included additional study information to address the adhesion-related concerns of the December 2017 Complete Response Letter. No other clinical data were submitted.
III. Clinical Pharmacology

Summary Statement
The applicant claims that AG200-15 is a “low dose” hormonal contraceptive. However, based on the comparison of EE exposure (area under the concentration-time curve or AUC) with AG200-15 versus the COC Ortho-Cyclen in the Applicant’s Study 14, the systemic EE exposure of AG200-15 is similar to that of Ortho-Cyclen, a product containing 35 mcg EE, and should not be designated as a low-dose estrogen contraceptive as there are CHCs containing 20 mcg or less of EE.

Study 14 Design
The single- and multiple-dose pharmacokinetics (PK) of EE and LNG after applications of AG200-15 were characterized in Study 14. In this study, 18 subjects in Group 1 received two consecutive cycles of AG200-15 and then one cycle of the marketed oral contraceptive Ortho-Cyclen that had 21 active tablets containing hormone and 7 placebo tablets. The other 16 subjects in Group 2 received one cycle of AG200-15, and then one cycle of Ortho-Cyclen followed by another cycle of AG200-15. The duration of each treatment cycle was 28 days. In each cycle, both AG200-15 and Ortho-Cyclen were administered over three consecutive weeks of drug-taking followed by a drug-free week. Each AG200-15 transdermal system was to be worn for 7 days and was applied to the buttocks only. In AG200-15 cycles, blood PK sampling was performed during the 1st and 3rd weeks and up to 72 hours following removal of the third transdermal system (4th week). In Ortho-Cyclen cycles, blood PK sampling was performed on Cycle Days 7 and 21 and up to 72 hours following the Day 21 dose.

Results of PK Parameters in Study 14
The mean PK parameters (C\text{max}, \text{AUC}_{0-168h}, T\text{max} and T\text{1/2}) for EE in Group 1 subjects are summarized in Table 1.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Parameters</th>
<th>AG200-15 (2.3 mg EE/ 2.6 mg LNG) (N=17)</th>
<th>Ortho-Cyclen (0.035 mg EE/0.25 mg Norgestimate) (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cycle 1</td>
<td>Cycle 2</td>
</tr>
<tr>
<td>EE</td>
<td>C\text{max} (pg/mL)</td>
<td>Week 1</td>
<td>Week 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 (14)</td>
<td>59 (16)</td>
</tr>
<tr>
<td></td>
<td>\text{AUC}_{0-168h} (ng·h/mL)</td>
<td>5.19 (1.73)</td>
<td>6.37 (2.07)</td>
</tr>
<tr>
<td></td>
<td>T\text{max} (h)*</td>
<td>60 (24-144)</td>
<td>24 (0-120)</td>
</tr>
<tr>
<td></td>
<td>T\text{1/2} (h)</td>
<td>N.A.</td>
<td>19.7 (3.7)</td>
</tr>
</tbody>
</table>

Presented as median (range)
Source: Modified from Tables 1 and 2 in the Summary of Clinical Pharmacology Studies submitted on 06/26/2017.
Discussion

Following two consecutive cycles of AG200-15, EE exhibited 10-20% within-cycle (Week 3 vs. Week 1) and between-cycle (Cycle 2/Week 1 vs. Cycle 1/Week 1) increases in AUC_{0-168h} (Table 1). The Applicant pooled Cycle 2/Week 3 PK data from Group 1 (AG200-15/AG200-15/Ortho-Cyclen) and Cycle 3/Week 3 data from Group 2 (AG200-15/Ortho-Cyclen/AG200-15). The Applicant’s analysis (using pooled data from Groups 1 and 2) showed that average AUC_{0-168h} of EE from AG200-15 (6.26 ng*h/mL) was 10% lower than that of EE (6.97 ng*h/mL) from Ortho Cyclen, a commonly prescribed 35 mcg EE oral contraceptive. The Applicant concluded that the calculated daily dose of the AG200-15 was equivalent to approximately 30 mcg EE.

Based on our analyses, AG200-15 exhibits between-cycle increases in EE exposure while Ortho-Cyclen does not. Consecutive cycles of AG200-15 using PK data from Group 1 rather than pooled PK data from Groups 1 and 2 should be used for the comparison between AG200-15 and Ortho-Cyclen (Table 1). The inclusion of an Ortho-Cyclen cycle between two AG200-15 cycles in Group 2 prevented the between-cycle increases in EE exposure and resulted in a Cycle 3/Week 3 AUC_{0-168h} of EE from AG200-15 of 5.18 ng*h/mL, which was 28% lower than Cycle 2/Week 3 AUC_{0-168h} of EE from AG200-15 in Group 1 (7.22 ng*h/mL) following two consecutive cycles of AG200-15 wear. Our analysis shows that the AUC_{0-168h} of EE from AG200-15 (7.22 ng*h/mL) was comparable to that of EE from Ortho-Cyclen (7.52 ng*h/mL and 6.97 ng*h/mL for Week 1 and Week 3, respectively). The C_{max} of EE from AG200-15 (58.7 pg/mL) was approximately 57 - 58% lower than that of EE from Ortho-Cyclen (140 pg/mL and 135 pg/mL for Week 1 and Week 3, respectively). The T_{1/2} of EE observed from both AG200-15 and Ortho-Cyclen was similar.

The mean PK parameters (C_{max}, AUC_{0-168} T_{max} and T_{1/2}) for LNG were also evaluated and did not raise any specific pharmacokinetic concerns.
IVA. Overall Effectiveness Assessment

Study Design

Study 23 was a U.S. only, single-arm, open-label, one year (thirteen 28-day cycles), multicenter phase 3 study of the contraceptive efficacy, safety, and tolerability of AG200-15 with no restriction on BMI of study participants. The Applicant designed Study 23 to have 90% power to establish a PI no larger than 3.5 with an upper bound of the two-sided 95% CI no larger than 5.

The trial design for Study 23 approximated that 1,900 enrolled women aged 18 to 35 years would generate about 16,000 cycles of exposure to AG200-15. The Applicant’s design also assumed that close to 21% of these cycles would not be included in the primary evaluation of efficacy due to use of back-up contraception or absence of sexual activity. Thus, the Applicant’s power calculation assumed that the 1,900 women would provide approximately 12,675 cycles to support the primary efficacy evaluation.

A total of 2,032 women of reproductive age at risk for pregnancy and desiring to use contraception were enrolled at 102 investigational sites. One woman enrolled in Study 23 discontinued prior to the application of the first TDS. Of the remaining 2,031 subjects, 1,830 subjects were 18-35 years of age and 201 were >35 years of age. Of the 1,830 subjects that were 18-35 years of age at enrollment, ninety-four subjects were excluded from the primary analysis population: seven subjects were excluded due to a positive test for pre-existing pregnancy; seven subjects were excluded because they did not provide information about bleeding and patch application in the eDiary; and 80 subjects were excluded because they were sexually inactive or backup contraceptives were used during the cycle. Therefore, 1,736 subjects contributed 15,165 cycles that were sufficiently characterized for analysis. In the subgroup of subjects > 35 years of age, 196 subjects contributed 1,961 evaluable cycles.

Efficacy Endpoints

The pre-specified primary efficacy endpoint was the pregnancy rate described by the PI (the pregnancy rate per 100 women-years of drug exposure as defined below) in subjects aged ≤35 years (at study entry) irrespective of BMI. The pre-specified secondary efficacy endpoints were the PIs by BMI (<30 kg/m² vs. ≥30 kg/m²), self-identified race (White vs. Black vs. Other), and ethnicity (Hispanic or Latino vs. Not Hispanic or Latino). Life table estimates of the probability of pregnancy were also provided as a supportive analysis.

\[
\text{Pearl Index} = \frac{(\text{number of pregnancies}) \times 13 \text{ cycles}}{\text{number of 28-day cycles as defined below}} \times 100
\]

- Calculation of the PI for primary efficacy evaluation includes:
  - Pregnancy with an estimated date of conception between the date of first AG200-15 system application through 7 days after the last system removal. This is also referred to as an “on treatment pregnancy”.

17
– Complete or incomplete on-treatment cycles in which vaginal intercourse occurred and no back-up or emergency contraception was used based on eDiary data. These are also referred to as “evaluable cycles”.

Subject Disposition

The Safety Population included 2,031 women. Of these 2,031 women, 1,042 (51%) subjects dropped out of the study prematurely. Table 2 summarizes the subject disposition information in study 23, including reasons for study discontinuations.

<table>
<thead>
<tr>
<th>Category</th>
<th>Safety Population (N=2,031)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Completed the study</td>
<td>989 (48.7)</td>
</tr>
<tr>
<td>Discontinued the study</td>
<td>1,042 (51.3)</td>
</tr>
<tr>
<td>Reason for discontinuation</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>222 (10.9)</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>116 (5.7)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>229 (11.3)</td>
</tr>
<tr>
<td>Subject’s decision</td>
<td>310 (15.3)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>73 (3.6)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>14 (0.7)</td>
</tr>
<tr>
<td>Investigator decision</td>
<td>17 (0.8)</td>
</tr>
<tr>
<td>Sponsor decision</td>
<td>18 (0.9)</td>
</tr>
<tr>
<td>Sponsor decision (study termination)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>41 (2.0)</td>
</tr>
</tbody>
</table>

1 Denominator for % calculation is the number of subjects in the Safety Population (N=2,031).
Source: FDA Analysis

Primary Efficacy Analysis based on the PI

The pre-specified primary analysis population for effectiveness included 1,736 subjects who were women aged ≤35 years, wore at least one AG200-15 system, had a negative enrollment serum β-hCG pregnancy test and had at least one evaluable cycle. In 15,165 evaluable cycles of AG200-15 use, we identified 68 on-treatment pregnancies.

The estimated PI in the primary analysis population is shown in Table 3. The treatment effect of AG200-15 did not achieve the trial objectives of a point estimate of 3.5 (or less) and an upper bound of the 95% CI of 5 (or less).
Table 3. Primary Efficacy Analysis (Age ≤35 years): PI (Study 23)

<table>
<thead>
<tr>
<th>N</th>
<th># On-Treatment pregnancies</th>
<th># Evaluable Cycles</th>
<th>PI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,736</td>
<td>68</td>
<td>15,165</td>
<td>5.83 (4.45, 7.21)</td>
</tr>
</tbody>
</table>

Source: FDA Analysis

Subgroup Analyses and Considerations Related to BMI and Weight

Table 4 presents PIs based on subgroup analyses of the primary analysis population for Study 23.

Table 4. Subgroup Efficacy Analysis (Age ≤35 years): PI (Study 23)

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th># On-Treatment Pregnancies</th>
<th># Evaluable Cycles</th>
<th>PI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI(^1) (kg/m(^2))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>1,123</td>
<td>33</td>
<td>9,888</td>
<td>4.34 (2.86, 5.82)</td>
</tr>
<tr>
<td>≥30</td>
<td>612</td>
<td>35</td>
<td>5,264</td>
<td>8.64 (5.79, 11.50)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;92</td>
<td>1,402</td>
<td>46</td>
<td>12,276</td>
<td>4.87 (3.47, 6.28)</td>
</tr>
<tr>
<td>≥92</td>
<td>334</td>
<td>22</td>
<td>2,889</td>
<td>9.90 (5.78, 14.02)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1,159</td>
<td>46</td>
<td>10,281</td>
<td>5.82 (4.14, 7.49)</td>
</tr>
<tr>
<td>Black</td>
<td>418</td>
<td>17</td>
<td>3,454</td>
<td>6.40 (3.36, 9.43)</td>
</tr>
<tr>
<td>Other</td>
<td>159</td>
<td>5</td>
<td>1,430</td>
<td>4.55 (0.57, 8.52)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>330</td>
<td>12</td>
<td>2,851</td>
<td>5.47 (2.38, 8.56)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>1,406</td>
<td>56</td>
<td>12,314</td>
<td>5.91 (4.37, 7.46)</td>
</tr>
</tbody>
</table>

\(^1\) One subject in the primary efficacy dataset does not have BMI information. Source: FDA Analysis

Generally, FDA does not support subgroup analyses when the primary analysis result does not demonstrate efficacy. There are multiple reasons to not consider subgroup analyses to support establishing efficacy when treatment benefit in the overall population is not significant (FDA 1998; FDA 2017b). The major statistical reason is inflation of type I error, that is, the heightened probability of incorrectly concluding treatment benefit. When such subgroup analyses are used to search for evidence of benefit, there is a high probability that any observed favorable subgroup results are due to chance alone. Therefore, FDA considers such analyses hypothesis-generating. However, FDA considered these subgroup analyses presented in Table 4 as informative. Some of the findings from the subgroup analyses included:

- Subgroup analysis was conducted using a weight subgroup of <202 pounds (92 kg) vs. ≥202 pounds (92 kg). This analysis was performed to evaluate the basis of the Applicant’s proposal of a limitation of use in the label for women “who weigh 202 lbs. (92 kg) or more and/or have a BMI of 30 kg/m\(^2\)”. It is unclear why the Applicant chose the cutoff of 202 pounds (92 kg) for these analyses.
- Other exploratory subgroup analyses did not demonstrate that AG200-15 had a favorable treatment effect, including in four large subgroups with over 5,000 evaluable cycles (BMI <30 kg/m\(^2\), weight <92 kg, White, and Not Hispanic or Latino).
Supportive Analysis using Life Table Method

The life table method efficacy results based on the primary efficacy population are shown in Table 5.

### Table 5. Supportive Efficacy Analysis (Age ≤35 years) Based on Life Table Method (Study 23)

| Population          | N     | # On-Treatment Pregnancies | # Evaluable Cycles | Cumulative Probability of Pregnancy²%
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1,736</td>
<td>68</td>
<td>15,165</td>
<td>5.48 (4.32, 6.04)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>1,123</td>
<td>33</td>
<td>9,888</td>
<td>4.08 (2.89, 5.74)</td>
</tr>
<tr>
<td>≥30</td>
<td>612</td>
<td>35</td>
<td>5,264</td>
<td>8.08 (5.82, 11.17)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;92</td>
<td>1,402</td>
<td>46</td>
<td>12,276</td>
<td>4.51 (3.37, 6.02)</td>
</tr>
<tr>
<td>≥92</td>
<td>334</td>
<td>22</td>
<td>2,889</td>
<td>9.52 (6.30, 14.26)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1,159</td>
<td>46</td>
<td>10,281</td>
<td>5.36 (4.02, 7.14)</td>
</tr>
<tr>
<td>Black</td>
<td>418</td>
<td>17</td>
<td>3,454</td>
<td>6.24 (3.85, 10.02)</td>
</tr>
<tr>
<td>Other</td>
<td>159</td>
<td>5</td>
<td>1,430</td>
<td>4.65 (1.91, 11.07)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>330</td>
<td>12</td>
<td>2,851</td>
<td>5.77 (3.27, 10.07)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>1,406</td>
<td>56</td>
<td>12,314</td>
<td>5.42 (4.17, 7.03)</td>
</tr>
</tbody>
</table>

¹ One subject in the primary efficacy dataset does not have BMI information.
² The cumulative estimates of pregnancy rates estimated by life table analysis were multiplied by 100; therefore, the probability of pregnancy is per 100 women.
Source: FDA Analysis

Discussion

In the October 10, 2013 meeting minutes, prior to the conduct of Study 23, the FDA communicated to the Applicant the following criteria regarding acceptability of the PI:

“The Division has never approved a combination hormonal contraceptive product for which the upper bound of the 95% confidence interval (CI) around the Pearl Index exceeds 5. The Division does not foresee a path by which it could agree that a Pearl Index in the range identified in the data provided to date for the patch would be considered proof of efficacy sufficient to inform a favorable risk-benefit assessment. Given the known serious adverse reactions associated with the use of combination hormonal contraceptives, the Division believes that a high level of efficacy in preventing pregnancy must be demonstrated in order to justify the risks.”

With this in mind, Study 23 was designed to demonstrate a PI no larger than 3.5 with an upper bound of the corresponding two-sided 95% CI not exceeding 5. In addition, the 10,000 cycles of exposure required by FDA is usually adequate to rule out an upper bound (95% CI) of 5 to evaluate a PI of 3.5 or less in a clinical trial. The overall PI and the upper bound of the 95% CI from Study 23 for AG200-15 did not meet FDA’s previously communicated criteria. AG200-15 in Study 23 reported a PI of 5.83 with an upper 95% CI bound of 7.21.
The Applicant has previously stated that Study 23 is a “real world study” and that this accounts for the high PI. We do not agree with this description. Real-world studies focus on data that come from routine health care interactions, as captured in electronic health records or claims databases, and patient populations that are seen for routine clinical care with few exclusions. In contrast, Study 23 had extensive enrollment criteria with patients excluded whom the investigator deemed might have poorer compliance with study procedures. Subjects who did not demonstrate ≥90% compliance during the run-in period were also excluded. Compliance was assessed at every study visit and this would not regularly occur in the post-marketing setting. In addition, the number of investigational site visits and telephone contacts is commensurate with other similar phase 3 studies. Therefore, we do not agree that Study 23 meets the description of a “real-world study”; rather it is a typical phase 3 study of a CHC.

The Applicant also states that the design (e.g., more thorough testing for pregnancy), population (e.g., more obese and ethnically/racially diverse) and analysis (e.g., exclusion of cycles where backup contraception was used) of their phase 3 trial differs from that of other recently completed CHC trials, and that their PI results more accurately reflect effectiveness whereas the lack of these features in older trials artificially lowered the PIs for those products.

While we agree that the design of contraceptive trials has been changing over time to better reflect the real-world use of these products, we note that all CHCs that have been approved, including recently approved CHC products, have an upper CI bound of the overall PI ≤5.0. We do not find support for marked differences between this study and other recently conducted hormonal contraceptive studies, nor is there convincing evidence that the higher PI seen in this study can be attributed to these factors. For example, the PI among Whites was 5.8 (95% CI 4.1, 7.5), which is clinically similar to the PI among Blacks of 6.4 (95% CI 3.4, 9.4) and to the PI among Hispanics/Latinos of 5.5 (95% CI 2.4, 8.6). In addition, even women who were not obese had an unacceptable PI. For example, the PI in overweight women (BMI ≥25 kg/m² to <30 kg/m²) was 5.7 (95% CI 3.0, 8.4). Therefore, the FDA does not believe that the trial differences noted by the Applicant clearly explain the suboptimal effectiveness results.

The Applicant states that AG200-15 is more effective in non-obese (i.e., BMI <30 kg/m² and/or body weight <202 pounds) women and proposes a Limitation of Use (LOU) for women who are obese. However, the PI in the non-obese subgroup was 4.34 (95% CI: 2.86, 5.82) and the PI among overweight women was 5.7 (95% CI 3.0, 8.4), i.e., the upper bound of the PI still exceeds 5 and the point estimate is above 3.5. Therefore, even if AG200-15 is limited to the non-obese population, the effectiveness data from Study 23 demonstrates an unacceptable PI based on the upper bound of the 95% CI exceeding 5.

Further discussion on the benefit-risk and limitation of use can be found in Section V of this document.
V. Safety

The safety data of AG200-15 was based on the safety population that was defined as all subjects who wore at least one TDS for any period of time during the clinical trial. As there were concerns about data collection and quality in Studies 12 and 13, the data from Study 23 was the focus of FDA’s safety analysis. Of the 2,031 subjects that were enrolled in Study 23, there were 989 subjects (49%) that completed thirteen 28-day cycles of treatment. The overall safety database includes 29,900 cycles from Studies 12, 13 and 23.

A total of 222 subjects (11%) in Study 23 discontinued due to adverse events.

Common adverse events (>2%) in Study 23 included nasopharyngitis, upper respiratory tract infection, headache, urinary tract infection, sinusitis, dysmenorrhea and increased weight.

Laboratory and vital signs data were collected during Study 23. Subjects were noted to have slight elevations in lipids and fasting glucose. No Hy’s Law cases were identified to suggest drug-related liver dysfunction/injury. There were some subjects who demonstrated clinically significant increases in blood pressures (defined as systolic ≥140 mm Hg and an increase of ≥20 mm Hg from baseline, or diastolic ≥90 mm Hg and an increase of ≥15 mm Hg from baseline). Based on the laboratory and vital sign changes, no new safety signals were identified. All the findings were consistent with trends well described in class labeling for CHCs.

A total of 40 serious adverse events (SAEs) were identified in Study 23 and are summarized in Table 6. As mentioned in the Regulatory History of this document, there were some discrepancies in the reporting of SAEs for Studies 12 and 13. For this reason, we are only considering the SAEs in Study 23. Table 6 shows treatment-emergent SAEs, which the Applicant defines as all SAEs with an onset date on or after the first TDS application through Day 28 of the subject’s final treatment cycle, regardless of whether the investigator attributed the SAE to use of the drug.

### Table 6. Treatment-Emergent SAEs of Special Interest – Safety Population for Study 23

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Cycles (N=2,031)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Colitis</td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td></td>
<td>Gastric fistula</td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis necrotizing</td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Cholecystitis</td>
<td>2 (0.10%)</td>
</tr>
<tr>
<td></td>
<td>Cholecystitis acute</td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td></td>
<td>Cholecystitis chronic</td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td></td>
<td>Cholelithiasis</td>
<td>4 (0.20%)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis</td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td>Pregnancy, puerperium, and perinatal conditions</td>
<td>Ectopic pregnancy</td>
<td>2 (0.10%)</td>
</tr>
<tr>
<td></td>
<td>Ruptured ectopic pregnancy</td>
<td>1 (0.05%)</td>
</tr>
</tbody>
</table>
Levonorgestrel and ethinyl estradiol transdermal system

### (Study 23) Cycles

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>All Cycles (N=2,031)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>6 (0.30%)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td></td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td>Major depression</td>
<td></td>
<td>3 (0.15%)</td>
</tr>
<tr>
<td>Substance abuse</td>
<td></td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td></td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td>Suicide attempt**</td>
<td></td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>4 (0.20%)</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td></td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td>Pulmonary embolism (PE)</td>
<td></td>
<td>3 (0.15%)</td>
</tr>
<tr>
<td>Vascular disorders**</td>
<td></td>
<td>3 (0.15%)</td>
</tr>
</tbody>
</table>

* Source: Adapted from NDA 204017, Module 5.3.5.3 Safety Update, Table 4.3.1 Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term
** See below for specific information on subjects with VTE.

All other serious adverse events reported for Study 23 did not demonstrate a new safety signal or trend that would indicate a different CHC profile from that addressed in class labeling.

### Venous Thromboembolism

VTE is an important adverse event associated with CHCs. Given the potential lethality associated with VTEs, the FDA focused on the incidence rate of these drug-related adverse events. For Study 23, the following VTEs were considered to calculate the incidence rate:

- **Subject 1**: A 25-year-old, White, non-Hispanic female with a BMI of 31.8 kg/m² and a weight of 92 kg was diagnosed with a pulmonary embolism (PE) after almost 5 months on treatment with AG200-15 while enrolled in Study 23.

- **Subject 2**: A 26-year-old, White, non-Hispanic female, former smoker, with a BMI of 34.3 kg/m² and weight of 92 kg was diagnosed with a PE of the left lower lobe after 4 months on AG200-15 while enrolled in Study 23.

- **Subject 3**: A 35-year-old White, non-Hispanic female with a BMI of 37.1 kg/m² and weight of 93 kg was diagnosed with a deep vein thrombosis (DVT) in the right leg and bilateral PE after almost 4 months on treatment with AG200-15 while enrolled in Study 23.

- **Subject 4**: A 33-year-old, Black, non-Hispanic female with a BMI of 36.3 kg/m² and a weight of 93 kg was diagnosed with an acute left DVT approximately 11 months on treatment with AG200-15 while enrolled in Study 23.

FDA is not counting a DVT that occurred in an obese subject (Subject 5) who was enrolled in Study 23 in the calculation of the final on-treatment VTE rate because it was considered unrelated to the study drug (pancreatitis and status post pancreatectomy). Therefore, four subjects had VTE considered probably-related to the study drug and all had BMIs >30
kg/m². Based on the number of safety cycles in Study 23 (18,841) the incidence rate of drug-related VTEs (4) based solely on Study 23 is approximately 28/10,000 women-years.

The Applicant concludes that the incidence rate of VTEs reported from a pooled analysis of safety data from Studies 12, 13 and 23 of 22 per 10,000 women years is generally in line with incidence rates between 15 and 19 per 10,000 woman-years for a population of women with similar mean BMI and age as recently described by Rabe and colleagues (Rabe et al. 2011). FDA does not agree with the Applicant’s pooling of VTE data from all three studies given the issues of the trial conduct and data quality of Study 12 and 13 referenced in Section II. Regulatory History of this document.

There is an inherent increased risk of VTEs in women using CHCs as compared to those who use non-hormonal contraceptives. The incidence rate of VTE in non-users of combined oral contraceptives (COCs)/combined hormonal contraceptives (CHCs) is estimated to be between 1 and 5 events per 10,000 woman-years, and 3 to 9 per 10,000 woman-years among COC/CHC users (Bayer HealthCare Pharmaceuticals Inc 2015). Although, most of the studies have used COCs, the currently available transdermal combined hormonal product (Xulane) may be associated with a higher risk for VTE compared to oral tablets (Tepper et al. 2017).

It is important to note that the incidence rates of VTEs from controlled clinical trials should not be compared to VTE incidence rates obtained from population-based observational studies. Besides differences in study populations and other study characteristics such as more intensive monitoring of adverse events in trials; missingness of some baseline risk factors in observational studies), clinical trials are typically not sufficiently sized to evaluate these rare safety events.

Based on the above considerations, the FDA is not reassured by the Applicant’s assertion that the VTE incidence rates reported in their clinical trials for AG200-15 are comparable to rates reported with other CHCs from postmarketing observational studies. The FDA does not agree that it is possible to directly apply information from the post-marketing setting for VTEs to what was identified in the clinical trial safety database.

The Applicant states that AG200-15 is a “low dose” combined hormonal contraceptive product. As discussed in Section III of this briefing document, AG200-15 has a similar EE exposure to that of Ortho-Cyclen, a product containing 35 mcg EE. In addition, AG200-15 exhibits between-cycle increases in EE exposure that may result in a different VTE risk.

The Applicant also claims that AG200-15 is safe because it contains levonorgestrel (LNG), a progestin that has been reported to have a lower VTE risk when compared to specific other progestin types in COC/CHCs. FDA is aware that VTE risk may vary by dose of estrogen and potentially by type of progestin in COC/CHC use (Oedingen et al. 2018). There is a large number of epidemiologic studies examining the risk of VTE associated with use of CHCs containing newer generation (third or fourth) progestins, compared to LNG-containing products (a second-generation progestin). These epidemiologic studies evaluated whether newer progestins, such as drospirenone (DRSP)-containing CHCs, are associated with a higher VTE risk than LNG-containing CHCs. The observational study results are inconsistent, with some studies reporting up to a three-fold increase in VTE risk while other studies reported no
differences in VTE risk between products. The crude incident VTE rate for LNG-containing CHCs with 30 to 40 mcg EE reported by these studies ranged from 0.9 to 7.2 per 10,000 women years for idiopathic VTEs\(^1\) and 1.6 to 10.9 per 10,000 women years for fatal and non-fatal VTEs. There is significant heterogeneity in these published studies and we conclude the slight increased risk in VTE observed by progestin types could be explained in part by study design issues and uncontrolled biases. A summary of the limitations of these studies include:

- **New users vs. Prior user designs:** Current evidence suggests that prevalent users (women with prior history of CHC use) may be at a lower baseline risk for VTE than new or first-time naïve users as prevalent users are deemed to be survivors (free of VTE risk). Recent studies also show that VTE risk is highest in the first three months of CHC use, with the risk decreasing after the first three months. Many studies compared current users of CHCs containing third generation progestins to LNG-containing products without considering their prior CHC use, which could over-estimate the true relative risk for VTE.

- **Residual confounding:** Measurement of and control for potential confounders varied across studies and may result in different risk estimates. Although most studies adjusted for age, many studies failed to measure and control for other established risk factors for VTE, such as BMI, personal or family history of VTE, and smoking. Lack of adjustment for these important variables could likely bias the observed estimate in either direction.

- **Selective prescribing or channeling bias:** There is evidence suggesting that physicians prescribed third-generation CHCs as their first-choice formulation to women with obesity, family history of VTE, and pre-existing arrhythmia as these progestins were considered safer when they were first approved for use. This practice of selective prescribing may result in channeling higher risk women to CHCs containing newer generation progestins and over-estimate the true relative risk for VTE associated with these products. Furthermore, publication of various observational study results may change the way that susceptible patients are channeled from newer products (initially believed to be safer) to older products (later reported to be safer). Drug utilization prescription data showed that in 2009, CHCs containing drospirenone were the second most commonly dispensed CHCs from U.S. retail pharmacies but their prescription has since decreased. By 2018, most prescriptions were dispensed in the U.S. for CHCs containing the progestins norethindrone, norgestimate, LNG, followed by drospirenone (see Figure 1 in the Appendix). Therefore, timing of channeling bias may also vary by the publications of different study results.

- **Misclassification of exposure:** Methods for ascertaining CHC exposure also varied across studies. In studies where patients were asked to recall contraceptive use history, exposure data such as type, dose, and duration of use may be self-reported but possibly reported inaccurately. In studies where prescription data were used to capture contraceptive exposure, prior contraceptive use may not be captured in the databases. In addition, these databases only provide information on prescriptions filled and not necessarily medication taken. Possible misclassification of CHC exposure could bias the observed risk estimate in either direction.

\(^1\) Idiopathic VTE are unprovoked venous thromboembolism occurring in the absence of any apparent provoking or triggering personal or environmental risk factors, such as cancer, pregnancy, surgery, trauma, and immobilization.
Misclassification of outcome: Type of VTE captured and definition of VTE varied across studies. Many studies limited evaluation to idiopathic VTE or non-fatal VTE. Fatal VTE cases are not always captured leading to underestimation of VTE cases. Although hospitalized VTE has been validated with hospital medical records when identified in U.S. claims data, some women diagnosed with only DVT are treated as outpatients in the U.S. and algorithms in the outpatient setting are not easily validated. Outcome misclassification could also bias the observed estimate in either direction.

Based on these considerations, we do not believe that LNG-containing products are safer than other CHCs containing newer generation progestins. Other risk factors (such as age, BMI, family history, smoking, and genetic factors), rather than progestin type alone, also need to be considered in advising women on which CHC would be optimal for use. Of these factors, the Applicant has attributed their VTE incidence rates reported in their clinical trials to high BMI.

In terms of BMI, epidemiologic studies show that, among normal-weight women (BMI < 25 kg/m²), CHC use appears to be associated with 3 to 4-fold increased risk of VTE compared to non-use (Abdollahi et al. 2003; Pomp et al. 2007)(Sidney et al. 2004). Overweight (BMI between 25 and 29 kg/m²) and obesity (BMI of 30 kg/m² or higher) are known risk factors for cardiovascular and VTE events. Many studies reported that the VTE risk with CHC use was substantially higher among overweight and obese women than among women with normal BMI (Horton et al. 2016).

In Study 23, all four subjects (as described above) with VTEs that were deemed probably drug-related had a BMI > 30 kg/m². However, given the small number of VTEs observed and the challenges with cross-study comparisons, there remains considerable uncertainty about the magnitude of VTE risk with AG200-15 and how that risk could compare to other CHC products.

In summary, there are reports of VTE in the clinical database for AG200-15 and it is not possible to conclude based on the limited existing data that the VTE profile of AG200-15 is safer than that of other CHCs.

Cycle Control

For Studies 23, the Applicant evaluated AG200-15’s ability to provide cycle control using eDiary data that collected unscheduled and scheduled vaginal bleeding and spotting. Unscheduled vaginal bleeding and spotting is an important consideration because lack of predictable bleeding can range from being bothersome to resulting in product discontinuation or suboptimal compliance.

Women were asked to record any vaginal bleeding episode once daily in their eDiaries. The Applicant defined the following bleeding parameters:

- **Bleeding**: Evidence of blood loss on any cycle that requires the use of a sanitary protection with at least one tampon or sanitary pad
- **Spotting**: Evidence of minimal blood loss on any cycle that requires the use of a pantyliner only or no sanitary pad
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- Episode: One or more consecutive days of bleeding and/or spotting bounded on either end by use of the TDS and \( \geq 2 \) days of no bleeding or spotting.

The Applicant further classified vaginal bleeding and spotting as either scheduled and unscheduled using the following definitions:

- Scheduled: Any bleeding or spotting that occurred when the woman is not wearing the TDS
- Unscheduled: Any bleeding or spotting that occurred when the woman was wearing the TDS

### Table 7. Summary of Incidence of Unscheduled Bleeding or Spotting Episodes for Study 23 Resubmission (Study 23)

<table>
<thead>
<tr>
<th>Cycle Number</th>
<th>All Cycles (N=2,017)</th>
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<tbody>
<tr>
<td>Cycle 1</td>
<td>1217/2014 (60%)</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>954/1875 (51%)</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>807/1745 (46%)</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>718/1627 (44%)</td>
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<tr>
<td>Cycle 5</td>
<td>678/1519 (45%)</td>
</tr>
<tr>
<td>Cycle 6</td>
<td>614/1428 (43%)</td>
</tr>
<tr>
<td>Cycle 7</td>
<td>562/1351 (42%)</td>
</tr>
<tr>
<td>Cycle 8</td>
<td>569/1277 (45%)</td>
</tr>
<tr>
<td>Cycle 9</td>
<td>524/1213 (43%)</td>
</tr>
<tr>
<td>Cycle 10</td>
<td>495/1143 (43%)</td>
</tr>
<tr>
<td>Cycle 11</td>
<td>473/1103 (43%)</td>
</tr>
<tr>
<td>Cycle 12</td>
<td>463/1065 (44%)</td>
</tr>
<tr>
<td>Cycle 13</td>
<td>423/1024 (41%)</td>
</tr>
</tbody>
</table>

Note: The number of subjects in Table 7 is based on the cycle control, not safety, population. These are subjects in the Contraceptive Efficacy Population [subjects who wore at least one TDS and were documented to have a negative enrollment serum \( \beta \)-hCG] who provided information on bleeding and TDS application.

The key results from the eDiary data regarding unscheduled vaginal bleeding/spotting from Study 23 are provided in Table 7. Unscheduled bleeding/spotting ranged from 60% of women in cycle 1 to 41% of women in cycle 13 (the final treatment cycle). It is unclear whether the vaginal bleeding and spotting rates reflect improved tolerability over time or whether these changes reflect subjects who prematurely discontinued AG200-15 or dropped out of the trial. The Applicant concludes in their proposed labeling that “for cycle 3-13, the majority of subjects did not report any unscheduled bleeding/spotting.” The FDA disagrees and has concerns that the rate of unscheduled vaginal bleeding and spotting may impact tolerability and compliance in real-world use.
VI. Applicant’s Labeling Proposal of a Limitation of Use

The Applicant is proposing the following Limitations of Use (LOU) to be included in the INDICATIONS AND USAGE section of labeling:

1. INDICATIONS AND USAGE
AG200-15 is indicated for use by females of reproductive potential to prevent pregnancy.

Limitations of Use:

AG200-15 has demonstrated reduced effectiveness in women who weigh 202 pounds (92 kg) or more and/or have a BMI of 30 kg/m² or more [see Use in Specific Populations (8.9) and Clinical Studies (14)].

The FDA has the following concerns with this approach:

- A LOU is included in the INDICATIONS AND USAGE section of labeling when there is reasonable concern or uncertainty about a drug’s benefit-risk profile. A LOU is generally based on some evidence suggesting that drug use in a population would be unsafe and/or ineffective. Usually, a LOU statement is included in labeling when data in a sub-population (i.e., pediatric population) are insufficient to warrant a definitive statement. In the case of AG200-15, the data are clear that the product’s effectiveness in women with BMI $\geq 30$ kg/m² is unacceptable. In situations where the risks outweigh the benefit (e.g., severe hypersensitivity reactions), the labeling would include, at a minimum, a contraindication. A contraindication in the CONTRAINDICATIONS section is a situation “in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit.”

- The Applicant’s labeling proposal of a LOU based on the efficacy data from AG200-15 does not address the FDA’s fundamental concerns about the high overall PI and upper bound of the 95% CI from Study 23, nor does it address the high PI in overweight women (BMI $\geq 25$ kg/m² to <30 kg/m²) of 5.7 (95% CI 3.0, 8.4) or the high PI among other races/ethnicities (Blacks, Hispanics). We do not believe the data are sufficient to conclude that the effectiveness demonstrated for AG200-15 is solely a reflection of the population recruited. Therefore, we remain concerned that the effectiveness demonstrated for this product is suboptimal in light of its risks and in the context of available therapy.

- The statistical analysis plan did not include a planned subgroup analysis by baseline weight less than 202 pounds (92 kg). It is unclear what methodology the Applicant used to add the additional criterion of 202 pounds (92 kg).

- The FDA acknowledges that a previously approved transdermal system (Ortho Evra) and its generic, Xulane, have a limitation of use that states, “ORTHO EVRA may be less effective in preventing pregnancy in women at or above 198 lbs. (90 kg).” This LOU was
based on a finding in less than 3% of the trial population. The limited data from the Ortho Evra registration trials conducted almost 20 years ago resulted in the use of the word “may” as opposed to more definitive phrasing. In contrast, the AG200-15 PI in obese subjects is based on more robust data and is more definitive in this regard. The FDA believes that the pre-planned analysis from Study 23 is clinically meaningful and would translate to potentially limiting or restricting use of AG200-15 in roughly a third of women.
VII. FDA Benefit/ Risk Considerations

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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| Analysis of Condition | • Unintended pregnancy affects millions of women in the United States each year with significant public health consequences including adverse maternal and child health outcomes as well as social and economic costs at the family and state level.  
• In 2011, nearly one-half (45% or 2.8 million) of the 6.1 million pregnancies in the U.S. were unintended (Guttmacher Institute 2019).  
• Women at risk for unintended pregnancy who use contraceptives consistently and correctly throughout the course of any given year account for only 5% of all unintended pregnancies. The 32% of women who use contraceptives inconsistently or incorrectly, who have gaps of >1 month or who do not practice contraception at all account for 95% of all unintended pregnancies (Guttmacher Institute 2018). | • Unintended pregnancy is a significant public health problem in the U.S. About 95% of unintended pregnancies occur in women who use contraceptives inconsistently or incorrectly or women who do not use contraception at all during the year.  
• Safe and effective contraception is crucial to women’s health and as many safe and effective options as possible should be made available, including those that are more convenient to use. |
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<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tr>
<td>Current Treatment Options</td>
<td>- A wide range of hormonal contraceptive products are currently available in the U.S., including oral tablets, intravaginal rings, implants, a transdermal system, and depot injections. &lt;br&gt;- COCs require women to take a pill daily for most days each month, which may be cumbersome for some patients. Implants, injectables, and IUSs and IUDs are administered less frequently than COCs but are invasive, require healthcare professional administration and may not be readily accessible to some women. Intravaginal ring insertion is invasive and may be cumbersome for some women. &lt;br&gt;- Venous thromboembolism (VTE) is one of the most important adverse events associated with CHCs. The other marketed transdermal CHC, Xulane, carries a Boxed Warning for a possible increased risk of VTE compared to women who use certain oral contraceptives. &lt;br&gt;- Progestin-only products may also be associated with side effects that can limit their use (e.g., irregular vaginal bleeding and spotting). The addition of an estrogen component in a CHCs can improve cycle control.</td>
<td>- Another transdermal system, if effective and safe, could provide an additional non-invasive option for women who do not want to use the other dosage forms of CHCs. We expect the convenience to be similar to that of the approved transdermal system, which is also applied once weekly for three weeks of the month. &lt;br&gt;- AG200-15 does not meet the FDA’s regulatory definition of an unmet need given there are other currently marketed CHC options available for women to use, including another transdermal system.</td>
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<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tr>
<td>Benefit</td>
<td>AG200-15 is a new transdermal contraceptive delivery system containing EE and LNG. AG200-15 is applied to the skin once weekly for 3 weeks of the month. This is less frequently administered than some of the other available contraceptives but must be maintained on the skin for a week at a time. AG200-15 reduces the risk of pregnancy compared to women not using contraception but the effectiveness is suboptimal for a CHC product in the context of available therapy in the U.S. In Study 23, the estimated overall PI, the standard measure of contraceptive failure was 5.83 (95% CI 4.45-7.21). This means the estimated pregnancy rate among women using AG200-15 was 5.83 per 100 women-years with a corresponding 95% CI interval upper bound of 7.21 pregnancies per 100 women-years. There are no FDA-approved CHC products with a PI 95% CI upper bound above 5. A subgroup analysis of non-obese women (BMI &lt;30 kg/m²) showed a PI of 4.34 (95% CI 2.86, 5.82). For overweight women (BMI ≥25 kg/m² to &lt;30 kg/m²) the PI was 5.7 (95% CI 3.0, 8.4). For obese women (BMI ≥30 kg/m²), the PI was 8.64 (95% CI 5.79, 11.50). A subgroup analysis of Black/African American subjects showed a PI of 6.40 (95% CI 3.36, 9.43). The PI among Hispanics/Latinos is 5.5 (95% CI 2.4, 8.6).</td>
<td>AG200-15 is administered less frequently than some of the approved contraceptive products but must remain on the skin for a week at a time. Based on the pharmacokinetics of AG200-15, it is not a low-dose estrogen-containing CHC. Also, the pharmacokinetic profile is not the same as that of an oral CHC product. Study 23 was designed to demonstrate a PI no larger than 3.5 with an upper bound of the corresponding two-sided 95% CI not exceeding 5. The Study failed to achieve this objective. The PI and the upper bound of the 95% CI for AG200-15 for the overall study population is concerning in the context of available therapies, which have upper bounds of the 95% CI for the PI ≤5. Almost 30% of women in the U.S. population ages 18-44 years are considered obese (BMI ≥30 kg/m²) (Vahraitian 2009). The estimated upper bound of the PI 95% CI of 11.5 in the subgroup of women with a BMI ≥30 kg/m² is very concerning. If the intended population were limited to the subgroup of non-obese women, the PI still has an unacceptable upper bound &gt;5. An exploratory analysis of Black/African American and Hispanic subjects is also concerning and raises further questions about the effectiveness of the product.</td>
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### Risk and Risk Management

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<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tr>
<td>One of the most significant safety concerns associated with CHC use is VTE, which can be life-threatening. In Study 23, four women experienced 5 drug-related VTEs. Contraceptive trials cannot reliably estimate the incidence of VTE that will occur in the postmarketing setting because these trials are substantially underpowered to evaluate these rare events and typically few events are reported, yielding unstable estimates. There remains considerable uncertainty about the magnitude of VTE risk with AG200-15 and how that risk compares to other CHC products. AG200-15 had a rate of unscheduled vaginal bleeding or spotting in 423 of 1,024 (41%) of women after a year on treatment. For Study 23, the common adverse events and laboratory findings did not identify any new safety signals or trends compared to other available CHC therapies.</td>
<td>The VTE incidence rates reported in clinical trials 23, 12 or 13 cannot inform the magnitude of risk of VTE with AG200-15 in the post-marketing setting. It is not possible to conclude that AG200-15 demonstrates improved safety compared to other CHC products in terms of VTEs using available clinical trial safety data. The VTE safety signal is based on 4 subjects with 5 VTEs in a clinical trial database. Even accounting for the fact that these women were considered obese, the rate does not assure similar risk to epidemiologic studies of oral CHCs. Unscheduled vaginal bleeding was reported in approximately 40% of women after 13 cycles of treatment in Study 23. This suboptimal bleeding profile from the eDiary data raises concerns regarding patient tolerability and compliance with real-world use.</td>
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### Conclusions Regarding the Benefits and Risks

- Unintended pregnancy is a significant public health problem in the U.S. While another transdermal CHC could provide an additional alternative for women seeking a non-invasive method of contraception, AG200-15 does not meet FDA’s regulatory definition of an unmet need.
- Given the significant impact of unintended pregnancy on a woman’s health, it is critical to ensure contraceptives are effective and have an acceptable benefit/risk profile.
- While AG200-15 reduces the risk of pregnancy as compared to women who do not use contraception, the effectiveness of AG200-15 raises concerns as the FDA has never approved a combined hormonal contraceptive with the upper bound 95% confidence interval for etonogestrel and estradiol.
CI of the PI above 5. An upper bound of 5 corresponds to 5 pregnancies per 100 women-years; whereas the upper bound of 7.21 seen for the overall PI with AG200-15 corresponds to more than 7 pregnancies per 100 women-years.

- The Applicant attributes the higher PI to the design (e.g., more thorough testing for pregnancy), population (e.g., more obese and ethnically/racially diverse) and analysis (e.g., exclusion of cycles where backup contraception was used) of their phase 3 trial, and states that their PI results more accurately reflect effectiveness whereas the lack of these features in older trials artificially lowered the PIs for those products. However, we do not find support for marked differences between this study and other recently conducted hormonal contraceptive studies, nor is there convincing evidence that the higher PI seen in this study can be attributed to these factors. For example, the PI among Whites was 5.8 (95% CI 4.1, 7.5), which is clinically similar to the PI among Blacks of 6.4 (95% CI 3.4, 9.4) and to the PI among Hispanics/Latinos of 5.5 (95% CI 2.4, 8.6). In addition, even women who were not obese had a high PI. For example, the PI in overweight women (BMI ≥25 kg/m² to <30 kg/m²) was 5.7 (95% CI 3.0, 8.4). Therefore, the FDA does not believe that the trial differences noted by the Applicant clearly explain the suboptimal effectiveness results.

- Based on the limitations of the available safety data on VTE risk, it is not possible to conclude that AG200-15 is a safer CHC product compared to available therapies. It is also not possible to infer the VTE risk of AG200-15 through extrapolation using safety profiles of oral CHC products containing similar amounts of EE and LNG.

- AG200-15 also has a clinically concerning rate of unscheduled vaginal bleeding, which raises concerns about tolerability and compliance with real world-use.

- While the convenience of a non-invasive combined hormonal transdermal system with a weekly dosing regimen may be attractive to some women, in the context of highly effective available CHC therapies, we conclude that the suboptimal effectiveness of AG200-15 does not outweigh its risks, which we anticipate will be comparable to the risks of other CHCs.

<table>
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<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tbody>
<tr>
<td>CI</td>
<td>5 pregnancies per 100 women-years</td>
<td>7.21 pregnancies per 100 women-years</td>
</tr>
<tr>
<td>Design</td>
<td>More thorough testing for pregnancy, more obese and ethnically/racially diverse, exclusion of cycles where backup contraception was used</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Whites 5.8 (95% CI 4.1, 7.5), Blacks 6.4 (95% CI 3.4, 9.4), Hispanics/Latinos 5.5 (95% CI 2.4, 8.6)</td>
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<tr>
<td>Analysis</td>
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<td>Safety</td>
<td>VTE risk not comparable</td>
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<td>CHCs</td>
<td>Suboptimal effectiveness</td>
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<td>Compliance</td>
<td>Concerns about tolerability and compliance</td>
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<tr>
<td>Risks</td>
<td>Anticipated to be comparable</td>
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VIII. Appendix: Hormonal Contraceptive Drug Utilization Review

The Division of Epidemiology II (DEPI II) summarized utilization data on hormonal contraceptives from 2006 through 2018 to provide context and background for the Advisory Committee discussion.

Annual sales of hormonal contraceptives (excluding intrauterine systems, or IUSs) appear relatively stable since 2006. An estimated 150 million packages (pill packs, vial/syringes, implants, or boxes) of hormonal contraceptives were sold in 2018. Combined hormonal contraceptives (CHCs) — which include combined oral contraceptives (COCs), the vaginal ring, and the transdermal system (Ortho Evra® and its generic) — comprised the largest proportion of sales or dispensed prescriptions compared to progestin-only contraceptives for the entire review period.

Products containing norethindrone or norgestimate were the most commonly dispensed CHCs from U.S. retail pharmacies in 2018 followed by levonorgestrel-containing COCs. Use of norethindrone- and norgestimate-containing COCs increased each year since 2010. In contrast, drospirenone-containing COCs and the transdermal system had the largest decreases in utilization for the review period. In 2018, the transdermal system accounted for approximately 2% of sales or dispensed prescriptions for CHC products.

An estimated 12.7 million patients filled a dispensed prescription for CHCs from U.S. retail pharmacies in 2018. Most patients were aged 25-34 years (36%), followed by patients aged 17-24 years (35%), 35 years or older (25%), and patients aged 16 years or younger (5%).2 The transdermal system accounted for 3.5% of use among patients aged 16 years or younger, and 3% or less among patients aged 17 years or older. Norgestimate had the highest proportion of use (40%) among patients aged 16 years or younger, while norethindrone had the highest proportion of use (37%) among patients 35 years and older. The proportion of patients with a dispensed prescription of COC products containing levonorgestrel, drospirenone, desogestrel, and other COCs (norgestrel, ethynodiol, and dienogest) was comparable across age groups.

Combined oral contraceptives remain the most widely used CHC products in women of reproductive age in the retail setting nationwide. Current use of the transdermal system is low, and prescription estimates fell steadily since 2006. An evaluation of trends of prescription use of the different CHCs is useful for reference purposes

Figure 1 below shows the timeline trend for different CHCs in the U.S.

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2 Prescription data is based on a calendar year. Some patients age into the next age group during that year, and therefore these patients are counted twice for that year. Patient-level data percentages like these will often add to slightly over 100%.
**Figure 1. Estimated Prescriptions of Combined Hormonal Contraceptives in the United States, 2006-2018**

*Of note, there was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology; therefore, the dotted line represents a trend break and any changes over time must be interpreted in the context of the changes in methodology. In 2017, an estimated 8% of total prescription claims for combined hormonal contraceptives dispensed from U.S. retail pharmacies appeared to have been voided or reversed.*

**Abbreviations:**
COC = Combined Oral Contraceptive. EE = ethinyl estradiol. NORE = norethindrone/EE or mestranol. NGM = norgestimate/EE. LNG = levonorgestrel/EE. DRSP = drospirenone/EE. DESO = desogestrel/EE. Other COCs = norgestrel, ethynodiol, and Dienogest/EE products. RING =etonogestrel/EE. TRANS-DERM. SYS. = transdermal system—norgestrel/etonogestrel/EE.

IX. References


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Tepper, NK, MV Dragoman, ME Gaffield, and KM Curtis, 2017, Nonoral combined hormonal contraceptives and thromboembolism: a systematic review, Contraception, 95(2):130-139.