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APPLICATION NUMBER:

204017Orig1s000

CLINICAL REVIEW(S)

MEMORANDUM TO FILE

Application Type	505(b)2 NDA
Application Number(s)	204017
Priority or Standard	Standard
Submit Date(s)	May 16,2019
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PDUFA Goal Date	November 16, 2019
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Division / Office	Division of Bone, Reproductive, and Urologic Products (DBRUP)/Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Nneka N. McNeal-Jackson, M.D.
Review Completion Date	February 14, 2020
Established Name	Ethinyl Estradiol and Levonorgestrel
(Proposed) Trade Name	Twirla
Therapeutic Class	Hormonal Contraceptive
Applicant	Agile Therapeutics, Inc.
Formulation(s)	Transdermal patch (transdermal contraceptive delivery system)
Dosing Regimen	One patch placed every seven days for three consecutive weeks

	followed by one week “patch-free” period
Indication(s)	Prevention of Pregnancy
Intended Population(s)	Women of reproductive age

Template Version: March 6, 2009

1.1 Recommendation on Regulatory Action

From a clinical perspective, this clinical reviewer recommends that AG200-15, the to-be-marketed transdermal contraceptive system (TDS) containing 2.6 mg levonorgestrel (LNG) and 2.3 mg ethinyl estradiol (EE) for the prevention of pregnancy in women of reproductive age, receive another Complete Response Letter (CRL). This clinical reviewer recommends that the Applicant conduct another clinical trial in the intended population to establish efficacy and safety of the AG200-15.

1.2 Risk Benefit Assessment

This clinical reviewer regards the benefit risk for the AG200-15 TDS to be unfavorable for the following reasons:

Efficacy Concerns: No new contraceptive efficacy data was included in this submission. The Division's determination on the acceptability of the Applicant's efficacy data is based on Study 23. This reviewer is concerned that Study 23 may have been enriched for compliance by including a 2-week run-in period that assessed for compliance with the eDiary. There were 625 subjects categorized as screen failures based on this compliance testing. Despite the possible enrichment of the Applicant's population, the overall Pearl Index is still higher than anything the Division has been approved and that the reduction of effectiveness could be even greater in a "real world" setting. Efficacy concerns have been conveyed to the Applicant numerous times regarding the expectations of the upper bound of the 95% confidence interval (UB95%CI) around the point estimate for the Pearl Index (PI) balanced by safety in October 2013 End of Review Meeting minutes. These concerns regarding efficacy were clearly communicated to the Applicant prior to the initiation of Study 23, after the review of Study 23 data, and during the Formal Dispute Resolution in the OND October 4, 2018 Denial Letter. This clinical reviewer's perspective has not changed given there was no new contraceptive efficacy data to consider.

Safety Concerns: The totality of the safety data includes two poorly conducted trials (Studies 12 and 13) that may have insufficiently captured adverse events and poor subject follow-up. Venous thromboembolic events (VTEs) is of special interest to the Division regarding the safety of combined hormonal contraceptives (CHCs). In Study 12, one VTE was detected in one normal weight subject with no obvious VTE risk factors. The concerns remains if more VTEs went undetected that may have better informed to the safety profile of this product. Study 23 had five VTEs, four of which occurred in relation to treatment. All four of these subjects had BMI ≥ 30 kg/m². The VTE incidence determination in Study 23 was 28/10,000 woman-years. This incidence is higher than any contraceptive registration trial in support of approval. The clinical reviewer prefers more safety information prior to its approval.

Adhesion Concerns: This clinical reviewer continues to have concerns regarding the adhesive property of this AG200-15. The Phase 3 trials provided the best evidence of how the product would perform in the actual use setting. The reader is referred to my prior clinical review dated December 21, 2017. This clinical reviewer is not convinced that an AG200-15 performance under the restrictive conditions outlined in the Phase 1 trials negates the concerns of how the product will perform in a real-world setting use free of those restrictions. During Study 23, 10-20% of subjects required four or more TDS per cycle. During this review cycle, the Clinical Pharmacology review dated February 4, 2020, suggests "that frequent reapplication of TDS could result in higher ethinyl estradiol exposure." Ideally, the adhesion quality of the product

should be optimized prior to approval. Given the link between estrogen levels and VTEs, the adhesion quality potential affect on safety remains a concern to this reviewer.

Unfavorable benefit risk: Based on aforementioned factors regarding reduced efficacy, VTE incidence, and adhesion concerns, the benefit risk is unfavorable. While this clinical reviewer agrees that AG200-15 could provide a more convenient option for women that desire a non-invasive, non-daily contraceptive, this clinical reviewer want to ensure that it demonstrates comparable effectiveness for the Applicant's intended population. While the Division encourages innovation to provide more contraceptive options to the public, a standard must be maintained to ensure that women relying on these options are achieving the ultimate goal of prevention of pregnancy well balanced by safety. The benefit risk for AG200-15 does not appear to support that objective.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarketing risk evaluation or mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

The Division is issuing a postmarketing requirement (PMR) to assess the risks of cardiovascular adverse events such as venous thromboembolism events (VTE) and arterial thromboembolism (ATE) by comparing new users of TWIRLA to new users of oral CHCs (primary comparator) to new users of Xulane (secondary comparator) in women from the United States of reproductive age using CHC primarily for contraception. The study should be designed to detect a 1.5 to 2-fold increased risk for VTEs in new users of TWIRLA and adequately measure for possible confounders such as age, BMI, and smoking status. The design of the study should be a prospective, controlled, non-interventional, observational cohort.

The Division is also issuing a postmarketing commitment (PMC) to accurately assess the residual drug and strength of TWIRLA by evaluating TWIRLA worn by 25 women subjects to analyze the EE and LNG content after the prescribed wear and TDS adhesion over time.

A more detailed review will follow in as a separate submission.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NNEKA N MCNEAL-JACKSON
02/14/2020 12:31:58 PM

GERALD D WILLETT
02/14/2020 12:35:43 PM

I do not concur with the primary reviewer. See the CDTL review dated 2/14/2020

Cross-Discipline Team Leader Review

Date	December 20, 2017
From	Catherine Sewell, MD, MPH
Through	Audrey Gassman, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	204017/SN38/SDN 40
Applicant	Agile Therapeutics, Inc.
Date of Submission	June 26, 2017
PDUFA Goal Date	December 26, 2017
Proprietary Name	Twirla
Established or Proper Name	levonorgestrel and ethinyl estradiol
Dosage Form(s)	Transdermal contraceptive delivery system (patch)
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy Women of reproductive age
Applicant Proposed Dosing Regimen(s)	LNG120/EE30 mcg/day, apply every 7 days for three weeks each cycle, with one patch-free week each cycle
Recommendation on Regulatory Action	Complete Response

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1 Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

AG200-15 is a new transdermal contraceptive delivery system (TCDS) containing the commonly used steroid hormones ethinyl estradiol (EE, 2.3 mg) and levonorgestrel (LNG, 2.6 mg). The doses are comparable to oral combined hormonal contraceptives (CHCs) which deliver 30 mcg/day EE and 120 mcg/day LNG over a period of seven days. The proposed dose regimen follows a 28-day cycle consisting of once-weekly applications of a 7-day patch for three weeks, followed by a one-week patch-free interval. Proposed application sites are the abdomen, buttock and upper torso.

I recommend a **COMPLETE RESPONSE** for AG200-15. There exist significant deficiencies in product quality, including patch adhesion and manufacturing concerns. The facility is not ready for commercial manufacturing. Further, the Applicant failed to demonstrate adequate efficacy and did not demonstrate a low enough risk profile to justify the reduced efficacy.

Unintended pregnancy is a significant public health problem in the US. In 2011, nearly half of all pregnancies in the US were unplanned.¹ 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 unplanned pregnancies.² Therefore, contraception is crucial to women's health. Development of contraceptives with lower doses, more convenient dosing schedules, optimized efficacy and improved safety is a priority. There are many contraceptive options available, but few with convenient dosing regimens. A low-dose TCDS with a weekly application schedule adds to the armamentarium for prevention of pregnancy. Long-acting reversible contraceptives include progestin-only injections, implants and intrauterine systems. While the dosing regimens are convenient and the methods highly effective, they carry the side effects of irregular bleeding. The addition of an estrogen component can improve cycle control. Currently there are multiple formulations of CHCs available, most of them being oral. There are only two non-invasive CHCs with convenient formulations and dosing regimens available. One is an intravaginal ring which is placed intravaginally for three weeks and removed for one week each cycle. There is one transdermal contraceptive delivery system [Xulane, generic of OrthoEvra® approved on April 16, 2014, under abbreviated new drug application (ANDA) 200910]. OrthoEvra® was withdrawn from market for commercial reasons (not for safety or efficacy). The Xulane patch is applied weekly for three weeks, with one patch-free week each cycle. As noted in the updated labeling for Ortho Evra® approved August 22, 2012, data from some epidemiologic studies suggested an increased risk of VTE with the use of Ortho Evra® compared to use of some oral CHCs. The relative risk estimates range from 1.2 to 2.2. None of the studies adjusted for potential confounders such as body mass index (BMI), smoking or family history of VTE. So the interpretations of these relative risk estimates range from no increase in risk to an approximate doubling of risk. There is a need for a convenient transdermal contraceptive comparable in safety and efficacy to low-dose oral CHCs.

The phase 3 studies for AG200-15 failed to demonstrate adequate efficacy in either review cycle, despite improvements in study conduct and data collection and reporting in the second review cycle. Pearl Indices in the first review cycle were 7.50 (95% CI 5.02, 9.97) and 8.19 (0.19, 16.19). In the second review cycle, the phase 3 trial showed a PI of 5.83 (95% CI 4.45-7.21). These calculations include additional FDA-identified on-treatment pregnancies that were not counted by the Applicant in their pregnancy rate calculations. In the second review cycle, in Study ATI-CL23, 75% of these additional pregnancies occurred in obese women. If the most recent efficacy analysis is restricted to women with a BMI<30, the PI is still high at 4.34 (2.86, 5.82). 67% of the additional pregnancies occurred in women who had delays in applying the next patch of >10 days. While a significant number of the FDA-adjudicated pregnancies occurred in women who had delays in applying patches, this reflects real-world, worst-case scenario contraceptive use. Therefore, PIs including these pregnancies more likely reflect the actual pregnancy rates in the postmarket setting. These Pearl Indices remain higher than those for any other approved contraceptives, as do the upper bound of the 95% confidence intervals (the Agency has never approved a contraceptive with the upper bound above 5). Though the Agency does not consider comparative efficacy in evaluating contraceptives, it is not clear that the reduced efficacy justifies the risks of AG200-15, which are similar to all CHCs. If the intended population were limited to non-obese women, the PI is still elevated above the level for any previously approved contraceptive.

The degree of cycle control, as measured by the rate of unscheduled bleeding or spotting is no better than other approved CHCs. In the first review cycle, studies demonstrated that 22% of women still had unscheduled bleeding or spotting after a year on AG200-15. 41.3% of women in Study 23 in the second review cycle still had unscheduled bleeding or spotting after a year on treatment.

As noted, the risks of AG200-15 are comparable to those of marketed CHCs. The rate of VTE is 3.18/10,000 woman-years, which is well within the range of 3-12/10,000 woman-years for approved CHCs. The rates of common adverse events, hepatobiliary disorders and mood disorders are on par with other hormonal contraceptives. Changes in vital signs and laboratory values revealed no new safety signals. Application site disorders (irritation, rash, dermatitis, discoloration, etc.), which are unique to transdermal systems and attributable to the adhesive, are lower than those reported in trials for other hormonal patches. It is unclear whether the reason for the lower rate of application site disorders is related to not having investigators perform standard methodology to monitor patch adhesion/sensitization and irritation. These unscheduled bleeding and risks are not offset by robust efficacy or even equivalent to marketed CHCs, even with a BMI restriction.

Equally important are significant deficiencies in patch adhesion. Adhesion data collected in Study ATI-CL23 demonstrated that over 11% of TCDS did not meet the Agency standard for adhesion during the seven-day patch wear period. 5% of all patches detached completely. 54.4% of patients experienced complete patch detachment at some point with 24.8% of subjects having complete TCDS detachment in the first cycle of use. 14.7% of patients required more than 4 patches per cycle during the most recent trial. If AG200-15 does not adhere, this could reduce patient compliance and increase the risk of unintended pregnancy. Further, procuring replacement patches places undue burden on women, their healthcare providers and insurers to cover the extra cost of additional supplies. Additional manufacturing concerns remain. The applicant has not established an adequate specification with respect to the adhesion or tack methods and acceptance criteria. A pre-approval inspection was performed of Corium International Inc., the contract drug product manufacturer. The facility was found not ready for commercial manufacturing in part due to inadequate in-process and finished product tests for tack and adhesion. On December 13, 2017, the OPF Division of Inspectional Assessment (DIA) review team entered a Withhold Approval recommendation. In summary, the demonstrated benefit of a more convenient dosing schedule has not been offset by the reduced efficacy of this product coupled with a comparable VTE risk to CHCs, a higher risk of unscheduled bleeding and a significant wearability issue related to adhesion. In fact, these Issues may actually be more pronounced in the real-world setting.

Due to concerns regarding adhesion of AG200-15 in Study ATI-CL23, the Applicant should assess whether the unacceptable in vivo adhesion properties are

the result of the current design and formulation of the drug product, or are due to some other factor(s). If the unacceptable adhesion is due to the design and formulation of the drug product, the Applicant should design a new TCDS and conduct another clinical trial with this product in the US population. The Applicant should also address all the other manufacturing deficiencies before addressing if there are any subpopulations for which the AG200-15 could be an appropriate product and demonstrate acceptable efficacy in that subgroup.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2011, nearly half (45% or 2.8 million) of the 6.1 million pregnancies in the US each year were unintended¹ • 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.¹	Contraception is crucial to women's health and as many options should be made available as possible. Development of contraceptives with lower doses, more convenient dosing schedules, optimized efficacy and improved safety is a priority. A low-dose TCDS with a weekly application schedule would add to the armamentarium for of available contraceptive products.
Current Treatment Options	• Many types of contraceptives are on the US market • Only one transdermal contraceptive delivery system (TCDS) is currently available (Xulane, generic of OrthoEvra®) • OrthoEvra® was withdrawn from market for commercial reasons (not for safety or efficacy) • Other marketed formulations for combined hormonal contraceptives include: oral, intravaginal ring	While there are many contraceptive options available, there are few with convenient dosing regimens. There are progestin-only injections, implants and intrauterine systems. These are associated with irregular bleeding. The addition of an estrogen component can improve cycle control. There are only two combined hormonal contraceptives (CHCs) available with convenient dosing regimens. The ring is placed intravaginally for three weeks and removed for one week each cycle. The Xulane patch is applied weekly for three weeks, with one patch-free week each cycle. There are no TCDS which are comparable to low-dose oral CHCs. The availability of a low-dose TCDS could provide a safe and effective method of

¹ <https://www.guttmacher.org/fact-sheet/unintended-pregnancy-united-states>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		contraception with convenient dosing intervals.
Benefit	• The drug substances (ethinyl estradiol and levonorgestrel) are well characterized and the information is adequate to support approval. • Convenience of dosing regimen: one patch every 7 days • First pass metabolism is eliminated increasing the amount of parent drug(s) available systemically to produce a therapeutic response • Pharmacokinetic data shows the product is comparable to a low-dose oral CHC • Adequate efficacy was not demonstrated in either review cycle. Study ATI-CL12 had a Pearl Index (PI) of 7.50 (95% CI 5.02, 9.97), Study ATI-CL13 had a PI of 8.19 (0.19, 16.19) and Study ATI-CL23 had a PI of 5.83 (95% CI 4.45-7.21). • Twelve (12) additional on-treatment pregnancies were identified in Study ATI-CL23 that were not counted by the Applicant in their original pregnancy rate calculations. 75% of these additional pregnancies occurred in obese women. If the efficacy analysis is restricted to women with a BMI<30, the PI is 4.34 (2.86, 5.82). 67% of the additional pregnancies occurred in women who had delays in applying the next patch of >10 days.	A low-dose TCDS with convenient dosing intervals could provide a safe and effective method of contraception. However, the Applicant failed to demonstrate adequate efficacy for AG200-15. The Pearl Indices are higher than those for any other approved contraceptive, as is the upper bound of the 95% confidence intervals (the Agency has never approved a contraceptive with the upper bound above 5). If the intended population were limited by the Applicant to non-obese women, the PI is still elevated above the level for any previously approved contraceptive. While a significant number of the FDA-adjudicated pregnancies occurred in women who had delays in applying patches, this reflects real-world, worst-case scenario contraceptive use. Therefore, an overall PI including all pregnancies more likely reflects the actual pregnancy rates in the postmarket setting and is not acceptable.
Risk and Risk Management	• Unscheduled bleeding: In the first review cycle, studies demonstrated that 22% of women still had unscheduled bleeding or spotting after a year on AG200-15. In this review cycle, 41.3% of women in Study ATI-CL23 had unscheduled bleeding or spotting after a year on treatment. This rate is higher than other approved CHCs. • There were no deaths among the women that used AG200-15 during the clinical development program. • The rate of VTE is 3.18/10,000 woman-years, which is well within the range	1. Unscheduled bleeding and spotting are known to occur with hormonal contraceptives. This occurs more commonly with progestin-only methods. The benefit of added estrogen mitigates this concern. AG200-15 has more unscheduled bleeding than some other CHCs, is concerning from a clinical perspective as it may lead to discontinuation of the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of 3-12/10,000 woman-years for approved CHCs. • The rates of hepatobiliary disorders and mood disorders are on par with other hormonal contraceptives. • Changes in vital signs and laboratory values revealed no new safety signals. • Application site disorders (irritation, rash, dermatitis, discoloration, etc.) occurred in 5.6% of study subjects in Study 23 in the second cycle, and led to discontinuation in 3.9% of subjects. This was comparable to the rates in the first review cycle. These cases were almost all attributed to the adhesive. The rates of application site disorders are lower than that reported in trials for other hormonal patches. • Adhesion issues: ○ The mean patch adhesion score (on a scale of 0—complete attachment, to 4—complete detachment) was 0.52 across all patches applied during cycles 1-13 and the mean worst score reported was 2.76. ○ 11.3% of all patches had less than 75% of the product surface area adhering during the seven-day wear period. This does not meet the Agency standard for patches which is that mean adherence of greater than 90% should be expected and no instances of detachment should be seen. ○ 24.8% of patients had complete patch detachment in Cycle 1; this decreased to 6.1% in Cycle 13. ○ 54.4% of subjects recorded at least one complete patch detachment (i.e. a score of 4) at some point in the study. ○ In 14.7% of 18,841 cycles, four or more patches were applied; some patients used up to nine individual TCDS in one cycle. ○ Specification with respect to the adhesion or tack methods and acceptance criteria are inadequate. ○ Pre-approval inspection was performed of Corium International Inc., the contract drug product manufacturer was conducted this cycle. The facility was found not ready for commercial manufacturing in part due to inadequate in-process and finished	method and subsequent pregnancy. 2. Patch adhesion is a significant clinical concern: • Over 11% of patches did not meet the Agency standard for adhesion during the seven-day patch wear period. • More than half of patients experienced complete patch detachment at some point. • 14.7% of patients required more than 4 patches per cycle during the most recent trial. • 10-20% of all users will require four or more TDS per cycle. If AG200-15 does not adequately adhere or multiple patches will be needed to complete a treatment cycle, this could significantly increase the risk of unintended pregnancy. Further, procuring replacement patches places undue burden on women, their healthcare providers and insurers to cover the extra cost of additional supplies. 3. Manufacturing of the patch remains a significant concern. Specifically, the adhesion or tack methods and acceptance criteria and the manufacturer has not demonstrated that it is ready for commercial manufacturing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	product tests for tack and adhesion. On December 13, 2017, the OPF Division of Inspectional Assessment (DIA) review team entered a Withhold Approval recommendation.	

2 Background

This application seeks approval for a new transdermal contraceptive delivery system (TCDS, alternatively described as a “patch” in this review), AG200-15, containing the commonly used steroid hormones ethinyl estradiol (EE) and levonorgestrel (LNG). The proposed dose regimen follows a 28-day cycle consisting of once-weekly applications of a 7-day patch for three weeks, followed by a one-week patch-free interval. Proposed application sites are the abdomen, buttock and upper torso.

There is currently only one TCDS marketed, Xulane, a generic equivalent of the discontinued Ortho Evra®, which delivers 0.035 mg EE and 0.15 mg norelgestromin per day, although there are multiple combined hormonal contraceptives (CHCs) containing EE and LNG on the market. The Applicant argues that AG200-15 is a “low dose” patch, as distinct from Xulane or Ortho Evra®. The TCDS contains 2.6 mg LNG (b) (4) and 2.3 mg EE (b) (4) and the Applicant maintains it is comparable to oral CHCs which deliver 30 mcg/day EE and 120 mcg/day LNG over a period of seven days.

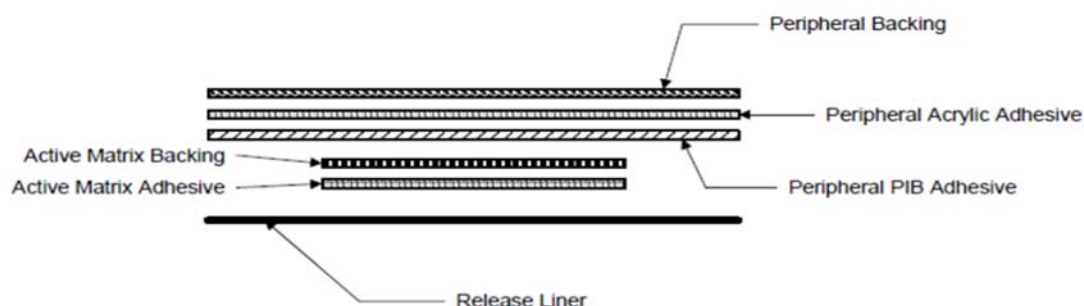
Because there are currently several EE/LNG combined hormonal contraceptives marketed in different formulations, LNG and EE are well-characterized progestin and estrogen products. These products reduce the risk of pregnancy mainly via the effect of the progestin on suppressing ovulation, changing cervical mucus such that it inhibits sperm motility and changing the endometrium in ways which may inhibit implantation. The estrogen component may make some contribution to the contraceptive action, and maintains cycle control.

2.1 Product Information

The proposed TCDS comprises a 15 cm² active acrylic adhesive matrix containing LNG, EE and skin permeation enhancers integrated into a larger (28 cm²) peripheral adhesive system. This larger adhesive system has bidirectional elasticity which the Applicant states is necessary to improve adhesion.

A cross-section of the TCDS is shown in Figure 1.

Figure 1 Diagram of AG200-15



Source: NDA 204017, Module 3.2.P.1 Description on Drug Product and Composition of the Drug Product

2.2 Regulatory History

The Applicant opened IND 57731 in 1999 to conduct their development program. On September 22, 2008, a Type B meeting (End of Phase 2) was held and the following issues were discussed:

- The Division agreed that no additional preclinical safety studies were needed, but requested additional information on chronic dermal safety and mutagenicity of capric acid, one of the excipients in the patch.
- The Division recommended additional pharmacokinetic (PK) studies:
 - o A relative bioavailability (BA) study comparing the AG200-15 to an oral contraceptive
 - o A study to assess the impact of different application sites on the PK of the TCDS. The study should include sufficient subjects to allow evaluation of site-specific safety and efficacy should the PK vary by application site.

- o A study assessing PK under different external conditions such as sauna, exercise, cold, etc.
 - o The Sponsor was encouraged to target the EE exposure toward that of a lower-dose combined oral CHC.
- The Division requested two phase 3 studies, one of 13 cycles duration, to provide 10,000 cycles of exposure with at least 200 women completing 13 cycles of use, and the other, to include an oral CHC comparator (30 µg EE/150 µg LNG). Details for the phase 3 trials discussed were:
 - o The definition of an on-treatment pregnancy and FDA adjudication of pregnancies
 - o Removal of any restrictions on BMI inclusion criteria--the Applicant proposed enrolling women of unrestricted BMI only in the CHC-comparator study which the Division found potentially acceptable provided there were at least 200 subjects per arm
 - o The need for formal dermal safety and cold flow studies

On June 22, 2009, The Applicant submitted a request for a Special Protocol Assessment (SPA) of the 13-cycle, 1,200 subject phase 3 Study ATI-CL12 (hereafter referred to as Study 12), which was also proposed to contain a low-dose oral CHC comparator (Levlite®, 20 µg EE/100 µg LNG). This was a six-month two-arm design with oral CHC users crossed-over to patch use in Month 7 for the remainder of the study. The SPA received a No Agreement letter on August 7, 2009, based on the following issues:

- Division disagreement with exclusion criteria related to body mass index ($\text{BMI} \geq 32$) and smoking (women under age 35 who smoked 10 or more cigarettes/day)
- Recommendation for the standard definition of evaluable cycles for Pearl Index calculation, which excludes 28-day cycles in which backup or emergency contraception was used or in which no sexual intercourse occurred
- Need for clearer definitions and quantification of bleeding and spotting
- Need for a more detailed plan for pregnancy follow-up
- Request for return to fertility data in a subset of women who discontinued with the intent to become pregnant

Another SPA was requested on November 24, 2009, for the six-month, 400 subject phase 3 Study ATI-CL13 (hereafter referred to as Study 13). The Applicant proposed use of a different oral CHC comparator (30 µg EE/150 µg LNG) in this study. A No Agreement letter was issued on January 7, 2010 based on the following:

- Nonconcurrency with the proposed exclusion of women with $\text{BMI} \geq 32$ and women under age 35 who smoked 10 or more cigarettes/day. The Division strongly recommended inclusion of women with $\text{BMI} \geq 32$ in at least one of the phase 3 studies; while the efficacy population could include only women below a specified BMI in the efficacy population, the safety and secondary evaluations of efficacy should be provided in all subjects.

- Nonconcurrency with the study objectives which were to characterize comparative safety, tolerability and PK of the two drug products; efficacy data would be collected but not compared statistically. The Division recommended that the trial should be considered supportive for efficacy and that Pearl Index and life table pregnancy rate estimates and 95% confidence intervals should be calculated.
- Revised bleeding and spotting definitions were recommended
- A standardized adherence scale was recommended to assess patch wearability

A Type A meeting was held on March 9, 2010 to discuss revisions made to the Study 12 protocol. At this time:

- It was agreed that there were no outstanding issues regarding the dermal safety of capric acid. The Division and the Applicant agreed that subjects should record instances of irritation and pruritis in the daily eDiary and that investigators should evaluate for skin irritation at all visits.
- The Division recommended against any upper limit on BMI and recommended that at least 170 women with BMI ≥ 35 should be enrolled in the patch arm of Study 13; the Applicant could exclude these women from the primary efficacy population, but efficacy in the extreme obese subgroup might be addressed in labeling. The Applicant was willing only to enroll women with BMI ≤ 32 and was asked to provide justification of BMI exclusions before submitting another SPA for Study 13.
- The Division had the following additional comments on Study 12 and the overall program:
 - o The sample size may need to be increased to assure 10,000 cycles of exposure
 - o The Applicant was asked to specify the proportion of enrollees who would be new users of hormonal contraception and might be at higher risk of venous thromboembolic events (VTEs) and other AEs than those who switched from another method. There should be an adequate number of cycles are from naïve users.
 - o The Division indicated it would consider the bleeding profile at all cycles; the Applicant agreed to this
 - o The Applicant was advised that comparative claims about drug levels or exposure with AG200-15 and oral CHCs would not likely be accepted in labeling
 - o Discussion about transdermal patch development standards

On April 21, 2010, the Applicant again requested a SPA of the revised protocol for Study 13, which continued to exclude women with BMI > 32 . While the Division sent an Agreement letter on June 3, 2010, the Division continued to recommend that women with BMI above 32 be included in at least one of the phase 3 studies. The Applicant was advised to collect daily eDiary information on bleeding with clear definitions of spotting, light, normal and heavy bleeding, and to follow previous recommendations in characterizing the bleeding profile.

Another SPA was submitted for Study 12 on June 21, 2010, and the Division provided an Agreement letter on July 13, 2010. This protocol proposed enrollment of about 500 women with a BMI ≥ 30 , but restricted the efficacy and safety subsets to women with BMI < 32 . The protocol proposed to enroll about 20% “new users” of hormonal contraception, defined as never-users or women who had not used hormonal contraception in the past six months.

The Applicant requested a pre-NDA meeting in 2011, but requested cancellation of the meeting after receipt of the Division’s preliminary comments on October 20, 2011. In those comments, the Division addressed:

- Questions about the 505(b)(2) pathway
- Requirement to submit narratives and case report forms (CRFs) for all pregnancies, and all pregnancy follow-up forms
- Request to collect information on venous thromboembolism in the phase 3 database

On April 13, 2012, the Applicant submitted the NDA 204017 and multiple amendments to the NDA dated April 19, June 1, July 10, 16, 18, August 3, 10, 15, 16, 31, October 17, 19, 31, November 29, December 4 and 12 of 2012; January 11, 16, 17, 18, and 29 of 2013.

On February 13, 2013, the Division issued a Complete Response Letter (CRL) citing the following key issues:

- Failure to establish drug efficacy. The Pearl Indices for the two pivotal trials were higher than any other approved combined hormonal contraceptive with similar risks. The Applicant provided no evidence that the product had a better safety profile than other CHCs that could justify acceptance of the higher PIs. The Division noted poor compliance, early discontinuations and loss to follow-up. The Division also had concerns about poor data quality, and the need for more rigorous study conduct, data collection, data cleaning and report preparation. The Applicant needed better information on pregnancy outcomes, dating of all suspected pregnancies and the timing of conception with respect to drug use and information on follow-up of SAEs. The Division advised the Applicant to conduct another pivotal trial.
- Numerous deficiencies regarding drug product quality.

On June 24, 2013, the Applicant sent in an NDA resubmission in an attempt to address all the issues outlined in the CRL.

On July 17, 2013, the Division issued Applicant an Incomplete Response Letter (ICRL) for the NDA resubmission reemphasizing the need to conduct an additional clinical trial to establish efficacy and to provide adequate responses to the product quality deficiencies.

On August 7, 2013, the Applicant requested a meeting to discuss whether the Division could reach agreement that the PIs for Studies 12 and 13 provided satisfactory proof of efficacy. The Division granted the meeting and provided preliminary

written responses to the Applicant's questions, reiterating that the Division has never approved a CHC for which the upper bound of the 95% CI around the PI exceeded 5 and that these PIs could not serve as sufficient proof of efficacy to offset the known safety risks associated with CHC use. In the October 10, 2013, face-to-face meeting, the Division re-iterated the need for improvements in study conduct with close communication with FDA during the course of the trial if any problems arose.

On January 10, 2014, in accordance with the July 17, 2013 ICRL, the Applicant requested a meeting to discuss the protocol for the new clinical trial. A Type C guidance meeting was scheduled for February 11, 2014 but the Applicant cancelled the meeting after receiving the February 7, 2014 preliminary comments containing recommendations on trial design, site selection, pregnancy adjudication and outcome measures for bleeding profiles and patch adherence—specifically on patient diary scoring and general information on clinical adhesion.

On June 7, 2014, the Applicant submitted the new clinical protocol ATI-CL23 (hereafter referred to as Study 23). This was a single-arm, open-label, multicenter, phase 3 trial to assess the 12-month contraceptive efficacy and safety of the AG200-15 TCDS. Key clinical comments and recommendations conveyed to the Applicant were as follows:

- Concerns that the Applicant's proposed strategies to minimize loss to follow up and poor compliance could result in contact fatigue and undermine the assessment of real-world use of the drug product
- Recommendation to not discourage patch exposure to water and to capture that information in daily eDiary
- Recommendations to capture and date pregnancies as accurately as possible, including home pregnancy testing and first trimester ultrasound
- Recommendations for subject selection criteria, including allowing females under the age of 18 years.
- Recommendations to include women who are 35 years of age at enrollment and turn 36 during the trial as part of the primary efficacy cohort and to also calculate efficacy for all women greater than 35 years of age
- Recommendation to record episodes where no bleeding occurs

Key CMC comments included:

- Advice on the Applicant's proposed plan for in vivo assessment of patch adhesion with patient-collected data in an electronic diary (eDiary), including:
 - o Definitions of the measurements in the patch adhesion scale
 - o Expectations that:
 - Mean adherence should be greater than 90% and there should be no instances of detachment seen.
 - The need to investigate events of poor adherence with elucidation of possible causes and risk factors.

- o Instructions that subjects should use the transdermal system as proposed and that they should not be permitted to use product reinforcement, such as taping the edges or use of overlays, nor should they occlude the product from water during bathing during the in vivo adhesion evaluation.
- o Reference to additional information regarding the design of in vivo adhesion studies

On October 10, 2014, the Applicant requested a meeting to discuss the CMC deficiencies identified in the February 2013 CRL. And Type C meetings were granted on December 15, 2014 and August 31, 2016. The Applicant requested cancellation of both meetings upon receipt of preliminary comments.

On December 16, 2016, the Applicant requested a Pre-NDA meeting to discuss the appropriateness of the NDA resubmission. The Type B meeting occurred on March 14, 2017. Key recommendations and comments provided to the Applicant were as follows:

- Not to pool safety and efficacy data from the previous performed phase 3 studies with Study 23 because of significant concerns about study conduct and data quality from the 2013 review cycle.
- To evaluate the potential effect of obesity on the effectiveness of the transdermal system subgroup analyses should be performed by body weight, median weight, and body weight quartiles. These analyses may have implications for labeling
- Additional clinical pharmacology and CMC topics were discussed along with the proposed content and format for the resubmission

On June 26, 2017, the Applicant submitted the Class 2 Resubmission – Complete Response to the Agency’s February 13, 2013 CRL.

On September 8, 2017, as part of the Class 2 resubmission, the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed proprietary name, Twirla, from a safety and misbranding perspective. On September 11, 2017, DMEPA sent the Applicant a Propriety Name Request Conditionally Acceptable letter deeming Twirla an acceptable proprietary name pending NDA approval.

3 Product Quality

Per the combined Office of Pharmaceutical Quality (OPQ) review by Mark Seggel, PhD, the CMC Technical Lead, dated December 13, 2017, a complete response is recommended for this application. “In its present form, Agile Therapeutics’

resubmission of 505(b)(2) New Drug Application #204017 for Twirla (levonorgestrel and ethinyl estradiol) Transdermal System is not ready for approval. While the applicant has addressed the product quality-related deficiencies noted in the February 13, 2013 Complete Response Letter, significant deficiencies with overall product quality have been identified. There is a significant problem with in vivo adhesion, which is likely to adversely impact the safe and efficacious use of the product. Tests for ensuring acceptable quality, and in particular tack and adhesion, of drug product intermediates and the finished drug products are inadequate.

During a recent inspection of the Corium International Inc. drug product manufacturing facility (FEI 3003693015) an FDA field investigator conveyed deficiencies to the representative of the facility. It has been determined that the Corium facility was not ready for the commercial manufacture of the drug product.”

Dr. Seggel does note in his summary review that adequate drug substance and biopharmaceutics information was provided.

3.1 Drug Substances

LNG and EE are well characterized and have long been used in the formulation of CHCs. The Drug Master Files (DMFs) document the chemistry, manufacturing and controls for LNG and EE; the DMFs were reviewed and found adequate. The information provided on both drug substances was adequate to support approval of the NDA.

3.2 Drug Product

During the 2013 review cycle, Per Dr. Seggel, several deficiencies in the chemistry, manufacturing and controls information were identified including “inadequate (b) (4) acceptable laser etching, inadequate finished product specification (tests and/or acceptance criteria for cold flow, shear, functional excipient (i.e., permeation enhancers) assays), incomplete characterization of impurities (b) (4), and insufficient information to support manufacturing equipment changes (b) (4) from the clinical trial batch process to commercial scale.” Per Dr. Seggel, OPQ expected that the product would be redesigned or reformulated; however, this was not done. The current drug product review dated November 15, 2017 by Dr. Strasinger describes the response by Agile Therapeutics, Inc. (hereafter referred to as “the Applicant”) regarding the product quality issues identified in the 2013 CRL. However, the CMC review found that the analysis of in vivo adhesion indicates inadequate performance (Refer to Section 3.3 for additional details). Further, based on information in the NDA submission and on an October 2017 inspection of the

Corium International drug product manufacturing site in Michigan, the finished drug product specification is inadequate with respect to ensuring adequate product adhesion (part tack and part adhesion tests). The proposed finished product specification lacks a validated test and appropriate acceptance criteria for part tack.

In summary, the CMC review team determined that the Applicant's data do not provide assurance that the finished drug product will consistently have the requisite quality (i.e., in vivo adhesion). On December 1, 2017, the Applicant did submit a response to an information request addressing the tack and adhesion methods, and stated they would submit the remainder of the information (method qualification reports) by December 15, 2017. The CMC team determined that a thorough review of this amendment could not be completed during this 6-month review cycle.

3.3 In vivo adhesion

Per the Quality in vivo Assessment Review by Caroline Strasinger, PhD, dated November 15, 2017, typical in vivo assessments of a transdermal system are conducted as part of the pharmacokinetic study or as an independent study, and performed in a clinical setting with regular observations of adhesion by a trained professional. Patient diaries provide supportive information on adhesivity and use of the product. As noted in Section 2.2, Regulatory History, on February 7, 2014 the Applicant received Preliminary Meeting Comments on patient diary scoring and general information on clinical adhesion as shown below. Upon receipt of this information the Applicant cancelled the meeting. After review of the June 7, 2014 submission of a proposed protocol for Study ATI-CL23 (hereafter referred to as Study 23), the following information was provided again:

- A mean adherence of greater than 90% should be expected and no instances of detachment should be seen.
- Poor adherence events should be investigated and possible causes and risk factors determined.
- The transdermal system should be used as proposed and product reinforcement, such as taping the edges or use of overlays, or occluding the product from water during bathing should not be permitted during the in vivo adhesion evaluation.

The Applicant was also referred to the European Medicines Agency Draft Guideline on the Quality of Transdermal Patches for additional information regarding the design of in vivo adhesion studies.

Per Dr. Strasinger's review, although the Applicant was not specifically instructed by FDA to conduct a formal adhesion study the Applicant had access to this information from publically available FDA bioequivalence draft guidances for transdermal systems describing formal adhesion studies, including the June 2016 draft guidance "Assessing Adhesion

with Transdermal Delivery Systems and Topical Patches for ANDAs,”. The Applicant also has access to industry-wide knowledge about the development of such TCPS formulations.

The Applicant did provide patient diary information on patch adhesion and a summary of investigator-reported adhesion data for evaluation of adhesion. In this study of patch adhesion, important information provided to subjects included:

- Recording of patch adhesion daily in the eDiary excluding the patch-free week, using this simplified scale:
 - 0: No lifting or small amount of lifting at the edges of the patch
 - 1: More than a small amount of lifting at the edges up to one-quarter of the patch lifting off
 - 2: More than one quarter of the patch lifting off up to half of the patch lifting off
 - 3: More than half of the patch is lifting off, but the patch is still on
 - 4: Patch has completely come off
- Instructions for managing patches that detach and details for different durations of detachment. Subjects were provided a reserve patch to use if needed due to detachment.

Team Leader comment:

I am concerned that patients manage patch issues with a reserve patch. If marketed, patches would be distributed with three patches per cycle. I do not see that the Applicant plans to address patch falloff by providing additional reserve patches.

The Applicant reported patch adhesion scores using summary statistics and tabulated the scores using frequency distributions. Per Dr. Strasinger’s review “The summaries were presented by patch application site, by treatment cycle and for all patches and all cycles combined. Poor patch adhesion in individual subjects, if observed, was investigated for potential risk factors and causes. A Patch Detachment Log summarizing the circumstances around patch detachment was completed by site personnel for reported patch detachment events (per eDiary data); and narratives were written for subjects who discontinue due to patch detachment.”

Dr. Strasinger found the study design adequate to allow for analysis of adhesive information on patches during clinical use but identified the following key issues:

- The Study relied solely on individual self-assessment – this resulted in over 2000 different evaluators (patients)

- The Study protocol did not specifying a precise time of day to make the adhesion assessment, nor did it specify when to record the adhesion assessment in cases of detachment (i.e. when a patch is detaching or after it is replaced due to complete detachment).
- 22% of all values had to be imputed due to missing data

3.3.1 Results of in vivo adhesion study

The in vivo study conducted during Study 23 yielded data on 2022 women and 18,841 cycles of wear.

Table 1 shows the subject reported patch adhesion scores overall.

Table 1 Subject Reported Adhesion Scores

Cycle	Patch Adhesion Score\$	Statistic	AG200-15 (N=2022)	
			Number of Subjects	Number of Patches
Overall	0	n/N (%)	230/2022 (11.4%)	40109/55900 (71.8%)
	1	n/N (%)	357/2022 (17.7%)	9462/55900 (16.9%)
	2	n/N (%)	174/2022 (8.6%)	2235/55900 (4.0%)
	3	n/N (%)	161/2022 (8.0%)	1305/55900 (2.3%)
	4	n/N (%)	1100/2022 (54.4%)	2789/55900 (5.0%)
		n	2022	55900
		Mean	2.76	0.52
		SD	1.518	1.034

SD = standard deviation.

\$ Worst score during a cycle or overall for each subject or patch.

Patch Adhesion Score: 0 = no lifting or small amount of lifting at edges of the patch.

1 = more than a small amount of lifting at the edges up to one-quarter of the patch lifting off, 2 = more than one quarter of the patch lifting off up to half of the patch lifting off,

3 = more than half of the patch is lifting off, but the patch is still on, 4 = patch has completely come off.

Adapted from Caroline Strasinger, PhD, Quality In vivo Adhesion Assessment Review dated November 15, 2017, based on NDA 204017 Table 14.3.7.1.2

- The mean patch adhesion score was 0.52 across all patches applied during cycles 1-13 and the mean worst score reported was 2.76.
- 11.3% of all patches result in less than 75% of the product surface area adhering during the seven-day wear period
- 5.0% of all patches applied during cycles 1-13 were given a score of 4 (complete detachment). The percentage of patches with complete detachment decreased over time, from 9.9% in Cycle 1 to 2.4% in Cycle 13.
- When analyzed by patients (which may be more clinically relevant), 24.8% of patients had complete patch detachment in Cycle 1; this decreased to 6.1% in Cycle 13.
- Over half, (54.4%) of subjects recorded at least one complete patch detachment (i.e. a score of 4) at some point in the study.
- Across the three application sites (abdomen, buttock and upper torso), the best mean adhesion scores were obtained for products worn on the abdomen, though the abdomen application site results in slightly lower absorption of the active pharmaceutical ingredients (APIs), the abdomen is still considered to be therapeutically equivalent. (See Sections 3.5 and 5 for the Biopharmaceutics review and Clinical Pharmacology Review).
- The adhesion scores were similar on days assessed by patients and providers.

Team Leader comment:

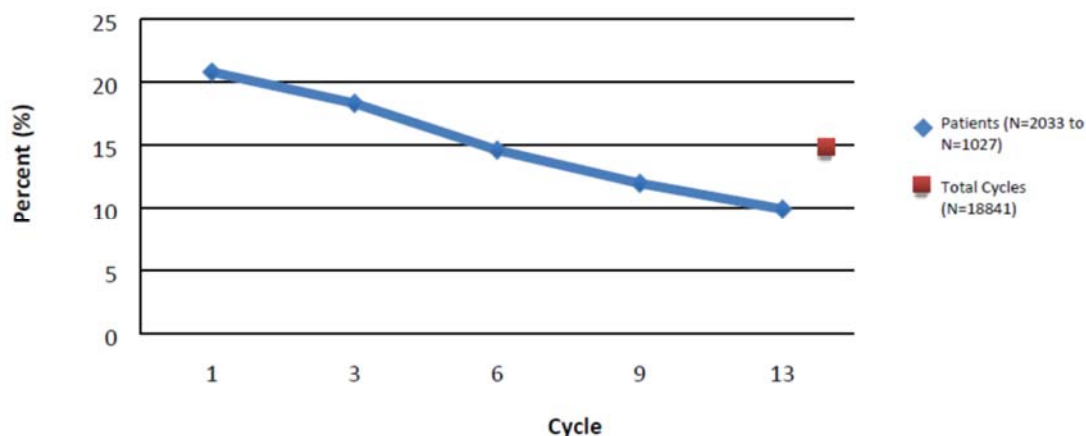
As the protocol did not to routinely have providers check patch adhesion in a systematic method, I have concerns that there may be higher patch detachment during actual use than what was reported in the study.

The data were also analyzed by number of patches used per cycle. The graph demonstrates that a significant percentage of users require extra patches each cycle, even up to a year of use, indicating that patch adhesion is independent of user familiarity with the product.

Figure 2 depicts the trend over the study period.

The graph demonstrates that a significant percentage of users require extra patches each cycle, even up to a year of use, indicating that patch adhesion is independent of user familiarity with the product.

Figure 2 Patient with Four or More TCDS Applied per Cycle*



*Adapted from Caroline Strasinger, PhD, Quality In vivo Adhesion Assessment Review dated November 15, 2017, based on NDA 204017 Table 14.3.7.1.2 page 8/15

These data demonstrate that:

- In 14.7% of 18,841 cycles, four or more patches were applied (red square). In fact, the Applicant-provided Table 14.3.7.1.2 noted by Dr. Strasinger showed that some patients used up to nine individual TCDS in one cycle.
- 10-20% of all users will require four or more TCDS per cycle.

The CMC product reviewer, Dr. Strasinger, identified that the final product will be packaged with three patches at a time, indicating patients will be forced to seek replacement product in order to use as prescribed and maintain adequate contraceptive protection. Patients are instructed to use a new TCDS if the patch does not stick completely. Dr. Strasinger finds these data are the most robust indicators of the true adhesion failure of the product. She finds the actual adhesion and potential patient experience could be even worse than 14.7%, as the figure generated above shows four or more products being utilized in each cycle.

Team Leader Comment:

These data demonstrating that up to 20% of users require more than three patches per cycle is clinically concerning; the adhesion failure of this product could translate into significant efficacy issues as women will not have access to reserve patches under the current proposed packaging.

Dr. Strasinger also obtained a statistics consult on the adhesion study in order to simulate the analysis of a more traditional adhesion study. A typical adhesion study includes 50 or 100 subjects; however, this study included thousands of patients with thousands of observations. The statistics reviewer analyzed random sub-populations of 50 subjects. (Refer to the statistical CMC review by Chao Wang, PhD, dated November 29, 2017). Dr. Wang stated that, "Assuming that a [TCDS] should have a score less than 2 (at least 75% adhered) throughout the entire wear period of 7 days to ensure proper adhesion, the analysis of the subject data shows that the probability of a [TCDS] passing the adhesion test is 0.89 with 95% lower confidence limit of 85.33%. This indicates that there is no strong evidence that at least 90% of the TDS will adhere at least 75% throughout the wear period. Nearly all tests based on random subsample of subject data, in an attempt to mimic a more traditional adhesion study could not reject the null hypothesis and thus also does not support acceptable adhesion. The analysis does confirm that adhesion performance improves when a subject becomes more experienced with the product."

After review, the CMC product review team concluded that the results of this yearlong supportive patch adhesion study do not support effective product adhesion for the required seven-day wear period. Ultimately, it is expected the product will need to be reformulated to address inadequate adhesion.

Team Leader comment:

The issue of inadequate patch adhesion with insufficient supportive clinical data will be outlined in the Complete Response letter.

3.4 Quality control

Per the OPQ Drug Product Review, the applicant has not established an adequate specification with respect to the adhesion or tack methods and acceptance criteria. These deficiencies will be outlined in the Complete Response letter. Refer to the OPQ Drug Product Review dated December 13, 2017 for more information.

3.5 Biopharmaceutics

The initial Biopharmaceutics review found the in vitro drug release method and the skin permeation report acceptable. The Biopharmaceutics review of the re-submission was acceptable. Overall, the Biopharmaceutics review team recommends approval of the NDA (Refer to OPQ review dated December 13, 2017).

3.6 Facilities

During this review cycle, a pre-approval inspection was performed October 23-27, 2017 of Corium International Inc., the contract drug product manufacturer. A three-item FDA Form 483 issued. The facility was found not ready for commercial manufacturing in part due to inadequate (b) (4) finished product tests for tack and adhesion. On December 13, 2017, the OPF Division of Inspectional Assessment (DIA) review team entered a Withhold Approval recommendation.

4 Nonclinical Pharmacology/Toxicology

Per the Pharmacology/Toxicology review by Mukesh Summan PhD, dated November 21, 2017, as a 505(b)2, NDA 20417 relies on the public literature that supports findings of safety and efficacy of approved oral combined hormonal contraceptives as well as clinical and clinical pharmacology studies conducted by the Applicant. The Applicant also relied upon published literature and dermal toxicity studies conducted under IND 57731 to support nonclinical pharmacology and toxicology.

A change in the drug product impurity specifications was noted during the review. The Applicant had revised the acceptance criteria of (b) (4) and the total LNG impurities, due an increase in these impurities under long term stability studies. Per the Applicant, 24- and 27-month old TCDS patches were used in Study 23. Exposure of clinical trial participants to the drug product also likely resulted in exposure to these LNG impurities. Therefore, these impurities are deemed qualified by their presence in the drug product and use in this clinical trial. Dr.

Summan also notes a PubMed.gov search yielded no toxicological concerns associated with [REDACTED] (b) (4)

[REDACTED] evaluated either singly or in combination.

Based on the extensive clinical experience with LNG/EE products and the nonclinical studies conducted by the Applicant, no nonclinical safety issues were identified during this resubmission which would precluded approval of this NDA. Hence, the Pharmacology and Toxicology team recommends approval.

5 Clinical Pharmacology

During the first review cycle, Hyunjin Kim PhD in his Clinical Pharmacology review dated January 11, 2013 evaluated information from the 19 clinical studies the Applicant had conducted up to that point, including 13 studies with the earlier formulations evaluating safety and/or pharmacokinetics (PK) and six studies with the to-be-marketed formulation AG200-15, including four PK studies and two phase 3 safety and efficacy studies. The four Clinical Pharmacology studies included an ovulation suppression and menstrual cycle control study, a comparative bioavailability study to compare the EE exposure with a marketed oral CHC, a PK study to evaluate the systemic exposure of EE and LNG following a single patch application to three different application sites, and a PK study to evaluate the effects of different external conditions such as dry sauna, whirlpool, treadmill exercise, and cold water.

The salient clinical pharmacology and biopharmaceutics findings in the first review cycle were:

- Dose-Finding: AG200-15 demonstrated the highest ovulation suppression with lowest breakthrough bleeding and/or spotting (BTB/S) in Cycle 3. Therefore, AG200-15 was studied in two phase 3 studies.
- EE exposure: In ATI-CL14 (hereafter referred to as Study 14), the Applicant compared EE exposure of AG200-15 with the oral contraceptive, Ortho-Cyclen® (containing 0.035 mg EE and 0.25 mg Norgestimate) in Weeks 1 and 3 during one cycle. Overall, the AUC and Cmax of EE from AG200-15 were about 10% and 61% lower than AUC and Cmax of EE from Ortho-Cyclen® based on the PK data observed in Week 3. However, due to the potential between-cycle accumulation of EE, there were concerns that the study result may not be reliable.
- In ATI-CL15 (hereafter referred to as Study 15), EE and LNG exposure in different application sites (abdomen, buttock, and upper torso) were compared following a patch application for one week at each site, including a wash-out period of one week. The study showed that both the buttock and upper torso were associated with higher Cmax and higher AUC₀₋₁₆₈ compared to the abdomen. However, the reviewer noted exposure change due to the treatment period for both EE and LNG indicating that the washout period again may have been too short to

eliminate both EE and LNG from the systemic circulation, thereby resulting in a carry-over effect. Therefore, the study results were considered to possibly not be reliable.

- In ATI-CL16 (also referred to as Study 16), EE and LNG exposures were compared under different external conditions (normal, dry sauna, whirlpool, treadmill, and cold water) following a patch application for one week. The study results showed that both EE and LNG exposures were comparable under cold water conditions compared to normal conditions and lower under other conditions including dry sauna, whirlpool and treadmill compared to normal conditions. However, it was again observed that there was exposure change due to the treatment period for both EE and LNG, indicating the washout period may have been too short.

At the end of the first review cycle the Applicant was asked to address the potential carry-over effects of both EE and LNG between adjacent treatment Cycles in Studies 14, 15 and 16. The Applicant was asked to provide a revised analysis that corrects for/compensates for the noted potential carry-over effect and provide details on how to obtain this information post-marketing along with suitable labeling to address this lack of information. In the June 21, 2013 response to the CRL the Applicant provided an assessment of potential carry-over effects of both EE and LNG using the pharmacokinetic data collected from Study 14. The clinical pharmacology reviewer for this resubmission concurred with the Applicant that steady-state concentrations of EE and LNG were achieved by Week 3 of the first cycle and the second cycle of a two consecutive cycles of patch therapy, respectively, and concluded that the exposure of EE and LNG would not significantly increase in subjects receiving three and more consecutive cycles of patch therapy. The potential carry-over effect in Studies 15 and 16 were not addressed.

The Applicant provided a clinical pharmacology update to address Studies 14, 15 and 16 in the current submission. Peng Zou, PhD, the clinical pharmacology reviewer for this resubmission, reviewed this update. Dr. Zou documented his analysis of these data in a memorandum dated December 1, 2017 as well as addressing the potential impact of the product quality deficiencies described in the CRL on the findings in clinical pharmacology studies. Dr. Zou found that the Clinical Pharmacology information to support this NDA resubmission is acceptable. His conclusions were based on the following information.

5.1 Study 14 – PK Assessment to determine Carry-over Effect between Cycles

To address the concerns of a carry-over effect when patches are reapplied to the same area, the Applicant analyzed PK data from Study 14. After review, the clinical pharmacology reviewer concurred with the Applicant that for subjects treated in the AG200-15/Ortho-Cyclen®/AG200-15 sequence, there were no carry-over effects for both EE and LNG and that one week washout is sufficient to eliminate the carry-over effects of EE between two consecutive cycles of patch therapy.

Based on the data from Study 14, a steady state was achieved after one cycle of patch therapy. Therefore, the clinical pharmacology reviewer concluded that it is unlikely that the systemic exposure of EE would significantly further increase in subjects receiving three or more consecutive cycles of patch therapy and the exposure to EE at steady state would be comparable to that in subjects treated with Ortho-Cyclen®.

After review of the data from Study 14, the clinical pharmacology review team concluded that any increase in EE and LNG exposure was determined to be unlikely to carry-over and therefore, would not affect the efficacy or safety of AG200-15 patch.

5.2 Study 15 – PK substudy to address Carry-over from different anatomical sites

To further support that there were no issues with carry-over between patches, the Applicant evaluated this issue in a PK substudy in Study 15. There were negligible pre-dose levels of LNG. The reviewer found that these analyses suggest that the inter-period increases in EE and LNG exposure observed in Study 15 were not due to carry-over effect. The Applicant's additional analyses to compare percent changes in exposure of EE and LNG across all study periods showed that the exposure of EE and LNG did not consistently increase across all three study periods. Therefore, repeated dosing of AG200-15 are not expected to result in sustained increases in EE or LNG exposure. The reviewer concluded that the three anatomical sites can be switched interchangeably without clinical consequences. Bioequivalence analysis did reveal that for buttock vs. abdomen and upper torso vs. abdomen, both AUC_{0-168} and C_{max} of EE failed to meet BE criteria, but the exposure of EE from three application sites was still comparable (90% CIs were within or close to 66.7- 150%). See Table 2 and Table 3.

Table 2 BE assessment for EE PK parameters Study 15

Comparison	% geometric mean ratio (90% CI)	
	C _{max}	AUC ₀₋₁₆₈
Buttock (B) vs. Lower abdomen (A)	130 (113 – 151)	123 (108 – 140)
Upper torso (C) vs. Lower abdomen (A)	115 (99.2 – 133)	121 (106 – 138)

Source: Clinical Pharmacology Review of NDA 204017, Peng Zou dated December 1, 2017, page 8/15

Table 3 BE assessment for LNG PK parameters Study 15

Comparison	% geometric mean ratio (90% CI)	
	C _{max}	AUC ₀₋₁₆₈
Buttock (B) vs. Lower abdomen (A)	107 (89.9-127)	107 (92.0-124)
Upper torso (C) vs. Lower abdomen (A)	117 (98.0-139)	117 (101-136)

Source: Clinical Pharmacology Review of NDA 204017, Peng Zou dated December 1, 2017, page 8/15

5.3 Study 16 External conditions

Again, the negligible pre-dose levels of EE and LNG suggested that the inter-period increases in EE and LNG exposure observed in Study 16 were not caused by carry-over effect. The data demonstrated that the exposure of EE and LNG did not consistently increase across all three study periods. Therefore, repeated dosing of AG200-15 should not result in sustained increases in EE or LNG exposure. The reviewer also concluded that “no clinically significant effect of any of the four environmental conditions (cold water, whirlpool, dry sauna and treadmill) on the drug delivery profiles is expected.”

6 Clinical Microbiology

No clinical microbiology consult was requested or necessary for this topically applied product.

7 Clinical/Statistical- Efficacy

7.1 Development Program

To date the development program for the AG200-15 patch included seven studies using the final formulation: three PK studies, one dose-finding PK/PD study, two open-label comparative phase 3 trials of the TCDS with active comparators of two EE/LNG oral combination hormonal contraceptives (CHCs) and one single arm phase 3 trial of the TCDS. These studies are briefly outlined in Table 4.

Table 4 Clinical Development Program for AG200-15 TCDS

Study ID	Design* Phase	Study and Control Arms	Objectives, Application Site	N	Endpoints
ATI-CL14	OL, R, 2-part XO Phase 1	AG200-15, OrthoCyclen (OC with 35 µg EE & 250 µg norgestimate)	Comparative PK	36 enrolled, 36 safety	Comparative EE & LNG PK, safety
ATI-CL15	OL, R, 3-period XO Phase 1	AG200-15	Application site PK Lower abdomen, upper torso, buttock	24 enrolled & safety	EE & LNG PK
ATI-CL16	OL, R, 3-period XO Phase 1	AG200-15	Extreme conditions PK Lower abdomen	24 enrolled & safety	EE & LNG PK, patch adhesion
ATI-CL11	OL, R, parallel group, 3-cycle Phase 2	AG200, AG200-LE, AG200-15	Dose-finding Lower abdomen	AG200: 45 enrolled, 44 safety AG200-LE: 45 enrolled, 44 safety AG200-15: 33 enrolled, 31 safety	EE & LNG PK, PD (ovulation inhibition), patch adhesion

ATI-CL12	OL, R, parallel group, 13-cycle Phase 3	AG200-15, Lessina (OC with 20 µg EE & 100 µg LNG)	Safety and efficacy, PK, PD effects on binding globulins, wearability Abdomen, upper torso, buttock	AG200-15: 1,378 enrolled, 1,278 safety (including 249 from OC at Cycle 7) Lessina: 375 enrolled, 344 safety	Pregnancy rate, safety, bleeding profile, EE & LNG PK, PD, patch adhesion
ATI-CL13	OL, R, parallel group, 6-cycle Phase 3	AG200-15, Levora (OC with 30 µg EE & 150 µg norgestimate)	Safety, efficacy, PK, PD effects on binding globulins, wearability Abdomen, upper torso, buttock	AG200-15: 201 enrolled, 177 safety Levlite: 206 enrolled, 188 safety	Pregnancy rate, safety, bleeding profile, EE & LNG PK, PD, patch adhesion
ATI-CL23	OL single arm 13 cycle Phase 3	AG200-15	Safety, efficacy, cycle control, subject compliance, and patch adhesion of AG200-15	2031 enrolled	Pregnancy rate, safety, bleeding profile, patch adhesion

Source: adapted from Table 1 CDTL Review NDA 204017 Lisa Soule dated February 13, 2013, based on Clinical Overview, Table 2, pp 10-12 & Tabular Listing of Studies in original submission, and from NDA 204017/S38 Table 5.2 Tabular Listing of Clinical Studies-Resubmission

7.2 First Review Cycle, 2013 – clinical efficacy and safety review

For a summary of the studies in the first review cycle, please see the CDTL by Lisa Soule, MD dated February 13, 2013 as well as the primary clinical review by Daniel Davis, MD dated January 23, 2013. Briefly, there were two phase 3 trials. The first phase 3 trial, Study 12, was a 13-cycle prospective, open-label, randomized, parallel-group multicenter trial including two phases of treatment allocation and enrolled 1,500 women. For the first six months, subjects were randomized 3:1 to AG200-15 or to Lessina, an oral CHC containing 20 µg of EE and 100 µg of LNG. After Cycle 6, women randomized to the oral CHC were allowed to cross-over to AG200-15 for the remainder of the study. The study compared efficacy, bleeding profile, compliance, plasma concentrations and safety of the patch vs. the oral CHC. Study 13 was a 6-cycle prospective, open-label, randomized, parallel-group multicenter trial of 400 women, randomized 1:1 to

AG200-15 or to Levora, an oral CHC that contains 30 µg of EE and 150 µg of LNG. The study compared exposure, bleeding profile, and safety and efficacy of the patch vs. the oral CHC.

Team Leader Comments:

Dr. Soule noted in her comments regarding the design of these two trials that the entry criteria were similar for hormonal contraceptive trials in general. In Study 12 the Applicant did not impose a BMI restriction, in accordance with the Division's request for the study populations to reflect the increasing burden of obesity in the general population. Though the primary efficacy population was restricted to women with a BMI<32, the data would allow the Division to review safety data on heavier women. Entry criteria for Study 13 did restrict BMI to <32.

7.2.1 Efficacy Results in the First Cycle

In Study 12, the Applicant reported a total of 40 on-treatment pregnancies on AG200-15, 30 of which were counted in the ITT2 population as agreed. Several pregnancies had no outcome information mentioned, and several were lost to follow-up. Further, the Applicant's categorization and description of potential pregnancies was inconsistent and often incomplete. The Division reviewed the pregnancies with the usual method, employing a "worst case" scenario approach, in which cases that are missing the information that would allow for a conclusive determination are considered "on-treatment" pregnancies. This is done because, as per Dr. Soule's review, "it is known that the pregnancies reported in a trial may be under-estimates; for example, pregnancy status is unknown for subjects lost to follow-up, but it is certainly possible that some subjects who stop communicating with a study site have become pregnant." The rate of agreement between the Applicant and the Division was low. Overall, of the 31 cases not counted by the Applicant, the Division Counted eight (26%) more on-treatment cases. In addition, there were another nine cases (29%) that the Division did not include because pregnancy dating information were so inadequate to make any determination. The Applicant also discounted six "false positive" pregnancy tests, which was highly unusual in a contraceptive trial. Of significant concern to the clinical review team was that there was inadequate evaluation of these results, further demonstrating poor study conduct. In Study 13, the Applicant reported four on-treatment pregnancies, and the Division did not identify any additional on-treatment pregnancies.

The Pearl Indices of 7.50 (95% upper bound of 9.97) and 8.19 (16.19) for the AG200-15 patch were well above that demonstrated for any approved combined hormonal contraceptive. Dr. Soule noted that although FDA does not consider comparative efficacy in the approval of contraceptive products, the unacceptably high Pearl Indices did not demonstrate

an acceptable level of efficacy in either trial. This led to a determination that the overall risk/benefit profile of this product was unfavorable. See Table 5 and Table 6.

Table 5 Pearl Index Calculation, Cycles 1-13, Study 12, ITT2 Population

	Population	N	# of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence
Applicant	Age 17-35 years	1,060	38	7,685	6.43	(4.39, 8.47)
	Age 17-35 with BMI < 32 kg/m²	827	30	6,070	6.43	(4.13, 8.27)
	Age 17-35 with BMI < 30 kg/m ²	767	27	5,645	6.22	(3.88, 8.56)
	All Subjects	1,158	40	8,446	6.16	(4.25, 8.06)
Reviewer	Age 17-35 years	1,060	45	7,685	7.61	(5.39, 9.83)
	Age 17-35 with BMI < 32 kg/m²	827	35	6,070	7.50	(5.02, 9.97)
	Age 17-35 with BMI < 30 kg/m ²	767	32	5,645	7.37	(4.82, 9.92)
	All Subjects	1,158	48	8,446	7.39	(5.30, 9.47)

Source: Lisa Soule, MD CDTL Review NDA 204017 Table 10, February 13, 2013

Table 6 Pearl Index Calculation, Cycles 1-6, Study 13, ITT2 Population

Variable	Statistic	OC	AG200-15
		N=179	N=158
ITT2	Number of subjects	163	147
Age 18-35 years	Number of cycles	765	635
	Number of on-therapy pregnancies	4	4
	Pearl Index	6.80	8.19
	95% CI	(0.15, 13.44)	(0.19, 16.19)

Source: Lisa Soule, MD CDTL Review NDA 204017 Table 13, February 13, 2013 based on Report for Study 13, Table 10, page 65.

Dr. Soule also commented on the following additional clinical concerns:

- **Unscheduled bleeding:** The CDTL noted that “by about Cycle 4, the rate of unscheduled bleeding and spotting combined decreased to about one day per cycle, and remained there until the conclusion of the treatment cycles in both arms.
- **Premature Discontinuation:** The CDTL also commented that in the studies almost 1% of subjects discontinued prematurely due to dissatisfaction with patch adhesion, suggesting that the adhesive properties of this patch may not be optimal.

Team Leader comment:

These clinical concerns identified during the first review cycle were taken into consideration when evaluating this resubmission.

7.3 Current Review Cycle

The Applicant addressed the clinical concerns in the 2013 CR letter by conducting Study 23. This study evaluated 2031 women over a total of 13 cycles. Below is a summary of the key descriptors and issues identified during the clinical review. For full details and review of Study 23, please refer to the clinical review by Nneka McNeal-Jackson, MD, dated December 15, 2017.

7.3.1 Design of Study 23

Study 23 was an open-label, single-arm, multicenter, clinical trial of approximately 2,300 women to evaluate the contraceptive efficacy of AG200-15 after 12 months of use. Additional objectives were to evaluate the safety and tolerability of AG200-15 and patch adhesion. Key inclusion criteria were healthy women age ≥ 18 with regular menses, who were sexually active and desiring hormonal contraception for at least 1 year, and who agreed not to use back-up contraception during the trial.

The Applicant addressed concerns of adhesion identified during the first review cycle by instructing subjects to record daily patch wear, patch adhesion data, patch exposure to water, application site irritation, and vaginal bleeding/spotting in a daily electronic diary (eDiary). The diary was also used to record information weekly on patch use, anatomic site of patch application, sexual activity, and whether or not they used a backup method of contraception. Women were given home pregnancy tests to use if they had any concern about a potential pregnancy.

Women returned to the clinical at monthly intervals unless adverse events were reported. At each routine clinic visit a urine pregnancy test was performed and the TCDS application site was inspected for irritation and adhesion. Adverse events and concomitant medications were reviewed. During each telephone visit, the trial medication and eDiary compliance data, adverse events, and concomitant medication were reviewed.

Subjects with a positive urine pregnancy test underwent a pelvic examination for assessment of uterine size, serum quantitative β -hCG testing and ultrasound evaluation to determine the estimated date of conception (EDC). An independent Pregnancy Review Committee (PRC) adjudicated all pregnancies and classified each pregnancy as pre-treatment, on-treatment, or post-treatment as follows:

- Pre-treatment: EDC prior to the first day of the first TCDS application of the trial
- Post-treatment: EDC after day seven from the last TCDS removal of the trial
- On-treatment: EDC falls between the date that the first TCDS of the trial is applied and the date that the last TCDS of the trial is removed

Table 7 Demographics of Study Population Study 23

Parameter	Category	Overall (n=2031)
Age (years)	≤ 35	90.1% (n=1830)
	>35	9.9% (n=201)
Race	Asian	3.2% (n=65)
	AI/AN	0.5% (n=11)
	Black	24.3% (n=493)
	NH/PI	0.4% (n=8)
	Other	4.7% (n=96)
	White	66.9% (n=1358)
Ethnicity	Hispanic	19.7% (n=400)
	Not Hispanic	80.3% (n=1631)
BMI (kg/m²)	Obese (≥ 30)	35.3% (n=717)
	Non-obese (<30)	64.7% (n=1313)
	≥ 30 to <35	17.5% (n=356)
	≥ 35 to <40	10.3% (n=209)
	≥40	7.5% (n=152)
Smoking Status	Current	11.6% (n=236)
	Past	12.8% (n=260)
	Non-Smoker	75.6% (n=1535)
Previous Contraceptive Use	Naïve	9.4% (n=190)
	Current	34.7% (n=704)
	Prior Use	43.1% (n=875)
	Recent Use	12.9% (n=262)
	Naïve to HC patch	82.7% (n=1680)

Source: Nneka McNeal-Jackson, MD Clinical Reviewer Review of NDA 204017/S38 table 6 page 39/87, adapted from NDA 204017, Module 5.3.5.1 ATI-CL23 Clinical Trial Report, Table 9 Demographics and Baseline Characteristics for Previous and Overall – Safety population, 5.3.5 Contraceptive Efficacy
AI/AN – American Indian/Alaskan Native, NH/PI – Native Hawaiian/Pacific Islander

Team Leader Comments:

According to the most recent US Census^{2,3} the US population is comprised of 64% Non- Hispanic Whites, 16% Hispanics, 13% African-Americans, 5% Asians and 7.1% “other.” Comparing the Census data with the data in Table 7, the Applicant oversampled African-Americans, and undersampled Asians just as in review cycle one. The sampling of Whites and Hispanics roughly mirrored the US Census data, which makes the findings particularly relevant to what will occur with real world use. Dr. Soule noted in her 2013 review that other recent contraceptive studies conducted in the US have generally oversampled Caucasians and undersampled Hispanics, Asians and “others.” In my judgement, the demographic sampling is improved in Study 23. The study included 35.4% obese women, which reflects the prevalence of obesity in the US, at 38.3%.⁴ The inclusion of obese women will allow for assessment of safety in this sub-population.

7.3.2 Disposition of Subjects Study 23

The Applicant provided a table of subject disposition. The discontinuation rate from the study was 51.3%. 10.9% of women discontinued due to an adverse event, 11.3% were lost to follow-up , and 15.4% discontinued due to subject decision, while only 0.8% were discontinued at the investigator’s discretion.

² Race, Combinations of Two Races, and Not Hispanic or Latino: Census.gov.<https://www.census.gov/prod/cen2010/briefs/c2010br-13.pdf>

³ Overview of Race and Hispanic Origin: 2010-Census.gov. <https://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf>

⁴ Ogden, CL et.al. (2015). Prevalence of Obesity among Adults and Youth: United States, 2011-2014. National Center of Health Statistics Data Brief. November; (219):1-8.

Table 8 Disposition of Subjects Study 23

<u>DispositionStatus</u>	<u>Subjects</u>
Screened Subjects	4033
Screen Failures	2001
Enrolled Subjects	2032
Safety Population	2031
Contraceptive Efficacy Population	2024 (99.7%)
Cycle Control Population	2017 (99.3%)
Completer Population	989 (48.7%)
Reason for Study Discontinuation	1042 (51.3%)
Any Reason	
Adverse Event	222 (10.9%)
Death	0
Non-Compliance	116 (5.7%)
Lost to Follow Up	229 (11.3%)
Subject Decision	310 (15.3%)
Pregnancy	73 (3.6%)
Protocol Violation	14 (0.7%)
Investigator Decision	17 (0.8%)
Sponsor Decision	18 (0.9%)
Sponsor Decision (Study Termination)	2 (0.1%)
Other	41(2.0%)

Source: NDA 204017 Module 5.3.5.1 ATI-CL23 Clinical Trial Report, Table 6: Subject Disposition and Analysis population, page 54/135

Safety Population = subjects who wore at least one patch for any length of time. Contraceptive Efficacy Population = subjects who wore at least one patch and had a negative enrollment serum β -hCG.

Cycle Control Population = subjects in Contraceptive Efficacy Population who provided information on bleeding and patch application.

Completer Population = subjects who completed the study.

Note: Denominator for percentages is number of subjects in the Safety Population.

Team Leader Comments:

The subject discontinuation rate of 51.3% is somewhat improved from Study 12, the other phase 3 trial of similar 13-cycle duration, where it was 57.0%. The lost-to-follow-up rate of 11.3% is also somewhat improved when compared to the rate of 16.2% for Study 12. The discontinuation rates due to AEs and to subject decision remained similar. These differences may demonstrate significant improvement in study conduct and recruitment between studies. However, the discontinuation rate for Study 23 remains higher than for almost all other submitted trials of oral CHCs over the last ten years. Subject Decision to withdraw is also 5-10% higher than for the other registration trials. See Table 9 for a summary of recent trials submitted to support US approval of oral CHCs.

Table 9 Discontinuation Rates in Pivotal Trials for AG200-15 versus Pivotal Trials for Recently Approved CHCs (2007-2017)

Drug/Trial	Year Approved	Trial Discontinuation			
		Total	Loss to Follow-up	Subject Decision	Others
Trial ATI-CL12	NA	57.0%	20.3%	16.2%	0.8%
Trial ATI-CL23	NA	51.3%	11.3%	15.3%	2.0%
Trial ATI-CL23	2013	40.4%	13.3%	6.0%	0.8%
Lo Loestrin Fe	2010	41.7%		8.9%	5.8%
Natazia		51.3%	13.0%	9.8%	11.6%
Generess	2010	40.9%	16.2%	8.9%	4.5%
Lo Seasonique	2008	37.1%		8.6%	1.4%

Source: Nneka McNeal-Jackson, MD Clinical Reviewer Review of NDA 204017/S38, Table 8, page 42/87, adapted from Biometrics Review prepared by K. Dwyer Ph.D. Adapted from Biometrics Review for Quartette (NDA 204061), Lo-Loestrin (NDA 22501), Natazia (NDA 22252), Generess (NDA 22573), and LoSeasonique (NDA 22262).

2010

14.1%

Team Leader comment:

It is concerning to me that a product that is supposedly an improvement in use demonstrates a relatively high discontinuation and withdrawal rate.

7.3.3 Efficacy Results

The primary efficacy endpoint for Study 23 is the Pearl Index based on all on-treatment pregnancies in women aged 18 to 35 years. Evaluable cycles were those in which no methods of back-up contraception were used and in which the subject had intercourse.

The Pearl Index is calculated as follows:

$$\text{Pearl Index} = \frac{100 \times \text{number of pregnancies} \times 13 \text{ cycles/year}}{\text{Number of 28-day cycles of treatment}}$$

The primary analysis population for Study 23 is the Intent-to-treat (ITT) Efficacy Dataset, which includes all complete or incomplete on-therapy cycles in which intercourse occurred and no back-up contraception was used. The ITT population includes women ≤ 35 at enrollment, regardless of BMI.

Secondary efficacy endpoints included calculation of the PI by BMI categories $<30 \text{ kg/m}^2$ or $\geq 30 \text{ kg/m}^2$. For selected endpoints, results were summarized by subgroups, including age ≤ 35 years old vs. > 35 years old; BMI categories: $< 25 \text{ kg/m}^2$, ≥ 25 to $<30 \text{ kg/m}^2$, $\geq 30 \text{ kg/m}^2$, non-obese: BMI $< 30 \text{ kg/m}^2$ vs. obese: BMI $\geq 30 \text{ kg/m}^2$, $\geq 30 \text{ kg/m}^2$, to $<35 \text{ kg/m}^2$, $\geq 35 \text{ kg/m}^2$ to $<40 \text{ kg/m}^2$, BMI $\geq 40 \text{ kg/m}^2$; weight summarized by quartiles and deciles; previous hormonal contraceptive use status; race and ethnicity.

The Applicant identified 56 on-treatment pregnancies. The clinical and statistical reviewers evaluated the pregnancies dataset with the usual method, employing a “worst case” scenario approach, in which cases that are missing the information that would allow for a conclusive determination are considered “on-treatment” pregnancies. The review team agreed with the on-treatment status of all 56 pregnancies. However, the clinical review in the Division of Bone, Reproductive and Urologic Products (hereafter referred to as DBRUP) identified 12 additional on-treatment pregnancies. The rationale supporting the review team’s determination is provided in Table 10.

Table 10 Adjudication of Additional Pregnancies

Subject ID	Applicant's Determination	DBRUP's Determination	Rationale
(b) (6) NA POST		ON	Ultrasound (US) report on March 7, 2016 gestational age 14 weeks. The gynecological exam on March 9, 2016 was consistent with a uterine size of 14 weeks. EDC was December 15, 2016. Last patch was removed March 28, 2016. EDC prior to last patch removal. This is on treatment.
		ON	Patient was noncompliant with treatment which represents a worst-case scenario. First patch was placed March 24, 2016. Last patch was removed March 6, 2016. EDC was February 14, 2016. This is on treatment.
	POST	ON	Patient was noncompliant with treatment which represents a worst-case scenario. First patch was placed December 19, 2014. Last patch was removed on February 1, 2016. EDC was January 12, 2016. This is on treatment.
		ON	March 19, 2016 US report showed gestational sac of 6 weeks. First patch was placed July 7, 2015. Last patch was removed May 5, 2016. EDC was April 21, 2016. This is on treatment.

POST

(b) (6)		ON	Patient was noncompliant with treatment which represents a worst-case scenario. First patch was placed September 25, 2015. Last patch was removed December 20, 2015. EDC was November 22, 2015. This is on treatment.
	T	ON	Patient was noncompliant with treatment which represents a worst-case scenario. September 12, 2016 US report 6 weeks and 5-day pregnancy. First patch was placed October 5, 2015. Last patch was removed on September 8, 2016. EDC was August 10, 2016. This is on treatment.
	T	ON	November 24, 2016 US report no gestational sac. Dropping HCG level (November 24, 2015: HCG 4879; November 25 2015: HCG 2495) consistent with a potential spontaneous abortion. First patch was placed March 3, 2015. Last patch was removed December 29, 2015. This is on treatment.
		ON	Patient is noncompliant with treatment which represents a worst-case scenario. First patch placed September 28, 2015. Last patch removed April 20, 2016. May 2, 2016 US report 7-week intrauterine pregnancy. EDC was March 30, 2016. This is on treatment.
	T	ON	Patient is noncompliant with treatment which represents a worst-case scenario. First patch placed April 2, 2015. Last patch removed August 16, 2015. August 28, 2015 US report 5 week and 6- day intrauterine pregnancy. EDC was August 1, 2015. This is on treatment.

POST

(b) (6)		ON	Patient is noncompliant with treatment which represents a worst-case scenario. First patch placed December 29, 2014. Last patch removed June 3, 2015. June 3 US report 8 week and 3-day intrauterine pregnancy. EDC was April 19, 2015. This is on treatment.
	T	ON	Patient is noncompliant with treatment which represents a worst-case scenario. First patch placed February 23, 2015. Last patch removed June 12, 2015. June 22, 2015 US report 6-week intrauterine pregnancy. EDC was May 25, 2015. This is on treatment.
	T	ON	First patch placed June 25, 2015. Last patch removed June 16, 2016. July 5, 2016 US report gestational sac 5 weeks and 6-day intrauterine pregnancy. EDC was June 8, 2016. This is on treatment.

Source: Adapted from NDA 204017, Module 5.3.5.1 ATI-CL23, Trial Report Body, Table 14.4.1.3 Pregnancy Narratives.

Eight of the 12 cases that the Applicant did not include as on-treatment pregnancies occurred in subjects who were reported to be noncompliant with patch use, i.e. with at least five of the women going > 10 days between patch applications (subjects (b) (6)). The Division sent the Applicant an information request on August 31, 2017 requesting a recalculation of the PI including these pregnancies. The Applicant responded on September 12, 2017 and acknowledged that eight of the twelve subjects considered on-treatment by the FDA were excluded in their original analysis due to “clinically significant interruptions in study drug.” The Applicant requested that the Division re-consider including those women in the PI because “there should be no clinical expectation that upon resumption of drug, the patch could provide protection at the time of conception.” The Applicant also noted that of the 12 additional pregnancies, nine (75%) occurred in subjects who were obese by BMI criteria (BMI ≥ 30 kg/m²) at study enrollment. The Applicant also recalculated weight- and BMI-specific PIs.

Team Leader Comments:

The Division stands by the decision to include compliant and non-compliant patients in the PI calculation as this more accurately reflects real-world use of contraceptives. The Division acknowledges that more of the additional pregnancies occurred in obese women, and acknowledges that obese women have tended to have a higher pregnancy rate during use of combined hormonal contraceptives (CHC) in general; FDA published a meta-analysis of this issue with real world use of contraceptives in 2015.^{5,6} Importantly, this 2015 FDA article stresses that clinicians should optimize hormonal contraceptive use by reinforcing the importance of using the contraceptives on the prescribed schedule, to handle missed doses according to labeled instructions and to use backup contraception when indicated. The real-world information on the efficacy of AG200-15 in women with a BMI greater than 30 is useful in ensuring safe and efficacious use of CHCs in obese women.

7.3.3.1 Primary Efficacy Analysis--Pearl Index Calculation

For the primary efficacy endpoint, using the ITT population, the Applicant calculated a PI of 4.80 (95% CI 3.55, 6.06). However, counting the additional on-treatment pregnancies, FDA calculated a PI of 5.83 (95% CI 4.45, 7.21). See Table 11.

⁵ Yamazaki M, Dwyer K, Sobhan M, Davis D, Kim MJ, Soule L, Willett G, Yu C. Effect of obesity on the effectiveness of hormonal contraceptives: an individual participant data meta-analysis. *Contraception* 2015;92:445-452).

⁶ Yamazaki M, Dwyer K, Sobhan M, Davis D, Kim MJ, Soule L, Willett G, Yu C. Response to Contraception Letter to the Editor (CONTRACEPTION_2015_94). *Contraception*. 2015; 92(6):602-3.

Table 11 Pregnancy Rates for All AG200-15 Treated Subjects (ITT): Study 23

	Population	N	# of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Applicant	Age ≤ 35 years	1,736	56	15,165	4.80	(3.55, 6.06)
	Age ≤ 35 with BMI < 30 kg/m ²	1,123	30	9,888	3.94	(2.53, 5.35)
	Age ≤ 35 with BMI ≥ 30 kg/m ²	612	26	5,264	6.42	(3.96, 8.88)
	All Subjects	1,932	62	17,126	4.71	(3.54, 5.88)
Reviewer	Age ≤ 35 years	1,736	68	15,165	5.83	(4.45, 7.21)
	Age ≤ 35 with BMI < 30 kg/m ²	1,123	33	9,888	4.34	(2.86, 5.82)
	Age ≤ 35 with BMI ≥ 30 kg/m ²	612	35	5,264	8.64	(5.79, 11.50)
	All Subjects	1,932	74	17,126	5.62	(4.34, 6.89)

Source: FDA analysis conducted by Kate Dwyer, Ph.D., Biometrics Reviewer.

Team Leader Comments:

The PI of 5.83 (95% CI 4.45, 7.21) is vastly lower than the PIs for the previously submitted Study 12 [7.50 (95% CI 5.02, 9.97)] and Study 13 [8.19 (95% CI 0.19, 16.19)]. However, the PI for Study 23 remains higher than that reported for any other approved oral CHC. The upper limit of the 95% CI remains above 5; the FDA has never approved a contraceptive with an upper bound of the PI above 5. Given that 75% of the additional pregnancies were in obese women, when efficacy is analyzed by BMI, if the population is restricted to women with a BMI <30 kg/m², the PI is 4.34 (95% CI 2.86, 5.82). These values are still well above those for any other approved CHCs. Again, while FDA does not consider comparative efficacy in the approval of contraceptive products, for this product, the PI remains unacceptably high and it is not clear that the benefit would outweigh the risks that all CHCs carry or that this product has a unique benefit for the intended population.

7.3.3.2 Secondary Efficacy Analyses

Life Table analysis is another methodology that the review team uses to estimating the pregnancy rates over time. Typically, life table estimates are slightly lower than PI results. Dr. Dwyer calculated the life table pregnancy rates in Table 12.

Table 12 Life Table Analyses for Study 23

	Population	# of On-Treatment Pregnancies	Cumulative Pregnancy Rate	95% Confidence Interval
Applicant	Age ≤ 35 years	56	4.22	(3.37, 8.88)
	Age ≤ 35 with BMI < 30 kg/m ²	30	3.54	(2.47, 5.07)
	Age ≤ 35 with BMI ≥ 30 kg/m ²	26	5.48	(3.74, 8.00)
	All Subjects	62	4.17	(3.25, 5.34)
FDA	Age ≤ 35 years	68	5.32	(4.20, 6.74)
	Age ≤ 35 with BMI < 30 kg/m ²	33	3.98	(2.82, 5.60)
	Age ≤ 35 with BMI ≥ 30 kg/m ²	35	7.79	(5.62, 10.77)
	All Subjects	74	5.13	(4.09, 6.44)

Source: Biometrics Review by Kate Dwyer, Ph.D. See the Biometrics Review finalized December 9, 2017.

Subgroup analyses by race, ethnicity and previous hormonal contraceptive use status further demonstrated unacceptable efficacy in all groups except for current hormonal contraceptive users [PI 3.16 (95% CI 1.51, 4.82)]. See Dr. McNeal-Jackson's review for full details of these analyses.

Team Leader Comments:

While the point estimates for the PI for all women ≤35 and women ≤35 and BMI <30 kg/m² are lower than the PIs, the upper bound of the 95% CI remains above the upper bound of 5. The Sponsor was told during drug development that this upper bound was not acceptable.

7.3.3.3 Cycle Control

Characterization of the bleeding profile was a secondary efficacy endpoint and also was an issue identified during the first review cycle. Unscheduled bleeding is an efficacy issue as it often results in discontinuation of the product and subsequent pregnancy. Subjects recorded daily the occurrence and intensity of bleeding or spotting in their eDiaries. Rates are shown in Table 13.

The Applicant defined bleeding as follows:

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

The Applicant classified the data as scheduled and unscheduled, relative to days of patch wear:

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

Table 13 Summary of Incidence of Unscheduled Bleeding or Spotting Episodes for all Phase 3 Trials

	Original NDA		New Data
	(ATI-CL13)	(ATI-CL12)	(ATI-CL23)
	Cycles 1-6 (N = 162)	All Cycles (N=715)	Cycles (N=2017)
Cycle 1	46/148 (31.1%)	168/649 (25.9%)	1217 (60.4%)
Cycle 2	33/127 (26.0%)	155/566 (27.4%)	954 (50.9%)
Cycle 3	28/119 (23.5%)	147/574 (25.6%)	807 (46.2%)
Cycle 4	23/118 (19.5%)	101/517 (19.5%)	718 (44.1%)
Cycle 5	25/114 (21.9%)	110/512 (21.5%)	678 (44.6%)
Cycle 6	24/105 (22.9%)	109/481 (22.7%)	614 (43.0%)
Cycle 7		86/459 (18.7%)	562 (41.6%)
Cycle 8		83/443 (18.7%)	569 (44.6%)
Cycle 9		88/387 (22.7%)	524 (43.2%)
Cycle 10		68/383 (17.8%)	495 (43.3%)
Cycle 11		65/368 (17.7%)	473 (42.9%)
Cycle 12		63/356 (17.7%)	463 (43.5%)
Cycle 13		77/338 (22.8%)	423 (41.3%)

Source: Clinical Review Nneka McNeal-Jackson, MD for NDA 204017/S38, Table 26, adapted from Module 5.3.5.1 ATI-CL23 Clinical Trial Report, Table 14.2.7.1.1, submitted June 26, 2017, Module 5.3.5.1 ATI-CL12 Table 14.2_3.1.1.1, Module Clinical Trial Report ATI-CL13 14.3.1 submitted April 13, 2012.

Team Leader Comments:

The collection of bleeding data in Study 23 was more in line with Division recommendations than the methods in Studies 12 and 13. Cycle control data for the new trial is notably different from that in the original trials. While the number of women that experienced bleeding/spotting episodes did decrease over time, it is concerning that 41.3% of women in the new trial still had unscheduled bleeding or spotting after a year on treatment. This rate is higher than other approved CHCs. Dr. McNeal-Jackson noted in her review that Ortho Evra® labeling shows a decrease in bleeding from 18.2% in cycle 1 to 8% -11.9% in cycles 2-13. The Generess® labeling shows 37% of the women experienced bleeding or spotting in cycle one, which decreased to 22.5% by cycle 13. Bleeding AEs only accounted for 3% of subject discontinuations. In a real-world setting, bleeding is an unwanted

side effect that results in product discontinuation and pregnancy. Therefore, this raises concerns regarding efficacy in the postmarket setting.

7.4 Overall Assessment of Efficacy

The Applicant conducted Study 23 to address the study conduct and monitoring issues raised after review of Studies 12 and 13. In Study 23, the discontinuation rate was lower as was the lost-to-follow-up rate, data collection was more thorough and the data were cleaner. The Division still identified several more on-treatment pregnancies in this trial; this is due to a difference in perspective between the Applicant and the Division about the value of representing the real-world, worst-case scenarios with the data.

Overall, I believe that the Applicant has still not demonstrated an acceptable level of efficacy for AG200-15. The Pearl Index in Study 23 is much lower than for the trials in the first review cycle, but the value of the PI and the upper bound of its 95% CI [5.83 (95% CI 4.45, 7.21)] remain higher than that for any other approved CHC. Even when the population is restricted to non-obese women, the values remain high at 4.34 (95% CI 2.86, 5.82). The only subgroup which demonstrated acceptable efficacy was women who were current contraceptive users [PI 3.16 (95% CI 1.51, 4.82)] per the reviews by the clinical and statistical reviewers (Nneka McNeal-Jackson, MD and Kate Dwyer, PhD, respectively). In addition, the unscheduled bleeding is a concern as it is higher than any other product and has a significant potential to result in product discontinuation and pregnancy.

At this point, the clinical reviewer and I believe we cannot identify a real-world subset of reproductive age women who could derive benefit from AG200-15. In addition, it is unclear whether concerns about poor patch adhesion necessitating use of extra patches each cycle would further negate the benefit of a once weekly application.

8 Safety

The safety database is comprised of subjects from all three phase 3 trials, and includes 3,481 women, with 230 of 3,481 (6.6%) being women who switched from an oral CHC to the AG200-15 patch in Study 12. Overall, the Applicant provided data on 29,900 cycles for AG200-15; in addition, over 400 women

completed a year of treatment in Studies ATI-CL12 and ATI-CL13, and 292 completing a year of treatment in ATI-CL23. Exposure is characterized as 28-day cycles and women-years (WY) in Table 14.

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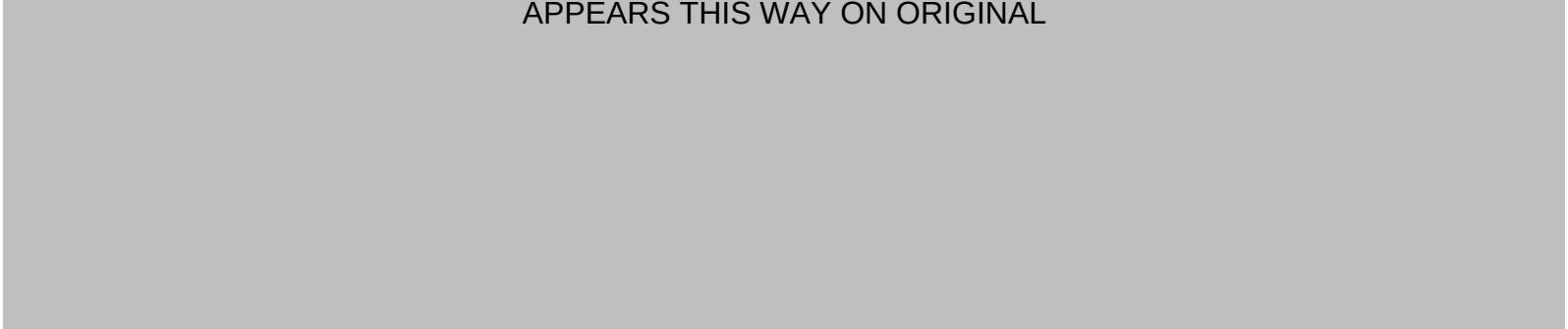


Table 14 Cycles in the Safety Database for AG200-15

	Original NDA (ATI-CL12/13)		New Data (ATI-CL23)	Overall
	Cycles @		Cycles	Cycles
Cycle	1-6 (N=1220)	1-13 (N=1450)	All Cycles (N=2031)	All Cycles (N=3481)
Cycle 1	1215 (99.6%)	1215 (83.8%)	2023 (99.6%)	3238 (93.0%)
Cycle 2	1060 (86.9%)	1060 (73.1%)	1878 (92.5%)	2938 (84.4%)
Cycle 3	990 (81.1%)	990 (68.3%)	1747 (86.0%)	2737 (78.6%)
Cycle 4	903 (74.0%)	903 (62.3%)	1629 (80.2%)	2532 (72.7%)
Cycle 5	857 (70.2%)	857 (59.1%)	1524 (75.0%)	2381 (68.4%)
Cycle 6	808 (66.2%)	808 (55.7%)	1430 (70.4%)	2238 (64.3%)
Cycles 1-6	1216 (99.7%)	1216 (83.9%)	2023 (99.6%)	3239 (93.0%)
Cycle 7		877 (60.5%)	1354 (66.7%)	2231 (64.1%)
Cycle 8		858 (59.2%)	1279 (63.0%)	2137 (61.4%)
Cycle 9		765 (52.8%)	1216 (59.9%)	1981 (56.9%)
Cycle 10		718 (49.5%)	1145 (56.4%)	1863 (53.5%)
Cycle 11		695 (47.9%)	1106 (54.5%)	1801 (51.7%)
Cycle 12		673 (46.4%)	1067 (52.5%)	1740 (50.0%)
Cycle 13		640 (44.1%)	1027 (50.6%)	1667 (47.9%)
>13 Cycles			292 (14.4%)	292 (8.4%)
All Cycles		1443 (99.5%)	2023 (99.6%)	3466 (99.6%)
Total Cycles		11059	18841	29900

Note: Denominator for percentages is number in the Safety Population.

@ Cycles 1-6 = Cycles 1-6 for subjects randomized to AG200-15 in studies ATI-CL13 and ATI-CL12. Cycles 1-13 = All cycles for subjects randomized to AG200-15 in studies ATI-CL13 (Cycles 1-6) and ATI-CL12 (Cycles 1-13), and Cycles 7-13 for ATI-CL12 subjects randomized to oral contraceptive who switched to AG200-15 after 6 cycles.

Source: NDA 204017/S38 Integrated Summary of Safety p.21/102

During the first review cycle, the clinical reviewer, Daniel Davis, MD, found the safety profile of AG200-15 acceptable; however, he noted that the high rate of discontinuation and loss-to-follow-up made it difficult to determine the true safety profile. The clinical reviewer for this cycle, Nneka McNeal-Jackson, MD, was aware of these outstanding study conduct issues and addressed them in her review dated December 15, 2017. The safety review below focuses on the data from Study 23 and review of the outstanding safety issues from the first cycle below.

Team Leader Comments:

- **In the first review cycle for this application, the Applicant was not able to meet the Division's request for at least 10,000 cycles of exposure to AG200-15 in Study 12; they obtained data on only 9,277 cycles of exposure. By combining Studies 12 and 13, they were able to obtain over 10,000 cycles. This deficiency was attributed to an inability to increase recruitment to mitigate the high discontinuation rates in Study 12 and 13. In Study 23, the subject retention rates were marginally better, with a rate of 51.3% as compared with 57.1% in the other 13-cycle trial, Study 12. For Study 23, the total available number of cycles met the Division's prespecified request for at least 10,000 cycles.**
- **The Applicant was successful in obtaining more than the requested 200 women who completed 13 cycles of patch use in both submissions which provides key safety information for review.**

8.1 Deaths and Other Serious Adverse Events

8.1.1 Deaths

There were no deaths among the women that used AG200-15 in the course of the clinical development program.

8.1.2 Nonfatal Serious Adverse Events

In the first review cycle, the review team identified several discrepancies in reported SAEs and narratives for AG200-15 vs. the oral CHC groups. Once these discrepancies were clarified with the Applicant, there were determined to be 16 SAEs in the patch arm with 14 SAEs being in Cycles 1-6 and two in Cycles 7-13 among patch subjects. No SAEs were reported in patch subjects in Study 13. In Study 23, there were 40 SAEs among subjects on AG200-15. Table 15 contains corrected information from the first review cycle as well as information from the most recent study, Study 23.

Table 15 Overall Summary of Treatment Emergent Adverse Events – Phase 3 Studies (12, 13 and 23)

Category	Original NDA (ATI-CL12/13)		New Data (ATI-CL23)	Overall
	Cycles @		Cycles	Cycles
	1-6 (N=1220)	1-13 (N=1450)	All Cycles (N=2031)	All Cycles (N=3481)
Subjects with Any TEAEs	580 (47.54%)	781 (53.86%)	1085 (53.42%)	1866 (53.61%)
Subjects with Any Study Drug-Related [*] TEAEs	261 (21.39%)	338 (23.31%)	552 (27.18%)	890 (25.57%)
Subjects with Severe TEAEs	50 (4.10%)	73 (5.03%)	92 (4.53%)	165 (4.74%)
Subjects with SAEs	14 (1.15%)	16 (1.10%)	40 (1.97%)	56 (1.61%)
Subjects with Study Drug-Related [*] SAEs	3 (0.25%)	3 (0.21%)	15 (0.74%)	18 (0.52%)
Subjects with TEAE Resulting in Study Drug Discontinuation	119 (9.75%)	151 (10.41%)	224 (11.03%)	375 (10.77%)
Subjects Who Died	0	0	0	0

Adverse events are coded using MedDRA version 18.1. TEAE = treatment emergent adverse event, SAE = serious adverse event.

Note: A TEAE is an adverse event with an onset date on or after the first patch application through Day 28 of the subject's final treatment cycle for ATI-CL23, and through the end of the study for ATI-CL12 and ATI-CL13.

^{*} Drug-related: definitely related, probably related, or possibly related.

@ Cycles 1-6 = TEAEs with onset date during Cycles 1-6 for subjects randomized to AG200-15 in studies ATI-CL13 and ATI-CL12. Cycles 1-13 = TEAEs for all cycles for subjects randomized to AG200-15 in studies ATI-CL13 (Cycles 1-6) and ATI-CL12 (Cycles 1-13), and Cycles 7-13 for ATI-CL12 subjects randomized to oral contraceptive who switched to AG200-15 after 6 cycles.

Source: NDA 204017/S38, Integrated Summary of Safety, p.34/102

Team Leader Comments:

Based on corrected information from the Applicant during the original review cycle, the overall rate of SAEs in Trials 12 and 13 in the first cycle is 1.1%. In Study 23, it is 1.97% (40/2031). The SAE rate is slightly higher in Study 23 for this review cycle than the previous cycle, and remains lower than in other contraceptive trials; however, the Applicant made efforts to improve study conduct, data collection, data cleaning and reporting as requested by the Division after cycle one. The clinical reviewer and I remain concerned about underreporting of SAEs in this trial.

The clinical reviewer Nneka McNeal-Jackson, MD provides detailed reviews of the individual treatment emergent SAEs in her memorandum dated December 15, 2017. Table 16 below highlights the SAEs that I believe are possibly drug-related, including hepatobiliary disorders, psychiatric disorders and vascular disorders. The Applicant finds that events are similar to those of currently marketed CHCs and that no new safety concerns are raised.

Table 16 Study 23 Select Treatment Emergent SAEs

	Original NDA Studies 12 and 13		Current Submission Study 23	Overall
	Cycles		Cycles	Cycles
System Organ Class Preferred Term	1-6 N=1220	7-13 N=1450	All Cycles N=2031	All Cycles N=3481
Gastrointestinal disorders				1 (0.03%)
Pancreatitis necrotizing	0	0	1 (0.05%)	
Hepatobiliary disorders				2 (0.06%)
Cholecystitis	0	0	2 (0.10%)	
Cholecystitis acute			1 (0.05%)	1 (0.03%)
Cholecystitis chronic			1 (0.05%)	1 (0.03%)
Cholelithiasis			4 (0.20%)	4 (0.11%)
Psychiatric disorders	1 (0.08%)	1 (0.07%)	6 (0.30%)	7 (0.20%)
Bipolar disorder	0	0	1 (0.05%)	1 (0.03%)
Major depression	0	0	3 (0.15%)	3 (0.09%)
Substance abuse	0	0	1 (0.05%)	1 (0.03%)
Suicidal ideation	1 (0.08%)	1 (0.07%)	1 (0.05%)	2 (0.06%)
Suicide attempt	0	0	1 (0.05%)	1 (0.03%)
Respiratory, thoracic and mediastinal disorders	1 (0.08%)	1 (0.07%)	4 (0.20%)	5 (0.14%)
Pulmonary embolism (PE)	0	0	3 (0.15%)	3 (0.09%)
Vascular disorders	1 (0.08%)	1 (0.07%)	3 (0.15%)	4 (0.11%)
Deep vein thrombosis (DVT)	0	0	3 (0.15%)	3 (0.09%)
Embolism venous	1 (0.08%)	1 (0.07%)	0	1 (0.03%)

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.

Team Leader Comments:

- The original Trials 12 and 13 included only one case of venous embolism and a case of compartment syndrome. These are discussed in Dr. Lisa Soule's CDTL review dated February 13, 2013 and in Dr.

Daniel Davis's clinical review dated January 23, 2013. Here, I review the cases pertaining to the most recent trial, Study 23. For a full analysis of the information in these cases, refer to the clinical reviewer memorandum by Dr. Nneka McNeal-Jackson dated December 15, 2017.

- **I consider five subjects in whom were reported three (3) deep vein thrombosis and three (3) pulmonary emboli, and one (1) left sided weakness to have drug-related vascular SAEs:**
 - **Subject (b) (6): Pulmonary embolism with infarction**
25-year-old, non-smoking White, non-Hispanic female with a BMI of 31.8 kg/m² with a remote history of hormonal contraceptive use and a family history of a clotting disorder in two grandparents. The subject applied her first patch on May 27, 2015. On (b) (6), she was admitted to the hospital with a four-day history of chest pain worse with inspiration. CT angiography of the chest showed an acute pulmonary embolus within the distal aspect of the right lower lobe artery and extending into the segmental and smaller right lower lobe arteries with a patchy consolidation within the posterior right lower lobe with small pleural effusion suspicious for a developing infarction. She was discharged from the hospital on (b) (6) fully anti-coagulated.
 - **Subject (b) (6): Small left lower lobe pulmonary embolus**
26-year-old, White, non-Hispanic female with a BMI of 34.3 kg/m². She had no pertinent medical history, had a several-year history of CHC use and was using NuvaRing before entering the study. She was a former smoker, having quit in 2012. She reported a family medical history of stroke in both elderly maternal and paternal grandmothers. She applied the first patch on September 23, 2015. On (b) (6), she complained of substernal chest pressure and shortness of breath. A CT scan showed a small left lower lobe pulmonary embolus with a small infarct.
 - **Subject (b) (6): Deep vein thrombosis right leg and bilateral pulmonary emboli**
35-year-old non-smoking White, non-Hispanic female with a BMI of 37.1 kg/m². She was a recent oral contraceptive user with a prior history of hormonal patch and progestin IUS use. She had no family history of clotting disorder. She applied the first patch on September 18, 2015. She took a flight on (b) (6) she was admitted to the hospital with worsening right leg pain and shortness of breath. CT scan demonstrated multiple emboli bilaterally, and a peripheral vascular laboratory (PVL) venous exam showed a

non-occlusive right femoral and posterior tibial DVT and an occlusive right popliteal and peroneal DVT.

- **Subject (b) (6): Acute left deep vein thrombosis**
33-year-old, Black, non-Hispanic female with a BMI of 36.3 kg/m² on Ortho-Evra prior to trial enrollment. She applied the first patch on May 27, 2015. She last wore the patch on April 26, 2016 and was discontinued from the study April 27, 2016 because she was pregnant. On (b) (6) (b) (6) she complained of a one week history of left leg pain an ultrasound revealed an acute, non-occlusive DVT in the left gastrocnemius vein.
- **Subject (b) (6): Bilateral Deep Venous Thrombosis, Necrotizing pancreatitis, cholelithiasis, acute respiratory distress syndrome, Klebsiella bacteremia, gastrocutaneous fistula, stage III pressure ulcers**
25-year-old, non-smoking Hispanic female with a BMI of 35.7 kg/m² with no pertinent medical history except recent oral CHC use. She applied the first patch on May 18, 2015. On (b) (6) (b) (6), she presented to the emergency room with pain and then loss of consciousness. She developed acute respiratory distress syndrome (ARDS) shortly after her ER arrival and was transferred to the intensive care unit (ICU). An abdominal ultrasound performed on (b) (6) (b) (6) showed cholelithiasis and ascites. CT scan of the abdomen and pelvis showed severe acute pancreatitis, known cholelithiasis, and moderate ascites. During the course of her hospitalization, she:
 - **Became oliguric with a creatinine of 3.9 mg/dL and required hemodialysis**
 - **Required several courses of antibiotics--on (b) (6) (b) (6) for spiking fevers, on (b) (6) (b) (6), for a paracentesis positive for *Klebsiella***
 - **Underwent a pancreatectomy on (b) (6) (b) (6). This surgery was complicated by prolonged ileus and development of a wound infection with a gastrocutaneous fistula on (b) (6) (b) (6). Repeat scan on (b) (6) (b) (6) showed fistula regression.**
 - **Was diagnosed with multiple DVTs: on (b) (6) (b) (6), venous Doppler showed a right partially occlusive DVT in the common femoral and saphenofemoral junction and left common femoral saphenofemoral junction, proximal and distal and popliteal DVTs. She was also diagnosed with splenic vein thrombosis.**
 - **Developed stage III pressure ulcers**

On (b) (6), she was transferred to a step down unit. She was discharged from the hospital to an acute care rehabilitation facility on (b) (6).

- o Subject (b) (6): Left sided weakness
25-year-old nonsmoking Black, non-Hispanic female with a BMI of 21.9 kg/m² and a past medical history of generalized arthritis, contact dermatitis, and discoid lupus. She reported prior use of oral hormonal and emergency contraception. She applied the first patch on July 22, 2015 and removed it one day later. On (b) (6), she reported to the ER with left-sided neck pain and left-sided facial burning, which resolved spontaneously but was followed by numbness in the left upper and lower extremities. She reported feeling unsteady on her feet with a “quivering and jerking sensation” in her legs and a sub-occipital headache. The subject’s initial blood pressure was (b) (6). CT of the head was normal. MRI of the head was inconclusive for artifact vs. infarction, showing a tiny focus of apparent diffusion restriction involving the left posterior lateral medulla. An MRA of the head and neck showed possible stenosis of the left vertebral artery and no evidence of stroke. Coronary computed tomography angiogram did not indicate stenosis or dissection. Neurological examination was normal except for some subjective “sensory impairment on the left side of the face.” Strength was 5/5 in both the upper and lower extremities, with normal tone and negative finger-to-nose test. Per the neurologist’s note, the subject’s symptoms and physical findings “did not fit” with the position of the artifact seen on MRI and his opinion was that the subject did not have a stroke or transient ischemic attack. Based on this information, the SAE term was changed by the Investigator on November 3, 2015, from “mini stroke” to left-sided weakness. The subject was discharged on (b) (6) with all symptoms resolved except some residual left-sided subjective weakness. She was discharged on Plavix and aspirin, with outpatient physical therapy and follow-up with her primary care physician for 3-5 days later. A neurological follow-up in 2 months was recommended.

Summary Team Leader Comments on Special Safety Issues related to hormonal contraceptive use regarding vascular SAEs:

The three VTEs in subjects (b) (6) are probably related to use of AG200-15, though case (b) (6) was confounded by the fact that she was on an airline flight.

For subject (b) (6), the investigator categorized this subject's DVT as unrelated to the drug while the Applicant categorized the AE as possibly related to the drug. Assessment is confounded by the fact that she was pregnant. The clinical reviewer assessed the AE as possibly related and I agree with her assessment.

Subject (b) (6) had an exceptionally complicated hospital course with multiple medical problems; the DVT is more likely related to prolonged bed rest and multiple medical comorbidities.

For subject (b) (6), given the temporal relationship between the AE and drug use, the clinical reviewer assessed the relationship as possibly related to the study drug though she only wore the patch for one day. The assessment is confounded by the fact that she had elevated blood pressure and symptoms suspicious for a rheumatologic disorder (discoid lupus, dermatitis, arthritis, and depression). I agree with her overall assessment, and think though possibly related, it is unlikely.

The common factor among all the women that experienced these VTEs was that they were almost all obese (only subject (b) (6) was not). While there were more VTEs in this new trial as compared with the original trials, overall, the rate of VTE is 3.18/10,000 woman-years, which is well within the range of 3-12/10,000 woman-years for approved CHCs.

- **Regarding hepatobiliary cases:**

- **Subject (b) (6): Cholelithiasis**

- 38-year-old, non-Hispanic, Caucasian female with a BMI of 39.9 kg/m². She applied the first patch on (b) (6). On (b) (6) (Cycle 5), the subject experienced acute right upper quadrant and epigastric pain and a subsequent abdominal ultrasound showed a 2.0 cm x 1.2 cm x 1.4 cm mobile calculus in the gallbladder fundus as well as gallbladder wall irregularity. She was diagnosed with gallstones. On (b) (6), the subject underwent laparoscopic cholecystectomy with cholangiogram. The cholangiogram was normal. The surgical pathology report revealed cholelithiasis and slight chronic cholecystitis.

- Subject (b) (6): Cholecystitis
29-year-old, white, non-Hispanic female with a BMI of 40 kg/m². She applied the first patch on November 1, 2014. On (b) (6), she experienced sudden onset sharp stabbing pain radiating to her back approximately two hours after eating. Laboratory tests revealed elevated liver enzymes (ALT 111 U/L and AST 150 U/L). Abdominal ultrasound showed multiple stones in the gallbladder with gallbladder wall thickening consistent with cholecystitis. On (b) (6), the subject underwent a cholecystectomy. Intraoperative findings included edema and inflammation of the gallbladder.
- Subject (b) (6): Acute/chronic cholecystitis without obstruction and cholelithiasis
28-year-old, white, non-Hispanic with a BMI of 39 kg/m². She applied the first patch on July 15, 2015. On (b) (6), the subject reported going to the ER with sharp and stabbing right upper quadrant abdominal pain, nausea, vomiting, blood in the stool, and anorexia. A CT of the abdomen indicated mild enteritis and cholelithiasis. She had an elevated WBC count (13,000/uL) and elevated glucose (133 mg/dL). She underwent a laparoscopic cholecystectomy on (b) (6). The final microscopic diagnosis was cholelithiasis, acute and chronic cholecystitis with prominent mural fibrosis and myoid changes.
- Subject (b) (6): Cholelithiasis
33-year-old, White, Hispanic female with a BMI of 38.8 kg/m² and a medical history of cholecystitis. She applied the first patch on March 12, 2015. On (b) (6), the subject presented to the ER with complaints of a 24-48-hour history of right upper quadrant abdominal pain, nausea, and vomiting. She was diagnosed with cholelithiasis with elevated liver enzymes. Her symptoms improved and she was discharged from the hospital; however, she was later re-admitted for the same symptoms and underwent a cholecystectomy and intraoperative cholangiogram. During the cholangiogram, no contrast was visualized in the duodenum. She underwent endoscopic retrograde cholangiopancreatography (ERCP) where a stone was found in the cystic duct. No stones were found in the common bile duct. The subject had a sphincterotomy and a stent placed in the common bile duct. She was stable for discharge on (b) (6), and was

instructed to follow up for liver function tests, post-operative checkup, ERCP, and stent removal.

- o Subject (b) (6): Acute cholecystitis
28-year-old, White, non-Hispanic female with a BMI 35.1 kg/m². She applied her first patch on May 19, 2015. On June 22, 2015, during her routine in clinic visit, she revealed that she was admitted to the hospital for acute cholecystitis and underwent an emergency laparoscopic cholecystectomy on (b) (6). She recovered without sequelae and was discharged on (b) (6). She continued taking the trial drug. Per her case report form, she removed her last patch on September 28, 2015. She was lost to follow up and discontinued from the trial on January 12, 2016.
- o Subject (b) (6): Cholecystitis
32-year-old non-Hispanic, Black female with a BMI of 44.4 kg/m². On September 16, 2015, she applied the first patch. On (b) (6), she reported to the emergency room with right upper quadrant pain, vomiting, diarrhea, and jaundice over the past month. The abdominal ultrasound showed gallstones but no biliary dilatation. Hepatobiliary iminodiacetic acid (HIDA) scan results showed retained hepatic parenchymal tracer which demonstrated liver dysfunction. ALT was 157 U/L, AST was 97 U/L alkaline phosphatase was 215 U/L, bilirubin was 0.7 mg/dL, and albumin was 2.8 g/dL. The subject's hepatitis panel was negative. She underwent a cholecystectomy and liver wedge biopsy which showed chronic cholecystitis with complete impaction and innumerable stones which distend the wall of the gallbladder. The lumen showed mucosal changes, suggesting cholesterolosis and mucosal ulceration. The liver wedge biopsy showed chronic hepatitis with minimal activity and stage 1 fibrosis possibly related to transient obstruction of the biliary tree and some background chronic changes secondary to a prior occurrence. Follow up ALT and AST levels, taken on (b) (6) were within normal limits.

Summary Team Leader Comments on hepatobiliary disorders:

Cholelithiasis and cholecystitis have been associated with obesity. In the reported cases above, subjects were all obese females. As the clinical reviewer, Dr. McNeal-Jackson points out in her review, literature does not demonstrate an added increase risk with exposure to the hormones contained in AG200-15. However, the timing of the incidents relative to drug administration makes an association possible in all five cases above.

- **Regarding mood disorder/adverse events related to depression:**
 - **Subject (b) (6): Major depressive disorder**
20-year-old, White, non-Hispanic female with a history of episodic anxiety, depression and cutting since age 14. She had a history of sexual, physical, and emotional abuse. She was a recent NuvaRing user. She applied the first patch on June 29, 2015. She was admitted to the hospital on (b) (6) for a suicide attempt after allegedly ingesting 18 Tylenol tablets. She was diagnosed with major depressive and post-traumatic stress disorder which was treated with a trial of sertraline.
 - **Subject (b) (6): Worsening of pre-existing depression with suicide attempt**
20-year-old, White, non-Hispanic female with a history of depression. She was naïve to hormonal contraception. She applied the first patch on August 30, 2015. She was hospitalized on (b) (6) for worsening depression with a suicide attempt. She tested positive for opiates and marijuana. She was hospitalized for five days, stabilized, and discharged on (b) (6) with follow up in outpatient counseling. The discharge diagnosis was adjustment disorder with mixed emotional features.
 - **Subject (b) (6): Major depressive episode – recurrent**
18-year-old, Hispanic female of Chinese and Mexican descent, with a history of an eating disorder, major depression since age 12, self-harm, suicidal behavior, child abuse, and chronic marijuana use. Her drug testing at screening was negative. She reported recent use of oral hormonal contraception and prior use of emergency contraception. Concomitant medication reported at screening included the contraceptive norethindrone. She applied the first patch on October 16, 2015. She was admitted on (b) (6) for severe depression and suicidal ideation. She was diagnosed with major depressive episode - recurrent.
 - **Subject (b) (6): Bipolar disorder with suicidal ideation**
24-year-old, White, non-Hispanic with a history of bipolar disorder and attention deficit hyperactivity disorder that was not reported to the Investigator prior to her entry into the trial. She had previously used the vaginal ring and was a current user of COCs. She applied the first patch on August 19, 2015. On (b) (6), she was admitted for bipolar disorder with suicidal ideation. She was discharged on (b) (6), and was referred for intensive outpatient counseling on (b) (6). Per the Investigator's

decision, the woman's last patch was removed and she was permanently discontinued from the trial on April 14, 2016.

- o Subject (b) (6): Major depressive disorder, recurrent, severe without psychosis 22-year-old, White, Hispanic female with a history of depression and cutting. She was a recent user of oral and injectable hormonal contraceptives. She applied her first patch on July 31, 2015. On (b) (6), the subject was admitted to the hospital for a suicide attempt after taking 100 propranolol pills. She was discharged from the hospital on (b) (6) with a diagnosis of major depressive disorder, recurrent and severe without psychosis. She was advised to continue taking fluoxetine and was given a referral for psychiatric counseling. The subject applied a patch on August 17, 2015; however, the removal date of the patch was unknown. She applied another patch on August 28, 2015; however, that patch was removed later that day during her discontinuation visit.

Summary Team Leader Comments Regarding Changes in Mood Disorders related to depression:

As the clinical reviewer points out, 20.7% of the safety population in Study 23 had a pre-existing psychiatric diagnosis and all of these subjects with mood-related SAEs had pre-existing mood disorders. The clinical reviewer and I are aware that there is a temporal relationship between the AG200-15 exposure and the worsening mood symptoms in these cases, but many of the subjects also had confounding life stressors. The percentage of cases of mood disorder changes resulting a serious AE is within the range of other contraceptive trials. Depression can be an adverse reaction to the progestin component of CHCs and the labeling for CHCs addresses the risk of exacerbation of mood disorders. If approved, this product would have similar labeling regarding depressive disorders.

8.2 Dropouts and/or Discontinuations in Study 23

In the first review cycle, the CDTL, Lisa Soule, MD reported that the discontinuation rate due to AEs was 10.2% in the AG200-15 arm (as compared with 4.7% in the oral CHC arm). In Study 12, several AEs common to CHCs led to discontinuation, while in Study 13, only menstrual bleeding complaints and application site reactions lead to subject withdrawal in more than a single subject.

Cross Discipline Team Leader Review
Catherine Sewell, MD, MPH
NDA 204017/SN38/SDN 40 Twirla TCDS
FINAL

In this resubmission review cycle, for Study 23, the discontinuation rate due to AEs was 11%. The average over all three trials for AG200-15 was 10.8%. Table 17 shows the most common AEs leading to subject discontinuation.

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Table 17 Phase 3 Treatment Emergent AEs with AG200-15 Leading to Discontinuation in >1 Subject

AE leading to withdrawal	AG200-15	AG200-15	AG200-15
	N=1043	N=177	N=2031
	N (%)	N (%)	N (%)
Any Event	106 (10.2%)	13 (7.3%)	224 (11.0%)
Application site complaint (dermatitis, discoloration, erythema, irritation, pain, pruritis, rash, reaction, vesicle)	46 (4.4%)	7 (4%)	80 (3.9%)
Menorrhagia/metrorrhagia/vagi nal hemorrhage/uterine hemorrhage	13 (1.2%)	2 (1%)	40 (3 %)
Headache/migraine	9 (0.9%)		8 (0.4%)
Nausea/vomiting	9 (0.9%)		18 (0.9%)
Affect lability/mood swings/mood altered	10 (1.0%)		13 (64%)
Ovarian cyst/ovarian cyst ruptured	5 (0.5%)		0
Depression	5 (0.5%)		3 (0.2%)
Dizziness	5 (0.5%)		4 (0.2%)
Breast pain/tenderness	4 (0.4%)		3 (0.2%)
Weight increased	4 (0.4%)		5 (0.3%)
Abdominal pain	3 (0.3%)		3 (0.2%)
Abdominal distension	3 (0.3%)		4 (0.2%)
Alopecia	3 (0.3%)		2 (0.1%)
Hypertension	3 (0.3%)		2 (0.1%)
Irregular menstruation	3 (0.3%)		2 (0.1%)
Abnormal Pap/cervical dysplasia	2 (0.2%)		
Acne	2 (0.2%)		7 (0.3%)
Fatigue	2 (0.2%)		5 (0.3%)
HPV test positive	2 (0.2%)		
Irritability	2 (0.2%)		2 (0.1%)

Source: adapted from CDTL NDA 204017 Lisa Soule dated February 13, 2013, Table 20 and from NDA 204017/S38 Table 4.5.1

Team Leader Comments:

- **The narratives for the subjects who discontinued from the study were generally complete, with good information on assessment of the condition and follow-up. As in the first review cycle, the narratives frequently use the passive “was discontinued from the study,” which does not differentiate whether subjects chose to discontinue due to the reported AE or were discontinued by the investigator. Most AEs were mild and resolved by the time of discontinuation.**
- **Most cases of application site complaints were noted as mild to severe, many persisted for some time before the subject was discontinued, as in the first phase 3 trials. Some had resolved by the day of discontinuation but many were ongoing at the time of discontinuation.**
- **Most cases of vaginal bleeding were mild or moderate. The vast majority were considered resolved by the time of study discontinuation.**
- **Most cases of changes in affect or mood were mild or moderate and most were considered resolved by the time of study discontinuation.**
- **Most migraines or headaches were moderate and most resolved by the time of study discontinuation.**

8.2.1 Application Site Disorders in Study 23

Application site disorders occurred in 5.6% of study subjects in Study 23 and led to discontinuation in 3.9% of subjects. These cases were almost all considered related to AG200-15, and attributed mostly to the adhesive, as in the first review cycle.

Table 18 Application Site Disorder TEAEs – Safety Population

PreferredTerm	Any TEAE (N=2031)	Severe TEAE (N=2031)	Drug-Rel TEAE (N=2031)	SAE (N=2031)	TEAE Resulting in Discontinuation (N=2031)
Application Site Disorder	126 (6.20%)	12 (0.59%)	123 (6.06%)	0	70 (3.45%)
Application site irritation	30 (1.48%)	0	30 (1.48%)	0	23 (1.13%)
Application site discolouration	29 (1.43%)	2 (0.10%)	29 (1.43%)	0	4 (0.20%)
Application site pruritus	19 (0.94%)	6 (0.30%)	18 (0.89%)	0	16 (0.79%)
Application site rash	17 (0.84%)	1 (0.05%)	17 (0.84%)	0	14 (0.69%)
Application site erythema	14 (0.69%)	4 (0.20%)	14 (0.69%)	0	9 (0.44%)
Application site dermatitis	12 (0.59%)	2 (0.10%)	12 (0.59%)	0	10 (0.49%)
Application site dryness	10 (0.49%)	0	10 (0.49%)	0	0
Application site pain	4 (0.20%)	0	4 (0.20%)	0	0
Application site acne	3 (0.15%)	0	3 (0.15%)	0	0
Application site reaction	3 (0.15%)	1 (0.05%)	3 (0.15%)	0	2 (0.10%)
Application site hypersensitivity	2 (0.10%)	0	2 (0.10%)	0	2 (0.10%)
Application site papules	2 (0.10%)	1 (0.05%)	2 (0.10%)	0	0
Application site urticaria	2 (0.10%)	1 (0.05%)	1 (0.05%)	0	0
Application site erosion	1 (0.05%)	0	1 (0.05%)	0	0
Application site exfoliation	1 (0.05%)	0	1 (0.05%)	0	0
Application site haemorrhage	1 (0.05%)	0	1 (0.05%)	0	1 (0.05%)
Application site induration	1 (0.05%)	0	1 (0.05%)	0	1 (0.05%)
Application site pustules	1 (0.05%)	0	0	0	0
Application site ulcer	1 (0.05%)	0	1 (0.05%)	0	0
Applicationsitevesicles	1(0.05%)	0	1(0.05%)	0	0

Adverse events are coded using MedDRA version 18.1. Application site disorder is a bundled term based on the subsumed preferred terms.

Note 1: Subjects are counted once for each system organ class and once for each preferred term under the closest relationship.

Note 2: A treatment emergent adverse event is an adverse event with an onset date on or after the first patch application through Day 28 of the subject's final treatment cycle. An SAE is treatment emergent if it has an onset date on or after the first patch application.

Note 3: Related adverse events have a relationship of definitely related, probably related, or possibly related to study drug.

Source: NDA 204017/S38 Study Report Table 32, p 113/135

Team Leader Comments:

The rates of application site disorders in this study, as in Studies 12 and 13 in the 2013 review cycle, are also lower than those reported in trials for other hormonal patches. As Dr. Soule points out in her 2013 review, the Climara Pro label reports rates of 34-40% in a one-year trial, and the Ortho Evra® label reports a rate of 17% in data pooled over six and 13-cycle trials. However, the collection of data was limited and no irritation/sensitization studies were embedded in the study. Without standardized evaluations, it is unclear whether the subjects were sufficiently trained to report application site disorders. I am especially concerned that without a standard investigator assessment of patch irritation and sensitization in these studies, the rate in Studies 12, 13 and 23 is likely significantly underreported.

8.3 Common Adverse Events in Study 23

The most common AEs with an incidence rate $\geq 2\%$ are listed below in Table 19.

Table 19 Incidence of the Most Common Treatment Emergent Adverse Events (≥ 2%)

	Original NDA (ATI- CL12/13)	New Data (ATI-CL23)	Overall
	Cycles	Cycles	Cycles
Preferred Term	1-6 (N=1220)	1-13 (N=1450)	All Cycles (N=2031)
Nasopharyngitis	64 (5.25%)	83 (5.72%)	116 (5.71%)
Upper respiratory tract infection	43 (3.52%)	55 (3.79%)	100 (4.92%)
Nausea	50 (4.10%)	64 (4.41%)	84 (4.14%)
Headache	52 (3.36%)	72 (3.55%)	124 (3.56%)
Urinary tract infection	26 (2.13%)	48 (3.31%)	72 (3.55%)
Cervical dysplasia	28 (2.30%)	90 (6.21%)	17 (0.84%)
Sinusitis	35 (2.87%)	52 (3.59%)	54 (2.66%)
⁴¹ Dysmenorrhea	22 (1.80%)	26 (1.79%)	47 (2.31%)
Weight increased	23 (1.89%)	30 (2.07%)	41 (2.02%)
			71 (2.04%)

Source: NDA 204017, Module 5.3.5.3 Safety Update, Table 14.4.2.3.1

Team Leader comments:

The rate of “any AE” is 53.42% for Study 23. This rate is similar to the previous Studies 12 and 13, and is lower than contraceptive trials in general, where AE incidence is 70-80%. With high drop-out and withdrawal rates, the clinical reviewer and I have concerns that AEs were under-reported by subjects in this trial. It is unclear why the rates of AEs are not consistent with other trials. Other

indicators of study conduct (overall discontinuation rate, lost-to-follow up, data collection) are improved over the first review cycle, so underreporting would be expected to be inconsistent with those improvements. My primary concern is that if the investigators failed to elucidate adverse events related to patch wear, that the AE results are not reflective of real world use.

The incidence rates of the most common AEs unrelated to CHCs were comparable across all the trials.

No new safety signals for a combined hormonal contraceptive were identified from the data in Study 23.

8.4 Laboratory Data and Vital Signs

Dr. Davis' review of the initial NDA submission addressed the evaluation of laboratory parameters and vital signs in the original phase 3 studies. There were no new safety signals of concern from the data in this resubmission identified by the clinical reviewer in laboratory parameters or vital sign data (See Clinical review dated December 13, 2017). Patch subjects demonstrated slight alterations in lipids, a known effect of hormonal contraceptive use. There was also a slightly greater chance of clinically significant changes in blood pressure (defined as systolic ≥ 140 mm Hg and an increase of ≥ 20 from baseline, or diastolic ≥ 90 and an increase of ≥ 15 from baseline). Hypertension is also described in class labeling for hormonal contraceptives. None of these changes were determined to be sufficiently concerning as to require a postmarketing required study or trial. Again, these changes are known for hormonal contraceptives and no new safety signals were identified.

Team leader comment:

I concur that there are no new safety issues regarding laboratory data or vital signs identified based on the safety data in the resubmission.

8.5 Overall Summary of Safety

The safety database includes 29,900 cycles for AG200-15, well over the requested 10,000 cycles. The Applicant surpassed the Division's requirements for numbers of completers of 13 cycles for evaluation of efficacy and safety. The Applicant made efforts to improve study conduct, data collection, data cleaning and reporting as requested by the Division after the 2013 review cycle in conducting Study 23.

My concerns with the safety of this product are as follows:

- The overall AE rate and SAE rate is slightly higher in Study 23 for this review cycle, and remains lower than in other contraceptive trials. While there may be an unresolved question of underreporting, this is overshadowed by the improvements in overall study conduct and data quality.
- The rate of VTE is 3.18/10,000 woman-years, which is well within the range of 3-12/10,000 woman-years for approved CHCs. The rates of hepatobiliary disorders and changes in mood are on par with other CHCs.
- Application site disorders occurred in 5.6% of study subjects in Study 23 and led to discontinuation in 3.9% of subjects. These cases were almost all considered related to AG200-15, and attributed mostly to the adhesive, as in the first review cycle. The rates of application site disorders are lower than that reported in trials for other hormonal patches.

Overall the safety profile for AG200-15 did not demonstrate any new safety issues. It is expected that the serious risks including hepatobiliary and other adverse events can be labeled in a similar manner. However, the outstanding AEs related to adhesive issues remain an unaddressed safety concern. In addition, it is important to recognize that VTE databases in clinical trials are small and may not be predictive of real world use. It is likely that if this product were approved that a significantly large postmarketing trial to evaluate the risk of VTE and other thrombotic events would be necessary.

9 Advisory Committee Meeting

There was no Advisory Committee meeting for this application. As the key issues to resolve are CMC related, this resubmission did not present issues that would benefit the need for outside clinical or statistical expert advice.

10 Pediatrics

In the first review cycle, per the review by Lisa Soule, MD dated February 13, 2013, the Applicant did request a waiver of pediatric studies in premenarcheal females < 17 years of age because the indication is not relevant to this population. The Applicant also requested a waiver of studies in postmenarcheal females < 17 years, with the justification that safety and

efficacy data for this population can be extrapolated from the adult data. The Division concurred that a partial waiver and extrapolation was appropriate. The Pediatric Review Committee (PeRC), on January 16, 2013, agreed to a partial waiver for patients from birth to 11 years of age, and to extrapolate efficacy for patients from 12 to 16 years of age. The NDA resubmission did not include an agreed-upon initial pediatric study plan (iPSP). For the resubmission, the Applicant submitted a request for a partial waiver for pediatric assessment in premenarcheal and postmenarcheal females less than 17 years of age based on assertions that “pediatric studies are not applicable in premenarcheal females because the claimed indication is not relevant to this pediatric subpopulation,” and that for postmenarcheal females less than 17 years of age, “the requirement for pediatric studies in this subpopulation may be fulfilled through extrapolation of efficacy data from adult trials.”

During this review cycle, on December 6, 2017, the Pediatric Review Committee (PeRC) met to discuss the iPSP proposed by the Applicant. Because of the pending Complete Response, the PeRC did not provide comments on the proposed iPSP and recommended that the Division include the iPSP requirement in the CRL to the Applicant. The iPSP will likely be a partial waiver for boys and for premenarcheal females < age 11 and an assessment for postmenarcheal females <17.

11 Other Relevant Regulatory Issues

There are no outstanding regulatory issues for this application identified by the regulatory project management team.

Team Leader comment:

I concur that there are no outstanding regulatory issues that require further resolution this cycle.

11.1 Ethics and Good Clinical Practice

The quality and integrity of the data and information in this NDA resubmission was acceptable. The clinical trial was conducted in compliance with Good Clinical Practices and provided appropriate financial disclosure information. On May 23, 2017, the Applicant certified the following debarment statement (Module 1.3.3 Debarment Statement): “Agile Therapeutics, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetic Act about this application, NDA 204017 for AG200-15.”

The Division of Scientific Investigations (DSI) conducted two clinical inspections per DBRUP's request. An overview of DSI's findings are outlined in Table 20 below:

Table 20 Clinical Inspection Summary by DSI

Clinical Trial	Indication	Investigator Site Number	Date of Inspection	Number Women Enrolled Number of Completers	Action
ATI-CL23	Contraception	Strout (Site 1082)	October 2-5, 2017	161 enrolled 32 completers	No Action Indicated (NAI)
		Kimble (Site 1079)	September 5-7, 2017	45 enrolled 14 completers	Voluntary Action Indicated (VAI)

Source: Clinical Review NDA 204017 Nneka McNeal-Jackson, MD dated December 15, 2017, adapted from Division of Scientific Investigation (DSI) Clinical Inspection Summary dated November 16, 2017

The inspector issued a Form 483 at the end of the inspection of site 1079 (Dr. Kimble), citing the following:

- Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation
- Sub-investigator participation in trial activities after his formal removal by the Applicant for potential financial conflict of interest

On September 26, 2017, Dr. Kimble addressed the inspector's observations in a written response noting that the site implemented "corrective actions to prevent the recurrence of the findings." DSI deemed Dr. Kimble's written response to be acceptable. Per the DSI, for site 1079, "neither the safety nor efficacy considerations appear to be affected;" further the "study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication."

For full details, see the Clinical Inspection Summary dated November 16, 2017.

Team leader comment:

I concur with DSI that there are no outstanding data integrity or site issues with the resubmission.

11.2 Labeling

No labeling negotiations regarding the content and format of the final product labeling as the Applicant has significant deficiencies. The proposed product labeling currently does not comply with the requirements for labels and labeling in 21 CFR 201. If the Applicant resubmits the Application and deficiencies are resolved, labeling will need to be revised from that in the resubmission.

12 Postmarketing Recommendations

At this time, no Risk Evaluation and Management Strategies (REMS), Postmarketing Requirements (PMRs) or Postmarketing Commitments (PMCs) are recommended.

Team Leader Comment:

I concur that no REMS, PMR or PMCs are necessary to convey to the Applicant at this time. However, it is likely that if the product will be approved, the Division would recommend that a large postmarketing requirement trial be designed to better evaluate the risk of serious VTE and thromboembolic risks.

13 Recommended Comments to the Applicant

The following comments will be conveyed to the Applicant in the regulatory action CR letter:

Data from your clinical trial (ATI-CL23) did not demonstrate acceptable efficacy for a combined hormonal contraceptive product. In addition, the rates of subject discontinuation in study ATI-CL23 was above 50% and unscheduled bleeding (cycle control) on treatment was over 40%. It is unclear whether the reduced product efficacy results and cycle control were a result of inadequate adhesion of your product, application site tolerability issues, unscheduled bleeding or other issues.

Twelve additional on-treatment pregnancies were identified from the data in Study ATI-CL23 which resulted in a calculation of a Pearl Index (PI) of 5.83 (95% CI 4.45-7.21). While a significant number of the FDA-adjudicated pregnancies occurred in women who had delays in applying patches, the Pearl Index in Study ATL-CL23 may

underrepresent real-world, worst-case scenario contraceptive use because of the significant withdrawal and drop-out rates.

The serious risks associated with combined hormonal contraceptives, including thromboembolic events, appear to be similar with use of your product. Given that your combined hormonal contraceptive product has a sole benefit of a more convenient dosing schedule, we do not concur that the benefit in the intended population is offset by the reduced efficacy, cycle control and adhesion issues that were identified.

Due to concerns regarding adhesion and efficacy with your levonorgestrel/ethinyl estradiol transdermal delivery System, 120/30 mcg/day, assess whether the unacceptable in vivo adhesion properties are the result of the current design and formulation of the drug product, or are due to some other factor(s) and how this may contribute to efficacy, cycle control and safety of your product. If the unacceptable adhesion is due to the design and formulation of the drug product, consider designing a new transdermal system and conduct another clinical trial with the new transdermal system in the US population.

In your next submission, include an initial Pediatric Study Plan (iPSP). This should likely be a partial waiver for boys and for premenarcheal females < age 11 and an assessment for postmenarcheal females <17.

Additional comments outlined in the reviews by the CMC, Compliance and statistical reviewers will also be conveyed to the Applicant.

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/s/

CATHERINE A SEWELL
12/20/2017

AUDREY L GASSMAN
12/21/2017

CLINICAL REVIEW

Application Type	505(b)2 NDA
Application Number(s)	204017
Priority or Standard	Standard

Submit Date(s)	June 26,2017
Received Date(s)	June 26, 2017
PDUFA Goal Date	December 26, 2017
Division / Office	Division of Bone, Reproductive, and Urologic Products (DBRUP)/Office of Drug Evaluation III (ODE III)

Reviewer Name(s)	Nneka N. McNeal-Jackson, M.D.
Review Completion Date	December 15, 2017

Established Name	Ethinyl Estradiol and Levonorgestrel
(Proposed) Trade Name	Twirla
Therapeutic Class	Hormonal Contraceptive
Applicant	Agile Therapeutics, Inc.

Formulation(s)	Transdermal patch (transdermal contraceptive delivery system)
Dosing Regimen	One patch placed every seven days for three consecutive weeks followed by one week “patch-

	free” period
Indication(s)	Prevention of Pregnancy
Intended Population(s)	Women of reproductive age

Template Version: March 6, 2009

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Nneka N. McNeal-Jackson, M.D.
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, the medical officer recommends that AG200-15, the to-be-marketed transdermal contraceptive system (TCDS) containing 2.6 mg levonorgestrel (LNG) and 2.3 mg ethinyl estradiol (EE) for the prevention of pregnancy in women of reproductive age, receive a Complete Response Letter (CRL).

1.2 Risk Benefit Assessment

The clinical reviewer regards the risk-benefit for the AG200-15 TCDS to be unfavorable. While the Applicant appeared to improve study conduct for trial ATI-CL23 from the previous review cycle, DBRUP discovered 12 additional on-treatment pregnancies in the trial. Using the intent-to-treat (ITT) population in women (age 18 to 35) yielded a Pearl Index (PI) of 5.83 [95% Confidence Interval (CI) 4.45, 7.21]. The Pearl Indices are still considerably higher than those for previously approved combined hormonal contraceptives (CHCs). It is plausible that this comparably lower efficacy is related to inadequate patch adhesion. Adhesion of the TCDSs to skin is critical to the effective delivery of the drug product. In this trial, for all TCDSs applied, at least 5% had complete detachment, with 2.1% of all TCDSs showing complete detachment on the first day of wear. 54.4% of women experienced complete patch detachment at some point during the 13-cycle trial. 10-20% of all users required four or more TCDSs per cycle to maintain therapy per labeled instructions; 14.7% of all cycles studied (N=18,841) required the use of four or more TCDSs. There remain several other significant deficiencies regarding the drug product quality.

The occurrence of adverse events (AEs) in trial ATI-CL23 differed from those for the previous trials, ATI-CL12 and ATI-CL13. For trial ATI-CL23, there were six venous thromboembolic events (VTEs), six psychiatric AEs, and seven hepatobiliary AEs. There was more unscheduled bleeding in this trial versus trial ATI-CL12. 41.3% of women experienced unscheduled bleeding/spotting episodes by cycle 13 in trial ATI-CL23 versus 22.8% of women by cycle 13 in trial ATI-CL12. This is higher than that seen with other approved CHCs. On balance, the safety profile of AG200-15 is similar to that of other approved CHCs, with the exception of more unscheduled bleeding. Given that the Applicant provided no evidence that the product offers a better safety profile than that of other approved CHCs, this does not justify the acceptance of a higher PI. This concern, coupled with concerns about product quality, result in an unfavorable risk-benefit assessment for this drug.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarketing risk evaluation or mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

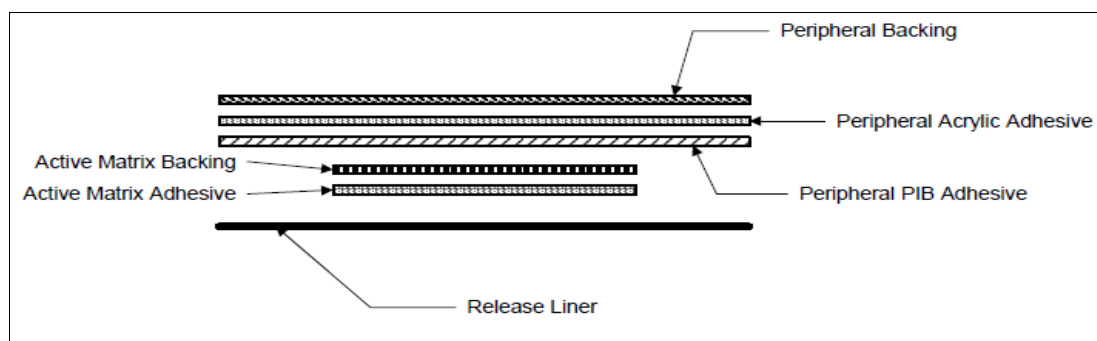
There are no recommendations for postmarketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

AG200-15 is a transdermal contraceptive system (TCDS), containing 2.6 mg LNG and 2.3 mg EE. Per the application, “it is designed to deliver daily hormone exposure, as measured by an area under the curve (AUC), of EE and LNG comparable to oral doses of 120 mcg LNG and 30 mcg of EE.” “AG200-15 is comprised of a 15 cm² active adhesive matrix integrated with a larger peripheral adhesive system (28 cm²).” The hormones LNG and EE, as well as skin permeation enhancers, are contained in the active uncross-linked acrylic adhesive matrix. The addition of skin permeation enhancers into the active matrix necessitates additional supporting adhesives. The peripheral adhesive system, with its bidirectional elasticity, is intended to enhance adhesion. The release liner is 40.33 cm². When viewed in cross-section, the AG200-15 TCDS appears as shown in Figure 1.

Figure 1: Schematic Depiction of the AG200-15 TCDS



Sources: NDA 204017, Module 3.2.P.1 Description on Drug Product and Composition of the Drug Product

2.2 Currently Available Treatments for Proposed Indications

Contraceptive methods for women include the following: barrier methods (female and male condoms, cervical cap, and diaphragm); intrauterine devices (levonorgestrel-containing, copper-containing); contraceptive implantable devices; contraceptive vaginal rings; combined oral contraceptive (COC) pills (including extended cycle); progestin only oral contraceptive

pills; injectable contraceptives; and surgical sterilization (tubal ligation and intra-tubal obstructive devices).

There are no currently approved TCDS that contains ethinyl estradiol and levonorgestrel.

Ortho-Evra[®] was the first brand-name TCDS approved in the United States under NDA 21180 on November 21, 2001. The company discontinued the manufacturing of Ortho-Evra for business reasons, not for reasons of safety or effectiveness, and the last lot expired in August 31, 2015.

Ortho-Evra[®] had a contact surface area of 20 cm². It contained 6 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE) with a delivery rate of approximately 150 mcg of NGMN and 35 mcg of EE per day. Per the prescribing information, in 3 large 12-month clinical trials in North America, Europe and South Africa, 3330 women (ages 18–45) completed 22,155 cycles of Ortho-Evra[®] use. The pregnancy rate in women aged 18 to 35 years was 1.07 (95% (CI) 0.60, 1.76) per 100 woman-years of Ortho-Evra use. The approved labeling had a limitation of use to women weighing less than 198 pounds (90 kg) due to possible reduced efficacy in heavier women. For patch adhesion, “approximately 2% of the cumulative number of patches used completely detached and 3% partially detached. The proportion of subjects with at least one patch that completely detached ranged from 2% to 6%, with a reduction from Cycle 1 (6%) to Cycle 13 (2%).”¹

In post marketing surveillance of Ortho-Evra[®], there was an increase in the reporting of thromboembolic events. Since its approval, the following five epidemiological studies were conducted:

- The (b) (4) study with norgestimate (NGM)-containing oral contraceptives as the comparator, including a 24-month extension, based on the (b) (4); this study included patient chart review to confirm the VTE occurrence.
- The Boston Collaborative Drug Surveillance Program (BCDSP) with NGM-containing oral contraceptives as the comparator (BCDSP NGM), including two extensions of 17 and 14 months, respectively, based on the Pharmetrics database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.^{3, 4, 6}
- BCDSP with LNG-containing oral contraceptives as the comparator, based on the Pharmetrics database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.⁵
- BCDSP with LNG-containing oral contraceptives as the comparator, based on the Marketscan database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.⁵
- FDA-funded study with two groups of comparators [1) LNG-containing oral contraceptives, and 2) oral contraceptives that contain LNG, norethindrone or norgestimate], based on Kaiser Permanente and Medicaid databases. This study used all cases of VTE (idiopathic and non-idiopathic) and included patient chart review to confirm the VTE occurrence.¹⁰

As noted in the updated labeling for Ortho Evra[®] approved August 22, 2012, some of the data from these studies with different designs suggest an increased risk of VTE with the use of Ortho Evra[®] compared to use of some combined oral contraceptives. The relative risk estimates range from 1.2 to 2.2. None of the studies have adjusted for potential confounders such as body mass index (BMI), smoking or family history of VTE. The interpretations of these relative risk estimates range from no increase in risk to an approximate doubling of risk.

Xulane, the generic of Ortho-Evra[®] approved on April 16, 2014 under abbreviated new drug application (ANDA) 200910, is the only TCDS currently marketed in the United States. It has a contact surface area of 14 cm². Per the prescribing information, Xulane contains 4.86 mg, USP (NGMN) and 0.53 mg, USP (EE) with a delivery rate of approximately 150 mcg of NGMN and 35 mcg of EE per day. A new patch is applied each week for three weeks with no patch applied on week four.

2.3 Availability of Proposed Active Ingredient in the United States

Ethinyl estradiol is available in many formulations of COCs that are currently being marketed.

Levonorgestrel is available alone in oral, intrauterine and dermal implantable formulations for the indications of emergency and long-acting reversible contraception and heavy vaginal bleeding. Levonorgestrel, in combination with estrogens, is available in oral formulations for the indications of contraception, vasomotor symptoms, and osteoporosis prevention.

2.4 Important Safety Issues with Consideration to Related Drugs

Combined hormonal contraceptives (CHC) are associated with the following adverse events:

- Vascular events
 - Venous [deep venous thrombosis (DVT), pulmonary embolism (PE)]
 - Arterial [(myocardial infarction (MI), cerebrovascular accident (CVA)]
- Hypertension
- Gall bladder disease
- Liver disease
- Worsening Mood disorders
- Carbohydrate and Lipid Metabolic effect
- Bleeding irregularities
- Headaches
- Nausea
- Breast tenderness
- Weight Gain

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 57731

- On January 19, 1999, the Applicant opened Investigational New Drug (IND) 57731 for the prevention of pregnancy.
- On September 22, 2008, DBRUP conducted an End-of-Phase 2 meeting with the Applicant and provided the following recommendations:
 - Conduct a relative bioavailability study comparing the to-be marketed TCDS to an oral comparator
 - Conduct trials assessing the effects of different application sites (buttock, abdomen, and upper arm) and external conditions (i.e. sauna, exercise, cold water) on the pharmacokinetic (PK) profile of the TCDS

DBRUP provided recommendations on the design of pivotal phase 3 trials in support of an NDA for AG200-15.

- On June 22, 2009, the Applicant submitted clinical protocol ATI-CL12 for a Special Protocol Assessment (SPA). This was an open-label, parallel-group, randomized, Phase 3 trial that compared the 12- month contraceptive efficacy and safety of the AG200-15 TCDS to a COC (Levlite[®]).
- On August 7, 2009, DBRUP sent the Applicant a Special Protocol No Agreement letter to clinical protocol ATI-CL12. Key comments and recommendations listed in the No Agreement Letter were as follows:
 - Recommendations
 - To enroll women less than 18 years of age
 - To use the earliest possible ultrasound to accurately assess the date of conception
 - To exclude cycles when back up contraception was used or when no sexual activity occurred
 - Clarification that pregnancy that occurred when additional contraception was used should be counted as on-treatment for the statistical analysis
 - Modification of Daily Diary card to capture 4 week cycles where no sexual activity occurred in order to exclude those evaluable cycles from the efficacy analysis and include in the safety analysis
 - Clarification of information needed for cycle control data
 - Need for
 - Clearer definitions of bleeding and spotting
 - More detailed plan for pregnancy follow-up

- o Request for return to fertility data in a subset of women who discontinued the trial with the intent to become pregnant
- On November 24, 2009, the Applicant submitted clinical protocol ATI-CL13 for a SPA. This was an open label, randomized, phase 3 trial that compared the 6- month contraceptive efficacy and safety of the AG200-15 TCDS to a COC (150 mcg LNG/30 mcg EE).
- On January 7, 2010, DBRUP sent the Applicant a Special Protocol No Agreement letter for clinical protocol ATI-CL13. In the No Agreement letter, DBRUP provided the following key comments and recommendations:
 - o Non-concurrence with exclusion criteria related to body mass index ($BMI \geq 32$) and smoking (women under age 35 who smoked 10 or more cigarettes/day)
 - o Recommendation to exclude 28-day cycles from the Pearl Index (PI) evaluation in which backup or emergency contraception was used or no sexual activity occurred
 - o Need for
 - Clearer definitions and quantification of bleeding and spotting
 - More detailed plan for pregnancy follow-up
 - o Request for return to fertility data in a subset of women who discontinued the trial with the intent to become pregnant
- On March 9, 2010, DBRUP conducted a Type A meeting with the Applicant to discuss the details of the November 24, 2009 Special Protocol No Agreement Letter for clinical protocol ATI-CL12. DBRUP provided the following key recommendations:
 - o Enrollment of a sufficient number of women into the trial to achieve a minimum 10,000 evaluable cycles of TCDS exposure including a percentage of truly naïve to hormonal contraceptive users (potentially at higher risk of thromboembolic events)
 - o Monitoring of enrollment and drop-out rates during the trial to increase recruitment, if needed
 - o Priority use of ultrasound for more accurate pregnancy dating
 - o Definitions of bleeding and spotting
 - o Consideration of breakthrough bleeding and spotting for all cycles of the clinical trial instead of selected number of cycles as initially proposed
 - o Inclusion of at least 200 women with a $BMI \geq 35 \text{ kg/m}^2$

DBRUP provided additional comments and recommendations to the Applicant to address clinical pharmacology and CMC deficiencies.

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- On April 21, 2010, the Applicant submitted revised clinical protocol ATI-CL13 for a SPA. On June 3, 2010, DBRUP sent the Applicant a Special Protocol Agreement Letter and provided key recommendations to enroll women with a higher BMI (≥ 32) and to use Mishell guidelines¹¹ to analyze the bleeding profiles of the trial participants.
- On June 21, 2010, DBRUP received revised clinical protocol ATI-CL12 for a SPA. On July 13, 2010, DBRUP sent the Applicant a Special Protocol Agreement letter.
- On August 11, 2011, the Applicant requested a pre-NDA meeting which DBRUP granted. The Applicant submitted their meeting package on September 23, 2011 to which DBRUP provided preliminary comments on October 20, 2011. On October 21, 2011, the Applicant cancelled the meeting based on the adequacy of the Agency's preliminary responses.

NDA 204017 (Original Submission, First Review Cycle)

- On April 13, 2012, the Applicant submitted the NDA for the Agile TCDS, composed of ethinyl estradiol and levonorgestrel with the proposed name TWIRLA[®], under NDA 204017.
- The Applicant submitted protocol amendments to the NDA dated April 19, June 1, July 10, 16, 18, August 3, 10, 15, 16, 31, October 17, 19, 31, November 29, December 4 and 12 of 2012; January 11, 16, 17, 18, and 29 of 2013.
- On February 13, 2013, DBRUP issued a Complete Response Letter (CRL) citing the following key issues:
 - Unproven drug efficacy. The Pearl Indices for the two pivotal trials (ATI-CL12 PI 7.50 with an upper bound of the 95% CI of 9.97; ATI-CL13 PI of 8.19 with an upper bound of the 95% CI of 16.19) were higher than any other approved combined hormonal contraceptive with similar risk. The Applicant provided no evidence that the product had a better safety profile than other combination hormonal contraceptives to justify acceptance of the higher Pearl Indices; therefore, the risk-benefit assessment for this drug was considered unfavorable. DBRUP advised the Applicant to conduct another pivotal trial with rigor and close oversight to establish efficacy.
 - Numerous deficiencies regarding drug product quality.
- On June 24, 2013, DBRUP received an NDA resubmission from the Applicant in an attempt to address all the issues outlined in DBRUP's February 2013 CRL.
- On July 17, 2013, DBRUP sent that Applicant an Incomplete Response Letter (ICRL) for the NDA resubmission reemphasizing the need to conduct an additional clinical trial to establish efficacy. DBRUP determined that the Applicant's responses to the product quality deficiencies were inadequate.
- On August 7, 2013, the Applicant requested a meeting to discuss whether DBRUP could reach agreement that the PI, in the ranges shown in trials ATI-CL-12 and ATI-

CL13, provided satisfactory proof of efficacy. DBRUP agreed to the meeting and provided preliminary written responses to the Applicant's questions, reiterating that the Agency has never approved a CHC for which the upper bound of the 95% CI around the PI exceeded 5.

DBRUP restated that it did not foresee a path to agreement where the PI, as presented in the current trials, could serve as sufficient proof of efficacy to inform a favorable risk-benefit assessment. Given the known safety risks associated with CHC use, DBRUP believed that a high level of efficacy in preventing pregnancy must be demonstrated in order to justify the risks.

- On October 10, 2013, during the face to face meeting, DBRUP noted that in addition to reaching agreement on a protocol for a new pivotal trial, the Applicant would need "to execute the study well and appropriately handle challenges in study conduct, such as recruitment, monitoring, discontinuations, missing data, etc." The Applicant was encouraged to monitor the study conduct closely and communicate with FDA during the course of the trial if any problems arose.
- On January 10, 2014, in accordance with the July 17, 2013 ICRL, the Applicant requested a meeting to discuss high-level issues of the protocol for the new clinical trial. A Type C guidance meeting was scheduled for February 11, 2014. In the preliminary comments dated February 7, 2014, DBRUP provided the Applicant recommendations on the trial design, site selection for patient recruitment, pregnancy adjudication for efficacy, outcome measures for bleeding profiles and patch adherence, and cervical cancer screening. The Applicant cancelled the face-to-face meeting upon receipt of the preliminary comments.

IND 57731 (Planning for new pivotal clinical trial)

- On June 7, 2014, the Applicant submitted the new clinical protocol ATI-CL23. This was a single-arm, open-label, multicenter, phase 3 trial to assess the 12-month contraceptive efficacy and safety of the AG200-15 TCDS. Key comments and recommendations conveyed to the Applicant were as follows:

Clinical

- Concerns that the Applicant's proposed strategies to minimize loss to follow up and poor compliance could result in contact fatigue and undermine the assessment of real-world use of the drug product
- Recommendation for less rigid start (within 48-72 hours of spontaneous menses) of hormonal contraception
- Recommendation to not discourage patch exposure to water and to capture that information in daily eDiary
- Recommendation to provide home pregnancy tests to the trial participants to capture pregnancy as early as possible and to confirm pregnancy at the clinical sites

- o Specification of a first trimester ultrasound as the most accurate dating method for pregnancy
- o Clarification to not censor the women who were 35 years of age at the time of trial enrollment and turn 36 during trial from the primary efficacy cohort
- o Recommendation to provide the PI for all women greater than 35 years of age
- o Inclusion of women under the age of 18 years
- o Clarification of inclusion/exclusion criteria to standardize the entry criteria
- o Recommendation to record episodes where no bleeding occurs

CMC

- o Advice on the Applicant's proposed plan for *in vivo* assessment of patch adhesion with patient-collected data in an electronic diary, including:
 - Definitions of the measurements in the patch adhesion scale
 - Expectations that:
 - Mean adherence should be greater than 90% and there should be no instances of detachment seen.
 - The need to investigate events of poor adherence with elucidation of possible causes and risk factors.
 - Instructions that subjects should use the transdermal system as proposed and that they should not be permitted to use product reinforcement, such as taping the edges or use of overlays, nor should they occlude the product from water during bathing during the *in vivo* adhesion evaluation.
 - Reference to additional information regarding the design of *in vivo* adhesion studies

NDA 204017 (Resubmission)

- On October 10, 2014, the Applicant requested a meeting to discuss the Chemistry, Manufacturing, and Controls (CMC) deficiencies identified in the February 2013 CRL. The Office of New Drug Product Quality (ONDPQ) granted Type C meetings to the Applicant on December 15, 2014 and August 31, 2016. The Office of New Drug Product Quality (ONDPQ) provided comments and recommendations regarding the numerous CMC deficiencies the Applicant attempted to address in their respective meeting packages. Due to the adequacy of responses, the Applicant cancelled each of the face-to-face meetings.
- On December 16, 2016, the Applicant requested a Pre-NDA meeting to discuss the appropriateness of the NDA submission. The Type B meeting occurred on March 14, 2017. Key recommendations and comments provided to the Applicant were as follows:
 - o Present subgroup analyses defined by body weight, median weight, and body weight quartiles

- o Include the data from trials ATI-CL12 and ATI-CL13 in the Clinical Overview of the new submission
 - o Include the data from trials ATI-CL23, ATI-CL12 and ATI-CL13 in the Summary of Clinical Safety
- On June 26, 2017, the Applicant submitted the Class 2 Resubmission – Complete Response to the Agency’s February 13, 2013 CRL.
- On September 8, 2017, as part of the Class 2 resubmission, the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed proprietary name, Twirla, from a safety and misbranding perspective. On September 11, 2017, DMEPA sent the Applicant a Propriety Name Request Conditionally Acceptable letter deeming Twirla an acceptable proprietary name pending NDA approval.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the NDA was good. The NDA was well organized with appropriately identified headings and subheadings that facilitated access to pertinent information for this clinical review.

The Applicant promptly responded to DBRUP’s clinical information request dated September 1, 2017.

In the cover letter dated September 12, 2017, the Applicant stated the following:

“The Information Request (Twirla IR 8 31 17) received from the Agency on September 1st, 2017 included requests for clinical information which are being addressed in this amendment. A response is provided in Module 1.11.1.”

The cover letter was hyperlinked to relevant section in the NDA that were well organized to address DBRUP’s inquiries.

3.2 Compliance with Good Clinical Practices

The clinical trial report for trial ATI-CL23 dated May 25, 2017 included the following Good Clinical Practice (GCP) Statement:

“This study was conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of the ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, 56, and 312 and Title 45, Part 164.”

The Applicant asserted that the clinical protocol [Trial ATI-CL23], informed consent form,

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Investigator Brochure, and any trial-related materials were reviewed and approved by a duly constituted Institutional Review Board (IRB). The IRB reviewed the ethical, scientific, and medical appropriateness of the clinical trial, and provided approval for the trial before authorization of drug shipment to a study site. A letter documenting the IRB approval was provided to the Applicant prior to initiation of the clinical trial. All amendments to the protocol were subject to the same requirements as the original protocol.

The Investigators asserted that all aspects of the IRB review were conducted in accordance with current institutional, local, and national regulations. Compliance with these regulations and guidelines also constituted compliance with the ethical principles described in the current revision of the Declaration of Helsinki.

The Applicant asserted that each potential trial participant provided written informed consent before the initiation of any trial-related activity and after the investigator explained the purpose and associated risk of the trial and answered all the trial participant's questions.

On May 23, 2017, the Applicant certified the following debarment statement (Module 1.3.3 Debarment Statement):

“Agile Therapeutics, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetic Act about this application, NDA 204017 for AG200-15.”

The Division of Scientific Investigations (DSI) conducted two clinical inspections per DBRUP's request. The reasons listed for the inspections were larger number of subjects enrolled relative to the other clinical sites, high discontinuation rates, and larger number of major protocol violations. The details of the clinical inspection are highlighted in **Table 1**. For full details, see the Clinical Inspection Summary dated November 16, 2017.

Table 1: Clinical Inspection Summary by DSI

Clinical Trial	Indication	Investigator Site Number	Date of Inspection	Number Women Enrolled Number of Completers	Action
ATI-CL23	Contraception	Strout (Site 1082)	October 2-5, 2017	161 enrolled 32 completers	No Action Indicated (NAI)
		Kimble (Site 1079)	September 5-7, 2017	45 enrolled 14 completers	Voluntary Action Indicated (VAI)

Source: Adapted from Division of Scientific Investigation (DSI) Clinical Inspection Summary dated November 16, 2017

For site 1082 (Dr. Strout), the inspector “did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.” No Form 483

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was issued at the end of the inspection. Per the DSI, Dr. Strout conducted the trial adequately and the data generated appeared acceptable for the indication.

For site 1079 (Dr. Kimble), the inspector issued a Form 483 at the end of the inspection citing the following:

- Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation
 - Subject (b) (6) with a non-serious adverse event of severe pelvic cramping attributed as definitely related to study treatment not included in the adverse events (AE) data listing
 - Subjects (b) (6)'s use of concomitant medications that were not included in the concomitant medication data listing. (Notes made by DSI inspector: Subject (b) (6) used Vyvanse 40 mg; Subject (b) (6) used Levaquin 500 mg and Biaxin 500 mg. Antibiotics, when used with hormonal contraceptives, can decrease contraceptive efficacy.)
- Sub-investigator participation in trial activities after his formal removal by the Applicant for potential financial conflict of interest
 - Sub-investigator conduct of four physical examinations on trial participants despite his removal from the trial

On September 26, 2017, Dr. Kimble addressed the inspector's observations in a written response noting that the site implemented "corrective actions to prevent the recurrence of the findings." DSI deemed Dr. Kimble's written response to be acceptable. Per the DSI, for site 1079, "neither the safety nor efficacy considerations appear to be affected;" further the "study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication."

Reviewer Comments:

The clinical reviewer confirmed that Subjects (b) (6), who took concomitant antibiotics, did not become pregnant during the trial. The clinical reviewer also confirmed that Subject (b) (6), who experienced severe pelvic pain, did not prematurely discontinue the trial due to an AE. The clinical reviewer agrees that the findings did not appear to affect the efficacy or safety profile of the drug.

3.3 Financial Disclosures

The applicant signed a Form 3454 that certifies "...[they] have not entered into any financial arrangements with the listed clinical investigators (list of names provided) whereby the value of compensation to the investigator could be affected by the outcome of the trial (as defined in 21 CFR 54.2(a)... that each listed clinical investigator required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose such interests... that no listed

investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Caroline Strasinger, Ph.D., the Product Quality reviewer for the NDA resubmission, completed the drug product review dated November 16, 2017. In her review, she referred to the February 2013 CRL which included eight deficiencies and three additional comments from Product Quality. The issues ranged “from concerns (b) (4) particularly related to the (b) (4) Laser Etching for the identifying label, the product release and stability specification (cold flow, shear, permeation enhancer content, etc.), and subsequent justification for acceptance criteria, impurities, inadequate Drug Master File (DMF), facility inspection, and concerns related to *in vivo* adhesion performance.” Further, there was insufficient information to support manufacturing equipment changes (b) (4) clinical trial batch process to commercial scale.

Due the numerous deficiencies noted during that CRL, other areas of the review [control of excipients (adhesives) manufacturing process, justification of specification for excipients (adhesives), process validation/evaluation and specification, justification of specification, shelf-life and post-approval stability protocol] were deferred to the next review cycle.

Per the Integrated Quality Assessment dated December 13, 2017, Mark Seggel, Ph.D., the acting Product Quality Team Lead, explained, “At the time that the CRL was issued, it was fully expected that the product would be re-designed or reformulated. The product was not reformulated, but another clinical study (ATI-CL23) was conducted.”

In the current review cycle, Dr. Seggel indicated that the DMFs for LNG and EE were reviewed and found adequate to support the approval of the NDA.

Dr. Strasinger, based on her review of the product quality data for ATI-CL23, concluded that “the formulation and product design of the drug product used in clinical study ATI-CL23 demonstrates inadequate *in vivo* adhesion for the prescribed seven-day wear period. The Quality recommendation to the Office of New Drugs for adhesion of Twirla (levonorgestrel and ethinyl estradiol) transdermal system is not approvable.”

Her conclusion was based on the following:

- The adhesion study relied solely on patient assessments rather than the assessments of trained investigators. Patient diaries are usually used as support of the real world/in-use experience.
- The study did not achieve the unofficial gold standard of 90% of all patients having at least 90% surface area adhered for the duration of wear, whether the data was analyzed

per patient, per individual system applied, per cycle, all cycles combined, or using simulated subpopulations.

- For all TCDSs applied, at least 5% completely detached, with 2.1% of all TCDSs completely detaching on the first day of wear.
- 54.4% of all patients of patients experienced at least one complete detachment during the course of the trial; 24.8% of all women in Cycle 1 down to 6.1% in Cycle 13 had such an occurrence.
- 10-20% of all users required four or more TCDS per cycle to maintain therapy per labeled instructions; some users required up to nine products in a single cycle. 14.7% of all cycles studied (N=18,841) required the use of four or more TCDS.

The Product Quality review further noted the following additional outstanding deficiencies:

- Failure to demonstrate (b) (4) adhesion and tack tests were suitable to ensuring the quality, and in particular the *in vivo* adhesion, of the commercial-scale product
- Inadequate drug product specification to ensure the tack and adhesion of the drug product at release and on stability. The current *in vitro* adhesion test did not ensure the *in vivo* adhesion requisite for the safe and efficacious use of the drug product
- Incomparable (b) (4) adhesion data for the clinical and commercial-scale intermediates which could not be used to bridge the pilot scale process used to manufacture the clinical batches to the commercial process

FDA conducted a recent inspection of Corium International Inc., one of the manufacturing facilities used by Agile, noting “objectionable conditions” at the facility. Based on the observations, the Facilities reviewer assessed that “the facility is not ready for commercial manufacturing.” For full details of those findings, see the Facilities review dated December 1, 2017.

On December 1, Agile attempted to address concerns regarding the tack and adhesion test methods. However, a thorough review of this amendment was not feasible during the current review cycle. Further, the Applicant did not identify drug product batches with adequate *in vivo* adhesion.

Reviewer Comment:

The clinical reviewer agrees that the *in vivo* adhesion quality data is inadequate to support the NDA approval. The quality deficiencies could have a significant impact on clinical efficacy. The clinical reviewer discusses the impact of the adhesion quality data in further detail in Section 6 Review of Efficacy.

4.2 Clinical Microbiology

The NDA submission contains no microbiological information. No microbiology review was conducted.

4.3 Preclinical Pharmacology/Toxicology

This resubmission contains no new preclinical pharmacology/toxicology information. Under the original NDA, the Applicant relied mostly on published literature and the results of a dermal study conducted in rabbits and guinea pigs using the (b) (4) (a 12.5 cm² prototype of AG200-15 patch) under IND 57731. During that review, the pharmacology/toxicology reviewer, Krishnan Raheja, Ph.D., recommended NDA approval of AG200-15. See the Pharmacology/Toxicology review for the original submission dated May 9, 2012.

During the review of the current NDA resubmission, the product quality reviewer apprised the pharmacology/toxicology reviewer of a change in the drug product impurity specifications for the LNG-related substances. Table 2 shows the LNG-related specifications for the original and resubmission.

Table 2: LNG-related drug impurities for AG200-15

Test	Method	Acceptance Criteria	
		Original	Resubmission
(b) (4)	(b) (4)	NMT (b) (4)	NMT (b) (4)
		NMT %	NMT %
Any individual unspecified LNG impurity		NMT	NMT %
Total LNG impurities		NMT %	NMT %

Source: Adapted from NDA 204017 Module 3.2.P.5.1 Specifications submitted June 24, 2013 and October 18, 2017.

Per the pharmacology/toxicology review by Mukesh Summan, Ph.D., dated November 21, 2017, the Applicant revised the acceptance criteria of (b) (4) and total LNG impurities due to an increase in the impurities noted in the long-term stability studies. Per the Applicant, 24- and 27- month old patches (drug lot numbers 35249, 35274, and 35260) were used in clinical trial ATI-CL23. Per his review, “Exposure of clinical trial participants to the drug product also likely resulted in exposure to these LNG impurities. Thus, these impurities are deemed qualified by their presence in the drug product and use in this clinical trial. In addition, on the basis of a PubMed.gov search for toxicity associated with (b) (4) evaluated either singly or in combination and without a date range restriction, revealed no toxicological concerns.”

Reviewer Comment:

There are no non-clinical safety issues that would preclude approval of this NDA resubmission. For full details see the Pharmacology/toxicology review dated November 21, 2017.

4.4 Clinical Pharmacology

No new clinical pharmacological studies were included in the NDA resubmission.

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AG200-15 (Ethinyl Estradiol and Levonorgestrel)

Clinical pharmacology studies were submitted with the original NDA and were reviewed by Hyunjin Kim, Ph.D. See the Clinical Pharmacology review for the original submission, dated January 13, 2013. In the original submission, the following trials were reviewed:

ATI-CL14: A two-part, open-label study to evaluate the pharmacokinetic (PK) profile of AG200-15 and to compare exposure to EE from AG200-15 to exposure to EE from Ortho Cyclen[®], an oral contraceptive (OC) containing 250 mcg of NGNM and 35 mcg EE.

- Part I of the study was a single-arm, run-in cycle with AG200-15 administered to all trial participants as a 21-7 day regimen (three consecutive weeks of patch wear followed by a patch-free week).
- Part II of the study employed a crossover design with trial participants randomly assigned to one of two treatment sequences. Each sequence included AG200-15 and the OC as follows:
 - o Sequence 1: AG200-15 (Period one) followed by OC (Period two)
 - o Sequence 2: OC (Period one) followed by AG200-15 (Period two)

Drug free weeks served as the washout period between the two treatment sequences.

ATI-CL15: An open-label, randomized, three-period crossover study to evaluate the safety and PK profile of AG200-15 following application at three different anatomical sites (abdomen, buttock, and upper torso). Twenty-four healthy females were randomly assigned to one of six treatment sequences. Each sequence included three patch application sites.

In each sequence, the woman wore a patch for seven days with each treatment period separated by a seven-day washout period.

ATI-CL16: An open-label, randomized, three-period, five-treatment, incomplete block design, crossover study to evaluate the PK profile, wearability and safety of AG200-15 under normal conditions and various external conditions (dry sauna, whirlpool, treadmill exercise, and cold water immersion). Twenty-four healthy females were randomly assigned to one of six external condition sequences. In each of the three treatment periods, women wore AG200-15 on the lower abdomen under normal wear conditions followed by two of the following four external conditions: treadmill, dry sauna, whirlpool, and cool water immersion. Women were randomly assigned to one of the six sequences of normal wear and external conditions.

In each sequence, the woman wore the patch for seven days and removed the patch following the 168-hour blood draw. Each period was separated by a seven-day washout period.

Dr. Kim provided the following recommendations in his January 13, 2013 review:

“The potential carry-over effects of both ethinyl estradiol (EE) and levonorgestrel (LNG) between adjacent treatment Cycles (in ATI-CL14) and adjacent Periods (in ATI-CL15 and ATI-CL16) were noted in the respective studies. As the FDA considers this to be important information for proper labeling, as part of your response to this Complete Response, you will need to provide a revised analysis which corrects for/compensates for the noted potential carry-over effect or provide details on how you will obtain this information post-marketing along with a suitable labeling to address this lack of information.”

In the CRL, DBRUP requested the following:

1. “Address whether the product quality deficiencies described above may have impacted the findings in your clinical pharmacology studies. You may need to repeat some of your clinical pharmacology studies if the existing data are unreliable due to product quality.”
2. “We identified potential carry-over effects of both ethinyl estradiol and levonorgestrel between adjacent treatment cycles (in Study ATI-CL14) and adjacent periods (in Study ATI-CL15 and ATI-CL16). This may also impact reliability of the study results. If the product quality deficiencies can be adequately addressed, provide a revised analysis that corrects for/compensates for this potential carry-over effect. If you are unable to adequately address carry-over with the available data, provide a proposal for how you will obtain reliable clinical pharmacology data.”

In accordance with the February 2013 CRL, Agile included a clinical pharmacology update in this NDA resubmission to address the Agency’s concern for the observed increases in EE and LNG exposure in trials ATI-CL15 and ATI-CL16. The clinical pharmacology reviewer for the resubmission, Peng Zou, Ph.D., reviewed the update provided by the Applicant. Additionally, he assessed the potential impact of the product quality deficiencies outlined in the CRL on the clinical pharmacology of the drug product.

Upon completion of his review December 1, 2017, he noted the following:

Agile’s reanalysis of PK data showed that the inter-period increases in EE and LNG exposure observed in trials ATI-CL15 and ATI-CL16 were not caused by carry-over effect. The reviewer concluded, “Overall it is unknown whether the increase in EE and LNG exposure seen [in Trial ATI-CL14] was caused by a carry-over effect. However, the increase in EE and LNG exposure is unlikely to affect the efficacy or safety of the drug.” He concluded that the repeat dosing of AG200-15 is not expected to result in sustained increases in EE or LNG exposure.

While bioequivalence for the three anatomic sites (abdomen, buttock, and upper torso) could not be established from trial ATI-CL15, the clinical pharmacology reviewer concluded that the AG200-15 user could switch the three anatomical sites interchangeably without appreciable clinical consequence.

Data for trial ATI-CL16 showed no clinically significant impact of any of the four external conditions (cold water, whirlpool, dry sauna and treadmill) on the drug delivery of AG200-15.

The February CRL identified the following product quality deficiencies: laser etching for the active backing of the product, cold flow and shear specifications, excipient specification, and manufacturing equipment used for the commercial product. In the opinion of the clinical pharmacology reviewer, none of the product quality deficiencies impacted the clinical pharmacology of the drug product.

Reviewer Comment:

The clinical pharmacology review issues are resolved. There are no outstanding clinical pharmacology safety issues that would preclude the approval of this NDA resubmission.

4.4.1 Mechanism of Action

The proposed mechanism of action is as follows:

“Combination hormonal contraceptives lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that may reduce the likelihood of implantation.”

Reviewer Comment:

The proposed mechanism of action is the same for CHCs in general.

4.4.2 Pharmacodynamics (PD)

No new clinical pharmacology studies were included in the NDA resubmission that assessed the pharmacodynamic properties of the AG200-15 TCDS. For full details, see the Clinical Pharmacology review of the original submission dated January 13, 2013.

4.4.3 Pharmacokinetics (PK)

No new clinical pharmacology studies were included in the NDA resubmission that assessed the pharmacokinetic properties of AG200-15. For full details, see the Clinical Pharmacology review of the original submission dated January 13, 2013.

5 Sources of Clinical Data

5.1 Table of Clinical Trials

Table 3 provides the summary information for Phase 2 and Phase 3 trials that used to assess the efficacy and safety of the AG200-15 TCDS.

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Table 3: Summary of Phase 2 and Phase 3 Trials for AG200-15

Name and Type of Clinical Trial	Objectives of the Clinical Trial	Trial Design and Type of Control	Test Product	Trial population Women enrolled/ Completers	Duration of Treatment
Phase 3 Trials					
ATI-CL23 Efficacy and Safety Trial	To evaluate contraceptive efficacy, safety, cycle control, treatment compliance, and patch adhesion of drug formulation AG200-15.	Open label, single arm, multicenter All 102 clinical sites are in the United States	AG200-15: 2.6 mg LNG and 2.3 mg EE Transdermal	Healthy sexually active females at risk for pregnancy age ≥ 18 years at the time of initial screening 2031 women were enrolled 989 women completed the clinical trial.	Thirteen 28-day cycles 1 patch applied every 7 days for 3 consecutive weeks followed by 1 patch free 7-day period
ATI-CL12 Efficacy and Safety Trial	To comparatively evaluate and compare of contraceptive efficacy, safety, cycle control, treatment compliance, and PK of EE/LNG of AG200-15 versus a low dose COC, and patch wearability	Open-label, randomized, comparative, parallel group, multicenter	AG200-15: 2.60 mg LNG and 2.30 mg EE 1 patch per 7-day period Transdermal Lessina® (OC): 0.1 mg LNG and 0.02 mg EE One tablet daily; Oral	Healthy sexually active females at risk for pregnancy age 17 to 40 AG200-15: 1378 women enrolled (249 women that switched from COC to patch at Cycle 7) 635 women completed the trial Lessina: 375 women enrolled in the trial 249 women completed the trial	AG200-15: Thirteen 28-day cycles (1 patch applied every 7 days for 3 consecutive weeks followed by 1 patch free 7- day period) Lessina® Six 28-day cycles (one tablet a day) followed by AG200-15 for Seven 28-day cycles (1 patch applied every 7 days for 3 consecutive weeks followed by 1 patch free 7- day period)

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ATI-CL13 Efficacy and Safety trial	To comparatively evaluate contraceptive efficacy, safety, cycle control, treatment compliance, PK of EE/LNG of AG200-15 versus a low dose COC, and patch wearability	Open-label, randomized, comparative, parallel group, multicenter,	AG200-15: 2.60 mg LNG and 2.30 mg EE 1 patch per 7-day period; Transdermal Levora® (OC): 0.15 mg LNG and 0.03 mg EE; One tablet daily; Oral	Healthy sexually active females at risk for pregnancy age between 18 to 40 years AG200-15 201 women enrolled in the trial 112 completed the trial Levora: 206 enrolled in the trial 145 completed the trial	AG200-15: six 28-day cycles (1 patch applied every 7 days for 3 consecutive weeks followed by 1 patch free 7- day period) Levora® Six 28 day cycles (one tablet a day)
Phase 2					
ATI-CL11 PK/PD Trial	To evaluate ovulation suppression, cycle control, PK profile and safety of TCDSs containing Two different doses of LNG and 3 different doses of EE	Multicenter, open-label, randomized, parallel group study followed by multicenter, open-label, single-arm extension	AG200: 2.17 mg LNG/ 1.92 mg EE/ 12.5cm ² AG200LE: 2.17 mg LNG/ 1.28 mg EE / 12.5 cm ² AG200-15: 2.60 mg LNG/ 2.30 mg EE / 15 cm ² 1 patch/7-day period; Transdermal	Healthy adult females age subjects 18-45 years of age AG200: 45 enrolled in the trial 41women completed the trial AG200-LE: 45 women enrolled in the trial 41 women enrolled in the trial AG200-15: 33 women enrolled in the trial 25 women completed the trial	Three 28-day cycles (21 days on Treatment 7 days off-treatment)

Source: Adapted from the NDA 204017 Module 5.2 Tabular Listing of all Clinical Trials submitted April 13, 2012 and June 26, 2017

5.2 Review Strategy

For the review of this resubmission, the clinical reviewer considered the clinical data for both review cycles, focusing on the Clinical Overview, Clinical Overviews for Safety and Efficacy, and the Clinical Trial Reports for trials ATI-CL23, ATI-CL12, and ATI-CL13.

For efficacy, the clinical reviewer, along with Kate Dwyer, Ph.D., the biometrics reviewer, reviewed the clinical data for the new pivotal trial, ATI-CL23. Because the women were exposed for the same duration of time (12 months), the clinical reviewer used the clinical data

from trials ATI-CL23 and ATI-CL12 to assess the drug's efficacy. ATI-CL13 was not included in the efficacy analysis because of the shorter AG200-15 exposure.

For safety, in addition to the Clinical Trial Reports, the clinical reviewer reviewed the Clinical Safety update included in this submission. The Safety update not only presented the safety data for trial ATI-CL23, it also included the pooled safety data for trials ATI-CL12, ATI-CL13, and ATI-CL23.

Trial ATI-CL11 was included in integrated summary of safety for the original submission.

5.3 Discussion of Clinical Trial ATI-CL23

Section 5.3 of this NDA review provides information about the pivotal contraceptive safety and efficacy clinical trial, ATI-CL23. Trials ATI-CL12 and ATI-CL13 were extensively reviewed by Daniel Davis, M.D. For full details of those clinical trials, see his review dated January 21, 2013.

5.3.1 Objectives

The primary objective of ATI-CL23 was to evaluate the contraceptive efficacy of AG200-15 after 12 months of use. Additionally, the overall safety and tolerability profile of AG200-15 was assessed (adverse events, cycle control, and patch application site reactions). Patch adhesion and women's compliance with the dosing regimen were also assessed.

5.3.2 Design

This was an open-label, single-arm, multicenter, clinical trial where women were treated for thirteen 28-day cycles. The protocol planned for 2100 (1900 women ages 18-35 years, 200 women age >35 years) heterosexually active women of reproductive age.

5.3.3 Eligibility Criteria

5.3.3.1 Key Inclusion Criteria

1. Sexually active woman $\geq$ 18 years and 0 days of age at initial screening, at risk for pregnancy, in good general health (as confirmed by medical history, physical examination, and screening laboratory values), with an intact uterus and fallopian tubes, regular menses every 21 - 38 days, and seeking to use hormonal contraception for at least 1 year
2. Willing to discontinue her current method of contraception and agrees to use AG200-15 as her sole method of contraception throughout the study, except when an alternate method is required for prevention of sexually transmitted

infection (STI) or back-up contraception in the setting of patch detachment/patch scheduling issues

3. Sexually active during each cycle throughout the trial and does not anticipate or plan on using alternative contraceptive methods for sexually transmitted infection (STI) prevention and/or emergency contraception
4. Not breastfeeding, with return of regular cycling for at least 3 menses, post-lactation
5. If previous injectable contraceptive use, must be at least 10 months since last injection with at least two spontaneous menses
6. Medically able and willing to forgo the use of other steroid hormonal therapy (other than topical or inhaled corticosteroids) for the duration of the trial
7. At least 90% compliance with electronic Diary entry and return two check-in phone calls from the Investigator site during the two-week Run-In Period of the trial
8. In the Investigator's assessment, woman must demonstrate ability and willingness to participate and adhere to the trial protocol for the full clinical trial
9. Willing and able to sign the informed consent form

5.3.3.2 *Key Exclusion criteria:*

1. Pregnancy
2. Currently lactating
3. Anticipates or plans use of condoms, emergency contraception, or any other form of backup contraception during the trial
4. Current use of a contraceptive implant without three, consecutive spontaneous menses and prior to date of consent
5. Current use of intrauterine device without one spontaneous menses following IUD removal and prior to date of consent
6. Recent surgical or medically induced abortion, spontaneous abortion, or ectopic pregnancy without three consecutive, spontaneous menses or withdrawal bleeding episodes and prior to date of consent
7. Recent vaginal or cesarean delivery without three, consecutive, spontaneous menses or withdrawal bleeding episodes and prior to date of consent
8. Unexplained vaginal bleeding
9. Known hypersensitivity or intolerance to progestins or estrogens (leading to discontinuation), including hormonal contraception; or history of serious or severe adverse event related to progestins or estrogens, including hormonal

contraception (e.g., worsening of a disease or condition while on hormonal contraception)

10. History of dermal hypersensitivity in response to medicated patches (e.g., nicotine patch) or topical applications (bandages, surgical tape, etc.) or known hypersensitivity to any components of the AG200-15 product
11. Has a contraindication to combined estrogen-progestin contraceptive use (as defined by a category 3 or 4 CDC U.S. Medical Eligibility Criteria for Contraceptive Use)
 - o Personal history of or existing deep venous thrombosis (DVT) or venous thromboembolism
 - o History of stroke, vascular or cerebral vascular disease including transient ischemic attacks (TIAs) or coronary artery disease
 - o Known inherited or acquired hypercoagulopathy, including thrombogenic mutations
 - o Systemic Lupus Erythematosus with positive or unknown antiphospholipid antibodies
 - o Known or suspected carcinoma of the breast, including past personal history of breast cancer
 - o Jaundice with prior combination hormonal contraceptive use
 - o Hepatocellular adenoma or carcinoma
 - o Severe cirrhosis
 - o Symptomatic current or medically treated gallbladder disease
 - o Smoker who is 35 years old or over, or smoker who will turn 35 years old during the course of the trial (Smoking includes cigarettes, cigars, smokeless tobacco, e-cigarettes, hookah, etc.)
 - o Headaches with focal neurological symptoms (i.e., migraines with auras). Migraines of any type in women over 35 years of age
 - o Diabetes mellitus with nephropathy, neuropathy, retinopathy, or other vascular disease; diabetes mellitus of >20 year's duration
 - o Plans for major surgery with anticipated prolonged immobilization during the study
 - o History of peripartum cardiomyopathy.
 - o Elevated blood pressure, defined as screening sitting blood pressure $\geq$ 140 mm Hg systolic or $\geq$ 90 mm Hg diastolic; or hypertension with known vascular disease

12. Known thrombophilia, including antiphospholipid antibody syndrome
13. History of any other condition that in the Investigator's opinion suggests an elevated risk of arterial or venous thromboembolic disease
14. Carcinoma of the endometrium, ovary, fallopian tubes, or other known or suspected estrogen-dependent malignant or pre-malignant neoplasia
15. Other active malignancy, excluding non-melanoma skin cancer
16. Acute or chronic hepatocellular disease with significantly abnormal liver function as measured by liver function tests (LFTs) $\geq 2 \times$ normal
17. Triglycerides ≥ 350 mg/dL
18. Thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease or atrial fibrillation)
19. Uncontrolled diabetes mellitus; subjects with a history of gestational diabetes are eligible for the study if they are currently euglycemic
20. Abnormal central laboratory fasting glucose ≥ 126 mg/dL and/or HbA1C value ($\geq 6.5\%$)
21. Uncontrolled thyroid disorder
22. Known human immunodeficiency virus (HIV) and/or hepatitis B or C infection, or positive test at screening
23. Positive screen for chlamydia or gonorrhea (subjects who screen fail due to positive results may be re-screened and enrolled in the study after standard medical treatment)
24. Significantly abnormal Papanicolaou (Pap) test
25. Current chronic use of any medication that might interfere with the efficacy of hormonal contraceptives, or be affected by the hormonal contraceptive (See Section 5.3.3.3)
26. History of suicidal ideation or attempt, or history of severe depression requiring hospitalization within the past year
27. Recent history (within prior 12 months) of drug or alcohol abuse or at Investigator's discretion, history greater than 12 months prior and at risk for noncompliance
28. Positive urine drug screen for Cocaine, Methamphetamine, Opiates, Phencyclidine unless there is a documented prescription with supporting medical history and diagnosis
29. Administration of any investigational drug and/or experimental device within 30 days prior to the date of consent or planned administration of such drug or

- device during the duration of the study; or current participation in any investigational studies
30. Previously enrolled in this protocol or prior Agile Protocols CL12 or CL 13 and dispensed study patch
 31. Deemed per the Investigator's discretion to have limited ability to comply with the protocol and to provide accurate information; subject previously on COCs and reports repeatedly missing pills and/or becoming pregnant while on COCs
 32. Subject is a dependent of (e.g., relative or family member) and/or is a member of the Investigator's staff

Reviewer Comment:

The subject selection criteria are appropriate.

5.3.3.3 Excluded and Concomitant Medications

During the course of the trial, the protocol prohibited the use of the following medications: other hormonal therapy (including other hormonal contraception/emergency contraception), human chorionic gonadotropin (hCG) supplements (due to the potential for false positive pregnancy testing), specific antibiotics (refer to the antibiotic package insert and/or WHO guidelines), barbiturates, primidone, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, rifabutin, St. John's Wort, topiramate, and ritonavir-boosted HIV protease inhibitors.

5.3.4 Trial conduct

Each woman underwent screening to determine her eligibility for participation in the clinical trial. Her eligibility was determined upon completion of the screening and run-in visits. The woman applied her first TCDS while in the office after confirmation of a negative pregnancy test.

For women not on hormonal contraception, the first TCDS was applied within 24 hours of day one of their menses. For women on hormonal contraception in a 21-day or 24-day cycle or an extended regimen (including ring and patch), the first TCDS was applied as follows: 1) any day of active treatment, or 2) the day after the last hormone-containing pill, patch, or ring, or 3) within 24 hours of the onset of withdrawal bleeding following an active treatment cycle. Women were to apply the patch by day 4 following discontinuations of previously used hormonal contraception.

On a daily basis, each woman recorded information on patch wear, patch adhesion data (using the numbered patch adhesion scale), patch exposure to water, application site irritation, and vaginal bleeding/spotting in their eDiaries. On a weekly basis, each woman recorded patch use information, anatomic site for patch application, sexual activity, and back up method of contraception information.

During the course of the clinical trial, women attended eight scheduled in person clinical visits and six telephone visits. Table 4 summarizes the schedule of events that occurred during the in-person clinic visit and Table 5 summarizes the schedule of events that occurred during the telephone contact visits.

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Table 4: ATI-CL23 Schedule of Events - In-person clinic visit

ATI-CL23 Schedule of Events										
Procedure	Visit 1 (Initial Screening)	Visit 2 (Run-In Visit)	Visit 3 (Enroll- ment) Cycle 1, Day 1	Visit 4 (Cycle 2, Days 1-8)	Visit 5 (Cycle 3, Days 1-8)	Visit 6 (Cycle 5, Days 8-20)	Visit 7 (Cycle 7, Days 8-20)	Visit 8 (Cycle 9, Days 8-20)	Visit 9 (Cycle 13, Days 8-20)	Visit 10 (Final/ Early D/C; 17 days [± 3] after last dose)*
Informed Consent Form	X									
Demographics, medical/gynecologic history including medications (prior 6 months) and contraceptive use (demographics and contraceptive use at screening only)	X		X							
Vital Signs	X		X	X	X	X	X	X	X	X
Height and Weight (height at Screening only)	X					X				X
Physical and Gynecological Examination	X									X
Pap Test (at Screening: documented Pap results (and HPV testing, if applicable) within 3 months prior to screening acceptable)	X									X
Fasting Hematology, Chemistry (including HbA1C at Screening), Lipid Panel and Urinalysis, urine drug screen (screening only)	X									X
HIV antibody, HBsAg, HCV antibody, thyroxine (Free T4), chlamydia and gonorrhea screening	X									
Serum Pregnancy Test			X							X
Urine β-hCG (from Visit 4 on: if positive, same-day serum β-hCG and pelvic examination must be performed; TVU should be performed as soon as possible, preferably same-day)	X	X	X	X	X	X	X	X	X	X
Confirm eligibility	X	X	X							
Application site (skin) evaluation (most recent application site); patch adhesion assessment			X	X	X	X	X	X	X	X
Dispense study medication/confirm subject has at least one reserve patch			X	X	X	X	X	X		
Dispense eDiary; Initial eDiary entry by subject		X								
Review subject eDiary instructions		X	X	X	X	X	X	X	X	
Provide home pregnancy test			X							
Dispense post-study contraceptive, if applicable									X	
AEs, CMEDs, Compliance (patch use, diary, back-up contraception, sexual activity)			X	X	X	X	X	X	X	X

Source: NDA 204017, Module 5.3.5.1 ATI-CL23, Protocol and Amendment, Protocol Amendment 2.0, updated December 18, 2014

Table 5: ATI-CL23 Schedule of Events – Telephone Contact

ATI-CL23 Schedule of Events - Telephone Contacts							
Procedure	Run-In Period Telephone Contact	Telephone Contact 1 Cycle 4	Telephone Contact 2 Cycle 6	Telephone Contact 3 Cycle 8	Telephone Contact 4 Cycle 10	Telephone Contact 5 Cycle 11	Telephone Contact 6 Cycle 12
Call subject x 2 for Run-In Period Check-In; document subject return of calls x 2	X						
Review AEs and CMEDs		X	X	X	X	X	X
Review sexual activity and back-up contraception use		X	X	X	X	X	X
Review subject patch use and eDiary compliance		X	X	X	X	X	X
Confirm subject has at least one reserve patch		X	X	X	X	X	X
Confirm subject contact information		X	X	X	X	X	X
Assess need for subject re-education; plan unscheduled visit if necessary		X	X	X	X	X	X

Source: NDA 204017, Section 5.3.5.1 ATI-CL23, Protocol and Amendment, Protocol Amendment 2.0, updated December 18, 2014

For each clinic visit, vital signs were collected and a urine pregnancy test was obtained. The TCDS application site was inspected for irritation and adhesion. Adverse events and concomitant medications were reviewed. During each telephone visit, the trial medication and eDiary compliance data, adverse events, and concomitant medication were reviewed.

Any woman with a positive urine pregnancy test underwent a pelvic examination for assessment of uterine size (weeks), serum quantitative β -hCG testing and prompt ultrasound evaluation to determine the estimated date of conception (EDC). Other data, including last withdrawal bleed, date of missed withdrawal bleed, and sexual activity, were utilized, as needed, to determine EDC. Repeat evaluations (e.g., repeat ultrasound if initial ultrasound done prior to presence of gestational sac and/or crown rump length for dating) were done as necessary to increase the accuracy of the EDC determination. Women were provided home pregnancy tests at Visit 3-Enrollment, and advised to test for pregnancy in the event of increased pregnancy risk (e.g. delayed patch application during a cycle without use of back-up contraception) and/or symptoms concerning for pregnancy. An independent Pregnancy Review Committee (PRC) adjudicated all pregnancies and classified each pregnancy as pre-treatment, on-treatment, or post-treatment as follows:

- Pre-treatment: EDC prior to the first day of the first TCDS application of the trial
- Post-treatment: EDC after day seven from the last TCDS removal of the trial

- On-treatment: EDC falls between the date that the first TCDS of the trial is applied and the date that the last TCDS of the trial is removed

5.3.5 Contraceptive Efficacy

The primary contraceptive efficacy analysis was based on the Pearl Index.

Pearl Index (PI) = $1300 \times \frac{\text{the number of pregnancies}}{\text{number of evaluable cycles of treatment}}$

5.3.6 Statistical Analysis Plan

Populations

The Applicant used three efficacy datasets for the analysis of the primary and secondary endpoints. The definitions of the efficacy datasets are as follows:

- Intent-to-treat (ITT) Efficacy Dataset: All complete or incomplete on-therapy cycles in which intercourse occurred and no back-up contraception was used.
- Per-Protocol-Instructions (PPI) Efficacy Dataset: All complete or incomplete on-therapy cycles in which intercourse occurred, excluding two cohorts of cycles:
 - Cohort 1: cycles in which a back-up method of contraception was used for reasons other than the protocol-specified procedures for missed days of TCDS use, unless pregnancy occurred
 - Cohort 2: cycles in which the woman missed ≥ 1 day of TCDS use and did not adhere to the recommended procedures for missed days of TCDS use
- Method Failure (MF) Efficacy Dataset: All complete or incomplete on-therapy cycles in which intercourse occurred, excluding three cohorts of cycles:
 - Cohort 1: cycles in which a back-up method of contraception was used for reasons other than the protocol-specified procedures for missed days of TCDS use
 - Cohort 2: cycles in which the woman missed ≥ 1 day of TCDS use and did not adhere to the recommended procedures for missed days of TCDS use
 - Cohort 3: cycles immediately following Cohort 2 cycles

Reviewer Comment:

DBRUP does not rely on the method failure dataset for efficacy analysis and considers any results from this analysis to be exploratory. DBRUP does not include such information in the labeling if a contraceptive is approved.

Endpoints:

Primary Efficacy Endpoints

- PI, based on the ITT population, in women ≤ 35 at enrollment, regardless of BMI. This excluded all cycles in which back-up contraception was used or intercourse did not occur.

Secondary Efficacy Endpoints

- The PI in women aged ≤ 35 years, with BMI $< 30 \text{ kg/m}^2$, utilizing the ITT efficacy cycle dataset (unless the woman became pregnant during the cycle)
- The PI in women aged ≤ 35 years, with BMI $< 30 \text{ kg/m}^2$ utilizing the PPI efficacy cycle dataset (unless the woman became pregnant during the cycle)
- The PI in women aged ≤ 35 years, regardless of BMI, utilizing the PPI efficacy cycle dataset (unless the woman became pregnant during the cycle)

For selected endpoints, results were summarized by subgroups, including:

Age at Enrollment:

- ≤ 35 years old
- > 35 years old

BMI and Weight:

- Normal: BMI $< 25 \text{ kg/m}^2$
- Overweight: BMI ≥ 25 to $< 30 \text{ kg/m}^2$
- Obese: BMI $\geq 30 \text{ kg/m}^2$
- Non-obese: BMI $< 30 \text{ kg/m}^2$
- Obese: BMI $\geq 30 \text{ kg/m}^2$
 - BMI $\geq 30 \text{ kg/m}^2$ to $< 35 \text{ kg/m}^2$
 - BMI $\geq 35 \text{ kg/m}^2$ to $< 40 \text{ kg/m}^2$
 - BMI $\geq 40 \text{ kg/m}^2$
- Weight summarized by quartiles and deciles

Previous hormonal contraceptive use status:

- Naïve Users: women who have not previously used any hormonal contraceptive
- Prior Users: women with previous use of hormonal contraceptives but not in the 6 months prior to enrollment
- Recent Users: women who are not currently using a hormonal contraceptive, but have used a hormonal contraceptive within 6 months prior to enrollment
- Current Users: women who are currently using a hormonal contraceptive

Race:

- White
- Black or African American
- Other

Ethnicity:

- Hispanic or Latino
- Not Hispanic or Latino

Reviewer Comments:

In the November 3, 2014 Advice Letter, DBRUP encouraged the Applicant to include females less than 18 years of age. The new protocol excluded these women from the trial.

Sample Size Determination

The clinical trial was sized to provide 90% power to establish that if an underlying PI is no larger than 3.5, the PI would have an upper bound of a two-sided 95% CI no larger than 5. The Applicant assumed each of the 1900 enrolled women 18 to ≤ 35 years of age would complete an average of 8.5 cycles on treatment to generate approximately 16,000 cycles of exposure to AG200-15 in the intended age group for efficacy analysis. The calculations also assumed a 21% drop out rate for the primary evaluation of efficacy due to back-up contraception use and absence of sexual activity. 12,675 cycles were used in the power calculations. As the clinical trial proceeded, Agile indicated they (or a designee) would monitor trial discontinuation and completion rates to increase the number of women enrolled in the clinical trial to achieve an adequate number of efficacy-evaluable cycles for pregnancy rate estimations.

6 Review of Efficacy

Efficacy Summary

The Applicant completed trial ATI-CL23. 2031 women enrolled in the trial; 1830 women of those women were between the ages of 18 to 35 years. There was no BMI restriction. The Applicant appeared to improve the trial conduct from the previous review cycle, as evidenced by the lower trial discontinuation and loss-to follow up rates. The loss to follow up rate for Trial ATI-CL23 was comparable to those rates seen in the registration trials of currently approved marketed drugs. The Applicant met the minimum requested 10,000 evaluable cycles of drug exposure to adequately assess for efficacy, attaining 15,165 cycles of drug exposure to calculate the primary outcome measure, the PI. During the adjudication of the pregnancy data, the clinical reviewer identified an additional twelve on-treatment pregnancies. Using the ITT population in women (age 18 to 35 years), this yielded a PI of 5.83 (95% CI 4.45, 7.21). For the secondary endpoints using the ITT population with a BMI restriction of $\leq 30 \text{ kg/m}^2$, the PI

was 4.34 (95% CI 2.86, 5.82). However, restricting the population to this group included only 9888 evaluable cycles, which is just shy of the minimum of 10,000 required cycles to calculate efficacy. Using the PPI population in women ≤ 35 , the PI was 5.25 (95% CI 3.89, 5.77); with a BMI restriction $\leq 30 \text{ kg/m}^2$ and age ≤ 35 , the PI was 3.94 (95% CI 2.48, 5.40). The Pearl Indices are still considerably higher than those for previously approved CHCs and the upper bound of the 95% CI remains above the established limit of 5.

It is plausible that this comparably lower efficacy is related to inadequate TCDS adhesion. As noted in the CMC section of this review, adhesion of the TCDS to skin is critical to the effective use of the drug product. In the new trial, for all TCDS applied, at least 5% completely detached, with 2.1% of all systems complete detaching on the first day of wear.

54.4% of women experienced complete patch detachment. 10-20% of all users required four or more TCDSs per cycle to maintain therapy per labeled instructions; some women required up to 9 TCDSs in a single cycle. 14.7% of all the evaluable cycles (N=18,841) required the use of four or more TCDS.

These findings suggest that women may not achieve the seven-day wear period for each patch that is required to achieve the desired contraceptive efficacy.

6.1 Indication

The proposed indication for AG200-15 is the prevention of pregnancy in women of reproductive age.

6.1.1 Methods

See Section 5.3. for details to clinical protocol ATI-CL23.

6.1.2 Demographics

Demographic and baseline characteristics of trial ATI-CL23 are shown in Table 6. Trial ATI-CL23 included 24.3% Black women and 35.3% obese women with BMI $\geq 30 \text{ kg/m}^2$. 90.7% of the women were current, recent, or former hormonal contraceptive users.

Table 6: Demographic Characteristics for Safety Populations for ATI-CL23

Parameter	Category	Overall (n=2031)
Age (years)	≤ 35	90.1% (n=1830)
	>35	9.9% (n=201)
Race	Asian	3.2% (n=65)
	AI/AN	0.5% (n=11)
	Black	24.3% (n=493)
	NH/PI	0.4% (n=8)
	Other	4.7% (n=96)
	White	66.9% (n=1358)
Ethnicity	Hispanic	19.7% (n=400)
	Not Hispanic	80.3% (n=1631)

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BMI (kg/m²)	Obese (≥ 30)	35.3% (n=717)
	Non-obese (<30)	64.7% (n=1313)
	≥ 30 to <35	17.5% (n=356)
	≥ 35 to <40	10.3% (n=209)
	≥ 40	7.5% (n=152)
Smoking Status	Current	11.6% (n=236)
	Past	12.8% (n=260)
	Non-Smoker	75.6% (n=1535)
Previous Contraceptive Use	Naïve	9.4% (n=190)
	Current	34.7% (n=704)
	Prior Use	43.1% (n=875)
	Recent Use	12.9% (n=262)
	Naïve to HC patch	82.7% (n=1680)

Source: Adapted from NDA 204017, Module 5.3.5.1 ATI-CL23 Clinical Trial Report, Table 9 Demographics and Baseline Characteristics for Previous and Overall – Safety population
 AI/AN – American Indian/Alaskan Native, NH/PI – Native Hawaiian/Pacific Islander
 BMI – Body Mass Index

Reviewer comments:

While most of the patient population for the clinical trial was White, other racial and ethnic groups were well-represented. When compared to the 2010 United States Census data: ^{12, 13} Black women were overrepresented for trial ATI-CL23 at 24.3% versus 14.6%; Asians were underrepresented at 3.2% versus 5.6%; other race was underrepresented at 4.7% versus 6.2%; and Hispanics were overrepresented at 19.6% versus 16.3%. The prevalence of obese women in ATI-CL23 at 35.4% is closely aligned with the prevalence of obesity of females in the United States which is 38.3%.¹⁴ This is acceptable.

While DBRUP recommended that the Applicant enroll sufficient number of truly naïve users to hormonal contraceptives, only 9.4% of the women were naïve users. While 82.7% women were naïve to the hormonal patch, most of the women were experienced contraceptive users and had a general awareness of dosing regimens needed to achieve the desired contraceptive effect.

6.1.3 Subject Disposition

Table 7 summarizes the disposition for the trial population. The number of women that completed the trial, ATI-CL23, was still low 48.7%.

Table 7: Disposition of Women for Trials ATI-CL23 and ATI-CL12

Category	ATI-CL23	ATI-CL12
Safety Population	2031	1129
Contraceptive Efficacy Population	2024 (99.7%)	998 (88.4%)
Cycle Control Population	2017 (99.3%)	918 (81.3%)
Completer Population	989 (48.7%)	485 (43.0%)
Reason for Study Discontinuation		
Any reason	1042 (51.3%)	644 (57%)
Adverse Event	222 (10.9%)	123 (10.9%)
Death	0	0
Non-compliance	116 (5.7%)	42 (3.7%)
Lost to Follow up	229 (11.3%)	229 (20.3%)
Subject Decision	310 (15.3%)	183 (16.2%)
Pregnancy	73 (3.6%)	34 (3%)
Protocol Violation	14 (0.7%)	11 (1%)
Investigator decision	17 (0.8%)	13 (1.2%)
Sponsor decision	18 (0.9%)	0
Sponsor decision (study termination)	2 (0.1%)	0
Other	41 (2%)	9 (0.8%)

Source: NDA 204017 Module 5.3.5.1 ATI-CL23 Clinical Trial Report, Table 6: Subject Disposition and Analysis population

Reviewer Comment:

For trial ATI-CL23, the top three reasons for trial discontinuation were subject decision (15.3%), lost to follow up (11.3 %), and adverse events (10.9%). Trial discontinuation for any reasons was 57% for trial ATI-CL12 versus 51.3% for trial ATI-CL23. Of those that discontinued the trial, the number of women lost to follow up was 20.3% for trial ATI-CL12 compared to 11.3% for trial ATI-CL23. Discontinuation rates due to subject decision were lower for trial ATI-CL23 at 15.3% than for trial ATI-CL12 at 16.2%. Similarly, discontinuation rates for adverse events in both trials were comparable at 10.9%. The clinical reviewer surmises that the aforementioned changes in subject disposition for the new trial might be attributed to improvements in trial conduct.

The biometrics reviewer compared the discontinuation rates for trials ATI-CL12 and ATI-CL23 to those discontinuation rates for oral CHCs approved within the past 10 years (Table 8). With the exception of Natazia, total discontinuation rates for trials ATI-CL12 and ATI-CL23 were approximately 10-20% higher than the discontinuation rates for the other registration trials. Subject Decision (Withdrawal of Consents) for Trials ATI-CL12 and ATI-CL23 were approximately 5.5-10% higher than the other registration trials. Lastly, the clinical reviewer noted that the dropout rate of women lost to follow up for trial ATI-CL23 was comparable to the dropout rate of women lost to follow up in registration trials for other approved oral contraceptives. Again, this finding may reflect the Applicant's efforts to improve conduct of this trial.

Table 8: Trial discontinuation in Pivotal Trials for AG200-15 versus Pivotal Registration Trials for Recently Approved Oral Contraceptives (From 2007-2017)

Drug/Trial	Year Approved	Trial Discontinuation			
		Total	Loss to Follow-up	Subject Decision	Others
Trial ATI-CL12	NA	57.0%	20.3%	16.2%	0.8%
Trial ATI-CL23	NA	51.3%	11.3%	15.3%	2.0%
Trial ATI-CL23	2013	40.4%	13.3%	6.0%	0.8%
Lo Loestrin Fe	2010	41.7%	13.7%	8.9%	5.8%
Natazia	2010	51.3%	13.0%	9.8%	11.6%
Generess	2010	40.9%	16.2%	8.9%	4.5%
Lo Seasonique	2008	37.1%	14.1%	8.6%	1.4%

Source: Adapted from Biometrics Review prepared by K. Dwyer Ph.D. Adapted from Biometrics Review for Quartette (NDA 204061), Lo-Loestrin (NDA 22501), Natazia (NDA 22252), Generess (NDA 22573), and LoSeasonique (NDA 22262).

6.1.4 Contraceptive Efficacy (primary endpoint)

The Applicant identified 56 on-treatment pregnancies. DBRUP classified 12 additional pregnancies as on-treatment. The rationale supporting DBRUP's determination is provided in Table 9.

Table 9: DBRUP's adjudication of the Pregnancy narratives provided by the Applicant

Subject ID	Applicant's Determination	DBRUP's Determination	Rationale
(b) (6)	NA	ON	Ultrasound (US) report on (b) (6) gestational age 14 weeks. The gynecological exam on (b) (6) was consistent with a uterine size of 14 weeks. A negative urine pregnancy test 2 weeks after the termination of pregnancy is reasonable. EDC was December 15, 2016. Last patch was removed March 28, 2016. EDC prior to last patch removal. This is on treatment.
	POST	ON	Patient was noncompliant with treatment which represents a worst-case scenario. First patch was placed March 24, 2016. Last patch was removed March 6, 2016. EDC was February 14, 2016. This is on treatment.

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(b) (6)	POST	ON	Patient was noncompliant with treatment which represents a worst-case scenario. First patch was placed December 19, 2014. Last patch was removed on February 1, 2016. EDC was January 12, 2016. This is on treatment.
	POST	ON	March 19, 2016 US report showed gestational sac of 6 weeks. First patch was placed July 7, 2015. Last patch was removed May 5, 2016. EDC was April 21, 2016. This is on treatment.
	POST	ON	Patient was noncompliant with treatment which represents a worst-case scenario. First patch was placed September 25, 2015. Last patch was removed December 20, 2015. EDC was November 22, 2015. This is on treatment.
	POST	ON	Patient was noncompliant with treatment which represents a worst-case scenario. September 12, 2016 US report 6 weeks and 5-day pregnancy. First patch was placed October 5, 2015. Last patch was removed on September 8, 2016. EDC was August 10, 2015. This is on treatment.
	NA	ON	November 24, 2016 US report no gestational sac. Dropping HCG level (November 24, 2015: HCG 4879; November 25 2015: HCG 2495) consistent with a potential spontaneous abortion. First patch was placed March 3, 2015. Last patch was removed December 29, 2015. This is on treatment.
	POST	ON	Patient is noncompliant with treatment which represents a worst-case scenario. First patch placed September 28, 2016. Last patch removed April 20, 2016. May 2, 2016 US report 7-week intrauterine pregnancy. EDC was March 30, 2016. This is on treatment.
	POST	ON	Patient is noncompliant with treatment which represents a worst-case scenario. First patch placed April 2, 2015. Last patch removed August 16, 2015. August 28, 2015 US report 5 week and 6- day intrauterine pregnancy. EDC was August 1, 2015. This is on treatment.

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(b) (6)	POST	ON	Patient is noncompliant with treatment which represents a worst-case scenario. First patch placed December 29, 2014. Last patch removed June 3, 2015. June 3 US report 8 week and 3-day intrauterine pregnancy. EDC was April 19, 2015. This is on treatment.
	POST	ON	Patient is noncompliant with treatment which represents a worst-case scenario. First patch placed February 23, 2015. Last patch removed June 12, 2015. June 22, 2015 US report 6-week intrauterine pregnancy. EDC was May 25, 2015. This is on treatment.
	POST	ON	First patch placed June 25, 2015. Last patch removed June 16, 2016. July 5, 2016 US report gestational sac 5 weeks and 6-day intrauterine pregnancy. EDC was June 8, 2016. This is on treatment.

Source: Adapted from NDA 204017, Module 5.3.5.1 ATI-CL23, Trial Report Body, Table 14.4.1.3 Pregnancy Narratives.

For the primary efficacy endpoint, using the ITT population, the Applicant calculated a PI of 4.80 (95% CI 3.55, 6.06). However, counting the additional on-treatment pregnancies, FDA calculated a PI of 5.83 (95% CI 4.45, 7.21). See Table 10.

Table 10: Contraceptive Efficacy for AG200-15 in Women ≤ 35 years of age -ITT dataset

	Total 28-day cycles of exposure	Total On-Treatment Pregnancies	PI (95% Confidence Interval)
Applicant	15165	56	4.80 (3.55, 6.06)
FDA	15165	68	5.83 (4.45, 7.21)

Source: Adapted from NDA 204017, Module 5.3.5.1 ATI-CL23 Trial Body Report, Table 14.2.1.2.2 Pregnancy Rates Based on PI by Age Group and Overall- ITT Dataset and FDA analysis conducted by Kate Dwyer, Ph.D., Biometrics Reviewer.

Reviewer Comments:

For the primary endpoint, the Applicant met the minimum 10,000 evaluable cycles as recommended in the March 9, 2010 Advice Letter.

In an Information Request (IR) letter to the Applicant dated September 1, DBRUP asked the Applicant to recalculate the PI based on the clinical reviewer's adjudication of the additional pregnancies. The results of their recalculated PI matched DBRUP's results. In the response letter to DBRUP's IR, the Applicant asked DBRUP to reevaluate the classification of several pregnancies. The Applicant requested that DBRUP reclassify eight

of the twelve pregnancies (Subjects (b) (6)) as “off treatment” “since there should be no clinical expectation that upon resumption of drug, the patch could provide protection at the time of conception.”

Reviewer Comments:

The clinical reviewer does not agree with the Application’s assertion. The clinical reviewer finds that these cases fit the *a priori* definition of on-treatment; they occurred within the pre-specified timeframe, i.e. the EDC fell between the date that the first patch of the trial was applied and the date that the last patch of the trial was removed. These pregnancies represent the worst-case scenario, which more accurately reflects pregnancy rates resulting from expected, real-world, use of this TCDS. The clinical investigators assessed the women for compliance on a monthly basis. Per the agreed upon protocol, the investigators could have considered discontinuing some of the women from the trial for noncompliance prior to their pregnancy diagnosis. Since they were not discontinued from the trial, they were counted in the efficacy analysis population.

For Subjects (b) (6), the Applicant requested that Division reconsider their on-treatment classification and provided the following explanation:

“Agile found that sufficiently conflicting information related to patch use and pregnancy dating strongly suggested conception while not using study drug. As such, we excluded the subjects from the analysis. We understand FDA’s rationale for considering (b) (6) as on-treatment despite the uncertain circumstances around her pregnancy, but request reconsideration of Subjects (b) (6), “who had even more notable discrepancies surrounding patch wear and timing of conception.”

Reviewer Comments:

The clinical reviewer does not find the information provided in the pregnancy narratives for these two women to be discrepant. For Subject (b) (6), the clinical reviewer gives greater credence the serum beta-hCG levels over the urine beta-hCG test given it is a more specific pregnancy test. Since no serum HCG was taken contemporaneously with the urine HCG on November 19, 2015, the clinical reviewer is more inclined to rely upon the serial serum HCGs that were taken on November 24th and 25th. The declining HCGs are supportive of a possible spontaneous abortion. The clinical reviewer’s rationale that this is an on-treatment pregnancy provided in Table 9 still applies.

The Applicant decided not to include a weight limitation of use in their primary endpoint. In the Applicant’s response letter, the Applicant attributed the higher PI, noted in the original efficacy analysis for Trial ATI-CL23, to the larger proportion of obese patients, (26/56 = 46.4%) included in the clinical trial. Further, the Applicant attributed the higher PI using the FDA calculations not only to the additional pregnancies (12), but also to the higher proportion of obese patients in those additional pregnancies (35/68 = 51.5%). Indeed, Table 11 below suggests that the pregnancy rates

are about twice as high in obese women (PI 8.64, 95% CI 5.79, 11.50 per the FDA analysis) as in non-obese women.

Table 11 Pregnancy Rates for All Subjects, ITT Population

	Population	N	# of On-Treatment Pregnancies	Number of Cycles	Pearl Index 95% CI
Applicant	Age ≤ 35 years	1,736	56	15,165	4.80 (3.55, 6.06)
	Age ≤ 35 with BMI < 30 kg/m ²	1,123	30	9,888	3.94 (2.53, 5.35)
	Age ≤ 35 with BMI ≥ 30 kg/m ²	612	26	5,264	6.42 (3.96, 8.88)
	All Subjects	1,932	62	17,126	4.71 (3.54, 5.88)
Reviewer	Age ≤ 35 years	1,736	68	15,165	5.83 (4.45, 7.21)
	Age ≤ 35 with BMI < 30 kg/m ²	1,123	33	9,888	4.34 (2.86, 5.82)
	Age ≤ 35 with BMI ≥ 30 kg/m ²	612	35	5,264	8.64 (5.79, 11.50)
	All Subjects	1,932	74	17,126	5.62 (4.34, 6.89)

Source: FDA analysis conducted by Kate Dwyer, Ph.D., Biometrics Reviewer.

Reviewer Comments:

The clinical reviewer finds that the drug product must demonstrate comparable efficacy and safety to the products that are currently being marketed and intended for the same population.

Table 12 demonstrates how other Applicants may have restricted BMI to facilitate the approval of their product. In comparing the PI of AG200-15 to other approved CHCs over the past 10 years (Table 12), the PIs for AG200-15 were still higher than any other FDA approved CHCs. Even with a weight restriction, the PI for AG200-15 was still higher than any other FDA approved CHCs. As previously explained in the October 9, 2013 Type C meeting minutes, the Agency has not approved any CHC with the upper bound of the 95% CI greater than 5.

In the statistical analysis plan dated December 20, 2016, the Applicant stated, “The study is sized to provide 90% power to establish that if the underlying Pearl Index is no larger than 3.5, the Pearl Index will have an upper limit of a two-sided 95% confidence interval no larger than 5%.” The PI did not meet the pre-specified endpoint set forth by the Applicant, regardless of whether a limitation of use is employed.

Table 12: Pearl Index for Approved Combined Hormonal Contraceptives (CHCs) from 2007-2017

Drug/Trial	# evaluable cycles without back up contraception	PI (95% CI)	BMI (kg/m²)
AG200-15 Trial ATI-CL12	6070	7.50 (5.02, 9.97)	BMI ≤ 32
AG200-15 Trial ATI-CL23	15165	5.83 (4.45, 7.21)	No Restriction
AG200-15 Trial ATI-CL23	9888	4.34 (2.86, 5.82)	BMI < 30
Quartette	28515	3.19 (2.49, 4.03)	No Restriction
Lo-Loestrin Fe	12482	2.92 (1.94, 4.21)	BMI ≤ 35
Natazia	3969	1.64 (NA, 3.82)	BMI ≤ 30
Generess	12297	2.01 (1.21, 3.14)	BMI ≤ 35
LoSeasonique	17068	2.74 (1.92, 3.78)	No Restriction

Source: Adapted from Biometrics Review for Quartette (NDA 204061), Lo-Loestrin (NDA 22501), Natazia (NDA 22252), Generess (NDA 22573), and LoSeasonique (NDA 22262)

6.1.5 Contraceptive Efficacy (supportive evidence)

The 12 additional pregnancies that DBRUP considered on-treatment also affected the secondary endpoints. For women ≤ 35 years of age and not obese, there were three additional pregnancies in the ITT population and two additional pregnancies in the PPI population. For the women ≤ 35 years of age, regardless of BMI, there were also twelve additional pregnancies in the PPI population. The biometrics reviewer summarized the PIs for the secondary endpoints in Table 13.

Table 13: Contraceptive efficacy for the secondary endpoints for Trial ATI-CL23

	Population	Subgroup	Number of Women	Number of On-treatment pregnancies	Number of evaluable cycles	PI (95% CI)
Applicant	ITT	Age $\leq$ 35, BMI < 30 kg/m ²	1123	30	9888	3.94 (2.53, 5.35)
	PPI	Age $\leq$ 35	1714	49	14118	4.51 (3.25, 5.77)
	PPI	Age $\leq$ 35, BMI < 30 kg/m ²	1109	26	9241	3.66 (2.25, 5.06)
FDA	ITT	Age $\leq$ 35, BMI < 30 kg/m ²	1123	33	9888	4.34 (2.86, 5.82)
	PPI	Age $\leq$ 35	1714	57	14118	5.25 (3.89, 6.61)
	PPI	Age $\leq$ 35, BMI < 30 kg/m ²	1109	28	9241	3.94 (2.48, 5.40)

Source: NDA 204017 Module 5.3.5.1 ATI-CL23 Trial Body Report, Table 14.2.1.2.3 Pregnancy Rates Based on PI by Age Group and Overall for each BMI category- ITT Dataset, 14.2.1.3.2 Pregnancy Rates Based on PI by Age Group and Overall- PPI Dataset, 14.2.1.3.3 Pregnancy Rates Based on PI by Age Group and Overall for each BMI category- PPI Dataset.

FDA analysis conducted by Kate Dwyer, Ph.D., Biometrics Reviewer.

Reviewer Comments:

For the secondary efficacy endpoint using the ITT population, the data reflects the effect of obesity on the PI. When the Applicant limited the efficacy population to women $\leq$ 35 years of age with a BMI < 30 kg/m², the number of evaluable cycles of drug exposure (n=9888) did not quite meet the minimum number of 10000. The point estimate was 4.34 with an upper bound of 95% CI of 5.82, which exceeds the pre-specified criteria in the Applicant's statistical analysis plan as well as that for approved CHCs. The difference above the point estimate was 1.48 which exceeds the value of 1 as recommended to the Applicant by DBRUP.

For the secondary efficacy endpoint using the PPI population, when the Applicant limited the efficacy population to women $\leq$ 35 years of age with a BMI < 30 kg/m², the number of evaluable cycles of drug exposure (n= 9241) did not meet the minimum number of 10000. The point estimate was 3.94 with an upper bound limit of the 95% CI of 5.4, which also exceeds pre-specified criteria.

The biometrics reviewer also calculated the cumulative pregnancy rate using life-table analysis after 13 cycles of treatment in Table 14.

Table 14: Life Table Analyses for Trial ATI-CL23

	Population	# of On-Treatment Pregnancies	Cumulative Pregnancy Rate	95% Confidence Interval
Applicant	Age ≤ 35 years	56	4.22	(3.37, 8.88)
	Age ≤ 35 with BMI < 30 kg/m2	30	3.54	(2.47, 5.07)
	Age ≤ 35 with BMI ≥ 30 kg/m2	26	5.48	(3.74, 8.00)
	All Subjects	62	4.17	(3.25, 5.34)
FDA	Age ≤ 35 years	68	5.32	(4.20, 6.74)
	Age ≤ 35 with BMI < 30 kg/m2	33	3.98	(2.82, 5.60)
	Age ≤ 35 with BMI ≥ 30 kg/m2	35	7.79	(5.62, 10.77)
	All Subjects	74	5.13	(4.09, 6.44)

Source: Biometrics Review by Kate Dwyer, Ph.D. See the Biometrics Review finalized December 9, 2017.

Reviewer Comments:

The life table analyses show that the data still does not meet the Applicant's pre-specified criteria nor FDA's previously applied standards for efficacy of CHCs.

6.1.6 Contraceptive Efficacy Based on Race/Ethnicity and Previous Hormonal Contraception (HC) Use

The biometrics reviewer performed sensitivity analyses to assess for differential efficacy in the subpopulations. The results are summarized in Table 15.

Table 15: Contraceptive Efficacy based on Race, Ethnicity, and Previous Hormonal Contraceptive Use for the ITT population ≤35 years old for Trial ATI-CL23

Population	N	# of On-Treatment Pregnancies	Number of Cycles	PI	95% Confidence Interval
Race					
White	1159	46	10281	5.82	(4.14, 7.49)
Black or African American	418	17	3454	6.4	(3.36, 9.43)
Other	159	5	1430	4.55	(0.57, 8.52)
Ethnicity					
Hispanic or Latino	330	12	2851	5.47	(2.38, 8.56)
Not Hispanic or Latino	1406	56	12314	5.91	(4.37, 7.46)
Previous HC Use Status					
Naïve	171	5	1415	4.59	(0.57, 8.61)
Former	726	35	6107	7.45	(4.99, 9.91)
Recent	227	14	1888	9.64	(4.61, 14.67)
Current	612	14	5755	3.16	(1.51, 4.82)

Source: FDA Analysis conducted by K. Dwyer, Ph.D. Biometrics Review finalized on December 9, 2017.

Reviewer Comments:

The White and non-Hispanic subpopulations had sufficient numbers of evaluable cycles on the drug. However, the PIs of 5.82 and 5.91 in White and non-Hispanic respectively, are higher than acceptable.

For the other race/ethnic groups the number of evaluable cycles on the drug ranged from 1415 to 6017, which is too small and the confidence intervals around the point estimates are too wide to draw any meaningful conclusions.

Similarly, in the subpopulations of previous hormonal contraceptive users and current hormonal contraceptive users, there are insufficient numbers of cycles of exposure to conclude whether a particular subpopulation could benefit from the drug. Some of the confidence intervals are also wide, precluding meaningful conclusions about differential drug efficacy in those subpopulations.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

6.1.7.1 Anatomic Site

In the original NDA submission, the Applicant conducted phase 1 trials to examine the PK profile of AG200-15 when applied to different anatomic sites. In the trial ATI-CL23, women applied the patch to the upper torso, abdomen, and buttocks. During the phase 3 trials, women chose to apply the patch to the anatomic region of their choice for the duration of that cycle. The Applicant claims, “While absorption from the abdomen was slightly lower than from other sites, absorption from all three anatomic sites was considered to be therapeutically equivalent.”

Table 16 summarizes the anatomic sites used for trial ATI-CL23.

Table 16: Distribution of Application Site for Trial ATI-CL23 for the Safety Population (n=2031)

	Patch	Number of Cycles (n=18425)		Number of Patches (n=57015)
		Applicant	FDA	
Cycles 1-13	Abdomen	11235 (61.0%)	7258 (39.4%)	22391 (39.3%)
	Buttock	8785 (47.7%)	8230 (44.7%)	25555 (44.8%)
	Upper Torso (Breast excluded)	2451 (13.3%)	2937 (15.9%)	9069 (15.9%)

Source: Adapted from Clinical Trial Report ATI-CL23, Table14.3.7.1.1, (b) (4) Analysis by the clinical reviewer using the (b) (4) dataset.

Reviewer Comments:

The clinical reviewer noted that the Applicant’s sum of percentages for all anatomic totaled 122% and not 100%. The clinical reviewer conducted a separate (b) (4) separate analysis using (b) (4) (Data for exposure Analyses –Cycle) dataset. The clinical reviewer presented the data side by side in Table 15. The sum of the data now equals

100% and the data matches the clinical picture of approximately 3 patches used per cycle. The overall conclusions did not change. The abdomen and buttock were the anatomic sites where the trial participants applied the most patches. The Applicant did not evaluate efficacy by anatomic site of patch application. The Applicant did not submit the data in manner that allowed such analysis. However, the Clinical Pharmacology reviewer Peng Zou, PhD, stated in his review dated December 1, 2017 that “although a bioequivalence conclusion among the three application sites (abdomen, buttock, and upper torso) cannot be drawn from Study ATI-CL15, it is concluded that the three anatomical sites can be switched interchangeably (as was done in the clinical trials) without appreciable clinical consequences.” Therefore, efficacy data by anatomical site is not required at this time.

6.1.7.2 Patch Adhesion

The trial participants applied one patch on the designated anatomic site every seven days for three consecutive weeks followed by one patch free week. Given that only three patches are included in the proposed packaging, it was important that each patch adheres to the skin for the entire seven-day patch wear period to ensure the drug’s efficacy.

Women used the following patch adhesion score to assess patch adhesion for all the days the patch was worn:

- 0: No lifting or small amount of lifting at the edges of the patch
- 1: More than a small amount of lifting at the edges up to one-quarter of the patch lifting off
- 2: More than one quarter of the patch lifting off up to half of the patch lifting off
- 3: More than half of the patch is lifting off, but the patch is still on
- 4: Patch has completely come off

The investigators provided a separate score for patch adhesion during the eight in person clinic visits using the following scale:

- 0: $\geq 90\%$ adhered (none to minimal lift)
- 1: $\geq 75\%$ adhered but $< 90\%$ (some edges showing lift)
- 2: $\geq 50\%$ adhered but $< 75\%$ (at least half of system lifts off)
- 3: $< 50\%$ (more than half of the patch lifts off, but the patch remains attached)
- 4: patch completely detached

The Applicant summarized the clinical data for subject-reported adhesion scores in Table 17:

Table 17: Subject Reported Patch Adhesion Data using Safety Population (N = 2031)

Adhesion Score	Statistics	Number of Women	Number of Patches
Cycle 1	N	2019	6361
0	n/N%	686 (34%)	3714 (58.4%)
1	n/N%	520 (25.8%)	1417 (22.3%)
2	n/N%	183 (9.1%)	385 (6.1%)
3	n/N%	129 (6.4%)	215 (3.4%)
4	n/N%	501 (24.8%)	630 (9.9%)
Cycle 13	N	1022	3055
0	n/N%	668 (65.4%)	2440 (79.9%)
1	n/N%	202 (19.8%)	386 (12.6%)
2	n/N%	49 (4.8%)	96 (3.1%)
3	n/N%	41 (4%)	61 (2%)
4	n/N%	62 (6.1%)	72 (2.4%)
Overall	N	2022	55900
0	n/N%	230 (11.4%)	40109 (71.8%)
1	n/N%	357 (17.7%)	9462 (16.9%)
2	n/N%	174 (8.6%)	2235 (4%)
3	n/N%	161 (8.0%)	1305 (2.3%)
4	n/N%	1100 (54.4%)	2789 (5%)
Ortho-Evra	N	3319	70552
Cycle 1	n/N%	196/3302 (5.9%)	234/11059 (2.1%)
Cycle 13	n/N%	12/643 (1.9%)	12/1990 (0.6%)
Overall	n/N%	826/3319 (24.9%)	1297/70552 (1.8%)

Source: Adapted from NDA 204017 ATI-CL23Clinical Trial Report, Table 14.3.7.7.1 Summary of Subject Reported Patch Adhesion Score, Clinical Review for Ortho-Evra by Daniel Davis, M.D. finalized on November 20, 2001.

Reviewer Comment:

As noted in Table 16 and in the CMC review by Dr. Strasinger, 54.4% of all women that participated in the trial experienced complete patch detachment at some point during the trial. The number of women that experienced complete detachment decreased from 24.8% during cycle 1 to 6.1% on cycle 13. By patch count, 9.9% versus 2.4% of the patches completely detached in cycle 1 versus cycle 13, respectively. Overall 5% of the AG200-15 patches completely detached during the 13-cycle trial period. The clinical reviewer attributes this decrease in detachment over time to the patient's increasing experience with patch use.

When subject assessment of patch adhesion for AG200-15 is compared to subject diary data for Ortho-Evra[®], the patch adhesion for this AG200-15 TCDS is much worse. Only 24.9% (826 of 3319) of the women in the Ortho-Evra[®] trials experienced at least one complete patch detachment during the 12-month trial. For Ortho-Evra[®], 2.1%

versus 0.6% of the patches completely detached in cycle 1 versus cycle 13, respectively, and only 1.8% of the Ortho-Evra® patches completely detached during the 12-month trial. These figures are also much lower than for AG200-15.

The Applicant assessed the number of patches that were distributed per cycle and overall. Key findings are summarized in Table 18.

Table 18: Number of Patch distributed per cycle for the Trial ATI-CL23

	Number of Patches	Number of cycles (N=18841)
Overall	1	756 (4%)
	2	621 (3.3%)
	3	14695 (78%)
	4	2185 (11.6%)
	5	452 (2.4%)
	6	108 (0.57%)
	7	16 (0.08%)
	8	6 (0.03%)
	9	2 (0.01%)

Source: Adapted from NDA 204017, Clinical Trial Report Table 14.3.7.1.2 Distribution of number of patches applied per treatment cycle.

Reviewer comment:

In 14.7% of the treatment cycles, women used four or more patches. This is concerning given that the proposed packaging would only include three patches. This supports concerns about reduced efficacy and undercuts any arguments for the convenience of the TCDS if the woman has to obtain unexpected refills for contraception secondary to underlying patch adhesion issues. Additionally, this could mean more out of pocket costs for the woman if health insurance does not cover early refills of the medication.

7 Review of Safety

Safety Summary

In ATI-CL23, 2031 women enrolled and 989 completed 13 28-day cycles of treatment, yielding 18,841 cycles. The overall safety database includes 29,900 cycles from all the phase 3 trials. These numbers are adequate for a thorough safety evaluation.

The AE profile for the ATI-CL23 differed from the combined ATI-CL12 and ATI-CL13 AE profile. The Applicant reported no deaths; however, there were 40 SAEs were reported in trial ATI-CL23 versus 16 total SAEs for both ATI-CL12 and ATI-CL13 combined (See Table 22). For trial ATI-CL23, there were six venous thromboembolic events (VTEs), six psychiatric AEs, and seven hepatobiliary AEs versus one VTE, one AE, and no hepatobiliary AEs in the original trials combined. Given the Applicant made no changes to the drug product, the clinical reviewer cannot explain why more SAEs were reported in the new trial. The

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unscheduled bleeding profile for women was more unfavorable in the ATI-CL23 with 41.3% of women experiencing bleeding/spotting episodes after a 1 year of exposure compared to 22.8% of women in the original trials combined. There were no significant changes in vitals, chemistry, or hematology parameters that represented any unexpected safety concern. On balance, the safety profile of AG200-15 is similar to that of other approved CHCs, with the exception of more unscheduled bleeding.

7.1 Methods

Dr. Davis' safety review in the previous cycle included three phase one trials (ATI-CL14, ATI-CL15, and ATI-CL16), one phase pharmacodynamic trial (ATI-CL11), and two phase 3 trials (ATI-CL12 and ATI-CL13). For full details, refer to his February 13, 2013 review. For this submission, safety was based on the following sources:

- Safety Update 2017
- Data from Clinical Trial Report for efficacy and safety trial ATI-CL-23
- Data from Clinical Trial Report for efficacy and safety trial ATI-CL12
- Data from Clinical Trial Report for efficacy and safety trial ATI-CL13

ATI-CL12 and ATI-CL13 were both comparative trials in which trial participants were randomized to AG200-15, COC, or COC/AG200-15. For the Safety Update, the Applicant excluded data for women treated with COC only from the safety analysis, as combined oral contraceptive use could be a confounder.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 19 summarizes the details of the Phase 3 trials that were used to assess safety.

Table 19: Summary of Phase 3 Trials used to assess the safety of AG200-15

Name and Type of Clinical Trial	Objectives of the Clinical Trial	Trial Design and Type of Control	Test Product(s) Dosing Regimen Route of Administration	Trial population	Duration of Treatment
ATI-CL23 Efficacy and Safety Trial	See details in Section 5.3.1				

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ATI-CL12 Efficacy and Safety Trial	To comparatively evaluate and compare of contraceptive efficacy, safety, cycle control, treatment compliance, and PK of EE/LNG of AG200-15 versus a low dose OC, and patch wearability	Open-label, randomized, comparative, parallel group, multicenter	AG200-15: 2.60 mg LNG and 2.30 mg EE 1 patch per 7-day period; Transdermal Lessina® (OC): 0.1 mg LNG and 0.02 mg EE One tablet daily; Oral	Healthy sexually active females at risk for pregnancy age 17 to 40 AG200-15: 1378 women enrolled (249 women that switched from OC to patch at Cycle7) 635 women completed the trial Lessina: 375 women enrolled in the trial 249 women completed the trial	AG200-15: Thirteen 28-day cycles (1 patch applied every 7 days for three consecutive weeks followed by 1 patch free 7- day period) Lessina® Six 28-day cycles (one tablet a day) followed by AG200-15 for seven 28-day cycles (1 patch applied every 7 days for three consecutive weeks followed by 1 patch free 7- day period)
ATI-CL13 Efficacy and Safety trial	To comparatively evaluate contraceptive efficacy, safety, cycle control, treatment compliance, PK of EE/LNG of AG200-15 versus a low dose OC, and patch wearability	Open-label, randomized, comparative, parallel group, multicenter,	AG200-15: 2.60 mg LNG and 2.30 mg EE 1 patch per 7-day period; Transdermal Levora® (OC): 0.15 mg LNG and 0.03 mg EE; One tablet daily; Oral	Healthy sexually active females at risk for pregnancy age between 18 to 40 years AG200-15 201 enrolled 112 completers Levora: 206 enrolled 145 completers	AG200-15: six 28-day cycles (1 patch applied every 7 days for three consecutive weeks followed by 1 patch free 7- day period) Levora® Six 28 day cycles (one tablet a day)

Source: Adapted from NDA 204017, Module 5.2 Tabular Listing of All Clinical Trials, submission date April 13, 2012 and submission date June 26, 2017.

7.1.2 Categorization of Adverse Events (AE)

The Applicant provided the definitions for serious adverse event (SAE) and treatment-emergent adverse event (TEAE).

A serious adverse event (SAE) was defined as:

- Any event that is fatal or life-threatening
- Any event requiring an inpatient hospitalization or prolongation of existing hospitalization
- Any event resulting in a persistent or significant disability or incapacity
- Any event resulting in a congenital anomaly/birth defect
- Any important medical event, based upon appropriate medical judgment that may jeopardize the subject requiring medical or surgical intervention to prevent one of the outcomes listed in this definition.

A treatment emergent AE (TEAE) was defined as an AE with an onset date on or after the application of the first patch application through twenty-eight days (28) of the woman's final treatment cycle.

SAEs were considered treatment emergent with an onset on or after the first patch application; however, to ensure reporting of SAEs, the Applicant considered SAEs treatment emergent even if the onset date was beyond Day 28 of the woman's final treatment cycle.

The Applicant provided the following definitions that were used to assign severity of reported AEs:

- Mild: discomfort noted, but no disruption of normal daily activity
- Moderate: discomfort noted of sufficient severity to reduce or adversely affect normal activity
- Severe: incapacitating, with inability to work or perform normal daily activity

The Applicant provided the following definitions that were used to categorize the relationship of observed AEs to the trial medication:

- Unrelated: There is strong evidence that the AE has an etiology other than the assigned study drug.
- Possibly Related: The AE has a temporal relationship to trial drug; however, an alternative etiology may be responsible. Information on drug/product withdrawal may be lacking or unclear.
- Probably Related: The AE has a temporal relationship to trial drug administration. The event is unlikely to be related to an alternative etiology. There is a reasonable response on withdrawal. Re-challenge information is not required.
- Definitely Related: The AE has a temporal relationship to trial drug administration and resolves when the drug is discontinued. An alternative etiology is not apparent. If the subject is re-challenged with the assigned study drug, the AE recurs. A re-challenge is not necessarily required.

7.1.3 Pooling of Data across Clinical Trials to Estimate and Compare Incidence

DBRUP advised the Applicant to submit an updated summary of safety to include safety information from trials ATI-CL12, ATI-CL13, and ATI-CL23. Per the Division's recommendation, the Applicant submitted the Safety Update in the following format, excluding the safety data for the women randomized to the COC treatment arms:

Original (ATI-CL12/13)		New (ATI-CL23)	Overall (Safety Update)
AG200-15 Cycles		AG200-15 Cycles	AG200-15
1-6	1-13	1-13	All Cycles

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 20 shows the drug exposure for all the phase 3 trials that contributed to the safety population.

Table 20: Summary of Safety Population by Treatment Cycle

Cycle	Original NDA (ATI-CL12/13)		New Data (ATI-CL23)	Overall
	Cycles @		Cycles	Cycles
	1-6 (N=1220)	1-13 (N=1450)	All Cycles (N=2031)	All Cycles (N=3481)
Cycle 1	1215 (99.6%)	1215 (83.8%)	2023 (99.6%)	3238 (93.0%)
Cycle 2	1060 (86.9%)	1060 (73.1%)	1878 (92.5%)	2938 (84.4%)
Cycle 3	990 (81.1%)	990 (68.3%)	1747 (86.0%)	2737 (78.6%)
Cycle 4	903 (74.0%)	903 (62.3%)	1629 (80.2%)	2532 (72.7%)
Cycle 5	857 (70.2%)	857 (59.1%)	1524 (75.0%)	2381 (68.4%)
Cycle 6	808 (66.2%)	808 (55.7%)	1430 (70.4%)	2238 (64.3%)
Cycles 1-6	1216 (99.7%)	1216 (83.9%)	2023 (99.6%)	3239 (93.0%)
Cycle 7		877 (60.5%)	1354 (66.7%)	2231 (64.1%)
Cycle 8		858 (59.2%)	1279 (63.0%)	2137 (61.4%)
Cycle 9		765 (52.8%)	1216 (59.9%)	1981 (56.9%)
Cycle 10		718 (49.5%)	1145 (56.4%)	1863 (53.5%)
Cycle 11		695 (47.9%)	1106 (54.5%)	1801 (51.7%)
Cycle 12		673 (46.4%)	1067 (52.5%)	1740 (50.0%)
Cycle 13		640 (44.1%)	1027 (50.6%)	1667 (47.9%)
>13 Cycles			292 (14.4%)	292 (8.4%)
All Cycles		1443 (99.5%)	2023 (99.6%)	3466 (99.6%)
Total Cycles		11059	18841	29900

Source: Module 5.3.5.3 Safety Update, Table 2 Safety Population by Treatment Cycle

Reviewer Comments:

There are 29900 evaluable cycles from all the phase 3 trials, which is adequate to sufficiently evaluate the safety of AG200-15. While the safety profile for the hormonal combination of levonorgestrel and ethinyl estradiol, in general is well understood, there are still important safety concerns to consider for this route of administration.

7.2.2 Explorations for Dose Response

There were no new Phase 2 trials conducted for the resubmission. See the clinical pharmacology review by Hyunjin Kim, Ph.D. of the original submission dated January 11, 2013.

7.2.3 Special Animal and/or In Vitro Testing

No special animals and/or in vitro testing were required for this application.

7.2.4 Routine Clinical Testing

At screening, the safety assessments included

- baseline characteristics (height, body weight, temperature)
- vital signs (heart rate, respiratory rate, sitting diastolic and diastolic pressure)
- urine pregnancy test, if positive excluded from the trial
- medical, gynecological, contraceptive use history
- concomitant medications (present and 6-month prior)
- physical including gynecological examination
- cervical cytology with HPV testing if applicable (waived if done within 3 months)
- clinical laboratory tests (hematology, chemistry, hemoglobin A1C, lipid panel) under fasting conditions
- urinalysis
- urine drug screen
- HIV antibody test, Hepatitis B surface antigen (HBsAg) test, Hepatitis C (HCV) antibody test, gonorrhea and chlamydia (GC/CT) test

For in-person clinical visit, safety assessments included

- urine pregnancy tests (if positive, further workup with serum beta-HCG, pelvic exam, and transvaginal ultrasound)
- vital signs
- review of concomitant medications
- skin assessment of patch application site
- patch adhesion assessment
- monitoring for adverse events

At the exit of the trial, the safety assessments included

- urine pregnancy test (if positive, see workup for in person clinic visit)
- serum beta-HCG
- weight and vital signs

- physical including gynecological examination
- cervical cytology
- clinical laboratory test (hematology, chemistry, lipid panel) under fasting conditions
- skin assessment of application site

Reviewer comment:

The routine clinical testing for this NDA is adequate; however, it is unclear why the Applicant conducted pap screening in women younger than 21 years of age. Guidelines set forth by the American Society of Colposcopy and Cervical Pathology (ASCCP)¹⁵ and the American Cancer Society¹⁶ recommend that women undergo pap screening starting at 21 years of age.

7.2.5 Metabolic, Clearance, and Interaction Workup

No metabolic, clearance, or interaction studies were conducted for this NDA.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events associated with this estrogen-progestin combination are well known. The clinical reviewer assessed the AEs identified by the Applicant during the conduct of the trial for any new safety concerns.

7.3 Major Safety Results

Overall, 53.6% of trial subjects experienced a TEAE and 1.6% experienced serious TEAEs. The Applicant assessed 0.52% of those serious TEAEs as trial drug-related. The Applicant summarized the data in Table 21.

Table 21: Overall Summary of Treatment Emergent Adverse Events (TEAEs)

	Original NDA (ATI-CL12/13)	New Data (ATI-CL23)	Overall
	Cycles	Cycles	Cycles
Category	1-6 (N=1220)	1-13 (N=1450)	All Cycles (N=2031)
Subjects with Any TEAEs	580 (47.54%)	781 (53.86%)	1085 (53.42%)
Subjects with Any Study Drug-Related TEAEs	261 (21.39%)	338 (23.31%)	552 (27.18%)
Subjects with Severe TEAEs	50 (4.10%)	73 (5.03%)	92 (4.53%) (4.74%)
Subjects with Serious TEAEs (SAE) (including death)	14 (1.15%)	16 (1.10%)	40 (1.97%) 56 (1.61%)
Subjects with Study Drug-Related Serious TEAEs (SAE)	3 (0.25%)	3 (0.21%)	15 (0.74%) 18 (0.52%)
Subjects with TEAE Resulting in Trial Drug Discontinuation	119 (9.75%)	151 (10.41%)	224 (11.03%)
Subjects Who Died	0	0	0

Source: NDA 204017 Module 5.3.5.3 Safety Update, Table 4.1.1 Overall Summary of Treatment Adverse Events.

Reviewer Comments:

The incidence of TEAEs was comparable across all categories with the exception of serious adverse events. For the ATI-CL23, the incidence for serious adverse events at 2.0% was almost twice the incidence of either of the original trials. See Section 7.3.2 for more a detailed discussion on this finding.

7.3.1 Deaths

There were no deaths among the women that used AG200-15 in the course of the clinical development program.

7.3.2 Nonfatal Serious Adverse Events

There were 40 SAEs in the trial ATI-CL23 versus 16 SAEs total in trials ATI-CL12 and ATI-CL13. After reviewing all of the SAEs presented in the Safety Update for all the clinical trials, the clinical reviewer further examined the SAEs that were classified under the following system organ classes: gastrointestinal, hepatobiliary, respiratory, pregnancy, psychiatric, and vascular. Those SAEs are summarized in Table 22. These categories were selected because of the potential lethality of associated AEs within those categories.

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Table 22: Treatment Emergent SAEs of Special Interest – Safety Population

	Original NDA (ATI-CL12/13)		New Data (ATI-CL23)	Overall
	Cycles		Cycles	Cycles
System Organ Class Preferred Term	1-6 (N=1220)	1-13 (N=1450)	All Cycles (N=2031)	All Cycles (N=3481)
<i>Any Adverse Event</i>	14 (1.15%)	16 (1.10%)	40 (1.97%)	56 (1.61%)
Gastrointestinal disorders	2 (0.16%)	2 (0.14%)	2 (0.10%)	4 (0.11%)
Colitis	0	0	1 (0.05%)	1 (0.03%)
Gastric fistula	0	0	1 (0.05%)	1 (0.03%)
Gastrointestinal motility disorder	1 (0.08%)	1 (0.07%)	0	1 (0.03%)
Pancreatitis necrotizing	0	0	1 (0.05%)	1 (0.03%)
Vomiting	1 (0.08%)	1 (0.07%)	0	1 (0.03%)
Hepatobiliary disorders	0	0	7 (0.34%)	7 (0.20%)
Cholecystitis	0	0	2 (0.10%)	2 (0.06%)
Cholecystitis acute	0	0	1 (0.05%)	1 (0.03%)
Cholecystitis chronic	0	0	1 (0.05%)	1 (0.03%)
Cholelithiasis	0	0	4 (0.20%)	4 (0.11%)
Hepatitis	0	0	1 (0.05%)	1 (0.03%)
Pregnancy, puerperium, and perinatal conditions	0	0	3 (0.15%)	3 (0.09%)
Ectopic pregnancy	0	0	2 (0.10%)	2 (0.06%)
Ruptured ectopic pregnancy	0	0	1 (0.05%)	1 (0.03%)
Psychiatric disorders	1 (0.08%)	1 (0.07%)	6 (0.30%)	7 (0.20%)
Bipolar disorder	0	0	1 (0.05%)	1 (0.03%)
Major depression	0	0	3 (0.15%)	3 (0.09%)
Substance abuse	0	0	1 (0.05%)	1 (0.03%)
Suicidal ideation	1 (0.08%)	1 (0.07%)	1 (0.05%)	2 (0.06%)
Suicide attempt	0	0	1 (0.05%)	1 (0.03%)
Respiratory, thoracic and mediastinal disorders	1 (0.08%)	1 (0.07%)	4 (0.20%)	5 (0.14%)
Acute respiratory distress syndrome	0	0	1 (0.05%)	1 (0.03%)
Asthma	1 (0.08%)	1 (0.07%)	0	1 (0.03%)
Pulmonary embolism (PE)	0	0	3 (0.15%)	3 (0.09%)
Vascular disorders	1 (0.08%)	1 (0.07%)	3 (0.15%)	4 (0.11%)
Deep vein thrombosis (DVT)	0	0	3 (0.15%)	3 (0.09%)
Embolism venous	1 (0.08%)	1 (0.07%)	0	1 (0.03%)

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

Reviewer Comments:

The AE profile for trial ATI-CL23 differed significantly from the AE profile for original trials. There were three cases of ectopic pregnancy in the new trial versus none in the original trial. The clinical reviewer does not believe the woman's use of the drug directly increased her risk of having an ectopic pregnancy. The increased risk of ectopic pregnancy is more likely a consequence of the drug's lack of efficacy. See Section 6 for detailed discussion the drug's efficacy.

There were six thromboembolic events (three DVTs and 3 PEs) in the new trial versus one in the new trial. These findings are discussed in further detail under Section 7.3.5 of this review.

There were seven hepatobiliary SAEs reported in the new trial versus none in the original trials and six psychiatric SAEs in the new trial versus one in original trials. The Applicant provided narratives of the SAEs which the clinical reviewer further examined for potential safety concerns.

7.3.2.1 Hepatobiliary disorders

Subject (b) (6): Cholelithiasis

The subject was a 38-year-old, non-Hispanic, Caucasian female with a BMI of 39.9 kg/m² and weight of 129.7 kg. She had abnormal screening laboratory assessments of cholesterol (5.87mmol/L) and LDL (3.52mmol/L). With the exception of a high BMI, vital signs were within normal limits. She applied the first patch on (b) (6). On (b) (6) (Cycle 5), the subject experienced acute right upper quadrant and epigastric pain. On (b) (6), an abdominal ultrasound showed a 2.0 cm x 1.2 cm x 1.4 cm mobile calculus in the gallbladder fundus as well as gallbladder wall irregularity. She was diagnosed with gallstones. Her last patch was removed on February 24, 2015. On (b) (6), the subject underwent laparoscopic cholecystectomy with cholangiogram. The cholangiogram was normal. The surgical pathology report revealed cholelithiasis and slight chronic cholecystitis. She was discharged with Colace and oxycodone. The event was considered resolved. She was discontinued from the trial on March 5, 2015.

Subject (b) (6): Cholecystitis

The subject was a 29-year-old, white, non-Hispanic female with a BMI of 40 kg/m² and weight of 116.1 kg. Her screening vitals, with the exception of BMI, were within normal limits. Abnormal screening laboratory assessments included the following: alkaline phosphatase (127 U/L), cholesterol (5.51mmol/L), and triglycerides (2.55mmol/L). She applied the first patch on November 1, 2014. On (b) (6), she presented to the emergency room when she started experiencing sudden onset sharp stabbing pain that radiated to her back approximately two hours after eating beef tacos. She was admitted for pain management and possible operative intervention. Laboratory tests revealed elevated liver enzymes (ALT 111 U/L and AST 150 U/L). Abdominal ultrasound showed multiple stones in the gallbladder with gallbladder wall

thickening consistent with cholecystitis. On (b) (6), the subject underwent a cholecystectomy. Intraoperative findings included edema and inflammation of the gallbladder. She was discharged to home later that day. No complications were noted and she recovered with no sequelae. The patch was removed on March 26, 2015, and she was discontinued from the study on April 27, 2015.

Subject (b) (6): Acute/chronic cholecystitis without obstruction and cholelithiasis

The subject was a 28-year-old, white, non-Hispanic with a BMI of 39 kg/m² and weight of 103 kg. Screening laboratory assessments and vitals, with the exception of BMI, were within normal limits. She reported prior use of oral hormonal contraception but none within the last 6 months. No concomitant medications were reported at screening. She applied the first patch on July 15, 2015. On (b) (6), the subject reported going to ER with sharp and stabbing abdominal pain in the right upper quadrant, nausea, vomiting, blood in stool, and anorexia. A CT of the abdomen indicated mild enteritis and cholelithiasis. She had an elevated WBC count (13,000/uL) and elevated glucose (133 mg/dL). She was treated with Toradol, Zofran, and morphine in the emergency room and discharged. Her last patch was removed on April 22, 2016. When her symptoms persisted, she underwent a laparoscopic cholecystectomy on (b) (6). The final microscopic diagnosis was cholelithiasis, acute and chronic cholecystitis with prominent mural fibrosis and myoid changes. She tolerated the procedure well and was discharged the same day. She was discontinued from the trial on May 2, 2016.

Subject (b) (6): Cholelithiasis

The subject was a 33-year-old, white, Hispanic female with a weight of 96.3 kg and a BMI of 38.8 kg/m². She reported a medical history cholecystitis in October 2014. No concomitant medications were reported at screening. She reported prior contraceptive use that included the contraceptive patch, vaginal ring, and emergency contraception. After trial enrollment, she applied the first patch on March 12, 2015. On (b) (6), the subject presented to the ER with complaints of a 24 to 48-hour history of right upper quadrant abdominal pain, nausea, and vomiting. She was diagnosed with cholelithiasis with elevated liver enzymes. Her symptoms improved and she was discharged from the hospital. She returned to the ER shortly thereafter with the same symptoms. She was admitted to the hospital for a cholecystectomy and intraoperative cholangiogram. During the cholangiogram, no contrast was visualized in the duodenum. She underwent an endoscopic retrograde cholangiopancreatography (ERCP) where a stone was found in the cystic duct. No stones were found in the common bile duct. The subject had a sphincterotomy and a stent placed in the common bile duct. She was stable for discharge on (b) (6), and was instructed to follow up for liver function tests, post-operative checkup, ERCP, and stent removal. The drug was temporarily interrupted from October 9, 2015, to October 12, 2015, but was not discontinued. The subject decided to withdraw consent and removed her last patch on January 13, 2016. She was discontinued from the trial on January 18, 2016.

Subject (b) (6): Acute Cholecystitis

The subject was a 28-year-old, white, non-Hispanic female with a BMI 35.1 kg/m² and weight of 101.6 kg. The subject reported prior user of oral hormonal contraception. She applied her first patch on May 19, 2015. On June 22, 2015, during her routine in clinic visit, she revealed that she was admitted to the hospital for acute cholecystitis and underwent an emergency laparoscopic cholecystectomy on (b) (6). She recovered without sequelae and was discharged on (b) (6). She continued taking the trial drug. Per her case report form, she removed her last patch on September 28, 2015. She was lost to follow up and discontinued from the trial on January 12, 2016.

Subject (b) (6): Cholecystitis

The subject was a 32-year-old non-Hispanic, black female with a weight of 128.4 kg and a BMI of 44.4 kg/m². Vital signs were otherwise within normal limits. The subject reported no significant medical history other than four cesarean sections. She reported prior oral contraception use, progestin IUD, and injectable contraception in the past but not in the last 6 months. On September 16, 2015, she applied the first patch. On (b) (6), she reported to the emergency room with severe abdominal pain and vomiting. She also reported right upper quadrant pain, vomiting, diarrhea, and jaundice over the past month prior to reporting to ER. The abdominal ultrasound showed gallstones but no biliary dilatation. Hepatobiliary iminodiacetic acid (HIDA) scan results showed retained hepatic parenchymal tracer which demonstrated liver dysfunction. ALT at 157 U/L and AST at 97 U/L was considered. Alkaline phosphatase was 215 U/L, bilirubin was 0.7 mg/dL, and albumin was 2.8 g/dL. The subject's hepatitis panel was negative. She underwent a cholecystectomy and liver wedge biopsy which showed chronic cholecystitis with complete impaction and innumerable stones which distend the wall of the gallbladder. The lumen showed mucosal changes, suggesting cholesterosis and mucosal ulceration. The liver wedge biopsy showed chronic hepatitis with minimal activity and stage 1 fibrosis possibly related to transient obstruction of the biliary tree and some background chronic changes secondary to a prior occurrence. Follow up ALT and AST levels, taken on (b) (6) were within normal limits. Her last patch was removed on January 7, 2016. She was discontinued from the trial on March 11, 2016.

Reviewer Comments:

All of these women were at increased risk for gallbladder disease given their obesity and female sex. According to published literature, for premenopausal women, exposure to the hormones found in AG200-15 does not increase the risk for developing gallbladder disease.^{17, 18} It is possible that the trial drug was responsible for the exacerbation of underlying gallbladder disease or the development of gallstones. However, the clinical reviewer notes in Table 20 that there were no hepatobiliary adverse events in the original submission.

Subject (b) (6): Bilateral Deep Venous Thrombosis, Necrotizing pancreatitis, cholelithiasis, acute respiratory distress syndrome, Klebsiella bacteremia, gastrocutaneous fistula, stage III pressure ulcers

The subject was a 25-year-old, race reported as “Other”, Hispanic female with a BMI of 35.7 kg/m² and weight of 97.3 kg. Vitals at screening were within normal limits. There was no pertinent medical history except obesity. She was a non-smoker and reported an alcohol intake of less than one drink per week. She had a history of oral contraceptive use within 6 months and emergency contraception use greater than 6 months from the screening exam. She applied the first patch on May 18, 2015. On (b) (6), she presented to the emergency room with pain and loss of consciousness. She developed acute respiratory distress syndrome (ARDS) shortly after her ER arrival and was transferred to the intensive care unit (ICU).

On (b) (6), blood work showed a bilirubin of 3.3. An abdominal ultrasound performed on (b) (6) showed cholelithiasis and ascites. CT scan of the abdomen and pelvis showed severe acute pancreatitis, known cholelithiasis, and moderate ascites.

On (b) (6), she was intubated secondary to ARDS. During the course of her hospitalization, she received required a blood transfusion for “her drop in hematocrit”. She experienced oliguria with a creatinine of 3.9 mg/dL which required hemodialysis until (b) (6).

On (b) (6), another CT scan of the abdomen and pelvis showed small perihepatic ascites, cholelithiasis with contracted gallbladder, and small right pleural effusion. On (b) (6), she experienced spiking fevers for which she received broad coverage antibiotics. She received a tracheostomy on (b) (6) because she still required mechanical ventilatory assistance.

When she became febrile, on (b) (6), she underwent a paracentesis that was positive for Klebsiella. She was treated with Meropenem IV from (b) (6) for suspected Klebsiella bacteremia; however, her blood cultures were negative on (b) (6).

On (b) (6), a repeat ultrasound showed multiple gallstones. That same day she underwent a pancreatectomy. On (b) (6), venous Doppler showed a right partially occlusive DVT in the common femoral and saphenofemoral junction and left common femoral saphenofemoral junction, proximal and distal and popliteal DVTs. She was placed on heparin and bivalirudin. On (b) (6), a CT scan showed a gastrocutaneous fistula. Repeat scan on (b) (6) showed fistula regression.

Her hospital course was complicated by prolonged ileus, splenic vein thrombosis, multiple DVTs, oliguria, multiorgan failure, stage III pressure ulcers, Klebsiella bacteremia, ARDs secondary to Pseudomonas, wound infection with gastrocutaneous fistula. (b) (6), she was transferred to a step-down unit. She was discharged from the hospital to an acute care rehabilitation facility on (b) (6). On (b) (6), she was deemed recovered was going to outpatient rehabilitation.

Reviewer Comments:

The investigator and Applicant considered the pancreatitis unrelated to the trial drug and the cholelithiasis to be possibly related to the trial drug considering the temporal association. The narrative notes that the subject wore the patch for only two days and stated she had preexisting cholelithiasis. Causality of the trial drug to her pancreatitis is cannot be established or ruled out. The investigator considered the rest of the listed AEs unrelated. The clinical reviewer agrees that the rest of the AEs were sequelae of the underlying disease and less likely the drug. For a discussion on the DVT, see Review comments under section 7.3.5.

7.3.2.2. Mood disorders

Subject (b) (6): Major depressive disorder

The subject was a 20-year-old, white, non-Hispanic female with a weight of 69.9 kg and a BMI of 22.1 kg/m². Her medical records revealed a history of episodic anxiety and depression as well as cutting since age 14. She had a history of sexual, physical, and emotional abuse. She was a recent Nuva Ring user. She applied the first patch on June 29, 2015. She was admitted to the hospital on (b) (6) for a suicidal attempt after allegedly ingesting 18 Tylenol tablets. She was diagnosed with major depressive and post-traumatic stress disorder for which was treated with a trial of sertraline. She was discharged on (b) (6) after her suicidal ideations resolved. Her discharge plan was outpatient counseling and monitoring. The patch was initially removed on July 6, 2015. Because of the suicidal ideation, she was no longer trial-eligible. She did not attend her discontinuation visit scheduled for July 27, 2015. After contacting the subject, she confirmed that she removed her last patch on August 2, 2015. Since the subject refused to attend her early termination visit, she was discontinued from the trial on September 2, 2015.

Subject (b) (6): Worsening of pre-existing depression with suicide attempt

The subject was a 20-year-old, white, non-Hispanic with a BMI of 19.3 kg/m² and weight 54.6 kg with a history of depression. She was naïve to hormonal contraception. She applied the first patch on August 30, 2015. She was hospitalized on (b) (6) for worsening depression with a suicide attempt by slashing her wrists. She tested positive for opiates and marijuana. She was hospitalized for five days, stabilized, and discharged on (b) (6) with follow up in outpatient counseling. The discharge diagnosis was adjustment disorder with mixed emotional features. By (b) (6), she reported her depression had abated. Her last patch was removed on May 13, 2016, and she was discontinued from the clinical trial on June 1, 2016. During her early termination visit, she was deemed stable and was still undergoing outpatient counseling.

Subject (b) (6): Major depressive episode - recurrent

The subject was an 18-year-old, Hispanic female of Chinese and Mexican descent, with a BMI of 30.3 kg/m² and a weight of 90.3 kg. She had a history of an eating disorder, self-harm, suicidal behavior, child abuse, and chronic marijuana use. Her drug testing at screening was negative. She reported recent use of oral hormonal contraception and prior use of emergency contraception. Concomitant medication reported at screening included the contraceptive norethindrone. She applied the first patch on October 16, 2015. On (b) (6), she reported her hospital admission on (b) (6) for severe depression and suicidal ideations. At the time, she reported a history of depression that started at age 12, resolved in 2014 and returned in August 2015. According to the subject's electronic diary, she removed the last patch on March 26, 2016, and did not apply another. She was diagnosed with major depressive episode - recurrent. She was discontinued from the trial on May 5, 2016.

Subject (b) (6): Bipolar disorder with suicidal ideation

The subject was a 24-year-old, white, non-Hispanic with a BMI of 30.7 kg/m² and a weight 98.4 kg. While her medical records revealed that she had a history of bipolar disorder and attention deficit hyperactivity disorder, she did not report this to the Investigator prior to her entry into the trial. She had previously used the vaginal ring and was a current user of COCs. She applied the first patch on August 19, 2015. On (b) (6), she was admitted for bipolar disorder with suicidal ideations. She continued wearing the patch and stated that she wished to continue in the trial. She was discharged on (b) (6), and was referred for intensive outpatient counseling on (b) (6). Per the Investigator's decision, the woman's last patch was removed and she was permanently discontinued from the trial on April 14, 2016.

Subject (b) (6): Major depressive disorder, recurrent, severe without psychosis

The subject was a 22-year-old, white, Hispanic female with a weight of 87.5 kg and a BMI of 36.5 kg/m². Screening laboratory assessments and vitals were within normal limits with the exception of BMI. Drug testing at screening was negative. She reported a history of depression and a history of cutting as a teenager; but, she denied any prior hospitalization or suicide attempts. She was a recent user of oral hormonal contraceptive and emergency contraception, and a prior user of injectable contraceptive. She applied her first patch on July 31, 2015. On (b) (6), the subject was admitted to the hospital for a suicide attempt after taking 100 propranolol pills. She was treated with ziprasidone and fluoxetine. The nursing staff removed the subject's patch on (b) (6). The subject was discharged from the hospital on (b) (6), with a diagnosis of major depressive disorder, recurrent and severe without psychosis. She was advised to continue taking fluoxetine and was given a referral for psychiatric counseling. The subject applied a patch on August 17, 2015; however, the removal date of the patch was unknown. She applied another patch on August 28, 2015; however, that patch was removed later that day during her discontinuation visit.

Reviewer Comments:

All of these subjects had significant underlying mental illness. For subjects (b) (6) the investigator ruled the adverse events as unrelated to the subject AG200-15 use. For the rest of the subjects described above, the investigator and Applicant ruled the psychiatric AEs as possibly related to the drug.

20.7% of the safety population had a psychiatric diagnosis prior to entering the trial ATI-CL23. Of those, 10.14% had depression and 9.2% had anxiety. Depression can be an adverse reaction to the progestin component of CHCs. While the clinical reviewer acknowledges the temporal relationship between the AG200-15 exposure and the worsening mood symptoms, causality cannot be definitively established. Several of the narratives suggested other cofounder for mood exacerbation such as life stressors or relationship difficulties. The labeling for CHCs in general addresses the risk of mood disorders exacerbation.

7.3.3 Dropouts and/or Discontinuations

Table 23 shows the subject disposition for all the trials. The number of women that discontinued trial ATI-CL23 was 51.3%. Overall, 50.1% discontinued the trials, which, as discussed in Section 6 of this review, is still higher than the discontinuation rates for most registration trials of other approved CHCs.

Table 23: Disposition of Women for all the Phase 3 Trials

	<u>Original NDA</u> <u>(ATI-CL12/13)</u>		<u>New Data</u> <u>(ATI-CL23)</u>	<u>Overall</u>
	Cycles		Cycles	Cycles
	1-6	1-13	All Cycles	All Cycles
Subjects Screened	2243	2523	4033	6556
Randomized/Enrolled	1330	1579	2032	3611
Safety Population	1220	1450	2031	3481
Completed Study	597 (48.9%)	747 (51.5%)	989 (48.7%)	1736 (49.9%)
<i>Reason for Discontinuation</i>				
Any	623 (51.1%)	703 (48.5%)	1042 (51.3%)	1745 (50.1%)
Adverse Events	135 (11.1%)	151 (10.4%)	222 (10.9%)	373 (10.7%)
Death	0	0	0	0
Non-compliance	41 (3.4%)	47 (3.2%)	116 (5.7%)	163 (4.7%)
Lost to Follow-up	207 (17.0%)	229 (15.8%)	229 (11.3%)	458 (13.2%)
Subject Decision	176 (14.4%)	200 (13.8%)	310 (15.3%)	510 (14.7%)
Pregnancy	38 (3.1%)	46 (3.2%)	73 (3.6%)	119 (3.4%)
Protocol Violation	4 (0.3%)	4 (0.3%)	14 (0.7%)	18 (0.5%)
Investigator's Decision	14 (1.1%)	16 (1.1%)	17 (0.8%)	33 (0.9%)
Sponsor Decision	0	0	18 (0.9%)	18 (0.5%)
Sponsor Decision (Study Termination)	0	0	2 (0.1%)	2 (0.1%)
Other	8 (0.7%)	10 (0.7%)	41 (2.0%)	51 (1.5%)

Source: NDA 204017 Module 5.3.5.3 Safety Update, Table 1 Subject Disposition

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Overall, 10.7% women discontinued the clinical trial due to adverse events. Table 24 shows only the top TEAEs that resulted in trial discontinuation.

Table 24: Treatment Emergent AEs that lead to trial discontinuation across all Phase 3 Trials

Preferred Term	Original NDA (ATI-CL12/13)		New Data (ATI-CL23)	Overall
	Cycles		Cycles	Cycles
	1-6 (N=1220)	1-13 (N=1450)	All Cycles (N=2031)	All Cycles (N=3481)
<i>Any Adverse Event</i>	119 (9.75%)	151 (10.41%)	224 (11.03%)	375 (10.77%)
Application site irritation	21 (1.72%)	29 (2.00%)	23 (1.13%)	52 (1.49%)
Application site pruritus	17 (1.39%)	21 (1.45%)	16 (0.79%)	37 (1.06%)
Nausea	7 (0.57%)	8 (0.55%)	18 (0.89%)	26 (0.75%)
Metrorrhagia	8 (0.66%)	8 (0.55%)	15 (0.74%)	23 (0.66%)
Mood swings	7 (0.57%)	9 (0.62%)	10 (0.49%)	19 (0.55%)
Application site rash	2 (0.16%)	4 (0.28%)	14 (0.69%)	18 (0.52%)
Application site erythema	5 (0.41%)	6 (0.41%)	9 (0.44%)	15 (0.43%)
Menorrhagia	4 (0.33%)	5 (0.34%)	10 (0.49%)	15 (0.43%)
Vaginal hemorrhage	2 (0.16%)	2 (0.14%)	13 (0.64%)	15 (0.43%)
Application site dermatitis	2 (0.16%)	3 (0.21%)	10 (0.49%)	13 (0.37%)
Headache	6 (0.49%)	6 (0.41%)	6 (0.30%)	12 (0.34%)
Dizziness	6 (0.49%)	6 (0.41%)	4 (0.20%)	10 (0.29%)
Dysmenorrhea	1 (0.08%)	3 (0.21%)	7 (0.34%)	10 (0.29%)
Migraine	3 (0.25%)	5 (0.34%)	5 (0.25%)	10 (0.29%)
Acne	2 (0.16%)	2 (0.14%)	7 (0.34%)	9 (0.26%)
Weight increased	4 (0.33%)	4 (0.28%)	5 (0.25%)	9 (0.26%)
Depression	5 (0.41%)	5 (0.34%)	3 (0.15%)	8 (0.23%)
Fatigue	2 (0.16%)	3 (0.21%)	5 (0.25%)	8 (0.23%)
Abdominal distension	3 (0.25%)	3 (0.21%)	4 (0.20%)	7 (0.20%)

Source: NDA 204017 Module 5.3.5.3 Safety Update, Table 4.5.1 TEAEs that lead to discontinuation in decreasing frequency order

The Applicant provided an analysis of two groups of adverse events that were of special interest to the clinical reviewer: application site and bleeding related disorders.

7.3.3.1 Application Site Disorders

The Applicant assessed for potential adverse events specific to the drug's transdermal route of administration. If women using the drug are discontinuing the trial drug due to skin related AEs associated with patch use, this would undermine the utility of such a route of drug delivery. The medical officer reviewed the Applicant's data in summarized in Table

25 to assess the types of application site disorders that women experienced during the trial for potential safety concerns.

Table 25: Incidence of TEAEs for Application Site Disorders for all the Phase 3 Trials

Preferred Term	Any TEAE (N = 3481)	Severe TEAE (N = 3481)	Drug- Related TEAE (N = 3481)	SAE (N = 3481)	TEAE Resulting in D/C Study Drug (N = 3481)
Application Site Disorder	197 (5.66%)	24 (0.69%)	193 (5.54%)	0	125 (3.59%)
Application site irritation	64 (1.84%)	6 (0.17%)	64 (1.84%)	0	52 (1.49%)
Application site pruritus	44 (1.26%)	9 (0.26%)	43 (1.24%)	0	37 (1.06%)
Application site discoloration	33 (0.95%)	2 (0.06%)	32 (0.92%)	0	6 (0.17%)
Application site erythema	24 (0.69%)	5 (0.14%)	24 (0.69%)	0	15 (0.43%)
Application site rash	22 (0.63%)	2 (0.06%)	22 (0.63%)	0	18 (0.52%)
Application site dermatitis	15 (0.43%)	3 (0.09%)	15 (0.43%)	0	13 (0.37%)
Application site dryness	10 (0.29%)	0	10 (0.29%)	0	0
Application site reaction	8 (0.23%)	2 (0.06%)	8 (0.23%)	0	6 (0.17%)
Application site pain	6 (0.17%)	0	6 (0.17%)	0	1 (0.03%)
Application site vesicles	4 (0.11%)	1 (0.03%)	4 (0.11%)	0	2 (0.06%)
Application site acne	3 (0.09%)	0	3 (0.09%)	0	0
Application site hypersensitivity	2 (0.06%)	0	2 (0.06%)	0	2 (0.06%)
Application site papules	2 (0.06%)	1 (0.03%)	2 (0.06%)	0	0
Application site urticaria	2 (0.06%)	1 (0.03%)	1 (0.03%)	0	0
Application site erosion	1 (0.03%)	0	1 (0.03%)	0	0
Application site exfoliation	1 (0.03%)	0	1 (0.03%)	0	0
Application site hemorrhage	1 (0.03%)	0	1 (0.03%)	0	1 (0.03%)
Application site induration	1 (0.03%)	0	1 (0.03%)	0	1 (0.03%)
Application site pustules	1 (0.03%)	0	0	0	0
Application site ulcer	1 (0.03%)	0	1 (0.03%)	0	0

Source: NDA 204017 Safety Update, Table 4.2.4.4 Incidence of Application Site Disorder TEAEs

Reviewer Comments:

3.59% of the TEAEs that resulted in discontinuation of the trial drug were related to the application site issues. Irritation (1.49%) and pruritus (1.06%) accounted for most of the discontinuation followed by erythema (0.43%), rash (0.52%), and dermatitis (0.37%). There were no SAEs. Only 6 reports of irritation and 9 cases pruritus were deemed severe. The data seems to suggest, overall, that women tolerated the patch well and that application site disorders posed no safety concerns.

7.3.3.2 Bleeding Related Adverse Events

The Applicant assessed discontinuation secondary to bleeding related adverse events summarized in Table 26.

Table 26: Bleeding Related Adverse Events for the Safety Population

Preferred Term	Original NDA (ATI- CL12/13) Cycles	1-13 (N=1450)	New Data (ATI- CL23) Cycles	Overall Cycles
	1-6 (N=1220)		All Cycles (N=2031)	All Cycles (N=3481)
Any Treatment-Emergent Bleeding or Spotting Adverse Events Leading to Drug Trial Discontinuation	19 (1.56%)	21 (1.45%)	45 (2.22%)	66 (1.90%)
Metrorrhagia	8 (0.66%)	8 (0.55%)	15 (0.74%)	23 (0.66%)
Menorrhagia	4 (0.33%)	5 (0.34%)	10 (0.49%)	15 (0.43%)
Vaginal hemorrhage	2 (0.16%)	2 (0.14%)	13 (0.64%)	15 (0.43%)
Dysmenorrhea	1 (0.08%)	3 (0.21%)	7 (0.34%)	10 (0.29%)
Menstruation irregular	4 (0.33%)	4 (0.28%)	2 (0.10%)	6 (0.17%)
Dysfunctional uterine bleeding	0	0	2 (0.10%)	2 (0.06%)
Menstrual disorder	0	0	1 (0.05%)	1 (0.03%)

Source: NDA 204017 Module 5.3.5.3 Safety Update, Table 4.7

Reviewer Comments:

Overall, 1.9% of subjects discontinued from the trial due to bleeding related TEAEs. Metrorrhagia (0.66%) and menorrhagia/vaginal hemorrhage combined (0.86%) were the top reasons for women discontinuing the trial. Overall, bleeding related disorders were not a major factor in women discontinuing the trial.

7.3.4 Significant Adverse Events

There were no additional significant adverse events that were reported in the clinical trials.

7.3.5 Submission Specific Primary Safety Concerns

Combined hormonal contraceptive use has long been associated with increased risk for arterial and/or venous thromboembolic events. For this reason, the incidences of these specific TEAEs are a particular interest when evaluating the safety of this drug.

In the original submission, there was only one case of venous embolism and a case of compartment syndrome. In the new trial, five women reported three (3) deep vein thrombosis and three (3) pulmonary emboli, and one (1) left sided weakness.

Subject (b) (6): Pulmonary Embolism with infarction

The subject was a 25-year-old, White, non-Hispanic female with a BMI of 31.8 kg/m² and a weight of 92.1 kg. She had a remote history of hormonal contraceptive use from November 2006 to February 2008. She also reported using emergency contraception in the past. She was a nonsmoker. She had a family history of a clotting disorder in two grandparents “who had clots in their legs and lungs.” Her mother tested negative for a clotting disorder. The subject applied the first patch on May 27, 2015. On (b) (6), she was admitted to the hospital with a four-day history of chest pain worse with inspiration. The patch was removed in the emergency room on (b) (6). The CT angiography of the chest showed an acute pulmonary embolus within the distal aspect of the right lower lobe artery and extending into the segmental and smaller right lower lobe arteries with a patchy consolidation within the posterior right lower lobe with small pleural effusion suspicious for a developing infarction. Bilateral lower extremity venous Doppler showed no evidence of a clot. She was treated with enoxaparin, warfarin, and Xarelto for the pulmonary embolus and oxycodone and ibuprofen for the pain. She was discharged from the hospital on (b) (6) fully coagulated with a discharge diagnosis of pulmonary embolism with pulmonary infarction. She was to continue warfarin for the 6 months. She was discontinued from the trial on December 7, 2015. On April 2016, she completed the anticoagulation therapy and was deemed recovered.

Subject (b) (6): Small left lower lobe pulmonary embolus

The subject was a 26-year-old, White, non-Hispanic female with a weight of 91.9 kg and BMI of 34.3 kg/m². Other than her obesity, she had no pertinent medical history. She reported a family medical history of stroke in both maternal and paternal grandmothers their 60s at the time of the event. She was a former smoker having stopped in 2012. Prior contraceptive use included Depo-Provera ((2009-2010) and Yaz (2010-2011). She was a current user of the Nuva-Ring. She applied the first patch on September 23, 2015. On (b) (6), she experienced substernal chest pressure and shortness of breath. A CT scan revealed a small left lower lobe pulmonary embolus with a small infarct. She was admitted to the hospital and treated with Xarelto. Her contraceptive patch was removed some time during her hospitalization; however, the narrative does not specify the exact date. She was discharged from the hospital (b) (6) with instruction to follow up with her primary care physician for medical management of her Xarelto anticoagulation therapy for six months. She was discontinued from the trial on February 11, 2016. No further follow up was provided.

Subject (b) (6): Deep vein thrombosis right leg and bilateral pulmonary emboli

The subject was a 35-year-old White, non-Hispanic female with a weight of 93.4 kg and BMI of 37.1 kg/m². She was a recent oral contraceptive user with a prior history of hormonal patch and progestin IUD. She did not report a history of smoking. She

denied any family history of clotting disorder. She applied the first patch on September 18, 2015. On (b) (6), she was admitted to the hospital with worsening right leg pain and shortness of breath that started after a (b) (6) flight. The narrative noted that her BMI increased from 37.1 kg/m² during her screening exam to 39 kg/m² during her hospitalization. Chest x-ray demonstrated a probable right upper lobe pneumonia. A CT scan showed multiple emboli bilaterally, and a peripheral vascular laboratory (PVL) venous exam showed a non-occlusive right femoral and posterior tibial DVT and an occlusive right popliteal and peroneal DVT. She was treated with hydrocodone/acetaminophen 5/325 mg for pain and enoxaparin and warfarin for the DVT. Her contraceptive patch was removed on (b) (6). She was discharged from the hospital on (b) (6) in stable condition and instructed to follow up for INR monitoring. She was counseled not to use hormonal birth control in the future due to her increased risk for blood clots. She was discontinued from the trial on February 1, 2016.

Subject (b) (6): Acute left deep vein thrombosis

The subject was a 33-year-old, Black, non-Hispanic female with a BMI of 36.3 kg/m² and a weight of 93 kg. Her medical history was notable for obesity status post gastric sleeve. She was current user of Ortho-Evra patch prior to trial enrollment. She applied the first patch on May 27, 2015. She last wore the patch on April 26, 2016. She was discontinued from the study on April 27, 2016 secondary to pregnancy. On (b) (6), she complained of a one week history of left leg pain over the last week and was sent the hospital. Ultrasound revealed an acute, non-occlusive DVT in the left gastrocnemius veins. On exam, she was hypotensive with a blood pressure of 98/48. She received IV heparin and transitioned to enoxaparin SC. She was discharged from the hospital on enoxaparin SC on (b) (6). According to the narrative, she has since recovered; however, the Applicant did not provide any further follow up.

Subject (b) (6): Bilateral DVTs with other comorbidities

See section 7.3.5.1 for the full details of this case.

Subject (b) (6): Left sided weakness

The subject is a 25-year-old black, non-Hispanic female with a weight was 61.4 kg and a BMI of 21.9 kg/m². The subject reported a past medical history of generalized arthritis, contact dermatitis, and discoid lupus. She was a non-smoker. She reported prior use of oral hormonal and emergency contraception. She applied the first patch on (b) (6) and removed that same patch on (b) (6). It is unclear why she removed since no patch related AEs or adhesion issues were reported. On September 8, 2015, she informed the site, via email, that she had a “mini stroke.” The site called the subject who reported that she went to the hospital on (b) (6). By that the time, an SAE had been reported to the Applicant.

On November 3, 2015, the site received the medical records from the hospital. The records indicated that the subject reported to the ER with left-sided neck pain and

associated left-sided facial burning, which resolved spontaneously. Subsequently, she experienced numbness in the left upper and lower extremities and reported feeling unsteady on her feet with a “quivering and jerking sensation” in her legs. She also reported a headache in the sub-occipital region. Of note, the subject reported to the ER; she was on an experimental patch for birth control but only wore it for one day because she was “afraid of getting a stroke.” The subject’s initial blood pressure was elevated to 160/117.

The subject received aspirin in the ER and had a CT of the head which was normal. MRI of the head was inconclusive for artifact vs. infarction, showing a tiny focus of apparent diffusion restriction involving the left posterior lateral medulla. An MRA of the head and neck was performed which showed possible stenosis of the left vertebral artery and no evidence of stroke. She received Plavix and low-dose aspirin. She underwent a coronary computed tomography angiogram to better visualize the artery, which did not indicate stenosis or dissection.

A neurological consultation was obtained. The subject’s neurological examination was normal except for some subjective “sensory impairment on the left side of the face.” Strength was 5/5 in both the upper and lower extremities, with normal tone and negative finger-to-nose test. Per the neurologist’s note, the subject’s symptoms and physical findings “did not fit” with the position of the artifact seen on MRI. His impression was that if her symptoms were due to a medullary stroke she should have sensory symptoms from one side of the body and symptoms on the opposite side of the face. His opinion was that the subject did not have a stroke or transient ischemic attack.

Based on this new information, the SAE term was changed by the Investigator on November 3, 2015, from “mini stroke” to left-sided weakness. The subject was discharged on (b) (6) with all symptoms resolved except some residual left-sided subjective weakness. She was discharged on Plavix and aspirin, with outpatient physical therapy and follow-up with her primary care physician for 3-5 days later. A neurological follow-up in 2 months was recommended.

Reviewer Comments:

For subjects (b) (6) both the investigator and Applicant ruled that the thromboembolic events were probably related to the AG200-15 use. After reviewing the narratives, the clinical reviewer agrees that these adverse events are probably related to the drug given the known risk of CHC use and VTEs.

For subject (b) (6), the investigator categorized this subjects’ DVT as unrelated to the drug while the Applicant categorized the AE as possibly related to the drug. The clinical reviewer assessed the AEs as possibly related. Causality between the AE and the drug use cannot be clearly established and is confounded by her pregnancy and recent cessation of the drug.

For subject (b) (6), the investigator ruled the DVT as unrelated to the trial drug. The clinical reviewer agrees with their assessment. The DVT is more likely related to her prolonged bed rest and poor state of health.

For subject (b) (6), the investigator and Applicant assessed the relationship to the drug as possibly related. Given the temporal relationship between the AE and drug use, the clinical reviewer assessed the relationship as possibly related to the drug use. The likelihood is low given she only took one dose of and removed the patch a day later. However, with her elevated blood pressure, age, and constellation of other symptoms (discoid lupus, dermatitis, arthritis, and depression) the clinical reviewer suspects an underlying pathology (i.e. rheumatologic disorder) that may have predisposed her to the symptoms she experienced. Causality between the drug and the AE of left sided weakness cannot be clearly established or ruled out.

It is unclear why there were so many more VTEs in this new trial versus the original trials given the drug product was the same. The common factor among all the women that experienced these VTEs was their obesity.

Overall, the rate of VTE is 3.18/10,000 woman-years, which is well within the range of 3-12/10,000 woman-years for approved CHCs.

7.3.5.1 Bleeding/spotting data using the cycle control population

Women recorded any uterine bleeding episode on a daily basis in their eDiaries.

The Applicant defined parameters as follows:

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

Episode: One or more consecutive days of bleeding/spotting bounded by on either end by patch ≥ 2 days of no bleeding or spotting.

The applicant classified the data as scheduled and unscheduled:

Scheduled: Any bleeding or spotting that occurred when the woman is not wearing the

Unscheduled: Any bleeding or spotting that occurred when the woman was wearing the patch

Bleeding/spotting reported during Days one to seven of cycle one of trial patch wear were not counted as either scheduled or unscheduled.

The clinical reviewer wanted to compare the cycle control of the AG200-15 for any changes in noted between the new trial and the original trials. Unscheduled bleeding/spotting was the focus since lack of cycle predictably can be bothersome for

women that take CHCs. Table 27 summarizes the unscheduled bleeding/spotting episodes for all trials.

Table 27: Summary of Incidence of Unscheduled Bleeding or Spotting Episodes for all Phase 3 Trials

	Original NDA		New Data
	(ATI-CL13)	(ATI-CL12)	(ATI-CL23)
	Cycles 1-6 (N = 162)	All Cycles (N=715)	Cycles (N=2017)
Cycle 1	46/148 (31.1%)	168/649 (25.9%)	1217 (60.4%)
Cycle 2	33/127 (26.0%)	155/566 (27.4%)	954 (50.9%)
Cycle 3	28/119 (23.5%)	147/574 (25.6%)	807 (46.2%)
Cycle 4	23/118 (19.5%)	101/517 (19.5%)	718 (44.1%)
Cycle 5	25/114 (21.9%)	110/512 (21.5%)	678 (44.6%)
Cycle 6	24/105 (22.9%)	109/481 (22.7%)	614 (43.0%)
Cycle 7		86/459 (18.7%)	562 (41.6%)
Cycle 8		83/443 (18.7%)	569 (44.6%)
Cycle 9		88/387 (22.7%)	524 (43.2%)
Cycle 10		68/383 (17.8%)	495 (43.3%)
Cycle 11		65/368 (17.7%)	473 (42.9%)
Cycle 12		63/356 (17.7%)	463 (43.5%)
Cycle 13		77/338 (22.8%)	423 (41.3%)

Source: Adapted from Module 5.3.5.1 ATI-CL23 Clinical Trial Report, Table 14.2.7.1.1, submitted June 26, 2017, Module 5.3.5.1 ATI-CL12 Table 14.2_3.1.1.1, Module Clinical Trial Report ATI-CL13 14.3.1 submitted April 13, 2012.

Reviewer Comments:

The cycle control data for the new trial differed from the original trials. While the number of women that experienced bleeding/spotting episodes did decrease over time, it is notable that 41.3% of women in the new trial still had unscheduled bleeding or spotting after a year on treatment. This rate is higher than other approved CHCs.

The clinical reviewer examined the labeling of other approved CHCs. Per Ortho Evra® labeling, 18.2% experienced bleeding or spotting in cycle 1. For cycles 2-13, the percent of women per cycle that experienced bleeding and/or spotting ranged from 8% to 11.9%. Per Generess® labeling, an FDA approved COC, for cycle 1 of use, 37% of the women experienced bleeding or spotting. For cycles 2-13, the percentage of women per cycle that experienced bleeding trended downward from 31.3% (cycle 2) to 22.5% (cycle 13).

While cycle control appeared to be less favorable in the new trial versus the original trial, it was not a major factor for women participating in the trial as discussed in section 7.3.3.2 of this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The clinical reviewer examined the most common AEs (see Table 28) with an incidence rate greater than or equal to two percent for any safety concerns.

Table 28: Incidence of the Most Common Treatment Emergent Adverse Events (≥ 2%)

	Original NDA (ATI- CL12/13) Cycles	New Data (ATI-CL23) Cycles	Overall Cycles
Preferred Term	1-6 (N=1220)	1-13 (N=1450)	All Cycles (N=2031)
Nasopharyngitis	64 (5.25%)	83 (5.72%)	116 (5.71%)
Upper respiratory tract infection	43 (3.52%)	55 (3.79%)	100 (4.92%)
Nausea	50 (4.10%)	64 (4.41%)	84 (4.14%)
Headache	41 (3.36%)	52 (3.59%)	72 (3.55%)
Urinary tract infection	26 (2.13%)	48 (3.31%)	72 (3.55%)
Cervical dysplasia	28 (2.30%)	90 (6.21%)	17 (0.84%)
Sinusitis	35 (2.87%)	52 (3.59%)	106 (3.05%)
Dysmenorrhea	22 (1.80%)	26 (1.79%)	47 (2.31%)
Weight increased	23 (1.89%)	30 (2.07%)	41 (2.02%)
			71 (2.04%)

Source: NDA 204017, Module 5.3.5.3 Safety Update, Table 14.4.2.3.1

Reviewer comments:

The incidence rates of the most common AEs were comparable across all the trials. Nausea, headache, dysmenorrhea and weight gain are known complaints associated with CHC use.

7.4.2 Laboratory Findings

7.4.2.1 Hematology

The clinical reviewer reviewed data from hematologic parameters which did not show any significant changes from baseline.

7.4.2.2 Chemistry panel

Table 29 shows the trends from clinical data for Trial ATI-CL23 and the combined phase 3 trials for the different chemistry parameters. Since CHCs have been shown to affect carbohydrate and lipid metabolism, the clinical reviewer focused on those specific parameters to determine if AG200-15 use was associated with such findings.

For cholesterol, the data from the original submission and resubmission was comparable; thus, trends for the pooled data were explored. 11.0% (299/2729) went from normal baseline to above normal at the end of the trial. 8.5% (232/2729) went from above normal baseline to normal baseline at the end of the trial.

For HDL cholesterol, the data for the new trial and original trials differed slightly. For the new trial, there were more women with baseline normal HDLs at 97.9% (1577/1611) vs. approximately 90% [cycles 1-6: 90.3 (831/920); cycles 1-13: 89.9% (1005/1118)] for the original trials. For the pooled data, only 1% (26/2729) went from normal to below normal at the end of the trial.

For LDL cholesterol, the data for the new trial and original trials differed. For the new trial, there were more women with normal baseline LDLs at 84.3% (1350/1602) vs. approximately 50% [cycle 1-6: 50.8% (466/917); cycle 1-13: 50.9% (568/1115)] for the original trials. For the pooled data, there were 7.4% (200/2717) went from normal baseline to above normal at the end of the trial. 7.6% (206/2717) went from above normal baseline to normal at the end of the trial.

For triglycerides, the data from the original submission and resubmission was comparable. For the new trial, there were more women with baseline normal triglyceride levels at 92.2% (1486/1611) vs. approximately 80% [cycle 1-6: 80.3% (739/920); cycle 1-13: 80.1% (895/1118)] for the original trials. For the pooled data, 6% (164/2729) went from normal baseline to above normal at the end of the trial. 2.7% (74/2729) went from above normal baseline to normal at the end of the trial.

For glucose, data for all the trials was comparable. Overall, 90.7% (2478/2732) were normal at the baseline and at end of the trial. 3.3% (90/2732) went from normal baseline to above normal at the end of the trial. 0.7% (18/2732) went from above normal baseline to normal at the end of trial.

Table 29: Shift Tables for Clinical Chemistry Parameters for AG200-15 Exposure

	Baseline Category	End of Study		
		Below Normal	Normal	Above Normal
		Cholesterol		
ATI-CL23	Below Normal	0	0	0
	Normal	0	1070	182
	Above Normal	0	131	228
Overall	Below Normal	0	0	0
	Normal	0	1834	299
	Above Normal	0	232	364
		HDL		
ATI-CL23	Below Normal	12	13	0
	Normal	9	1577	0
	Above Normal	0	0	0
Overall	Below Normal	39	82	0
	Normal	26	2582	0
	Above Normal	0	0	0
		LDL		
ATI-CL23	Below Normal	0	0	0
	Normal	0	1350	95
	Above Normal	0	65	92
Overall	Below Normal	0	0	0
	Normal	0	1918	200
	Above Normal	0	206	393
		Triglycerides		
ATI-CL23	Below Normal	0	0	0
	Normal	0	1486	71
	Above Normal	0	19	35
Overall	Below Normal	0	0	0
	Normal	0	2381	164
	Above Normal	0	74	110
		Glucose		
ATI-CL23	Below Normal	2	31	0
	Normal	40	1495	41
	Above Normal	0	3	1
Overall	Below Normal	5	56	3
	Normal	71	2478	90
	Above Normal	0	18	11

Source: Adapted from NDA 204017 Module 5.3.5.1 Safety Update, Table 7.2.2 Shift from Baseline to End of Trial in Clinical Chemistry Parameters

Reviewer Comments:

Based on a review of these data, there were no consistent trends to suggest that use of the drug adversely affects lipid or glucose metabolism or poses such a safety concern.

7.4.2.3 Liver Function Tests

The clinical reviewer examined the liver function test data to for assess for evidence of possible drug induced liver injury. Since there were no abnormal findings identified in Dr. Davis' clinical review of the original submission, the clinical reviewer only assessed the data the new trial. Table 30 shows all the abnormal liver function tests for Trial ATI-CL23 that went from normal baseline to abnormal high at the end of the trial.

Table 30: Abnormal Liver Function Tests (LFTs) for Trial ATI-CL23

Subject ID	Parameter	Baseline	Baseline Change	Reference (Low)	Reference (High)	EOT Value
(b) (6)	BILI	15	12	0	22	27
	AST	42	32	0	42	74
	AST	21	25	0	42	46
	ALT	29	32	0	48	61
	ALT	14	156	0	48	170
	AST	14	50	0	42	64
	BILI	22	28	0	22	50
	BILI	22	10	0	22	32
	BILI	9	15	0	22	24
	ALT	40	22	0	48	62
	AST	28	15	0	42	43
	BILI	15	12	0	22	27
	AST	34	9	0	42	43
	ALT	18	31	0	48	49
	ALT	14	66	0	48	80
	AST	15	33	0	42	48
	ALT	48	22	0	48	70
	AST	37	13	0	42	50

Source: (b) (4) analysis by the clinical reviewer using the (b) (4) (Data from laboratory test analyses) dataset
 BILI – Total bilirubin AST – aspartate transaminase ALT – alanine transaminase EOT- End of Trial

Reviewer Comments:

The highlighted data (ALT greater than three times the upper limit and a TB greater than two times the upper limit) seems to fit a Hy's law case; however, further review of the case confirms this is not a case of drug induced liver injury. The lab abnormalities are most likely the result of extensive gallbladder disease for which she underwent a cholecystectomy. For full details of this case, see section 7.5.3 Serious Adverse Events.

Based on the review of the data liver function test, the changes are not of clinical significance and do not represent a safety concern.

7.4.3 Vital Signs

Vital signs were recorded at the baseline visit and at each in-person clinic visit.

The Applicant presented summarized the data of all the clinically significant changes in vital signs for all the women exposed to the drug across all the trials. Table 31 summarizes that clinical information.

Table 31: Incidence of Clinical Significant Changes to Vital Signs for all Phase 3 Trials

		Original NDA (ATI- CL12/13)		New Data (ATI- CL23)	Overall
		Cycles		Cycles	Cycles
Parameter	Criterion	1-6 (N=1220)	1-13 (N=1450)	All Cycles (N=2031)	All Cycles (N=3481)
Systolic Blood Pressure (mmHg)	Increased ≥ 20 mmHg from baseline and is ≥ 140 mmHg	21/1131 (1.9%)	25/1356 (1.8%)	40/1956 (2.0%)	65/3312 (2.0%)
Diastolic Blood Pressure (mmHg)	Increased ≥ 15 mmHg from baseline and is ≥ 90 mmHg	26/1131 (2.3%)	31/1356 (2.3%)	73/1956 (3.7%)	104/3312 (3.1%)
Heart Rate (bpm)	Increased ≥ 20 bpm from baseline and is ≥ 120 bpm	2/1131 (0.2%)	2/1356 (0.1%)	3/1956 (0.2%)	5/3312 (0.2%)
Body Weight (kg)	Low: decreased ≥ 4.54 kg (10 lb) from baseline	130/1131 (11.5%)	163/1357 (12.0%)	180/1803 (10.0%)	343/3160 (10.9%)
	High: Increased ≥ 4.54 kg (10 lb) from baseline	192/1131 (17.0%)	206/1357 (15.2%)	303/1803 (16.8%)	509/3160 (16.1%)

Source: NDA 204017 Module 5.3.5.3 Safety Update, Table 8.2 Incidence of Clinically Significant Changes in vital signs.

Reviewer Comments:

Review of the vital signs did not reveal any unexpected safety concerns compared with CHC users in general. Weight gain and changes in blood pressure (BP) are common.

7.4.4 Electrocardiograms (ECGs)

No ECGs were performed for any of the phase 3 Trials.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials conducted for this resubmission.

7.4.6 Immunogenicity

There was no immunogenicity studies conducted for this resubmission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There is no dose dependency for adverse events for this resubmission given women received the same dose of the patch for throughout the trial.

7.5.2 Time Dependency for Adverse Events

Aside from characterizing AEs in the 13-cycle trial and the 6-cycle trial, exploration for time dependency of adverse events was not performed.

7.5.3 Drug Demographic Interactions

The product is intended for women of reproductive age. See section 6 of the review where the drug effect was discussed in different populations (BMI, age, race, and previous hormonal use). As discussed in Section 7 of this review, the hepatobiliary AEs and VTEs occurred in women that were obese women only in trial ATI-CL23.

7.5.4 Drug-Disease Interactions

There were no drug-disease interactions studies conducted for this NDA resubmission.

7.5.5 Drug-Drug Interactions

There were no drug-drug interactions studies conducted for this NDA resubmission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity trials were performed for this submission.

7.6.2 Human Reproduction and Pregnancy Data

No human reproductive reproduction or pregnancy data was required for this resubmission.

7.6.3 Pediatrics and Assessment of Effects on Growth

The NDA resubmission did not include an agreed-upon initial pediatric study plan (iPSP) because it was not required when the Applicant filed the original NDA. For the

resubmission, the Applicant submitted a request for a partial waiver for pediatric assessment in premenarcheal and postmenarcheal females less than 17 years of age. The Applicant asserts that “pediatric studies are not applicable in premenarcheal females because the claimed indication is not relevant to this pediatric subpopulation.” For postmenarcheal females less than 17 years of age, the Applicant asserts that “the requirement for pediatric studies in this subpopulation may be fulfilled through extrapolation of efficacy data from adult trials.”

Reviewer comments:

On December 6, 2017, the Pediatric Review Committee (PeRC) met to discuss the iPSP proposed by the Applicant. Since the Division had apprised PeRC of the resubmission pending Complete Response prior to the meeting, the PeRC did not provide comments on the proposed iPSP and recommended that the Division include the iPSP requirement in the CRL to the Applicant. The iPSP will likely be a partial waiver for boys and for premenarcheal females < age 11 and an assessment for postmenarcheal females <17.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdose in the NDA resubmission. Drug abuse potential is low. Overdose of the drug could result in nausea, vomiting, or abnormal vaginal bleeding. The primary withdrawal effect is physiologic withdrawal bleeding. No rebound effect would be expected.

8 Postmarket Experience

No post marketing data is currently available for this proposed drug formulation given the transdermal contraceptive system containing levonorgestrel and ethinyl estradiol has yet to be approved.

9 Appendices

9.1 Literature Review/References

- ¹ Ortho-Evra product labeling last revised November 2017.
- ² Cole JA, et.al. (2007). Venous Thromboembolism, Myocardial Infarction, and Stroke among Transdermal Contraceptive System Users. *Obstetrics & Gynecology*; 109(2):339–346.
- ³ Jick S, et. al. (2006). Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol. *Contraception*; 73: 223–228.
- ⁴ Jick S, et.al. (2007). Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 µg of EE. *Contraception*; 76: 4–7.
- ⁵ Jick S, et. al. (2010). Postmarketing study of Ortho-Evra[®] and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism. *Contraception* 2010; 81: 16–21.
- ⁶ Jick S, et. al. (2010) Ortho-Evra[®] and venous thromboembolism: an update. Letter to the Editor. *Contraception*; 81: 452–453.
- ⁷ Dore D, et. al. (2010) Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. *Contraception* 2010; 81: 408–413.
- ⁸ Cole JA, et. al. (2008). Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users [published erratum appears in *Obstetrics & Gynecology*; 111:1449].
- ⁹ Dore D, et. al. Eligibility criteria in venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Letter to the Editor. *Obstetrics & Gynecology* 2009; 114(1):175.
- ¹⁰ Combined hormonal contraceptives (CHCs) and the risk of cardiovascular endpoints. Sidney, S. (primary author) <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf>, accessed Oct 27, 2011.
- ¹¹ Mishell et. al. (2007) “Recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials. *Contraception*; 75(1): 11-15.
- ¹² Race, Combinations of Two Races, and Not Hispanic or Latino: Census.gov. <https://www.census.gov/prod/cen2010/briefs/c2010br-13.pdf>
- ¹³ Overview of Race and Hispanic Origin: 2010-Census.gov. <https://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf>
- ¹⁴ Ogden, CL et.al. (2015). Prevalence of Obesity among Adults and Youth: United States, 2011-2014. National Center of Health Statistics Data Brief. November; (219):1-8.
- ¹⁵ American Society of Colposcopy and Cervical Cytology guidelines <http://www.asccp.org/asccp-guidelines>
- ¹⁶ American Cancer Society Cervical Cancer Screening Guidelines <https://www.cancer.org/cancer/cervical-cancer/prevention-and-early-detection/cervical-cancer-screening-guidelines.html>

Clinical Review for NDA 204017
Nneka N. McNeal-Jackson, M.D.
AG200-15 (Ethinyl Estradiol and Levonorgestrel)

¹⁷Wang, S. et. al. (2017). Is the oral contraceptive or hormone replacement therapy a risk factor for cholelithiasis: A systematic review and meta-analysis. *Medicine*; Apr: 96(14). p. e6556

¹⁸Jick, S. et al. (2012). Drospirenone- and levonorgestrel-containing oral contraceptives and the risk of gallbladder disease. *Contraception*; 86(3):220-3.

9.2 Labeling Recommendations

Both the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) deferred comments on the proposed drug product labeling, patient package insert, and instructions for use for this cycle.

9.3 Advisory Committee Meeting

No advisory committee was conducted for NDA 204017.

APPEARS THIS WAY ON ORIGINAL



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/s/

NNEKA N MCNEAL-JACKSON
12/15/2017

CATHERINE A SEWELL
12/15/2017

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA/BLA #	NDA 204017
Applicant Name	Agile Therapeutics, Inc.
Date of Submission	April 13, 2012
PDUFA Goal Date	February 13, 2013
Proprietary Name / Established (USAN) Name	Twirla Levonorgestrel/ethinyl estradiol transdermal system
Dosage Forms / Strength	2.3 mg ethinyl estradiol and 2.6 mg levonorgestrel
Proposed Indication(s)	Prevention of pregnancy
Action	Complete Response

Material Reviewed/Consulted Action Package, including:	Names of discipline reviewers
Medical Officer Review	Daniel Davis, M.D. and Lisa Soule, M.D.
Statistical Review	Kate Dwyer, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Krishan Raheja, D.V.M., Ph.D. and Alex Jordan, Ph.D.
CMC Review	Caroline Strasinger, Ph.D. and Terrance Ocheltree, Ph.D.
Microbiology Review	None
Clinical Pharmacology Review	Hyunjin Kim, Pharm.D., M.S. and Myong-Jin Kim, Pharm.D.
Biopharmaceutics Review	Tapash Ghosh, Ph.D. and John Duan, Ph.D.

Signatory Authority Review

1. Introduction

Agile Therapeutics, Inc. has submitted this 505(b)(2) New Drug Application (NDA) for a transdermal contraceptive delivery system known as AG200-15 (proposed tradename, Twirla) and is seeking an indication for the prevention of pregnancy. This transdermal system contains ethinyl estradiol and levonorgestrel, which are commonly used together in combination hormonal contraceptives. The mechanism of action is primarily suppression of ovulation, although other possible mechanisms include cervical mucus changes that inhibit sperm penetration and endometrial changes that may reduce the likelihood of sperm transport and implantation. There are many approved combined hormonal contraceptives, but Ortho Evra (which contains ethinyl estradiol and norelgestromin) is currently the only FDA-approved transdermal contraceptive patch. The Applicant is proposing a once-weekly application of the 7-day patch for 3 weeks followed by a 1-week patch-free interval. This is the same dosing regimen used for Ortho Evra.

This document serves as the decisional memorandum for the application.

2. Background

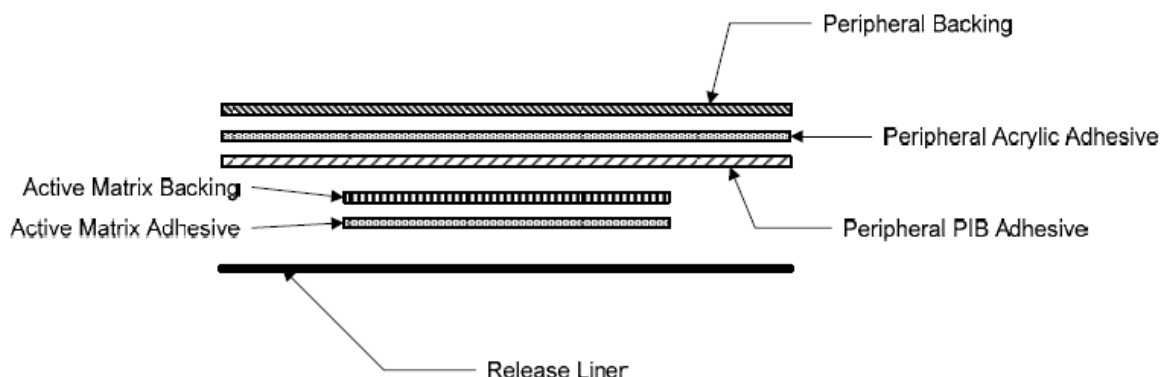
This 505(b)(2) NDA relies on published literature for ethinyl estradiol and levonorgestrel to support the nonclinical and selected clinical pharmacology sections of the label.

Additional background is provided, where needed, in the sections below in context of the issues being discussed.

3. CMC

The Chemistry/Manufacturing/Controls (CMC) reviewers find the drug substances (ethinyl estradiol and levonorgestrel) and their accompanying Drug Master Files to be acceptable. The drug product is comprised of a 15 cm² active adhesive matrix containing 2.3 mg ethinyl estradiol, 2.6 mg levonorgestrel and skin permeation enhancers (dimethyl sulfoxide, ethyl lactate, capric acid and lauryl lactate). The active adhesive matrix is integrated with a 28 cm² peripheral adhesive system designed for 7-day adherence to the skin. A schematic depiction of the patch is shown below:

Figure 1: Schematic Depiction of the AG200-15 Transdermal Patch System



The CMC reviewers recommend that this NDA receive a Complete Response. See the reviews by Drs. Caroline Strasinger and Terrance Ocheltree for details. The deficiencies include the following, all of which will be included in the Complete Response letter:

- Drug Master File (b) (4) which relates to (b) (4), an excipient in the patch, could not be reviewed because of administrative issues related to the Letter of Authorization. In the next review cycle, the Applicant will need to assure that the Letter of Authorization is adequate and active.
- The Applicant is proposing a laser etching process for labeling the marketed product (laser etching was not used for the clinical trial material). However, the NDA does not contain adequate (b) (4) laser etching process. (b) (4)
- The provided specifications do not contain a test for cold flow or shear. Additionally, acceptance criteria for several tests are not adequate, have not been adequately updated as previously requested, or have not been adequately justified. For example, the Applicant has not adequately justified the upper and lower bounds of the acceptance criteria for the excipient assay with either *in vivo* or *in vitro* skin permeation data. This is a concern given that the permeation enhancers are critical for proper functioning of the patch.
- Impurities have not been adequately characterized. The Applicant will need to test for (b) (4) in the final product and provide acceptance criteria for these (b) (4) (if toxicologically relevant levels are detected) or justify why a test for (b) (4) is not needed.

The Office of Compliance issued an “acceptable” recommendation for all facilities involved in the manufacture and testing of the drug product. However, the inspected equipment was used for the manufacture of clinical trial product and different equipment is proposed for the to-be-marketed product. In the Complete Response letter, the CMC reviewers are requesting additional information to support the adequacy of the new processes and equipment proposed for the manufacturing of the commercial product.

4. Nonclinical Pharmacology/Toxicology

The Applicant conducted local toxicity studies using a prototype patch, which adequately bridge the oral and patch formulations of ethinyl estradiol and levonorgestrel. The Applicant did not conduct nonclinical local toxicity studies with the final drug product but this is acceptable to the nonclinical pharmacology/toxicology reviewers because local toxicity has been evaluated in the phase 3 trials using the to-be-marketed formulation.

The NDA also contains an integrated summary of the literature for ethinyl estradiol and levonorgestrel to inform on single and repeat dose animal toxicity, reproductive and developmental toxicology, genotoxicity and carcinogenicity.

During the IND stage, the nonclinical pharmacology reviewers expressed concerns with the capric acid excipient. The Applicant subsequently provided adequate data to address this concern.

The nonclinical pharmacology/toxicology reviewers have determined that no additional nonclinical data are needed and recommend approval of the NDA. See the review by Dr. Krishan Raheja for details.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted the following four clinical pharmacology studies involving the to-be-marketed (AG200-15) formulation:

Study ATI-CL15: This 3-period cross-over study compared ethinyl estradiol and levonorgestrel exposures when AG200-15 was applied for one week to different application sites – abdomen, buttock and upper torso. For both ethinyl estradiol and levonorgestrel, results show numerically higher AUC_{0-168h} and C_{max} for buttock and upper torso compared to lower abdomen (Table 1). However, as discussed by the clinical pharmacology reviewers, there appears to be accumulation of ethinyl estradiol and levonorgestrel between treatment periods due to a washout period that was too short, which may have impacted the reliability of the findings.

Table 1. Pharmacokinetic comparisons at different application sites

	Ethinyl Estradiol		Levonorgestrel	
	Geometric Mean Ratio (90% CI)		Geometric Mean Ratio (90% CI)	
	C _{max}	AUC _{0-168h}	C _{max}	AUC _{0-168h}
Buttock vs. abdomen	1.30 (1.13-1.51)	1.23 (1.08-1.40)	1.07 (0.90-1.27)	1.07 (0.92-1.24)
Upper torso vs. abdomen	1.15 (0.99-1.33)	1.21 (1.06-1.38)	1.17 (0.98-1.39)	1.17 (1.01-1.36)

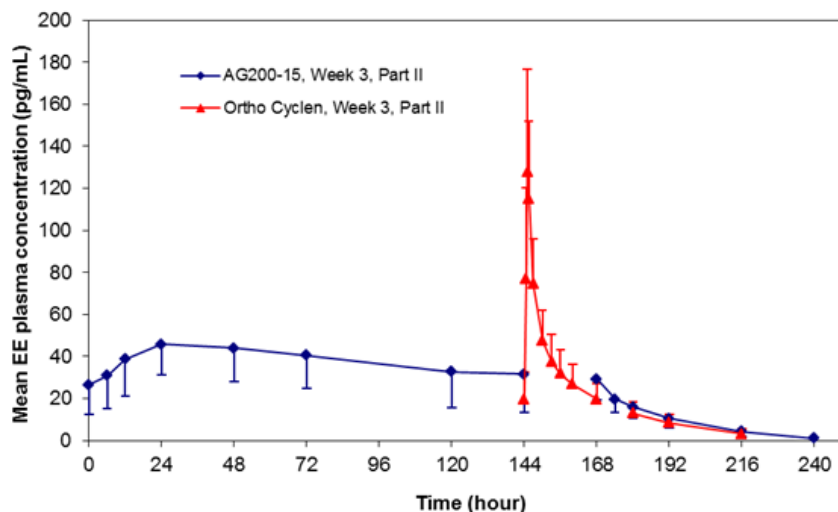
Study ATI-CL11: This study compared AG200-15 to two other formulations (all applied to the lower abdomen) with respect to ovulation suppression. The primary efficacy endpoint was possible ovulation defined as the highest measured progesterone concentration ≥ 4.7 ng/mL. AG200-15 performed better than the two other formulations with an incidence of possible ovulation of 11-12% among compliant subjects with body mass index ≤ 32 kg/m² and 18-19% among compliant subjects regardless of body mass index. Based on our experience with other approved contraceptive products, this is considered acceptable preliminary evidence of efficacy to support confirmatory testing in phase 3 trials. This formulation also had more favorable effects on menstrual cycle control compared to the two other formulations. Therefore, we agreed with the Applicant's decision to take AG200-15 into phase 3 testing.

Study ATI-CL14: This study compared ethinyl estradiol exposures with AG200-15 (applied to the buttock) to exposures seen with Ortho-Cyclen, an approved oral contraceptive containing 35 mcg of ethinyl estradiol and 250 mcg norgestimate (a different progestin to the levonorgestrel in AG200-15). In Part I of the study, all subjects received AG200-15 for one cycle. Part II of the study had a cross-over design that randomized subjects to AG200-15 followed by Ortho-Cyclen or Ortho-Cyclen followed by AG200-15. Study drug was administered for 3-weeks of each treatment period followed by a 1-week drug-free period.

As shown in Figure 2, the pharmacokinetic profile for ethinyl estradiol with AG200-15 is distinctly different from that seen with Ortho-Cyclen. In the AG200-15 arm, mean C_{max} for ethinyl estradiol increased by about 13% from Week 1 to 3 whereas no increase in mean C_{max} occurred in the Ortho-Cyclen arm. At Week 3, the ethinyl estradiol AUC_{0-168h} was about 14% lower and C_{max} was about 60% lower with AG200-15 compared to Ortho-Cyclen. However, as discussed by the clinical pharmacology reviewers, there appears to be accumulation of ethinyl estradiol in the AG200-15 treatment arm that may impact reliability of the findings.

Although there are limitations with cross-study comparisons, when Ortho Evra was compared to a combined oral contraceptive containing 35 mcg of ethinyl estradiol, the AUC_{0-168h} for ethinyl estradiol was 55% higher for the patch and C_{max} was about 35% higher for the oral contraceptive.

Figure 2. Pharmacokinetic profile of ethinyl estradiol at Week 3 for AG200-15 compared to Ortho-Cyclen (Figure produced by Dr. Hyunjin Kim).



Study ATI-CL16: This study compared ethinyl estradiol and levonorgestrel exposures when AG200-15 was applied to the lower abdomen and used under different external conditions – normal use or in the setting of daily dry sauna, whirlpool, treadmill or immersion in cold water. Findings with cold water were most similar to normal use whereas there was some reduction in the pharmacokinetics for both ethinyl estradiol and levonorgestrel when dry sauna, whirlpool and treadmill were compared to normal use (Tables 14 and 17 in Dr. Kim’s review). However, as discussed by the clinical pharmacology reviewers, there appears to be accumulation of ethinyl estradiol and levonorgestrel between treatment periods due to a washout period that was too short, which may impact reliability of the findings.

Based on these studies, the clinical pharmacology reviewers conclude that the NDA is acceptable although concern was raised about potential carry-over effects of ethinyl estradiol and levonorgestrel in three of the four studies. In addition, it is presently unclear whether the CMC deficiencies may also have impacted the clinical pharmacology findings. Based on discussions with the clinical pharmacology reviewer we are including the following text in the Complete Response letter.

1. Address whether the product quality deficiencies may have impacted the findings in your clinical pharmacology studies. You may need to repeat some of your clinical pharmacology studies if the existing data are unreliable due to product quality.
2. We identified potential carry-over effects of both ethinyl estradiol and levonorgestrel between adjacent treatment cycles (in Study ATI-CL14) and adjacent periods (in Study ATI-CL15 and ATI-CL16). This may also impact reliability of the study results. If the product quality deficiencies can be adequately addressed, provide a revised analysis that corrects for/compensates for this potential carry-over effect. If you are unable to

adequately address carry-over with the available data, provide a proposal for how you will obtain reliable clinical pharmacology data.

See the review by Drs. Hyunjin Kim and Myong-Jin Kim for details.

Biopharmaceutics reviewed the *in vitro* drug release method and specifications. They recommend that the *in vitro* drug release criteria for ethinyl estradiol and levonorgestrel be adjusted from not less than (NLT) (b) (4) % to NLT (b) (4) % at the 72 hour timepoint. Otherwise, they found the NDA to be acceptable. See the review by Drs. Tapash Ghosh and John Duan for details.

6. Clinical Microbiology

This NDA does not contain clinical microbiology data.

7. Clinical/Statistical-Efficacy

The phase 3 program consists of two clinical trials, both of which used the proposed to-be-marketed formulation. FDA reached agreement with the Applicant on the study design for both trials under Special Protocol Agreement. For each treatment cycle, a new AG200-15 patch was applied weekly for three weeks followed by a one-week patch-free period.

Study ATI-CL12 was a 13-cycle, open-label trial conducted across 102 sites in the United States. The study randomized subjects in a 3:1 ratio to AG200-15 (n=1129) or to Lessina (n=375), which is an approved oral contraceptive containing 20 mcg ethinyl estradiol and 100 mcg levonorgestrel. Subjects randomized to AG200-15 were to receive one-year (13 cycles) of treatment. Subjects randomized to Lessina were to receive 6 cycles of treatment then cross-over to AG200-15 for cycles 7-13. In this trial, AG200-15 was applied to the abdomen for 40% of cycles, to the buttock for 47% of cycles and to the upper torso for 12% of cycles.

Study ATI-CL13 was a randomized, 6-cycle, open-label trial conducted across 21 sites in the United States. This study also included an oral contraceptive comparator (ethinyl estradiol 30 mcg/levonorgestrel 150 mcg). A total of 201 subjects were randomized to AG200-15 and 206 subjects were randomized to the oral contraceptive.

This section will mostly focus on Study CL12 as it is the pivotal phase 3 trial. Study CL13 was smaller and only 6 months in duration. As shown in Table 3, the efficacy findings in Study CL13 are comparable to those seen in Study CL12. For further details, see the clinical review by Dr. Daniel Davis, the Cross-Discipline Team Leader review by Dr. Lisa Soule and the statistical review by Dr. Kate Dwyer.

Study CL12 enrolled sexually active women 17-40 years old who were in good health and who were requesting contraception. The primary efficacy endpoint was the Pearl Index calculated

as the number of on-treatment pregnancies (those occurring while the subject was using the patch or within 7 days after last use of the patch) multiplied by 1300 and divided by the number of 28-day on-treatment cycles. The Pearl Index provides an estimate of the number of pregnancies per 100 women-years of product use and is the standard endpoint for contraceptive trials. The pre-specified primary efficacy analysis was based on the Pearl Index for all on-treatment pregnancies in women 17-35 years old with body mass index $<32 \text{ kg/m}^2$, having intercourse and not using other birth control methods.

In Study CL12, 485 (43%) subjects randomized to AG200-15 completed all 13 cycles (Table 2). Of the 375 subjects randomized to the oral contraceptive, 249 (66%) completed 6 cycles then switched over to AG200-15 at Cycle 7. Of these 249 subjects, 150 (60% of those who started AG200-15 at Cycle 7 and 40% of those originally randomized to the oral contraceptive) completed Cycle 13. The most common reasons for premature discontinuation from the trial included loss to follow-up (discussed later), subject decision and adverse events (see Section 8 for further details). As discussed by Dr. Soule, some of the discontinuations due to “subject decision” appear to have been due to adverse events, such as vaginal bleeding or application site reactions. It is unclear why the safety population included only 92% of randomized subjects (i.e., nearly 10% of randomized subjects did not receive at least one dose of study medication). About 60% of subjects randomized to AG200-15 or switched to AG200-15 from the oral contraceptive were included in the primary efficacy population.

Table 2. Patient disposition in Study CL12

	Oral Contraceptive Cycles 1-6	AG200-15 Cycles 7-13¹	AG200-15 Cycles 1-13
Randomized	375	249	1129
Safety population ²	344 (92%)	230 (92%)	1043 (92%)
Primary efficacy population ³	-	152 (61%)	675 (60%)
Completed	249 (66%)	150 (60%)	485 (43%)
Reason for discontinuation			
Lost to follow-up	61 (16%)	37 (15%)	229 (20%)
Subject decision	30 (8.0%)	28 (11%)	183 (16%)
Adverse events	16 (4.3%)	16 (6.4%)	123 (11%)
Non-compliance	9 (2.4%)	6 (2.4%)	42 (3.7%)
On-treatment pregnancy	4 (1.1%)	8 (3.2%)	34 (3.0%)
Other	6 (1.6%)	4 (1.6%)	33 (2.9%)
¹ Reflects subjects who switched to AG200-15 after completing 6 cycles of the oral contraceptive			
² Randomized subjects who received at least one dose of study medication			
³ 17-35 years old with body mass index $<32 \text{ kg/m}^2$ having intercourse and no other birth control			

As discussed by Drs. Davis and Soule, the mean age of women in Study CL12 was about 26 years with 9% of subjects >35 years old. The mean body mass index was 27.5 kg/m^2 and about 28% of subjects had a body mass index $\geq 30 \text{ kg/m}^2$. The racial/ethnic make-up was 57% White

(non-Hispanic), 16% White (Hispanic), 21% Black, 3.5% Asian and 2.4% other. The highest level of education achieved by most subjects was high school (40%), undergraduate college (40%) or graduate school (10%). About one-half of the subjects were nulliparous. About 57% of subjects were either naïve to hormonal contraceptives or not recent users of hormonal contraceptives (last use more than 6 months prior to receiving study medication). In the Applicant's demographics table for Study CL12 (Table 14.1.2.1), about 25% of subjects were current users of hormonal contraceptives and the remaining 18% were recent (within 6 months prior to receiving study medication) users of hormonal contraceptives. However, the Applicant's summary of current contraceptive methods (Table 14.1_4.1) shows that about 90% of subjects were using some form of contraception at enrollment – with about 6% using a contraceptive patch, 35% using an oral contraceptive, 5% using a vaginal contraceptive ring and 50% of subjects had partners using a male condom with or without spermicide. The reason for the discrepancy between tables with regard to the percentage of women currently using hormonal contraception is unclear.

The primary efficacy results for Study CL12 are shown in Table 3. The Pearl Index for most approved hormonal contraceptives is in the 1-2 range, with the highest approved Pearl Index for a hormonal contraceptive of 2.9. The Pearl Index for AG200-15 and the upper bound of its associated 95% confidence interval are well beyond that for any of the approved hormonal contraceptive products, including the Ortho Evra patch. FDA's clinical reviewers identified at least 8 additional on-treatment pregnancies, 5 of which occurred in the primary efficacy population (see Dr. Soule's Table 9 for details). These additional pregnancies increased the Pearl Index beyond that calculated by the Applicant. However, even based on the Applicant's analysis, the Pearl Index is well above that of approved combination hormonal contraceptives.

There are several additional noteworthy findings:

- The primary efficacy analysis excluded cycles during which subjects were abstinent. In contrast, other contraception trials have typically included such cycles in the primary efficacy analysis. As a sensitivity analysis, we recalculated the Pearl Index for Study CL12 including these cycles. The results still show an unacceptably high Pearl Index of 6.7 with an upper bound of 9.4 for the associated 95% confidence interval.
- Ethinyl estradiol and levonorgestrel concentrations were measured at one timepoint during patch use in Cycles 2, 6, and 13. Based on these data, there was a trend of decreasing ethinyl estradiol and levonorgestrel concentrations with increasing baseline body mass index (see Figure 7 in Dr. Kim's review). However, these clinical pharmacology findings do not appear to translate into meaningful differences with regard to efficacy as measured using the Pearl Index. For example, efficacy analyses that excluded obese women (i.e., those with body mass index ≥ 30 kg/m²) and analyses that included all women regardless of body mass index yielded comparable results to the primary efficacy analysis.
- The Pearl Index was considerably lower among Whites (not Hispanic) than among Whites (Hispanic) and Blacks, although the confidence intervals are wide for the minority subgroups, reflecting small sample sizes. This is discussed further below.

- The Pearl Index was considerably lower among women who were using hormonal contraceptives at baseline or within the preceding 6 months compared to those who had remote (use more than 6 months prior to the start of study medication) or no prior use of hormonal contraceptives. This is discussed further below.
- About 40% (n=19) of the 48 on-treatment pregnancies identified by FDA occurred across five of the 102 sites. One of these sites (Dr. Hazen – 033) was an outlier with 8 pregnancies among 69 subjects. In total, these five sites enrolled about 15% of the AG200-15 subjects. The Office of Scientific Investigations (OSI) investigated Dr. Hazen's site as well as one of the other sites and did not identify an explanation for the findings.

In Study CL13, the Applicant's calculated Pearl Index (8.2; 95% confidence interval 0.2-16.2) was numerically higher than that seen in Study CL12.

Table 3. Efficacy results for Study CL12 (adapted from Table 4 in Dr. Kate Dwyer's review)

	N	On-Treatment Pregnancies	Evaluable Cycles	Pearl Index (95% CI)
Primary efficacy analysis				
Applicant's analysis ¹	827	30	6070	6.4 (4.1, 8.7)
FDA's analysis (5 additional pregnancies) ¹	827	35	6070	7.5 (5.0, 10.0)
Other analyses (FDA findings)				
17-35 years old; BMI <30 kg/m ²	767	32	5645	7.4 (4.8, 9.9)
17-35 years old; any BMI	1060	45	7685	7.6 (5.4, 9.8)
All subjects, regardless of age, BMI	1158	48	8446	7.4 (5.3, 9.5)
Race/Ethnicity ¹				
White (not Hispanic)	512	13	3749	4.5 (2.1, 7.0)
White (Hispanic)	124	8	924	11.3 (3.5, 19.0)
Black	137	11	960	14.9 (6.1, 23.7)
Other	54	3	437	8.9 (0.0, 19.0)
Remote or naïve hormonal contraceptive user ^{1,2}	413	25	2921	11.1 (6.8, 15.5)
Current or recent hormonal contraceptive user ^{1,3}	414	10	3149	4.1 (1.6, 6.7)
Excluding sites 023, 033, 044, 076, 081 ^{1,4}	714	22	5252	5.5 (3.2, 7.7)
Other analyses (Applicant's findings)				
Oral contraceptive comparator ^{1,5}	220	5	975	6.7 (0.8, 12.5)
BMI = body mass index; CI = confidence interval ¹ Analyses in subjects 17-35 years old with BMI <32 kg/m ² having intercourse and not using other birth control ² No use of hormonal contraceptives for at least 6 months prior to starting study medication ³ Recent = use of hormonal contraceptives within 6 months of starting study medication ⁴ Post hoc analysis performed by Dr. Dwyer at my request. These 5 sites enrolled 15% of the subjects but contributed 40% of the pregnancies. ⁵ The Applicant did not pre-specify a statistical comparison between AG200-15 and the oral contraceptive arm				

The Applicant claims that the efficacy findings in these trials reflect inclusion of women who are more representative of hormonal contraceptive users in the United States compared to registration trials for other hormonal contraceptives. Table 4 compares selected features of Study CL12 and four other phase 3 registration trials for hormonal contraceptives conducted only or predominantly in the United States.

Table 4. Comparison of registration trials in the United States for selected hormonal contraceptive products					
	Study CL12 (CL13 not included)	NDA 21180 Ortho Evra¹	NDA 22501 Lo Loestrin Fe	NDA 2252 Natazia¹	NDA 22573
Approval year	Pending	2001	2010	2010	2010
Components	Ethinyl estradiol Levonorgestrel	Ethinyl estradiol Norelgestromin	Ethinyl estradiol Norethindrone acetate Ferrous fumarate	Estradiol valerate Dienogest	Ethinyl estradiol Norethindrone Ferrous fumarate
Body mass index (BMI)	Mean 27.5 kg/m ² 28% ≥30 kg/m ²	Mean 23.8 kg/m ²	Mean ? Excluded >35 kg/m ²	Mean 23.3 kg/m ² Excluded >30 kg/m ²	Mean 25.0 kg/m ² 16% >30 kg/m ²
Duration	13 cycles	6 or 13 cycles	13 cycles	Up to 28 cycles	13 cycles
Completion rate	43%	70%	58%	50% (for 28-cycles)	59%
Primary efficacy endpoint	≤35 years old BMI <32 kg/m ²	All subjects (18-45 years old)	≤35 years old	All subjects (18-35 years old)	≤35 years old
Additional pregnancies identified by FDA	5	1 in another trial	4	0	1
Primary efficacy findings in the main United States trial					
Pregnancies/cycles	35/6070	4/5240	28/12482	5/3969	19/12297
Pearl Index (95% CI)	7.5 (5.0, 10.0)	1.2 (0.2, 2.3)	2.9 (1.9, 4.2)	1.6 (X, 3.8)	2.0 (1.2, 3.1)
Pearl Index by BMI	7.4 (4.8, 9.9) ≤30 kg/m ²	No analysis available	3.0 (1.9, 5.3) ≥24 kg/m ²	No analysis available	1.9 (1.0, 3.1) ≤30 kg/m ²
Hormonal contraceptive use	57% naïve/remote use	73% switched from an oral contraceptive	51% with no immediate prior use	59% had prior use; 3% naïve	48% not immediate switchers
Race/ethnicity					
White (non-Hispanic)	57%	86%	75%	76%	72%
White (Hispanic)	16%	<5%	10%	13%	11%
Black	21%	5%	12%	7%	13%
Asian	4%	4%	1%	3%	2%
Other	2%	<5%	2%	1%	2%
Active comparator	Yes	Yes	No	No	No
Major United States trial	102 sites	39 sites (plus 6 in Canada)	68 sites	22 sites (plus 9 in Canada)	69 sites
¹ NDA included European trials – data shown in this table are limited to trials conducted exclusively in the United States (with or without Canadian sites)					

The Applicant puts forth the following explanations for why their efficacy findings are substantially different from that of approved hormonal contraceptives.

- No restrictions on body mass index:** Study CL12 enrolled subjects with higher body mass index compared to that seen in other recent contraceptive trials. However, body mass index does not appear to explain the considerably higher Pearl Index in Study CL12. For example, among the 17-35 year old age group, the Pearl Index (and the upper bound of its associated 95% confidence interval) is 7.5 (10.0) for the primary efficacy analysis (which was restricted to subjects with body mass index $<32 \text{ kg/m}^2$), 7.4 (9.9) when analyses were limited to those with body mass index $<30 \text{ kg/m}^2$, and 7.6 (9.8) when analyses were not restricted based on body mass index (Table 3).
- Trials conducted entirely in the United States:** The Applicant notes that European trials often have considerably lower Pearl Indices and partially attributes the higher Pearl Indices in Study CL12 and CL13 to the fact that these studies were conducted exclusively in the United States. However, as shown in Table 4, the registration trials for other hormonal contraceptives that were conducted exclusively in the United States or in the United States plus Canada all have Pearl Indices well below that seen in Study CL12. Therefore, the fact that Study CL12 and CL13 were conducted exclusively within the United States does not explain the substantially higher Pearl Indices seen in these trials.
- Compliance data:** The Applicant measured ethinyl estradiol and levonorgestrel concentrations at a single timepoint in Cycle 2, Cycle 6 and Cycle 13. The Applicant classified subjects as non-compliant if both ethinyl estradiol and levonorgestrel concentrations were less than the lower limit of quantification. At the 3 sampled timepoints, Hispanics and Blacks had a higher incidence of undetectable ethinyl estradiol and levonorgestrel concentrations compared to Whites (Table 5). The Pearl Index in these minority populations was considerably higher than that seen with Whites although confidence intervals are wide (Table 3). The Applicant states that these pharmacokinetic data are a novel approach for evaluating correct and compliant use of study medication and interpreting the Pearl Index. However, these data represent only a snapshot in time and do not inform on the extent of compliance at other timepoints. In addition, the Applicant's efficacy assessment that excludes these subjects with undetectable ethinyl estradiol and levonorgestrel concentrations was neither prespecified in the statistical analysis plan nor agreed to by FDA.

Table 5. Subjects with available pharmacokinetic data in Study CL12 who had ethinyl estradiol and levonorgestrel concentrations below the lower limit of quantification

	All	Whites	Hispanics	Blacks
Cycle 2 (Visit 3)	92/921 (10%)	31/533 (6%)	18/135 (13%)	40/202 (20%)
Cycle 6 (Visit 5)	69/629 (11%)	25/364 (7%)	10/95 (11%)	30/132 (23%)
Cycle 13 (Visit 7)	65/605 (11%)	18/356 (5%)	13/85 (15%)	29/119 (24%)

- **Better minority representation:** In Study CL12, about 57% of subjects who received at least one dose of AG200-15 were White, 16% were Hispanic and 21% were Black. It is noteworthy, however, that two hormonal contraceptives approved in 2010 had reasonable representation of Hispanics (10-11%) and Blacks (12-13%) yet still had an overall acceptable Pearl Index in the 2-3 range (Table 4).
- **“Pearl Creep”:** The Applicant postulates that Pearl Indices have increased over time as trials have incorporated modern-day standards of enrollment and pregnancy ascertainment. For example, the Applicant reports a Pearl Index of 3.8 in 2003 for Seasonale and 4.4 in 2006 for Seasonique. However, the approved labels show a Pearl Index of 2.0 for Seasonale and Pearl Indices of 1.3 to 1.8 for Seasonique. In addition, as shown in Table 4, the Pearl Index is about 2.0-3.0 for the three hormonal contraceptives approved as recently as 2010.
- **Inclusion of an oral contraceptive active comparator treatment arm:** The oral contraceptive arm also performed poorly in the phase 3 trials. For example, in Study CL12, the Pearl Index for the oral contraceptive was 6.7 (95% confidence interval 0.8-12.5). These data are limited because the oral contraceptive was administered to a small number of subjects for only 6 cycles, as reflected by the wide confidence interval. In addition, the Applicant did not prespecify between-treatment efficacy comparisons.
- **A high proportion of new users:** The Applicant states that their phase 3 trial enrolled a higher proportion of new hormonal contraceptive users compared to other NDAs. However, as discussed above, the Applicant defines new users as those who have not used hormonal contraception in the 6 months prior to receiving study medication. This definition does not necessarily reflect truly naïve users. The proportion of treatment naïve subjects is not specified.

FDA values when clinical trials include populations that are representative of subjects who will use the product, if approved. However, it is not possible to solely attribute the findings in the AG200-15 phase 3 program to a more representative population for the reasons discussed above and because there are substantial problems with study conduct, as described below. Dr. Soule discusses several concerns, including the quality of the NDA submission and problems related to reporting of adverse events. Below I focus on the low completion rate, poor follow-up and poor data collection.

- **Low completion rate:** The completion rate in Study CL12 was about 42% for subjects treated with AG200-15. The Applicant states *“Nearly 50% of discontinuations in Study ATI-CL13, and a somewhat lower percentage in Study ATI-CL12, occurred in the first cycle, suggesting that these subjects never intended to be in the study. This may be a reflection of the bad economic times where many women have no health insurance. This is also reflected in the unexpectedly high lack of compliance in both studies.”* The Applicant also states that the findings support *“the possibility that a significant number of these subjects were primarily motivated to participate in the study for the benefits associated with the initial health care assessment, less so the full rigors of the entire trial.”* Given the

high dropout rates early in the trial, I question whether subjects were poorly selected for inclusion in the trial. For example, if poor economic times were the primary reason for subject enrollment, I would anticipate that subjects not desiring pregnancy would choose to remain in the trial for the long-term to continue to obtain free access to study medication. Poor subject selection could also potentially be explained by the rapid enrollment – there was only 15 months from the start of screening until completion of the 1-year study. This is unusually short. For comparison, completion rates in other recent 13 cycle (1-year) hormonal contraceptive trials are in the 60-70% range (Table 4; the 50% completion rate is for a 28-cycle trial). The Applicant stated in the protocol for Study CL12 that it would monitor discontinuation rates and, if necessary, increase the number of enrolled subjects. They did not do so even though discontinuations exceeded the assumed dropout rate of 25% for 6 cycles and 40% for 13 cycles. This extent of missing data substantially limits conclusions, as would be the case for any trial with a considerable amount of missing data.

- Poor follow-up and poor data collection:** As discussed by Dr. Soule, the Applicant reported a total of 31 pregnancies that were not counted as on-treatment pregnancies. The clinical reviewers counted 8 of these 31 cases (26%) as on-treatment pregnancies based on strongly suggestive data, such as hCG concentrations or sonogram results. There were another 9 cases that had poor data pertaining to last patch use and pregnancy dating. The clinical reviewers concluded that the inadequacy of this information precludes a determination of whether they reflected on-treatment pregnancies. In addition, about 20% of subjects were lost to follow-up over the course of the trial. As discussed by Dr. Soule, 17 of the 31 pregnancies not counted as on-treatment by the Applicant were either lost to follow-up or discontinued by the investigator such that the gestational age of the fetus and estimated conception date were not obtained. These examples illustrate concerns with regard to subject follow-up and data collection and further lower our confidence in the study results.

Bleeding profile

The Applicant assessed spotting (bloody discharge requiring only panty liners) and bleeding (bloody discharge requiring use of at least one tampon/sanitary napkin per day) as secondary efficacy endpoints. Drs. Davis and Soule discuss the results for unscheduled spotting and bleeding (events occurring during Days 1-21 of a cycle). As shown in Table 12 in Dr. Soule's review, the mean number of unscheduled spotting days with AG200-15 was 0.84 in Cycle 1, 0.65 in Cycle 2, 0.60 in Cycle 3 then 0.46-0.57 in Cycles 4-13. The mean number of unscheduled bleeding days with AG200-15 was 0.67 in Cycle 1, 0.78 in Cycle 2, 0.70 in Cycle 3 and then 0.35-0.48 in Cycles 4-13. Dr. Soule notes that by about Cycle 4 the rate of unscheduled spotting and bleeding combined had decreased to about one day per cycle and remained relatively stable through Cycle 13. Dr. Soule also notes that unscheduled bleeding and spotting occurred numerically more frequently with AG200-15 than with the oral contraceptive during Cycles 1-3 but that the two treatment groups had a more comparable incidence of unscheduled bleeding and spotting events during Cycles 4-6.

8. Safety

Safety Database: Safety data for AG200-15 are available for 10,027 28-day cycles across the two phase 3 trials. These data are derived from a total of 1450 women treated with AG200-15, 230 of whom switched from the oral contraceptive to AG200-15 at the beginning of Cycle 7 in Study CL12. A total of 438 women received AG200-15 for 13 cycles. Across Study CL12 and CL13, a total of 532 women received at least one dose of the oral contraceptive comparator.

Deaths: Drs. Davis and Soule note that there were no reported deaths in women treated with AG200-15.

Serious Adverse Events: During the 6-cycles of controlled data in Study CL12 and CL13 combined, serious adverse events were reported in 1.3% of AG200-15 treated subjects and 1.1% of oral contraceptive treated subjects. Dr. Soule notes several serious adverse events of interest among the AG200-15 treated subjects including one report each of suicide ideation and attempted suicide (depression is associated with hormonal contraception), and subclavian vein thrombosis. This deep vein thrombosis was diagnosed in Cycle 5. A thrombophilia workup was unrevealing. The patient was a weight lifter and kick boxer and consideration was given to a diagnosis of Effort-Thrombosis (Paget-Schroetter Syndrome). Relationship to AG200-15 cannot be excluded given the known hypercoagulable effects of hormonal contraceptives and the fact that the patient's exercise activity level was unchanged over the preceding 4-5 years. Another patient had acute compartment syndrome of unclear etiology.

Adverse Events Leading to Discontinuation: As shown in Table 20 in Dr. Soule's memorandum, the most common adverse events leading to premature discontinuation during the first 6 months of Study CL12 were application site reactions such as erythema, irritation, pain, rash (4.4% with AG200-15 vs. 0% with the oral contraceptive), vaginal bleeding events such as menorrhagia (1.2% vs. 0.9%), headache/migraine (0.9% vs. 0.3%), nausea/vomiting (0.9% vs. 0.3%), and affect lability/mood swings (0.8% vs. 0%). In addition, another 2% of subjects were reported to have discontinued due to "subject decision" but appear to have been discontinued due to either bleeding events or application site reactions. Nonetheless, the overall incidence of these events leading to discontinuation remains generally low and acceptable.

Skin Irritation: As noted in Dr. Soule's memorandum, most subjects in Study CL12 and CL13 had no (~60%) or mild skin irritation (~30%) as assessed by investigators at the clinic visits. Dr. Soule notes discrepancies in the severity of skin irritation assessed by investigators compared to the daily assessments made by the subjects themselves (e.g., ~20% with no irritation, ~35% mild, ~30% moderate and ~14% severe in Study CL12).

Patch Adhesion: As shown in Table 17 in Dr. Soule's memorandum, the vast majority of subjects (~96%) in Study CL 12 had minimal problems with patch adhesion as assessed by site personnel at each study visit. For about 83% of subjects, the patch had $\geq 90\%$ adherence with none of the edges showing lift at all clinic evaluations. An additional 13% of subjects had at least one visit with 75% to $< 90\%$ patch adherence and some edges showing lift. About 1% of

subjects discontinued prematurely due to dissatisfaction with patch adhesion. It is unclear whether poor patch adhesion contributed to the number of pregnancies.

9. Advisory Committee Meeting

This NDA was not taken to advisory committee. Ethinyl estradiol and levonorgestrel are commonly used drug substances in hormonal contraceptives and there is already an approved contraceptive patch. In addition, we did not identify efficacy or safety issues that needed input from an advisory panel.

10. Pediatrics

This NDA triggers the Pediatric Research Equity Act (PREA). We are granting a waiver of pediatric studies for premenarcheal females <17 years of age because the indication is not applicable to this population. After discussions with the Pediatric Review Committee, we will fulfill PREA in the 12 to 16 (inclusive) year old population by extrapolating efficacy and safety from adults and grant a partial waiver for premenarcheal females from birth to 11 years of age.

11. Other Relevant Regulatory Issues

Tradename: The proposed tradename (Twirla) was found to be acceptable by the Division of Medication Error Prevention and Analysis but will need to undergo re-review during the next review cycle.

Office of Scientific Investigations (OSI): OSI inspected three of the 102 clinic sites that participated in Study CL12. These three sites enrolled a total of 241 subjects. OSI noted numerous deficiencies as delineated in the reviews by Drs. Davis and Soule but concluded that these deficiencies do not appear to seriously affect data integrity or the safety of study subjects.

There are no other outstanding regulatory issues.

12. Labeling

Labeling has been deferred because the application will receive a Complete Response.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

The CMC reviewers, the primary clinical reviewer and the Cross-Discipline Team Leader recommend that this NDA receive a Complete Response. I agree that the NDA cannot be approved on this cycle. The Pearl Index and the upper bound of its associated 95% confidence interval are substantially higher than that seen with any of the approved hormonal contraceptives. The Applicant is attributing this higher Pearl Index to a trial population that is more generalizable compared to the trial populations of other approved hormonal contraceptive products. FDA values trials that include populations that are representative of subjects who will use the product, if approved. However, several of the Applicant's assertions with regard to generalizability are not supported by the available data. In addition, it is not possible to attribute the AG200-15 efficacy findings solely to a more representative trial population because there are substantial problems with study conduct, including low completion rates, poor follow-up and poor data collection. Section 7 discusses the generalizability and study conduct issues in detail. The Applicant states that the higher Pearl Index could be offset by a possible reduction in the risk of venous thromboembolism because of lower ethinyl estradiol concentrations compared to Ortho Evra. However, there are no head-to-head data comparing these products and it would not be possible to definitively show differences in the risk of venous thromboembolism in a pre-approval trial given the infrequency of such events, even among hormonal contraceptive users. It is noteworthy that there was one event of venous thromboembolism associated with AG200-15 in Study CL12. In addition,

The Applicant is encouraged to conduct further analyses to identify possible explanations for some of the observed findings in Study CL12, such as the clustering of pregnancies at 5 clinic sites, the impact of incentives for patients to stay in the study, and the adequacy of investigator training. These exploratory analyses will not salvage the NDA application but may yield useful information that can be incorporated into the design of another trial. The Applicant should ensure that the new trial uses the to-be-marketed product that adequately addresses the quality issues described in the CMC deficiencies.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Not applicable.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable.

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/s/

HYLTON V JOFFE
02/13/2013

Cross-Discipline Team Leader Review

Date	February 12, 2013
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	204-017
Applicant	Agile Therapeutics, Inc.
Date of Submission	April 13, 2012
PDUFA Goal Date	February 12, 2013
Proprietary Name / Established (USAN) names	To be determined Ethinyl estradiol (EE) and Levonorgestrel (LNG)
Dosage forms / Strength	Transdermal patch containing 2.6 mg of LNG and 2.3 mg EE, applied once weekly
Proposed Indication(s)	Prevention of pregnancy
Recommended:	<i>Complete Response</i>

1. Introduction

Although there are a large number of combination hormonal contraceptives (CHCs) available, there is currently only a single transdermal patch marketed. This application seeks approval for a new transdermal contraceptive patch, one that contains the commonly used steroid hormones ethinyl estradiol (EE) and levonorgestrel (LNG). The formulation used in the phase 3 trials and proposed for marketing is referred to as the AG200-15 transdermal contraceptive delivery system (TCDS); the numeric designation distinguishes it from different formulations evaluated earlier in the development program. Like the other approved contraceptive patch, the proposed dose regimen follows a 28-day cycle consisting of once-weekly applications of a 7-day patch for three weeks, followed by a one-week patch-free interval. Proposed application sites are the abdomen, buttock and upper torso.

2. Background

2.1 DESCRIPTION OF PRODUCT

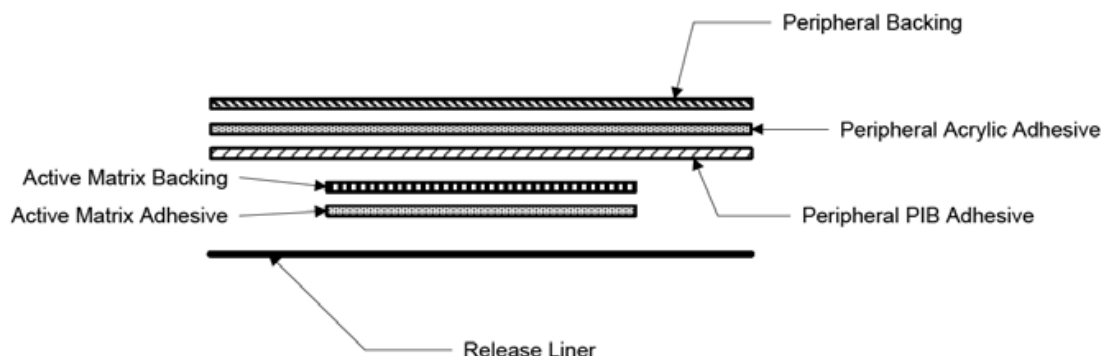
The TCDS contains 2.6 mg LNG (0.867 w/w%) and 2.3 mg EE (0.767 w/w%). LNG and EE are well-characterized progestin and estrogen products, respectively, that are widely used in combined hormonal contraceptive products. These products reduce the risk of pregnancy mainly via the effect of the progestin on suppressing ovulation, along with changes in cervical mucus that inhibit sperm motility and endometrial changes that may inhibit implantation. The estrogen component may make some contribution to the contraceptive action, and mainly acts to maintain cycle control and provide an acceptable bleeding profile.

The TCDS comprises a 15 cm² active matrix that contains LNG and EE in an acrylic adhesive matrix integrated into a larger (28 cm²) peripheral adhesive system. The peripheral adhesive system is necessary due to the inclusion of skin permeation enhancers in the active matrix.

A cross-section of the TCDS is shown in Figure 1.

Figure 1 Cross Section of AG200-15 Transdermal Patch

Figure 1: Schematic Depiction of the AG200-15 Transdermal Patch System



Source: NDA 204-017, Module 2.3.P, Figure 1, p 3

2.2 REGULATORY HISTORY

The Applicant conducted the drug development program for this indication under IND 57,731, which was opened in 1999. A Type B meeting (End of Phase 2) was held on September 22, 2008. The following issues were discussed:

- The Division agreed that no additional preclinical safety studies were needed, but noted a safety concern with respect to capric acid, one of the excipients in the patch and requested additional information regarding chronic dermal safety and mutagenicity. The Division noted that the lauryl lactate and ethyl lactate excipients were safe for use as proposed, and that no additional studies were needed to support inclusion of dimethyl sulfoxide (DMSO).
- The Division further recommended that the Sponsor conduct a relative bioavailability (BA) study comparing the AG200-15 to an oral contraceptive, a study to assess the impact of different application sites on the pharmacokinetics (PK) of the patch, and a study assessing PK under different external conditions such as sauna, exercise, cold water, etc. The Sponsor was encouraged to target the EE exposure toward that of a lower-dose combined oral contraceptive (COC).
- The application site study should be designed to provide sufficient subjects using each site to allow evaluation of site-specific safety and efficacy should the PK vary by application site. An acceptable number of subjects using the sites providing the highest and lowest exposure would allow for bracketing of safety and efficacy data. In phase 3, subjects should be instructed to use the same site for each 21-day patch use cycle, and to document application site in the diary.
- The Division requested two phase 3 studies, one of 13 cycles duration, to provide 10,000 cycles of exposure with at least 200 women completing 13 cycles of use, and the other, which could be a six-month study, to include a COC comparator (30 µg EE/150 µg LNG) to compare the exposure, common adverse events (AEs) and bleeding profile of the two products. At least 200 women per arm were requested to be randomized in this smaller study. The Division requested collection of PK data at Months 3 and 6 in the six-month trial and Months 6 and 12 in the 12-month trial.

- The definition and evaluation of on-treatment pregnancies was discussed and the Division stated that “in case of uncertain or conflicting data, the Division may determine that a pregnancy occurred ‘in-treatment’.”
- The exclusion of women based on body mass index (BMI) was discussed; the Division requested removal of any restrictions and the Sponsor proposed enrolling women of unrestricted BMI only in the COC-comparator study. The Division found this potentially acceptable provided that more than 200 women/arm were enrolled.
- The need for formal dermal safety and cold flow studies was discussed; the Sponsor believed that Studies 10 and 11, as well as data collected in phase 3 would adequately characterize dermal safety. Because the patch is a matrix, not a reservoir, the Sponsor did not anticipate that cold flow would be an issue, but agreed to monitor for the impact of cold flow on stability.

The Applicant submitted a request for a Special Protocol Assessment (SPA) of the 13-cycle, 1,200 subject phase 3 Study ATI-CL12 (hereafter referred to as Study 12), which was also proposed to contain a low-dose COC comparator (Levlite, 20 µg EE/100 µg LNG) on June 22, 2009. The design entailed a six-month two-arm phase, with COC users crossed-over to patch use in Month 7 for the remainder of the study. The Division responded with a No Agreement letter on August 7, 2009, due to the following issues:

- Nonconcurrency with exclusion criteria related to body mass index ($\text{BMI} \geq 32$) and smoking (women under age 35 who smoked 10 or more cigarettes/day)
- Recommendation to exclude 28-day cycles from Pearl Index evaluation in which back-up or emergency contraception was used or in which no sexual activity had occurred
- Need for clearer definitions and quantification of bleeding and spotting
- Need for a more detailed plan for pregnancy follow-up
- Request for return to fertility data in a subset of women who discontinued with the intent to become pregnant

Another SPA was requested on November 24, 2009, for the six-month, 400 subject phase 3 Study ATI-CL13 (hereafter referred to as Study 13). The Sponsor proposed use of a different COC comparator (30 µg EE/150 µg LNG) in this study. Again, the Sponsor proposed to exclude women with $\text{BMI} \geq 32$ and women under age 35 who smoked 10 or more cigarettes/day. The study objectives were to characterize comparative safety, tolerability and PK of the two drug products; efficacy data would be collected but not compared statistically. A No Agreement letter was issued on January 7, 2010 based on the following:

- The Division strongly recommended inclusion of women with $\text{BMI} \geq 32$ in at least one of the phase 3 studies; it would be acceptable to include only women below a specified BMI in the efficacy population, but safety and a secondary evaluation of efficacy should be provided in all subjects
- Exclusion of smokers < 35 years would likely result in exclusionary labeling
- The trial should be considered supportive for the overall demonstration of contraceptive efficacy; therefore, Pearl Index and life table pregnancy rate estimates and 95% confidence intervals should be calculated; statistical hypothesis testing to compare the treatment arms would not be necessary
- Revised bleeding and spotting definitions were recommended

- A standardized adhesion scale was recommended to assess patch wearability

Subsequently, a Type A meeting was held on March 9, 2010 to discuss revisions made to the Study 12 protocol. At this time, the Division agreed that there were no outstanding issues with respect to the dermal safety of capric acid. The Division requested specific inquiries be made about dermal irritation in phase 3, rather than relying on spontaneous complaints; the Division agreed to the Sponsor's proposal for checkboxes in the daily diary for irritation and pruritis and investigator evaluation of irritation at all visits. Regarding BMI, the Division recommended against any upper limit on BMI and suggested that, based on current US data and recent clinical trial experience, at least 170 women with BMI ≥ 35 should be enrolled in the patch arm of Study 13. It would be acceptable to exclude these women from the primary efficacy population, but the Division would consider the efficacy demonstrated in this subgroup and might address it in labeling. The Sponsor was willing to enroll women with BMI up to 32, but expressed concern about the safety of combined hormonal contraceptives in heavier women. The Division asked the Sponsor to provide justification of BMI exclusions before submitting another SPA for Study 13. The Division had the following additional comments on Study 12 and the overall program:

- The sample size may need to be increased to assure 10,000 cycles of exposure
- The Sponsor was asked to specify the proportion of enrollees who would be new users of hormonal contraception; the Division was concerned that the COC users who cross-over to patch use a Month 7 are "switchers" who are at lower risk of venous thromboembolic events (VTEs) and other AEs. If the Sponsor plans to include the cross-over subjects in its 10,000 cycles of exposure, it must ensure that an adequate number of cycles are from naïve users.
- The Division did not agree with the proposal to evaluate bleeding in Cycles 3, 5 and 12 only, and indicated it would consider the bleeding profile at all cycles; the Sponsor agreed to this
- The plan to measure drug concentrations in the patch and COC arms in two cycles in each phase 3 study may not provide a meaningful quantitative comparison, due to the different PK profiles of the two formulations; it is not likely that comparative claims about drug levels or exposure would be accepted in labeling
- Although the Sponsor had data on a comparative PK study of the patch and norgestimate-containing OrthoCyclen, the Division requested a comparison between the patch and a LNG-containing COC
- Investigation of different batches in phase 3 was discussed; the Sponsor anticipates using one batch in Study 13 and at least two batches in Study 12. The Division asked that the age of patches used in phase 3 be characterized and performance of fresh vs. aged patches be evaluated; the Sponsor should use patches aged to at least 12 months and preferably up to the end of expiry in the trials.
- A CMC pre-NDA meeting would allow provision of more current advice regarding transdermal patch development standards, which are evolving

On April 21, 2010, the Sponsor again requested an SPA of the revised protocol for Study 13, which continued to exclude women with BMI > 32 . On June 3, 2010, the Division sent an Agreement letter for this protocol, but included some comments. The Division continued to

recommend that women with BMI above 32 be included in at least one of the phase 3 studies, but stated that it would be acceptable for the efficacy population to have some BMI restriction (e.g., < 32), provided that a secondary efficacy analysis was done for heavier women. The Sponsor was asked to provide definitions of spotting, light, normal and heavy bleeding on the daily diary cards, and to follow the recommendations of Mishell et al¹ in characterizing the bleeding profile. The Division continued to express concern that the planned measurement of PK in two treatment cycles might not provide a meaningful quantitative comparison of the patch and the comparator COC.

Another SPA was submitted for Study 12 on June 21, 2010, and the Division provided an Agreement letter on July 13, 2010. Revisions to this protocol included enrollment of about 500 women with BMI ≥ 30 , but restriction of efficacy and safety subsets to women with BMI < 32 . The protocol proposed to enroll up to 1,500 women aged 17 - 40 years in a 3:1 randomization (patch:COC), with 20% to be “new users” of hormonal contraception, defined as never-users or women who had not used hormonal contraception in the past six months.

Minor revisions to both protocols were submitted on February 3, 2011; the medical reviewer determined that these did not impact the SPA agreements.

The Sponsor requested a pre-NDA meeting in 2011, but requested cancellation of the meeting after receipt of the Division’s preliminary comments on October 20, 2011. In those comments, the Division addressed:

- Advice about the 505(b)(2) pathway
- Requirement to submit narratives and case report forms (CRFs) for all pregnancies, and all pregnancy follow-up forms
- Request to conduct a Standardized MedDRA Query (SMQ) for venous thromboembolism in the phase 3 database
- Submission of datasets and efficacy analysis programs
- Submission of information on all formulations evaluated during the development program, not merely a tabular listing

2.3 PRIMARY MEDICAL REVIEWER’S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Dan Davis, stated in his review dated January 23, 2013:

I do not recommend approval for this NDA 204017 application for a 7-day combination hormonal transdermal patch for contraception. According to the FDA calculations based on 5 additional on-treatment pregnancies identified during the review, the Pearl Index for the prespecified primary efficacy dataset is 7.50 with an upper bound of the 95% confidence interval of 9.97. A total of 8 additional on-treatment pregnancies were identified, but only 5 were in the primary efficacy dataset. This is unacceptable for a combination hormonal contraceptive (CHC) product with all the known and expected safety issues associated with CHCs, especially thromboembolic events. The risk/benefit for this combination transdermal patch is not favorable compared to the other FDA-approved combination products currently on the market. Furthermore, there are

¹ Mishell D et al. Recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials. *Contraception*, 2007; 75: 11-15

significant unresolved chemistry and manufacturing (CMC) issues and several issues with the overall quality of the clinical trials and the data in the submission as commented on throughout this review.

Team Leader Comment:

I concur with Dr. Davis' recommendation. Although FDA does not consider comparative efficacy in the approval of contraceptive products, I agree that the unacceptable level of efficacy demonstrated by a Pearl Index of 7.5 leads to a determination that the overall risk/benefit profile of this product is unfavorable.

Dr. Davis indicated that it was premature to recommend any postmarketing risk evaluation and mitigation strategies or postmarketing requirements/commitments.

3. CMC/Device

3.1 CMC

Information about the drug substances (EE and LNG) was cross-referenced to two DMFs, which have been reviewed several times and determined to be adequate. The quality of the drug product, the TTDS, is controlled by tests for appearance, assay, content uniformity, identification, related substances, excipient assay, adhesion, release liner removal force, drug release and pouch seal strength. However, the primary Chemistry Reviewer, Caroline Strasinger, Ph.D., identified several deficiencies related to specifications, and the specification table was not properly updated in this review cycle.

Dr. Strasinger noted the following additional deficiencies:

- Administrative deficiencies in DMF (b) (4)
- Inadequate (b) (4) need for release test and specifications to identify compromised systems after (b) (4) laser etching
- Inadequate specification and acceptance criteria; need for test for cold flow or shear
- Inadequate justification of upper and lower bounds of acceptance criteria for the excipient assay; justify with *in vivo* or *in vitro* skin permeation data
- Need to identify the strength as a transdermal flux
- Identifying label on the drug product backing membrane insufficient to assure the product can be appropriately identified during use
- Inadequate characterization of impurities, including test for (b) (4) in final product and acceptance criteria for (b) (4) if toxicologically relevant levels are detected
- Need to update post-approval stability protocol with new tests added to the specification

She made the following recommendations in her review dated January 14, 2013:

NDA 204017 for Twirla (levonorgestrel, ethinyl estradiol) transdermal system is recommended for Complete Response from the CMC perspective. The Applicant has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Applicant needs to respond adequately to the CMC issues outlined in this review. Deficiencies to be communicated to the Applicant can be found on pages 85 – 89.

An overall “PENDING” recommendation has been issued for the manufacturing and testing sites by the Office of Compliance.

Labeling was not reviewed in this cycle. No post-marketing commitments or risk management steps were recommended.

Dr. Strasinger identified issues that were deferred during this review cycle that would need to be addressed in a future review cycle, including:

- Adequacy of the chosen adhesive platform (DMFs for the adhesives was not reviewed)
- The manufacturing process remains unclear; concerns include (b) (4) laser etching steps and controls to insure the integrity of the active matrix backing, and the integrity of the manufacturing process
- A downward trend in excipient assay and attention to differences volatile excipients in systems that did and did not use the (b) (4) etching process.
- Additional recommendations pertaining to specifications and justification of specifications, control of excipients and process validation

Shortly before the action date, the Office of Compliance provided an “Acceptable” recommendation despite the fact that at the initial attempt at inspection, the drug product manufacturer facility was not ready for inspection. Inspectors returned and were able to complete the inspection; however, the Applicant did not have commercial production-level equipment in place at this time. Other individual facilities (drug substances manufacturer, packager and release testers) were found acceptable on profile.

Because the inspection did not evaluate the facility as it will be configured in order to perform commercial production, the CMC reviewer made recommendations on the data needed to bridge the manufacturing equipment and process changes and noted that an inspection may be requested when the Applicant responds to the Complete Response.

Following completion of the Office of Compliance inspection, Dr. Strasinger submitted an addendum to her review on February 12, 2013. She made the following recommendations:

*From the ONDQA perspective, this NDA is recommended for **COMPLETE RESPONSE**.*

The Applicant has not provided sufficient information on raw material controls, manufacturing processes and process controls, and specifications for assuring consistent product quality of the drug product. The applicant has not provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the proposed expiration dating period. The identifying label on the drug product backing membrane is insufficient to assure the product can be appropriately identified during use.

The Office of Compliance has issued an “ACCEPTABLE” overall recommendation on all the manufacturing facilities.

Labels and Labeling were not reviewed in this review cycle.

3.2 Biopharmaceutics

The ONDQA Biopharmaceutics reviewer, Tapash Ghosh, Ph.D., reviewed the *in vitro* drug release method and specifications and the *ex vivo* skin permeation study results. He noted

that the LNG drug release results did not meet acceptance criteria at accelerated storage conditions for 24 and 72 hour sampling times, and recommended that the 72 hour *in vitro* release specifications at release and at stability be revised. The EE drug release results met acceptance criteria at all sampling times. Results of the skin flux study that used three TCDS lots of different ages (2, 6 and 18 months) showed that the patch provided adequate containment of actives and excipients such that flux would not impact performance of the drug product over its shelf life and storage conditions.

Dr. Ghosh made the following recommendation in his review dated January 3, 2013:

*ONDQA/Biopharmaceutics has reviewed NDA 204-017 for Twirla™ (Levonorgestrel/Ethinyl estradiol Transdermal system 15 cm²/28 cm²). Based on the evaluation of the overall information included in the original submission and subsequent amendments/communications, the NDA 204-017 is acceptable from biopharmaceutics perspective (except the *in vitro* release acceptance criterion at 72 hour time) as noted below:*

- The following proposed *in vitro* release method is acceptable.*

In Vitro Release Method for Evaluation of Twirla™ (Levonorgestrel/ Ethinyl estradiol Transdermal system

Apparatus	USP Type 5
Rotation Speed	75 rpm
Medium Temperature	32 ± 0.5 ⁰ C
Dissolution Medium	Deaerated 0.25% HPCD in water
Dissolution Medium Volume	500 mL
Sampling Times	2, 24 and 72 hrs

Analytical Method : HPLC with UV detector at 225 nm

Typical Operation Parameters	
Wavelength	(b) (4)
Flow Rate	
Injection Volume	
Column Temperature	
Run Time	
Isocratic or Gradient	

- The proposed *in vitro* drug release criterion at 72 hour time point as outlined below is recommended to be adjusted as per the Agency's recommendation described below in the next submission:*

The **Applicant's** proposed Specifications for TCDS AG200-15

Test	Method	Acceptance Criteria
Drug Release Ethinyl Estradiol 2hr 24hr 72hr	(b) (4)	NMT $\frac{(b) (4)}{(4)}\%$ (b) (4) % NLT $\frac{(b) (4)}{(4)}\%$
Drug Release Levonorgestrel 2hr 24hr 72hr		NMT $\frac{(b) (4)}{(4)}\%$ (b) (4) % NLT $\frac{(b) (4)}{(4)}\%$

The **Agency's** proposed Specifications for TCDS AG200-15

Test	Method	Acceptance Criteria
Drug Release Ethinyl Estradiol 2 hr 24 hr 72 hr	(b) (4)	NMT $\frac{(b) (4)}{(4)}\%$ (b) (4) % NLT $\frac{(b) (4)}{(4)}\%$
Drug Release Levonorgestrel 2 hr 24 hr 72 hr		NMT $\frac{(b) (4)}{(4)}\%$ (b) (4) % NLT $\frac{(b) (4)}{(4)}\%$

4. Nonclinical Pharmacology/Toxicology

The current submission is a 505(b)(2) application that relies in part on data from published literature. The Applicant also referred to dermal toxicity studies conducted under IND 57,731. These studies were conducted using a 12.5 cm² prototype patch of the AG200-15 formulation, and evaluated irritation in rabbits and sensitization potential in guinea pigs. No additional preclinical studies were conducted for this NDA.

The primary Toxicology Reviewer, Krishan Raheja, D.V.M., Ph.D., reviewed the dermal toxicity studies in 1999 and noted in a summary memo dated November 3, 2008 that "there were no significant signs of irritation in the primary skin irritation study in rabbits and no skin sensitization in Buchler sensitization test in guinea pig."

Dr. Raheja made the following recommendations in his NDA review dated May 9, 2012:

Recommendations on approvability: Pharmacology/Toxicology recommends approval of NDA 204017 for EE/LNG transdermal patch for prevention of pregnancy.

Recommendations for nonclinical studies: None

Recommendations on labeling: Sponsor has submitted draft labeling text.

5. Clinical Pharmacology/Biopharmaceutics

A number of formulations were evaluated over the drug development program; problems with various early formulations included crystal formation in the patches, adhesion

difficulties and delivery of lower than expected LNG serum levels. The Applicant submitted 13 clinical studies with earlier formulations and four PK studies using the to-be-marketed formulation; the latter studies included a dose-finding ovulation suppression/cycle control study, a comparative BA study to compare EE exposure to that with a COC, and PK studies to evaluate various application sites and external conditions.

The dose-finding study, ATI-CL11, evaluated three formulations:

- AG200LE: a 12.5 cm² patch containing 1.28 mg EE/2.17 mg LNG
- AG200: a 12.5 cm² patch containing 1.92 mg EE/2.17 mg LNG
- AG200-15: a 15 cm² patch containing 2.3 mg EE/2.6 mg LNG

Subjects received each formulation for three cycles; initially, subjects were randomized to either AG200 or AG200LE for three cycles; then all subjects received AG200-15 for an additional three cycles. The application site was on the abdomen. Ovulation was defined as a progesterone concentration ≥ 4.7 ng/mL in a given cycle; cycle control was evaluated based on the occurrence of “breakthrough” or unscheduled bleeding and spotting in Cycle 3. The AG200-15 patch demonstrated the best ovulation suppression (19% rate of “possible ovulation” compared to 20% for the AG200 and 37% for the AG200LE) with the lowest rate of unscheduled bleeding/spotting (15% compared to 29% each for the AG200 and AG200LE patches), and therefore, was taken forward into phase 3.

Study ATI-CL14 was the BA study comparing EE exposure of the AG200-15 patch to that of OrthoCyclen (35 µg EE/250 µg norgestimate) at Weeks 1 and 3 during a single cycle. In the patch arm, mean C_{max} for EE increased about 13% from Week 1 to 3; there was no increase over time in the COC arm. At Week 3, the mean C_{max} for EE for the patch (51 pg/ml) was about 39% of the mean C_{max} observed for the COC (131 pg/ml), and the AUC for the patch (6.3 ng·h/ml) was about 86% of that for the COC (7.0 ng·h/ml). However, the primary Clinical Pharmacology Reviewer, Hyunjin Kim, Pharm.D., noted that due to potential between-cycle accumulation of EE, these results may not be reliable.

Team Leader Comment:

Although cross-study comparisons are problematic, it is interesting to note that the Ortho Evra patch has also been compared to a similar 35 µg EE COC; that study (NED-1) found a Week 3 C_{max} of 97 pg/ml for Ortho Evra vs. 133 pg/ml for the COC, and Week 3 AUC of about 13.0 ng·h/ml for Ortho Evra vs. 8.3 ng·h/ml for the COC, resulting in a conclusion (described in Ortho Evra labeling) that the AUC for Ortho Evra was about 60% higher than that associated with use of a 35 µg EE COC, while C_{max} was about 25% lower.

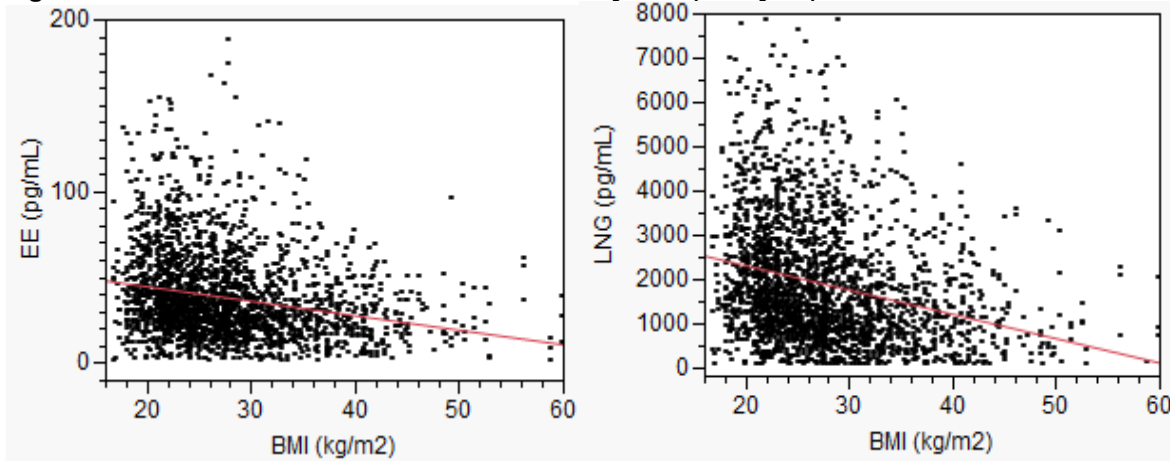
The application site study (ATI-CL15) compared EE and LNG exposure following a one-week application to abdomen, buttock and upper torso, with a one-week wash-out between treatment weeks. C_{max} and AUC₀₋₁₆₈ for both LNG and EE were higher for the buttock and upper torso compared to the abdomen. For buttock vs. abdomen, LNG C_{max} and AUC were each 7% higher, and the upper limit of the 90% confidence interval (CI) for C_{max} exceeded 125%. For upper torso vs. abdomen, LNG C_{max} and AUC were each 17% higher, and the upper limit of both the 90% CIs exceeded 125%. Results were more discrepant for EE. However, Dr. Kim noted that the wash-out period may not have been long enough and therefore, the results may not be reliable.

Study ATI-CL16 compared EE and LNG exposure under different external conditions, including normal, dry sauna, whirlpool, treadmill, and cold water) following one-week

exposure. EE and LNG exposures were similar for normal and cold water conditions, but lower for the other external conditions. Again, Dr. Kim noted that reliability of results is in question due to the inadequacy of the one-week washout period.

Intrinsic factors (i.e., weight and organ dysfunction) were evaluated in the phase 3 Study 12. Trough concentrations of both EE and LNG at Cycles 2, 6 and 13 showed a statistically significant trend of decreasing concentration with increasing BMI (see Figure 2). However, the mean BMI between pregnant and non-pregnant subjects did not vary substantially. The impact of BMI on efficacy is discussed further in Section 7.4.4.

Figure 2 AG200-15 EE and LE Concentrations by BMI (Study 12)



Source: Clinical Pharmacology review by Hyunjin Kim, Ph.D., dated January 11, 2013, Figure 7, p 19

Studies in renally or hepatically impaired subjects were not done, nor were drug-drug interaction (DDI) studies. Class labeling for hormonal contraceptives addresses hepatic impairment and DDIs.

Dr. Kim stated the following in his review dated January 11, 2013:

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 204017 acceptable provided that the issues identified by the Office of New Drug Quality Assessments for the recommendation for Complete Response are resolved.

Dr. Kim did not recommend any phase 4 commitments. He did recommend that the following comment be conveyed to the Applicant:

The potential carry-over effects of both ethinyl estradiol (EE) and levonorgestrel (LNG) between adjacent treatment Cycles (in ATI-CL14) and adjacent Periods (in ATI-CL15 and ATI-CL16) were noted in the respective studies. As the FDA considers this to be important information for proper labeling, as part of your response to this Complete Response, you will need to provide a revised analysis which corrects for/compensates for the noted potential carry-over effect or provide details on how you will obtain this information post-marketing along with a suitable labeling to address this lack of information.

6. Clinical Microbiology

No clinical microbiology consult was requested for this product.

7. Clinical/Statistical – Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The development program for the AG200-15 patch included six studies that utilized the final formulation: three PK studies, one dose-finding PK/PD study, and two open-label comparative phase 3 trials of the patch with active comparators of two EE/LNG combination oral contraceptives (COCs). These studies are briefly outlined in Table 1.

In both studies, subjects began using study drug on Cycle Day 1, defined as first day of menses for subjects without current or recent hormonal contraceptive use, or, for current users, as any day during the active pill-taking interval of their current method, or the first day of menses following an active pill cycle (Study 12) or no later than the third day of the pill-free intervals (Study 13). AG200-15 subjects were provided with three reserve patches to use in case unscheduled patch replacement was needed. Patches were to be applied to the abdomen, buttock or upper torso (excluding the breasts). Subjects were instructed to apply a missed patch as soon as the mistake was noted; COC subjects were to follow labeled instructions with respect to missed pills.

Table 1 Clinical Development Program for AG200-15 TCDS

Study ID	Design* Phase	Study and Control Arms	Objectives, Application Site	N	Endpoints
ATI-CL14	OL, R, 2-part XO Phase 1	AG200-15, OrthoCyclen (OC with 35 µg EE & 250 µg norgestimate)	Comparative PK	36 enrolled, 36 safety	Comparative EE & LNG PK, safety
ATI-CL15	OL, R, 3-period XO Phase 1	AG200-15	Application site PK Lower abdomen, upper torso, buttock	24 enrolled & safety	EE & LNG PK
ATI-CL16	OL, R, 3-period XO Phase 1	AG200-15	Extreme conditions PK Lower abdomen	24 enrolled & safety	EE & LNG PK, patch adhesion
ATI-CL11	OL, R, parallel group, 3-cycle Phase 2	AG200, AG200-LE, AG200-15	Dose-finding Lower abdomen	AG200: 45 enrolled, 44 safety AG200-LE: 45 enrolled, 44 safety AG200-15: 33 enrolled, 31 safety	EE & LNG PK, PD (ovulation inhibition), patch adhesion
ATI-CL12	OL, R, parallel group, 13-cycle Phase 3	AG200-15, Lessina (OC with 20 µg EE & 100 µg LNG)	Safety and efficacy, PK, PD effects on binding globulins, wearability Abdomen, upper torso, buttock	AG200-15: 1,378 enrolled, 1,278 safety (including 249 from OC at Cycle 7) Lessina: 375 enrolled, 344 safety	Pregnancy rate, safety, bleeding profile, EE & LNG PK, PD, patch adhesion
ATI-CL13	OL, R, parallel group, 6-cycle Phase 3	AG200-15, Levora (OC with 30 µg EE & 150 µg norgestimate)	Safety, efficacy, PK, PD effects on binding globulins, wearability Abdomen, upper torso, buttock	AG200-15: 201 enrolled, 177 safety Levlite: 206 enrolled, 188 safety	Pregnancy rate, safety, bleeding profile, EE & LNG PK, PD, patch adhesion

* OL= open label, R = randomized, XO = cross-over

Source: Based on Clinical Overview, Table 2, pp 10-12 & Tabular Listing of Studies

7.1.1 Study ATI-CL12

Study 12 was a 13-cycle prospective, open-label, randomized, parallel-group multicenter trial that included two phases of treatment allocation and enrolled 1,500 women. For the first six months, subjects were randomized 3:1 to AG200-15 or to Lessina, a COC that contains 20 µg of EE and 100 µg of LNG. After Cycle 6, women randomized to the COC were allowed to cross-over to AG200-15 for the remainder of the study.

Blood samples were drawn for trough concentrations of LNG and EE prior to the third patch application in Cycles 2, 6 and 13. The objective of the study was a comparative evaluation of efficacy, bleeding profile, compliance, plasma concentrations and safety of the patch vs.

the COC. The Applicant also intended this study to meet the Division's requirement for 10,000 cycles of exposure with at least 200 women completing a year of treatment.

Entry criteria specified inclusion of sexually active women ages 17 to 40 years, with regular menstrual cycles and general good health. Exclusion criteria included smokers ≥ 35 years and other common exclusions for contraceptive trials that reflect contraindications to use of hormonal contraception. Women were enrolled without restriction on BMI; however, several exclusion criteria were modified on the basis of BMI (e.g., women with BMI < 32 were excluded if they had uncontrolled hypertension [$\geq 140/90$] or diabetes with vascular disease, while women with BMI ≥ 32 were excluded if they had presence or history of hypertension or diabetes Type 1 or 2). The Applicant used centralized stratified randomization in an attempt to enroll 33% of subjects in each arm with BMI ≥ 30 and 50% of those to have BMI ≥ 35 .

Team Leader Comment:

The entry criteria were those generally utilized in hormonal contraception trials; however, per the Division's request, the Applicant did not impose a BMI restriction in Study 12. The Division has been urging sponsors to avoid BMI restrictions, so the study populations will be more reflective of the general population, with the increasing burden of obesity. As negotiated prior to submission of the NDA, the primary efficacy population did exclude women with BMI ≥ 32 , but the Division valued the opportunity to review safety data on the entire population, including a substantial number of heavier women.

7.1.2 Study ATI-CL13

Study 13 was a 6-cycle prospective, open-label, randomized, parallel-group multicenter trial that enrolled 400 women, randomized 1:1 to AG200-15 or to Levora, a COC that contains 30 μg of EE and 150 μg of LNG. Blood samples were drawn for concentrations of LNG and EE after that week's patch application in Cycles 3, and 6. The objectives of the study were comparative evaluations of exposure, bleeding profile, and safety and efficacy of the patch vs. the COC.

Entry criteria were generally similar to those for Study 12, with the following exceptions:

- Entry age was 18 to 40 years
- BMI was restricted to $< 32 \text{ kg/m}^2$

Team Leader Comments:

Despite the Division's requests to avoid BMI restrictions, many sponsors of contraceptive trials continue to exclude women with BMI above 30 or 35. The entry criteria for Study 13 were similar to those utilized in the majority of contraceptive trials submitted to the Division in recent years.

7.2 DEMOGRAPHICS

Demographics were similar over both studies and across the arms of each study. The mean age was about 27 years. About 56-60% of the subjects were Caucasian, with 15-20% Hispanic, 16-22% Black, 1-4% Asian and 2-4% "other." About half the women in each arm and study were nulliparous. Subjects in Study 13 weighed less on average (66 vs. 74 kg) and had lower average BMIs (25 vs. 27), as would be expected given BMI restrictions employed in Study 13.

Table 2 shows the demographics of the Safety population in Study A12, which is defined as all randomized subjects who received any amount of study drug, and Table 3 shows the

Table 2 Study 12 – Demographics and Baseline Characteristics – Safety Population

Variable	COC Cycles 1-6 N=344	COC →AG200-15* Cycles 7-13 N=230	AG200-15 Cycles 1-13 N=1,273
Age (years; mean (SD) and range)	26.4 (5.7) 17-40	26.9 (5.7) 17-40	26.5 (5.7) 17-40
≤ 35 years (N, %)	313 (91.0)	208 (90.4)	1,163 (91.4)
> 35 years (N, %)	31 (9.0)	22 (9.6)	110 (8.6)
Weight (kg; mean (SD) and range)	73.7 (19.6) 34.8-149.7	72.8 (18.6) 45.5-147.2	73.9 (19.9) 41.1-172.3
BMI (kg/m ² ; mean (SD) and range)	27.5 (6.8) 15.6-56.6	27.3 (6.6) 17.6-52.4	27.5 (7.1) 16.5-59.8
< 30 (N, %)	245 (71.2)	168 (73.0)	912 (71.6)
≥ 30 (N, %)	99 (28.8)	62 (27.0)	361 (28.4)
Race/ethnicity (N, %)			
White (non-Hispanic)	191 (55.5)	140 (60.9)	733 (57.6)
Hispanic (White)	61 (17.7)	37 (16.1)	191 (15.0)
Black	71 (20.6)	36 (15.7)	275 (21.6)
Asian	12 (3.5)	9 (3.9)	44 (3.5)
Other	9 (2.6)	8 (3.5)	30 (2.4)
Parity			
Nulliparous	162 (47.1)	114 (49.6)	623 (48.9)
Parous	182 (52.9)	116 (50.4)	650 (51.1)
Previous hormonal contraceptive use (N, %)			
New user (no use in last 6 months)	198 (57.6)	116 (50.4)	710 (55.8)
Current user (use immediately prior to study drug)	57 (16.6)	45 (19.6)	228 (17.9)
Recent user (used in last 6 months, but not Current User)	89 (25.9)	69 (30.0)	335 (26.3)

* The women who crossed-over at Cycle 7 from COC to AG200-15 are a subset of the subjects listed in the COC column.

Source: Based on Applicant's Report for Study 12, Tables 6 and 7, pp 76-8

Table 3 Study 13 – Demographics and Baseline Characteristics –Safety Population

Variable	COC N=188	AG200-15 N=177
Age (years; mean (SD) and range)	26.7 (5.7) 18-40	25.9 (5.4) 18-40
≤ 35 years (N, %)	172 (91.5)	164 (92.7)
> 35 years (N, %)	16 (8.5)	13 (7.3)
Weight (kg; mean (SD) and range)	66.2 (10.9) 46.0-99.0	65.9 (11.1) 43.2-94.1
BMI (kg/m ² ; mean (SD) and range)	24.8 (3.6) 17.0-32.0	24.6 (4.0) 17.2-31.9
Race/ethnicity (N, %)		
White (non-Hispanic)	111 (59.0)	106 (59.9)
Hispanic (White)	37 (19.7)	28 (15.8)
Black	30 (16.0)	34 (19.2)
Asian	2 (1.1)	6 (3.4)
Other	8 (4.3)	3 (1.7)
Parity		
Nulliparous	105 (55.9)	100 (56.5)
Parous	83 (44.1)	77 (43.5)
Previous contraceptive use (N, %)		
New user	100 (53.2)	107 (60.5)
Current user	65 (34.6)	44 (24.9)
Recent user	23 (12.2)	26 (17.4)

Source: Based on Applicant's Report for Study 13, Tables 6 and 7, pp 60-2

Team Leader Comments:

- The Applicant did not attain its goal in Study 12 of enrolling about one-third of subjects with BMI ≥ 30; about 27-29% of subjects were in this category. About 15% of subjects in each arm had BMI ≥ 35.
- During the development program, the Division had emphasized the need for sufficient numbers of naïve users. Over the two studies, the proportion of “new users” ranged from 50 to 60%; however, the Applicant's definition did not identify true naïve users who had no previous exposure to hormonal contraceptives; rather, the “new user” category included some women who previously used hormonal contraception prior to enrolling in the study. It appears that women who did not meet the criteria for current or recent use were categorized as new users, although they may have used hormonal contraception more than six months before entering the trial. In reading narratives, it is clear that a number of women who were categorized as “new users” had previous use of hormonal contraception. It is not entirely clear how the Applicant obtained the data used to categorize previous contraceptive use, but based on the CRF, it appears that subjects were asked during screening if they were currently using hormonal contraception; those who replied “yes,” were then asked for the date of their last dose.
- Current Census figures² report that the US population comprises 64% Non-Hispanic Whites, 16% Hispanics, 13% African-Americans, 5% Asians and 7.1%

² 2010 Census Shows America's Diversity, <http://www.census.gov/2010census/news/releases/operations/cb11-cn125.html>, accessed January 25, 2013. Numbers sum to > 100% because data on Hispanic ethnicity was

“other.” By this measure, the Applicant enrolled slightly higher percentages of African-Americans, and slightly lower percentages of Asians and “others” compared to the US population.

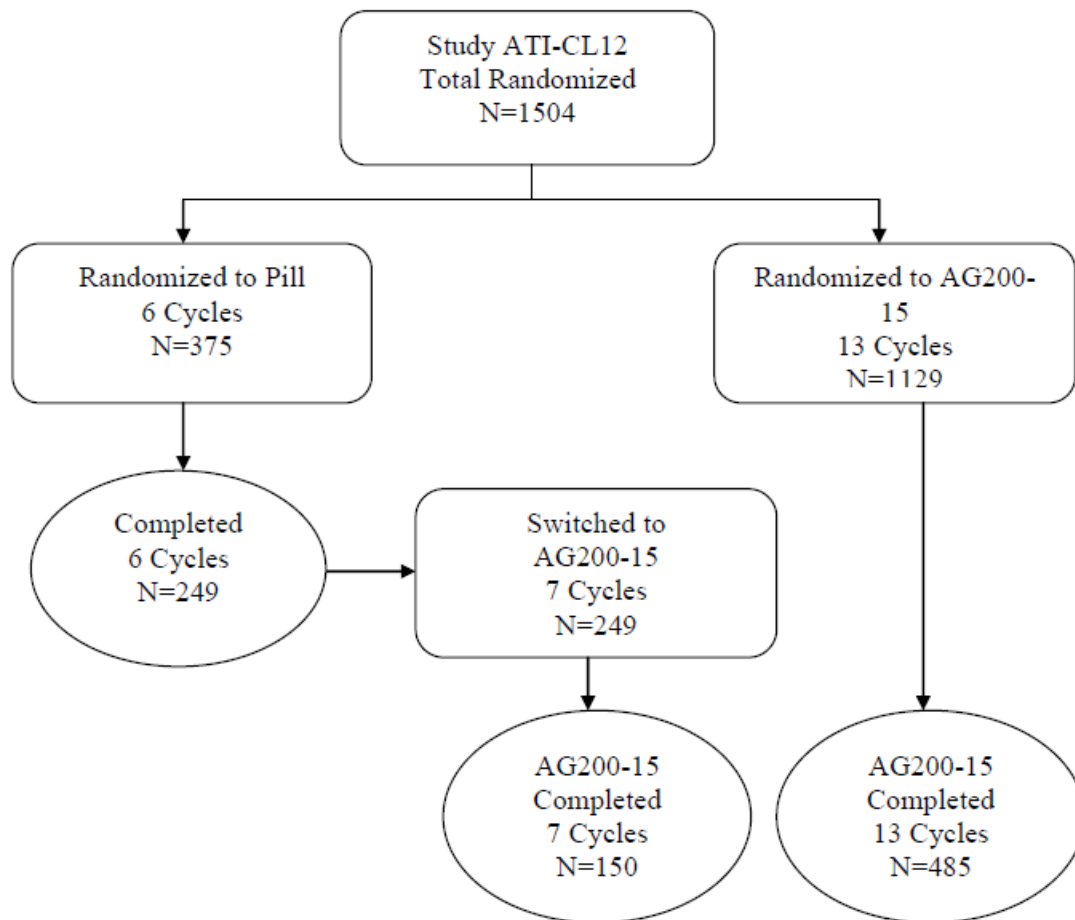
- **Compared to other recent contraceptive studies conducted in the US (see NDAs 22-252, 22-501 and 22-573), which enrolled about 75% Caucasians, 10-13% Hispanics, 7-13% Blacks, 1-3% Asians and 1-3% “other,” the proportion of Caucasians is lower and the proportions of Hispanics and Blacks are higher in this study. Compared to the US population, it appears that contraception studies have generally oversampled Caucasians and undersampled Hispanics, Asians and “others,” while the AG200-15 studies under-represented Caucasians, Asians and “others” and oversampled Blacks.**

7.3 DISPOSITION OF SUBJECTS

A flow diagram of treatment assignment for Study 12 is shown in Figure 3. Based on the various treatment groups, overall study completion rates were 66% for subjects who were randomized to the COC for six cycles, 60% for subjects who completed six cycles on the COC and then crossed-over to the patch for Cycles 7-13, and 43% for subjects who were randomized to the patch for 13 cycles.

collected by a separate questionnaire than that used to determine race; Hispanic ethnicity is not included in the 5 racial groups tabulated by Census, and Hispanics may be of any race.

Figure 3 Treatment Allocation in Study 12
Flow Diagram



Source: Applicant response dated January 9, 2013 to Division Information Request

Among reasons for withdrawal of a subject from either study at the investigator's discretion, the Applicant included "first signs of venous inflammation or blood clots," "repeated, excessive and persistent intracyclic bleeding." Other reasons for discontinuation included "non-compliance."

Team Leader Comment:

The specific reasons for study withdrawal noted above are not commonly utilized in contraceptive trials. Women with symptoms suggestive of a VTE are typically worked up and the event confirmed before they are completely withdrawn from the study, although they may discontinue study drug during the evaluation process. While unacceptable bleeding is a common reason women elect to discontinue from a trial, this is not typically a reason for which an investigator would be allowed to discontinue a subject. The definition of non-compliance is not provided, so it is unclear whether this refers to undetectable blood levels, or how extensive the "non-compliance" would have to be to result in study withdrawal.

At the Division's request, the Applicant provided a revised disposition table; in the initial study report, the subgroup of women who crossed-over from COC to patch at Cycle 7 was

included in all three treatment columns. In the present table, these cross-over subjects are still included in both the COC and COC→patch columns (see Table 4), but the columns reflect different cycles of participation. The AG200-15 13-cycle column reflects only those women assigned to the patch from the initiation of the study.

Table 4 Study 12: Disposition of Subjects

Category	COC Cycle 1-6		COC →patch Cycles 7-13		AG200-15 Cycle 1-13	
	N	%	N	%	N	%
Randomized	375	100	249	100	1,129	100
Safety Population	344	91.7	230	92.4	1,043	92.4
Efficacy Population (ITT1)	330	88.0	228	91.6	998	88.4
Cycle Control Population	324	86.4	216	86.7	918	81.3
PK Population	326	86.9	144	57.8	933	82.6
Completed the Study	249	66.4	150	60.2	485	43.0
Reason for Discontinuation:						
Lost to follow-up	61	16.3	37	14.9	229	20.3
Subject's decision	30	8.0	28	11.2	183	16.2
Adverse Events	16*	4.3	16	6.4	123	10.9
Non-compliance	9	2.4	6	2.4	42	3.7
On-treatment pregnancy	4	1.1	8	3.2	34	3.0
Investigator's decision	1	0.3	2	0.8	13	1.2
Protocol violation	4	1.1	0	0	11	1.0
Other	1	0.3	2	0.8	9	0.8

* includes one death

Source: Based on Table 2, Applicant's response dated January 9, 2013 to Division's Information Request

Team Leader Comments:

- It is unclear why the Safety Population, which includes all randomized subjects who took any study drug, is only about 92% of the Randomized Subjects. In typical contraception trials, virtually all randomized subjects take at least one dose of study drug. This may again reflect poor quality control in the enrollment process, in that subjects may have been determined to be ineligible after having been randomized.
- The rate of premature discontinuation was higher in the AG200-15 Cycle 1-13 population, but this reflects, in part, the longer duration of treatment in this cohort.
- I reviewed some other recent hormonal contraceptive NDAs (NDAs 22-252, 22-501 and 22-573) that submitted studies lasting at least 13 cycles and found study completion rates that ranged from 50-78%, loss to follow-up rates of 2-16%, discontinuations due to AEs of 9-15%, subject-determined withdrawal of 2-10% and "other" reasons for discontinuation ranging from 5-8%. Thus, the study completion rate of 43% in the 13-cycle patch arm was well below that typically observed for contraception trials, and discontinuations due to loss to follow-up (20%) and subject's decision (16%) were higher than usually seen. Discontinuations due to "other" were less common, but the Applicant provided more explanatory categories than did other NDAs, which likely resulted in fewer attributed to this non-specific reason.

- The reasons of “subject’s decision” and “other” were explored to find additional information about what led to these discontinuations. The Applicant provided a listing in the appendix of the study report that purportedly provided discontinuation information on all women treated with AG200-15. However, the numbers do not match those for the AG200-15 Cycle 1-13 cohort above, or for the total when the cohort who switched from COC to patch at Cycle 7 is added to the initial users.
- In Study 12, there were 10 listings for AG200-15 subjects who discontinued due to “other” reasons (as opposed to nine or 11 listed in the table above). Of these 10 women, six withdrew because they were found to be pregnant prior to starting the study and four withdrew because they had a suspected pregnancy on-treatment that was not confirmed. For the “subject’s decision” category, only 18 subjects were listed. Of these, two were related to adverse events (including patch-related skin irritation), three to bleeding complaints, two because subjects didn’t like the patch (including problems with adhesion), five due to moves/inconvenient travel to the study site, four due to unspecified “personal reasons” and two were listed only as “consent withdrawn.”
- Of the 183 women who withdrew due to “subject’s decision,” the following reasons were provided in the more detailed listing in the appendix of the study report:
 - Moved/transportation problems – 47
 - Withdrew consent (no further information) – 34
 - Didn’t like the patch – 30 (of these, eight specifically noted problems with patch adhesion)
 - Personal – 29
 - Adverse events – 18 (of these 12 specifically noted application site- or patch-related problems; three also noted bleeding problems in addition to other adverse events)
 - Desired pregnancy – 13
 - Bleeding – 11
 - Not sexually active - 1
- Although the Applicant identifies the “Efficacy Population” as the ITT1 population, the actual population used in the primary efficacy analysis was the ITT2 population, which was considerably smaller. It is not clear why this is. The Applicant sometimes refers to analysis “populations” and other times to “datasets.” However, as defined, the difference in the ITT1 and ITT2 datasets is the inclusion of “all complete or incomplete on-therapy cycles” in ITT1, vs. “all complete or incomplete on-therapy cycles with intercourse and no other birth control methods” in ITT2. The two datasets would be expected to differ on the number of cycles included, but not on the number of subjects, unless there were subjects who had all of their data excluded either because they did not have intercourse or used back-up contraception throughout their participation in the trial.

The disposition of subjects in Study 13 is shown in Table 5.

Table 5 Study 13: Disposition of Subjects

Category	COC Cycle 1-6		AG200-15 Cycle 1-6	
	N	%	N	%
Randomized	206	100	201	100
Safety Population	188	91.3	177	88.1
Efficacy Population (ITT1)	186	90.3	170	84.6
Cycle Control Population	182	88.3	162	80.6
PK Population	147	71.4	117	58.2
Completed the Study	145	70.4	112	55.7
Reason for Discontinuation:				
Lost to follow-up	32	15.5	44	21.9
Subject's decision	13	6.3	21	10.4
Adverse Events	4	1.9	14	7.0
Non-compliance	5	2.4	2	1.0
On-treatment pregnancy	1	0.5	4	2.0
Investigator's decision	1	0.5	1	0.5
Protocol violation	3	1.5	2	1.0
Other	2	1.0	1	0.5

* includes one death

Source: Based on Applicant's Report for Study 13, Table 4, p 56

Team Leader Comments:

- **Again, the Safety Population is only 88-91% of the randomized population, indicating a substantial loss of subjects from randomization to first dose.**
- **In each population subsequent to the Safety Population, there were greater decrements in the AG200-15 arm than in the COC arm.**
- **Discontinuations overall were more common in the AG200-15 arm, with particularly notable discrepancies in discontinuations due to adverse events (7% vs. 2%) and lost to follow-up (22 vs. 16%)**
- **Again, the reasons of "subject's decision" and "other" were explored further. In Study 13, there was no listing for an AG200-15 subject who discontinued due to "other" reasons, despite one being listed in the table above. For the "subject's decision" category, only 18 subjects were listed (rather than the 21 listed in the table). Of these 18, two were related to adverse events (including patch-related skin irritation), three to bleeding complaints, two because subjects didn't like the patch (including problems with adhesion), five due to moves/inconvenient travel to the study site, four due to unspecified "personal reasons" and two were listed only as "consent withdrawn."**
- **Of interest is that among those subjects listed under "subject's decision," one subject discontinued due to skin irritation and one because the patch would not stay on.**
- **Thus, over both studies, an additional 41 subjects (3.3%) discontinued due to relevant complaints such as bleeding (1.4%), patch-related adverse events (1.0%) and adhesion problems (0.9%), but these reasons were obscured by being categorized merely as "subject's decision" to withdraw.**

- A study completion rate of 56% for a six-month trial is unusually low. In NDA 22-261, which was also a six-month US contraceptive trial, the completion rate was 69%. In that study, loss to follow-up was 12% (vs. 22% in Study 13), subject request 5.5% (vs. 10.4%) and adverse event 5.4% (vs. 7%). Investigator-requested withdrawals were <1% in both studies.
- Over both studies, regardless of length, more than 20% of subjects were lost to follow-up. It was also noted in reviewing the “questionable” pregnancies (see Section 7.4.4) that many of these cases were lost to follow-up and therefore did not have the appropriate evaluation and follow-up that would have determined whether or not the woman was indeed pregnant. I believe this is another indicator of the very poor quality of these studies.

7.4 EFFICACY FINDINGS

7.4.1 Application Site

In both studies, the most common site of application was the buttock, followed by the abdomen (see Table 6).

Table 6 Site of Application, Study 12 (Cycles 1-13) and Study 13 (Cycles 1-6)

-----AG200-15 (N=1273)-----			
Cycle	Application Site	Number of Cycles	Number of Patches
Cycles 1-13 combined	Abdomen	4103/10180 (40.3%)	12597/32508 (38.8%)
	Buttock	4825/10180 (47.4%)	15503/32508 (47.7%)
	Upper Torso (Excluding Breasts)	1187/10180 (11.7%)	3842/32508 (11.8%)
	No data	65/10180 (0.6%)	566/32508 (1.7%)
-----AG200-15 (N=177)-----			
Cycle	Application Site	Number of Cycles	Number of Patches
Cycles 1-6 combined	Abdomen	271/829 (32.7%)	860/2668 (32.2%)
	Buttock	422/829 (50.9%)	1367/2668 (51.2%)
	Upper Torso (Excluding Breasts)	129/829 (15.6%)	418/2668 (15.7%)
	No data	7/829 (0.8%)	23/2668 (0.9%)

Source: Applicant's Study Reports for Study 12 and Study 13, Tables 40, p 393 and 27, p 139, respectively

Team Leader Comment:

The Applicant did not evaluate efficacy by site of application, and the data were not provided in a format that would allow the FDA statistician to do these calculations. Given the apparent lower exposure using the abdomen site, this should be explored in the future.

7.4.2 Assessment of Efficacy

Primary Endpoint

For both studies, the primary efficacy endpoint was the Pearl Index based on all on-treatment pregnancies in women aged 17 (18 in Study 13) to 35 years with BMI < 32 kg/m². Evaluable cycles were those in which no methods of back-up contraception were used and in which the subject had intercourse (and any cycle in which a conception occurred was considered evaluable). The prespecified analysis did not exclude laboratory-verified noncompliant subjects; however, the Applicant conducted additional analyses to exclude these subjects (10-14%).

Subjects in Study 12 had study visits at Cycles 2, 4, 6, 9, 13 and 14 days after final dose (End of Study or Early Discontinuation visit), while subjects in Study 13 had visits at Cycle 2, 3, 6 and 14 days after final dose. Serum pregnancy testing was done at each visit (excluding Cycle 2 in Study 12). Urine pregnancy testing was to be done by women who did not experience a scheduled bleed before start of the next treatment cycle.

Subjects recorded use of back-up contraception in the subject diary card, which was provided for each cycle. Subjects were to indicate whether back-up was used for reasons other than missed days of study drug, and whether they had intercourse during the treatment cycle. The diary card was also used to record drug taking, days of patch application and removal, weekly reports of skin irritation and pruritis and daily bleeding information.

Pregnancy cases were to be followed up and information collected about the course and outcome of the pregnancy, including information about the neonate's status.

Team Leader Comments:

- **The primary efficacy endpoint is that used in contraception trials. Appropriate exclusions were made of cycles in which back-up contraception was used. Although other sponsors have not typically excluded cycles in which no intercourse occurred, this was recommended by the medical reviewer during review of the phase 3 protocols, and is also considered appropriate.**
- **The Applicant did not provide summary data about pregnancy/neonatal outcomes. In some cases, the pregnancy narrative discussed the pregnancy outcome (most commonly where the subject had a miscarriage or abortion), and a limited amount of follow-up was presented in the 120-day Safety Update.**

7.4.3 Primary Efficacy Analysis

The primary endpoint was the Pearl Index, calculated as:

$$\text{Pearl Index} = \frac{100 \times \text{number of pregnancies} \times 13 \text{ cycles/year}}{\text{Number of 28-day cycles of treatment}^*}$$

* Only cycles in which subjects had intercourse and used no back-up contraceptive methods were included.

The primary analysis population was based on the Intent to Treat 2 (ITT2) dataset, defined as all cycles in which subjects had intercourse and did not use any back-up contraception. Within the ITT2 dataset, the primary analysis population included women aged 17-35 years with BMI < 32. The ITT1 population consisted of all women and all cycles, regardless of

age, BMI or use of back-up contraception. The number of subjects in each population for Study 12 is shown in Table 7.

Table 7 Study 12 Analysis Populations

Population	AG200-15		OC/AG200-15		AG200-15 Total	
ITT1	998		228		1,226	
ITT2	940	94.2%	218	95.6%	1,158	94.5%
ITT2 with Age 17-35	863	86.5%	197	86.4%	1,060	86.5%
ITT2 with Age 17-35 and BMI < 32 kg/m²	675	67.6%	152	66.7%	827	67.5%
ITT2 with Age 17-35 and BMI < 30 kg/m ²	621	62.2%	146	64.0%	767	62.6%

Bold = primary analysis population

Source: Table 3, Statistical review by Kate Dwyer, Ph.D., dated January 22, 2013

As requested by the Division, the Applicant also provided Pearl Index data in the entire population, with BMI limitation. Finally, the Applicant calculated Pearl Indices in Study 12 for both Cycles 1-6 and Cycles 1-13. The Applicant also calculated pregnancy rates and Pearl Indices for the OC comparators. The Division did not review these cases or calculations, as it does not rely upon comparative efficacy in considering the approvability of a contraceptive product.

In addition to the ITT analysis, the Applicant also conducted a Method Failure analysis that excluded cycles in which subjects missed more than two days of study drug AND the following cycle (in Study 13, subjects who missed more than one day had that cycle and the following cycle excluded). In Study 12, the Applicant also calculated Pearl Indices based on various subsets of the efficacy population, including subsets that excluded all women who had undetectable EE and LNG concentrations at one or more visits during the study; this was added as an amendment to the original protocols. In addition, the Applicant evaluated Pearl Indices by racial/ethnic subgroups and by study site.

Pregnancies conceived on treatment, or within 7 days after last use of the patch, were included in calculation of the Pearl Index. Any conception that occurred in what would otherwise have been a nonevaluable cycle (e.g., due to use of back-up contraception) was also counted.

Team Leader Comment:

Although the Applicant reported that it followed the Division's recommended "7-day window" rule for defining on-treatment pregnancies, in at least one case (Subject (b) (6) in Study 12), the Applicant characterized as post-treatment a conception dated to two days after patch removal.

Life table methods are also commonly used to assess contraceptive efficacy; the Applicant used these to provide cumulative probability of pregnancy at the end of Cycle 6 (for both studies), and at the end of Cycle 13 (for Study 12). Life table methods do not typically exclude individual cycles for a given subject, such as a cycle in which an alternate method of birth control was used, but more commonly censor a subject from the remainder of the trial as soon as she uses back-up contraception, or include all of a woman's cycles without regard to use of back-up contraception. For this reason, these analyses are often not directly comparable to the Pearl Index.

7.4.4 Primary Efficacy Results

Study 12

The Applicant reported a total of 40 on-treatment pregnancies among all women using the patch in Study 12, 30 of which were counted in the ITT2 population. Of the reported pregnancies, six had no outcome information mentioned, seven were lost to follow-up and 27 had some information on pregnancy outcome. Of this latter group, 12 had a healthy infant, one had a premature infant, three had a spontaneous abortion, two had a D&C for a non-viable pregnancy and nine had an elective abortion.

As with any contraception NDA, the clinical reviewers evaluated all potential pregnancies, including those considered by the Applicant to have occurred pre- or post-treatment. However, the Applicant's categorization and description of potential pregnancies was disjointed, inconsistent and often lacked information necessary to make a valid determination of whether a pregnancy should be considered on-treatment. For example, the study report contained the following two tables: Table 16, which listed seven patch subjects with "positive HCG and no Pregnancy Report" and Table 17, which included eight patch subjects with "Form A Pregnancy Report but Deemed not Pregnant." In the pregnancy narrative section, the Applicant reported 12 "not verified" pregnancies (seven of which were in Table 17), four post-treatment pregnancies, seven pre-treatment pregnancies and 40 on-treatment pregnancies.

When the Division reviews potential pregnancies, it typically uses a "worst case" scenario approach, in which cases that are missing the information that would allow for a conclusive determination are considered "on-treatment" pregnancies. This is done because it is known that the pregnancies reported in a trial may be under-estimates; for example, pregnancy status is unknown for subjects lost to follow-up, but it is certainly possible that some subjects who stop communicating with a study site have become pregnant.

Table 8 outlines all 31 possible pregnancies (i.e., 15 subjects listed in Tables 16 and 17, five subjects from "not verified narratives" who were not included in Table 17, and 11 subjects reported to have pre- or post-treatment pregnancies) reported by the Applicant that were not counted by the Applicant as on-treatment pregnancies.

Table 8 Applicant's vs. Division's Classification of Potential Pregnancies

Subject ID	Listed in NDA	Applicant's Classification	FDA Classification	Comments
Study 12				
(b) (6)	Table 16	False positive	Indeterminate	Would count under strict "worst case"
	Pre-tx narratives	Pre-tx	Pre-tx	Subject LTFU
	Post-tx narratives	Post-tx	On-tx	See Table 9 Subject was discontinued
	Table 17 and "not verified" narratives	Not pregnant	On-tx	See Table 9 Subject was discontinued
	"Not verified" narratives	Not verified, pre-tx vs. not pregnant	Likely pre-tx	
	Pre-tx narratives	Pre-tx	Pre-tx	Subject LTFU
	Table 16	Pre-tx	Pre-tx	Discontinued prior to patch application
	"Not verified" narratives	Not verified	Indeterminate	Would count under strict "worst case" Subject was discontinued for "suspicion of pregnancy not confirmed"
	Table 17 and "not verified" narratives	Not verified	On-tx	See Table 9 Subject LTFU
	Table 16	False positive	Indeterminate	Would count under strict "worst case"
	Pre-tx narratives	Pre-tx	On-tx	See Table 9 Subject LTFU
	Table 17 and "not verified" narratives	Not verified	On-tx	See Table 9
	Pre-tx narratives	Pre-tx	Pre-tx	Pregnancy dated to one day before patch started Delivered health infant
	Table 17 and "not verified" narratives	Not verified	Likely not pregnant	Subject was discontinued due to noncompliance
	Table 16	False positive	False positive	Serum HCG of 21 followed by negative urine pregnancy test
	Post-tx narratives	Post-tx	On-tx	See Table 9 Subject LTFU
	Pre-tx narratives	Pre-tx	Pre-tx	Subject LTFU
	Post-tx narratives	Post-tx	Post-tx	Subject LTFU
	Table 17	Not verified	Indeterminate	Would count under strict "worst case"
	Table 17 and "not verified" narratives	Not verified	Indeterminate	Would count under strict "worst case" Subject reported a positive pregnancy test then LTFU
	"Not verified" narratives	Not verified	On-tx	See Table 9 Subject was discontinued
	Table 17 and "not verified" narratives	Not verified, then false positive	Indeterminate	Would count under strict "worst case"
	Pre-tx narratives	Pre-tx	Pre-tx	Spontaneous abortion

Subject ID	Listed in NDA	Applicant's Classification	FDA Classification	Comments
(b) (6)	Table 16	False positive	False positive	Ingested HCG drops
	Table 16	False positive	Indeterminate	Would count under strict "worst case"
	"Not verified" narratives	Not verified	False positive	Ingested HCG drops
	Pre-tx narratives	Pre-tx	Pre-tx	Spontaneous abortion
	"Not verified" narratives	Not verified	Likely post-tx	Subject was discontinued due to noncompliance
	Table 16	False positive	Indeterminate	Would count under strict "worst case"
	Table 17 and "not verified" narratives	Not verified	Indeterminate	Would count under strict "worst case" Subject LTFU
	Post-tx narratives	Post-tx	On-tx	See Table 9 Subject LTFU

LTFU = lost to follow-up

Team Leader Comments:

- As shown in Table 8, the rate of agreement between the Applicant and the Division was low. Overall, of the 31 cases not counted by the Applicant, the Division considered eight (26%) to have been on-treatment cases. In most of these cases, the evidence was not completely definitive, but information like HCG level was strongly suggestive that the conception occurred on-treatment.
- In addition, there were another nine cases (29%) that the Division did not include in its calculation of the Pearl Index, but that would have been included under a strict "worst case" evaluation. These were cases in which the data about last patch use or pregnancy dating information were so inadequate that no determination could be made as to whether or not they should be considered on-treatment. On the one hand, it does not seem appropriate to write them off due to inadequate data collection and documentation by the Applicant. On the other hand, inclusion of these additional pregnancies would not tip the Pearl Index from an acceptable to an unacceptable value; even without these pregnancies counted, the data from the two trials demonstrate an unacceptable level of contraceptive efficacy.
- This is an extremely high number of potential on-treatment pregnancies, and an unusually high level of discrepancy between Applicant's and the Division's assessments. In only 14 of the 31 cases (45%) did the Division agree with the Applicant's conclusion that the potential pregnancy should not be considered on-treatment.
- An additional notable feature of the pregnancy data is the large number of potential pregnancies in which the subject was lost to follow-up or discontinued from the trial; these are both scenarios in which the usual appropriate follow-up to determine the gestational age of the fetus and calculate the estimated conception date was not obtained. Seventeen of the 31 cases noted above (including seven of the eight additional cases the Division counted as on-treatment) were either lost to follow-up or discontinued by the investigator. I have not observed this magnitude of inadequate follow-up in a previous contraception trial.

Of the seven cases with positive HCG levels reported in Applicant Table 16, the Applicant declared six cases as "false positives;" these women had one or more HCG levels < 100 mU/ml, but > 5 mU/ml, which is commonly used to define non-pregnant levels. The majority of these women had no further work-up, although in some cases a "normal" pelvic exam was reported. With levels this low, it is unlikely that ultrasound would be useful.

Team Leader Comments:

- The finding of six “false positive” pregnancy tests is highly unusual in a contraceptive trial. In cases of a potential false positive serum pregnancy test, administration of a urine pregnancy test will often resolve the question; the urine test is not subject to the same cross-reactivity, and will be negative in women who are truly not pregnant. It does not appear that this was done for five of the six “false positive” subjects in the trial. Although the inadequate work-up and follow-up of these cases precludes a clear decision as to whether or not they should be considered on-treatment pregnancies, in view of the high Pearl Index, my index of suspicion is high. At a minimum, these cases exemplify poor study conduct.
- Four of these women had a repeat HCG drawn within days to a month, which was lower or negative, and “normal withdrawal bleeding” was reported in all. While the clinical pictures could indeed represent a false positive pregnancy test, they could also characterize a very early, nonviable conception, or a “chemical pregnancy.” Although the Division did not count any of these as on-treatment pregnancies, in four cases ((b) (6)), there is insufficient information to be sure that these were not on-treatment conceptions, and they would have been counted under a strict “worst case” analysis.
- One of the “false positives” ((b) (6)) reportedly used HCG drops for weight loss beginning 2-3 weeks before her positive HCG. I agree that she is likely to represent a false positive.
- Another woman listed on Table 16 ((b) (6)) was further described in a response to an Information Request from the Division. She had a low HCG (21 mU/ml) 14 days after last patch use and two negative urine pregnancy tests 4 and 7 days later. I agree that she is likely to represent a false positive.
- The final woman on Table 16 ((b) (6)) was listed as a pre-treatment pregnancy, but did not appear in the pre-treatment narratives, likely because she discontinued prior to using the patch. I agree that she was a pre-treatment pregnancy.
- Overall, then, the Division agreed on three cases from Table 16; one pre-treatment pregnancy and two false-positives. The four remaining cases may have represented on-treatment pregnancies.

Of the eight cases reported in Applicant Table 17, the Division considered three cases to be on-treatment pregnancies (see Table 9), four (Subjects (b) (6)) had insufficient information to determine and were not counted by the Division, and the Division agrees that the remaining case ((b) (6)) does not appear to be an on-treatment pregnancy. The four subjects with insufficient information would be counted under a strict “worst case” classification.

Team Leader Comments:

- Subject (b) (6) stopped using the patch on 7/11/11, stating that she’d had a positive pregnancy test. HCG and ultrasound done by site on 7/20/11 were both negative and pelvic exam on 7/26/11 was normal. It does not appear that this subject was pregnant.
- Subject (b) (6) was randomized on 8/17/10, but never returned diary cards and was lost to follow-up with no information on whether/when she had started patch use. She called the site on 9/21/10 to report a positive pregnancy test at the end of August, but did not return for further evaluation.
- Subject (b) (6) used her last known patch on 12/28/10; she was dispensed more patches at that visit but did not provide further data. She had drug levels below LLOQ on 11/1/10. The subject called and reported a positive home pregnancy test on 2/28/11 but failed to return for follow-up and no HCG or ultrasound results were available.

- **Subject (b) (6) (who is discussed further in Section 8.1) used her last patch on 3/28/11, and had an HCG of 912 mU/ml on (b) (6), but a “bedside ultrasound” done in the emergency room on (b) (6) reportedly showed no intrauterine pregnancy. This ultrasound was done during her admission for compartment syndrome that resulted in bilateral above-the-knee amputations. There was no further discussion of possible pregnancy in her narrative; she is discussed further in Dr. Davis’ review in the section on SAEs.**
Upon request from the Division, the Applicant provided the emergency room notes and a copy of an inpatient ultrasound report dated (b) (6). The emergency room notes state “threatened miscarriage” under Impression. The “history” section of the (b) (6) ultrasound report states “pregnant and heavy bleeding.” The Impression is “Prominent free pelvic fluid. Involuting left ovarian cyst. No intrauterine pregnancy.” The Comment notes “No intrauterine fetus is seen... Prominent free fluid is noted throughout the pelvis. Correlate with the patient’s beta-hCG levels and clinical exam.” No further HCG values were provided; it is unclear whether her pregnancy status received further attention given the deterioration of her condition relative to her lower extremities.
- **Subject (b) (6) had unknown date of last patch use, but had patches dispensed on 12/10/10. The Pregnancy Follow-up Form states that she had an 8-week pregnancy terminated on 2/18/11, which would suggest a conception date of 1/7/11. If she used her patch beginning on 12/11/10, the conception date would fall within the seven-day conception window.**

Of the five “not verified” pregnancies included in the narratives but not already discussed in Applicant Table 17, the Division considered one (b) (6) to be a likely pre-treatment pregnancy, and one (b) (6) to be a likely post-treatment pregnancy. Another case was counted as on-treatment (see Table 9) and one (b) (6) was considered an indeterminate case that would have been counted under a strict “worst case” approach. The remaining case (b) (6) was noted to have “admitted to use of HCG diet.” It is unclear why she was not also reported on Table 16 as a false positive, like Subject (b) (6), who also used HCG drops, but the Division agreed that this likely was a false positive result.

Team Leader Comment:

In addition to those pregnancies identified by Dr. Davis, I would also include Subject (b) (6) as an on-treatment pregnancy. This subject used her last patch on 11/6/10, which was Week 1, Day 4 of her fourth cycle. She had an HCG of 163 on 11/10/10, and does not appear to have further follow-up until 12/10/10, at which time she had a negative HCG and an ultrasound. The pregnancy narrative reports ultrasound results of “no evidence of IUP. ?spontaneous abortion; ?ectopic pregnancy.” Thus, it appears that she had an early pregnancy conceived during patch use, and that the pregnancy was lost by the next evaluation one month later.

However, because the review decision would not be changed by the addition of one more pregnancy, I did not request a recalculation of the Pearl Index to include this subject.

Of the four post-treatment pregnancies, the Division considered three to have been on-treatment (see Table 9). The fourth, Subject (b) (6), had no data on patch use from Cycle 2 (beginning about 10/11/10) on, but she had a positive HCG and an ultrasound that documented a conception date of 12/4/10. It is unclear when she actually stopped using the patch but she had drug levels above the lower limit of quantitation (LLOQ) on 10/19/10. Because there was insufficient information to conclude that the conception occurred while she was using the patch, the Division did not count this.

Of the seven pre-treatment pregnancies, the Division considered one to have occurred on-treatment (Subject (b) (6)), and agreed that the remaining six cases were pre-treatment conceptions.

Of the 12 pre- and post-treatment pregnancies reported by the Applicant (this number exceeds the number of narratives by one because one pre-treatment pregnancy was reported in Table 16 only), outcome information was available on only three. Of the remaining nine cases, seven subjects were lost to follow-up and two were discontinued with no follow-up information provided.

As discussed in the comments above, following careful review of the data, subject narratives and case report forms (CRFs), the Division identified another eight pregnancies it considered to be on-treatment, five of these in the ITT2 population. Some of these are cases in which complete information was not available, but the Division made a “worst case” determination to call the pregnancy on-treatment. In other cases, it is not clear why the Applicant failed to identify it as an on-treatment pregnancy. Details of these additional pregnancies considered on-treatment by the Division are shown in Table 9.

Team Leader Comments:

- **As mentioned for several cases above, there were a number of instances noted in the pregnancy narratives in which the diary cards used to document dates of drug use were not returned to the site by the subject. It is unclear how prevalent this was in the total study population, but it certainly was a contributing factor in the high number of “potential” pregnancies for which it could not be definitively determined whether conception occurred on-treatment.**
- **Including the additional on-treatment pregnancies identified by the clinical reviewer, there were 48 on-treatment pregnancies in patch subjects in Study 12. Nineteen of these (40%) occurred in five sites. A single site (Dr. Hazen’s Site #033) accounted for eight pregnancies among 69 subjects. The other 11 pregnancies occurred at sites that enrolled < 40 subjects and each had only 2-3 pregnancies among patch subjects.**

Table 9 Study 12: Details of Pregnancies Added by FDA, AG200-15 Arm

Subject ID	Applicant's Designation	Last patch	Conception Date	Basis for diagnosis/dating; other comments
(b) (6)	Post-treatment pregnancy	6/28/11	Not reported	HCG of 251 on 7/1/11 with pregnancy confirmed by ultrasound on 7/7/11, immediately prior to medical abortion. Per the investigator, and according to Dr. Davis' consideration of the HCG level and ultrasound, conception likely occurred between 6/9-6/17, on-treatment. Subject was discontinued due to adverse events and non-compliance.
	Not verified/ Deemed not pregnant	5/12/11	Not reported	Negative HCG on 5/13/11 study visit; 6/23/11 HCG of 9,191 with sono showing gestational sac but no pregnancy. Based on HCG level, this represents a conception date likely to be within 5/18-6/1; thus, within 7 day window and considered on-treatment under worst case scenario. Subject was discontinued due to adverse events.
	Not verified/ Deemed not pregnant	1/20/11	Not reported	CRF states no positive pregnancy tests, but narrative reports the following HCG levels: 1/13/11 – 44, 1/21/11 – 11, 1/28/11 – 0. Pregnancy Follow-up Form states “pregnancy ended in early spontaneous abortion;” narrative states “no confirmation subject was pregnant.” No record of ultrasound. Based on positive HCG results prior to last patch use, considered on-treatment. Subject lost to follow-up.
	Pre-treatment pregnancy	10/9/10	9/20/10	First patch applied 8/21/10. HCG of 20,454 on 10/15/10, no ultrasound or pelvic exam. This HCG level is consistent with a gestation of ≥ 4 weeks. Investigator and Dr. Davis believe conception date is 9/20/10, or on-treatment. Subject lost to follow-up.
	Not verified/ Deemed not pregnant	7/14/11	Not reported	No CRF submitted; Pregnancy Follow-up Form has lab reports of HCG as follows: 7/27/11 – 2,118, 7/29/11 – 1,415. Narrative reports HCG as follows: 8/16/11 – 140 and 132, no record of ultrasound. Based on HCG results, conception likely to be within 6/29-7/13; thus, considered on-treatment.
	Post-treatment pregnancy	9/17/11 (Day 18 of cycle)	Not reported	HCG of 68 on 10/6/11; no ultrasound or follow-up. Based on HCG, conception likely from 9/22-9/29, or within 7 day window; therefore considered on-treatment. Subject lost to follow-up.
	Not verified	6/23/11	Not reported	HCG of 5,567 on 6/23/11, ultrasound showed 9 x 6 cm hyperechoic focus in lower uterine segment and site discontinued her as a “suspected but unconfirmed pregnancy.”
	Not verified/ Deemed not pregnant	8/14/11	Not reported	HCG of 236 on 9/1/11, with pelvic exam reported as “pregnant uterus.” Ultrasound on 9/13/11 showed probable miscarriage and HCG dropped to 7. Based on initial HCG, conception likely occurred 8/11-8/25, or on-treatment. Subject lost to follow-up.

* Pregnancy NOT included in ITT2 Pearl Index calculation because BMI was > 32

Team Leader Comment:

There were several cases in which it seems very clear that the subject had an on-treatment pregnancy, including at least one case (b) (6) in which the investigator made this determination. The Applicant did not provide an explanation for why these women were not counted as on-treatment pregnancies.

Study 13

In Study 13, the Applicant reported four on-treatment pregnancies, and the Division did not identify any additional pregnancies that clearly occurred on-treatment. The Applicant reported that Subject (b) (6) was lost to follow-up after randomization, but returned to the clinic for a pregnancy ultrasound. The Applicant did not count this as an on-treatment pregnancy.

Team Leader Comment:

Again, although the Division also did not count this pregnancy, due to inadequate information, it is at least possible that this could be an on-treatment pregnancy. The subject was given six patches at the randomization visit on 11/10/10. If she initiated use on that data and used them as directed, she would have used the last patch on 12/29/10. Based on an ultrasound she requested when she returned to the Planned Parenthood clinic on 3/24/11, she was 13 6/7 weeks pregnant, which gave an estimated conception date of 12/30/10, within the seven-day window the Division uses for on-treatment pregnancies. In response to an Information Request from the Division, the Applicant provided the Pregnancy Follow-up Form A for this subject, which documents that her last patch use was on 1/6/11. The basis for citing this date is unknown, but this case demonstrates the multiple inconsistencies found in reviewing the data in this NDA.

Pearl Index

The statistical reviewer, Kate Dwyer, Ph.D., focused her review on the data from Study 12, the major study intended to evaluate efficacy of AG200-15, and she did not calculate Pearl Indices for the COC comparator. Her calculations, which include the additional pregnancies identified by the clinical reviewers, are shown in Table 10, along with the original Applicant calculations.

Table 10 Pearl Index Calculation, Cycles 1-13, Study 12, ITT2 Population

	Population	N	# of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Sponsor	Age 17-35 years	1,060	38	7,685	6.43	(4.39, 8.47)
	Age 17-35 with BMI < 32 kg/m²	827	30	6,070	6.43	(4.13, 8.27)
	Age 17-35 with BMI < 30 kg/m ²	767	27	5,645	6.22	(3.88, 8.56)
	All Subjects	1,158	40	8,446	6.16	(4.25, 8.06)
Reviewer	Age 17-35 years	1,060	45	7,685	7.61	(5.39, 9.83)
	Age 17-35 with BMI < 32 kg/m²	827	35	6,070	7.50	(5.02, 9.97)
	Age 17-35 with BMI < 30 kg/m ²	767	32	5,645	7.37	(4.82, 9.92)
	All Subjects	1,158	48	8,446	7.39	(5.30, 9.47)

Bold = primary efficacy analysis

Source: Table 4, Statistical review by Kate Dwyer, Ph.D., dated January 22, 2013

Because the subjects who switched from the OC comparator to the patch at Cycle 7 may not be comparable to patch users in Cycle 1-6, Dr. Dwyer also calculated Pearl Indices excluding these switchers (see Table 11).

Table 11 Sensitivity Analysis of Pearl Index, Cycles 1-13, Study 12, ITT2 Population, Exclusive of Switchers

	Population	N	# of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Using Sponsor Reported Pregnancies	Age 17-35 years	863	32	6,673	6.23	(4.08, 8.39)
	Age 17-35 with BMI < 32 kg/m²	675	25	5,278	6.16	(3.75, 8.57)
	Age 17-35 with BMI < 30 kg/m ²	621	22	4,885	5.85	(3.41, 8.30)
	All Subjects	940	33	7,320	5.86	(3.87, 7.86)
Using Agency Identified Pregnancies	Age 17-35 years	863	37	6,673	7.21	(4.89, 9.52)
	Age 17-35 with BMI < 32 kg/m²	675	29	5,278	7.14	(4.55, 9.74)
	Age 17-35 with BMI < 30 kg/m ²	621	26	4,885	6.92	(4.27, 9.57)
	All Subjects	940	39	7,320	6.93	(4.76, 9.09)

Bold = primary efficacy analysis

Source: Table 5, Statistical review by Kate Dwyer, Ph.D., dated January 22, 2013

Team Leader Comments:

- In Study 12, there is a slight increase in Pearl Index as the analysis population is expanded to include heavier subjects, but 95% confidence intervals for all estimates overlap, precluding any definitive statement about an impact of BMI on efficacy.
- It is of interest to note in the Applicant's analysis (data not shown) that the Pearl Index for Cycles 1-13 in Study 12 (6.43) is higher than that in Cycles 1-6 (5.41). Typically, shorter contraceptive trials provide higher Pearl Index estimates, because women with higher fertility or more difficulty complying with the dose regimen tend to conceive earlier in a trial and drop out; as the trial progresses, the population becomes enriched with less fertile and more compliant subjects, who contribute fewer pregnancies. The inclusion of experienced "switchers" who crossed-over to use the patch in Cycle 7 may have some impact on this (their patch data would be counted under Cycles 1-6, even though their use began in Cycle 7). However, exclusion of these "switchers" as shown in Table 11 would then be expected to result in higher Pearl Indices; in fact, the Pearl Indices drop when COC→patch users are excluded, for reasons that are not clear.

Finally, because contraception trials have not typically excluded cycles in which no intercourse occurred, Dr. Dwyer did a sensitivity analysis that included cycles with no intercourse in the denominator of evaluable cycles. For Study 12, this provided about 700 more cycles (for a total of 6,763) and a Pearl Index of 6.73 with an upper bound of 9.35.

Team Leader Comments:

- It does not appear that the high Pearl Index for AG200-15 is due to exclusion of these cycles.
- However it is surprising that subjects did not have intercourse in up to 10% of cycles; this suggests that the usual entry criterion of "sexually active" women was not strictly met in this population.

Dr. Dwyer also looked at efficacy in subgroups by race (see Table 12). Age and region were not explored because the study only enrolled reproductive-aged women and was conducted in the US only.

Table 12 Pearl Index by Race, Study 12, ITT2 Population

	Population	N	# of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Sponsor	White (not Hispanic)	512	12	3,749	4.16	(1.81, 6.51)
	White (Hispanic)	124	7	924	9.85	(2.58, 17.12)
	Black	137	8	960	10.83	(3.36, 18.31)
	Other	54	3	437	8.92	(0.00, 18.99)
Reviewer	White (not Hispanic)	512	13	3,749	4.51	(2.06, 6.95)
	White (Hispanic)	124	8	924	11.26	(3.49, 19.02)
	Black	137	11	960	14.90	(6.14, 23.65)
	Other	54	3	437	8.92	(0.00, 18.99)

Source: Table 7, Statistical review by Kate Dwyer, Ph.D., dated January 22, 2013

Team Leader Comment:

Although there appear to be some racial disparities in Pearl Indices, the 95% confidence intervals are very wide. Only for Whites does the upper bound exclude the point estimates for the other racial/ethnic subgroups, and only for Blacks does the lower bound exclude the point estimate for White women. A larger study, specifically powered to evaluate racial/ethnic differences would be needed to make any definitive statements about any impact of race/ethnicity on efficacy.

The Applicant's Pearl Index calculation for Study 13 is shown in Table 13; because the Division did not identify additional pregnancies, the FDA statistician did not recalculate the data.

Table 13 Pearl Index Calculation, Cycles 1-6, Study 13, ITT2 Population

Variable	Statistic	OC N=179	AG200-15 N=158
ITT2	Number of subjects	163	147
Age 18-35 years	Number of cycles	765	635
	Number of on-therapy pregnancies	4	4
	Pearl Index	6.80	8.19
	95% CI	(0.15, 13.44)	(0.19, 16.19)

Source: Report for Study 13, Table 10, page 65

Team Leader Comment:

Over both studies, the Pearl Indices of 7.50 (95% upper bound of 9.97) and 8.19 (16.19) for the AG200-15 patch are well above that demonstrated for any approved combined hormonal contraceptive. An acceptable level of efficacy has not been demonstrated in either trial.

Life Table Analysis

The Applicant also provided Life Table analyses estimates of the pregnancy rate and Dr. Dwyer recalculated these including the additional Division-identified pregnancies. As typically observed, the life table estimates are slightly lower than Pearl Index results, but continue to show a high pregnancy rate over 13 cycles in Study 12 (see Table 14).

Table 14 Life Table Analysis of Pregnancy Rates, Study 12, ITT2 Population

		Number of On-Treatment Pregnancies	Cumulative Pregnancy Rate	95% Confidence Interval
Sponsor	Cycles 1-6	12	2.54	(1.05, 4.03)
	Cycles 1-13	25	6.12	(3.37, 8.88)
Reviewer	Cycles 1-6	12	2.54	(1.05, 4.03)
	Cycles 1-13	29	7.30	(4.31, 10.29)

Source: Table 6, Statistical review by Kate Dwyer, Ph.D., dated January 22, 2013

Statistician's Conclusion

Dr. Dwyer did not identify any statistical issues in the application, but did include in her analyses the additional pregnancies identified by the clinical reviewer. She made the following conclusions and recommendations regarding contraceptive efficacy in her review dated January 22, 2013:

There were no statistical issues with this submission. However, the Clinical Reviewer identified eight additional pregnancies in study ATI-CL12. Therefore, these additional pregnancies were included in the efficacy evaluation.

Efficacy was evaluated by the pregnancy rate based on the Pearl Index in women aged 17 to 35 years with a BMI <32 kg/m² and excluding cycles with no intercourse and where other birth control methods are used. In study ATI-CL12, the Pearl Index for the AG200-15 patch was 7.50% (95% Confidence Interval: 5.02% to 9.97%). Although the Applicant amended the datasets to exclude laboratory verified non-compliant subjects, these datasets were not pre-specified in the statistical analysis plan and conclusions cannot be based on these post-hoc datasets.

From a statistical perspective, the Applicant reported efficacy results based on pre-specified endpoint and statistical methods. Both the Pearl Index and life table method consistently showed much higher pregnancy rate in this population than seen in support of other contraceptives. However, the use of AG200-15 in the prevention of pregnancy with large Pearl Index is the clinical Division's decision.

7.4.5 Secondary Efficacy Analysis - Bleeding Profile

Characterization of the bleeding profile was a secondary efficacy endpoint. Subjects completed a diary card for each cycle that recorded occurrence and intensity of bleeding or spotting. Spotting was defined as any bloody discharge that required only panty liners; bleeding was defined as any bloody discharge requiring use of at least one tampon/sanitary napkin per day. There were no definitions provided to distinguish intensity of bleeding, although women were asked to indicate "None, Spotting, Light, Normal or Heavy" for each

cycle day. The Applicant considered any bleeding during Days 22-28 to be scheduled (or withdrawal) bleeding; bleeding during Days 1-21 was considered unscheduled.

The Applicant defined the cycle control population as all subjects who took study drug and provided diary cards with relevant bleeding and drug-taking information; however, it defined the incidence of unscheduled bleeding/spotting episodes in subjects with BMI < 32 as the primary endpoint for the cycle control analysis. Cycles were excluded from the analysis if they had missing bleeding information or had no drug-free interval.

Although the Division had requested that the Applicant provide data according to standard recommendations (see Section 2.2) that use 28-day cycles as the reference period, in the study report, the Applicant reported bleeding data by 84-day reference periods, each consisting of three treatment cycles. However, the Applicant also provided the bleeding data based on 28-day cycles.

Team Leader Comments:

- The Division had informed the Applicant prior to NDA submission that it did not concur with presenting bleeding data only for particular cycles.
- The Division also did not explicitly agree with the limitation of the cycle control analysis to women with BMI < 32.

Table 15 and Table 16 present unscheduled bleeding and spotting data from Study 12 by 28-day cycles for all subjects, not merely women with BMI < 32. For clarity, data by cycle is presented for only the cohort of AG200-15 users who were assigned to the patch for the full study duration; women who switched from COC to the patch at Cycle 7 are not included here.

Table 15 Study 12: Unscheduled Bleeding Days per 28-Day Cycle

	AG200-15 N=918			COC N=324		
Cycle	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
1	830	0.67 (1.6)	0 (0, 11)	298	0.44 (1.4)	0 (0, 8)
2	730	0.78 (1.9)	0 (0, 13)	269	0.65 (1.9)	0 (0, 14)
3	731	0.70 (1.8)	0 (0, 12)	271	0.62 (1.6)	0 (0, 9)
4	663	0.36 (1.2)	0 (0, 8)	248	0.59 (1.6)	0 (0, 11)
5	653	0.43 (1.3)	0 (0, 10)	247	0.48 (1.4)	0 (0, 11)
6	614	0.48 (1.4)	0 (0, 8)	90	0.47 (1.3)	0 (0, 6)
7	590	0.45 (1.5)	0 (0, 15)	--	--	--
8	568	0.32 (1.1)	0 (0, 7)	--	--	--
9	494	0.36 (1.4)	0 (0, 9)	--	--	--
10	490	0.35 (1.2)	0 (0, 8)	--	--	--
11	471	0.37 (1.2)	0 (0, 8)	--	--	--
12	460	0.41 (1.4)	0 (0, 10)	--	--	--
13	438	0.46 (1.4)	0 (0, 7)	--	--	--

Source: Study Report for Study 12, Table 14.2_3.6.2

Table 16 Study 12: Unscheduled Spotting Days per 28-Day Cycle

	AG200-15 N=918			COC N=324		
Cycle	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
1	830	0.84 (1.5)	0 (0, 9)	298	0.72 (1.7)	0 (0, 11)
2	730	0.65 (1.4)	0 (0, 12)	269	0.58 (1.5)	0 (0, 12)
3	731	0.60 (1.4)	0 (0, 14)	271	0.45 (1.1)	0 (0, 7)
4	663	0.47 (1.2)	0 (0, 9)	248	0.48 (1.4)	0 (0, 12)
5	653	0.56 (1.3)	0 (0, 9)	247	0.51 (1.3)	0 (0, 11)
6	614	0.54 (1.3)	0 (0, 9)	90	0.61 (1.3)	0 (0, 7)
7	590	0.48 (1.3)	0 (0, 10)	--	--	--
8	568	0.49 (1.3)	0 (0, 10)	--	--	--
9	494	0.57 (1.3)	0 (0, 9)	--	--	--
10	490	0.48 (1.3)	0 (0, 15)	--	--	--
11	471	0.46 (1.1)	0 (0, 7)	--	--	--
12	460	0.51 (1.5)	0 (0, 18)	--	--	--
13	438	0.54 (1.3)	0 (0, 10)	--	--	--

Source: Study Report for Study 12, Table 14.2_3.7.2

Team Leader Comments:

- The high rate of treatment discontinuations in the patch arm in the first three cycles is evident, particularly in Cycle 1. By Cycle 4, only 72% of the original patch subjects remained in the study. The rate was only slightly better (77%) in the COC arm.
- Although subjects on the patch initially had more unscheduled bleeding and spotting, by Cycle 4, they had equivalent or slightly lower amounts of bleeding and spotting. It is uncertain whether this was due in part to early withdrawal of women who were dissatisfied with the bleeding profile.
- By about Cycle 4, the rate of unscheduled bleeding and spotting combined (data not shown) decreased to about one day per cycle, and remained there until the conclusion of the treatment cycles in both arms.

7.4.6 Other Efficacy Data

PK Findings and Compliance

In Study 12, plasma concentrations of EE and LNG were assessed at Cycles 2, 6 and 13. Levels below the LLOQ (< 50 pg/mL for LNG and < 2.0 pg/mL for EE) were defined as zero levels and were considered indicative of non-compliance. EE levels defined as non-compliance were detected in 12% of COC subjects at Cycle 2 and 14% at Cycle 6, and in 12%, 14% and 14% of patch subjects at Cycles 2, 6 and 13, respectively. For LNG, levels indicating noncompliance were detected in 9% and 13% of COC subjects and in 11%, 12% and 13% of patch subjects at Cycles 2, 6 and 13, respectively. Overall, about 15% of COC subjects and 18% of patch subjects had zero levels for both hormones at one or more visits.

In Study 13, these parameters were assessed at Cycles 3 and 6. EE levels defined as non-compliance were detected in 12% of COC subjects at both cycles, and in 10% and 7% of patch subjects at Cycles 3 and 6, respectively. For LNG, levels indicating noncompliance were detected in 11% and 13% of COC subjects and in 9% and 5% of patch subjects at Cycles 3 and 6, respectively. Overall, about 14% of COC subjects and 9% of patch subjects had zero levels for both hormones at one or both visits.

Team Leader Comments:

- The Applicant's reported overall rates of zero drug levels for both EE and LNG at any visit exceed the highest rate of zero levels for either hormone at any visit. This appears to be due to the fact that not all subjects were sampled at each of the three cycles; when calculating the rate of zero hormone levels at any visit, the number of subjects with zero levels and the number of subjects evaluated are both higher than the numbers in any single cycle.
- The utility of these measures for evaluating compliance is limited, as the results represent only a snapshot of a few days' drug use at two cycles over the trials. In the case of AG200-15, as a weekly patch, the clinical pharmacology reviewer indicated that, based on usual concentrations after 24-48 hours of patch wear and the half-lives of LNG and EE, levels <LLOQ likely suggest that the subject has not worn the patch for at least three days prior to the blood draw.

Patch Adhesion and Tolerability

Adhesion was assessed by site personnel at each study visit, on a 0-4 scale (0 for $\geq 90\%$ adherence, 4 for complete detachment). Over all evaluations, based on the subject's worst score in an individual cycle, results are shown in Table 17. Site of application did not influence the adhesion scores.

Table 17 Summary of Patch Adhesion Scores, All Visits

Patch Adhesion Score (n, %)	Study 12 N=1,273	Study 13 N=177
0 ($\geq 90\%$ adherence, no lift)	942 (83%)	126 (79%)
1 ($\geq 75\%$ adherence but < 90%, some edges showing lift)	142 (13%)	19 (12%)
2 ($\geq 50\%$ adherence but < 75%, half of the system lifts off)	6 (0.5%)	1 (0.6%)
3 (< 50% adherence, > half of the system lifts off, but not detached)	5 (0.4%)	0
4 (complete detachment)	41 (3.6%)	13 (8%)

Source: Study Report for Study 12, Table 41, p 395 and Study Report for Study 13, Table 28, p 140

Team Leader Comment:

For Study 13 and part of Study 12, the eCRF was designed in a manner in which investigators had to record a 4 if a subject presented to the visit without a patch (even if this was during her drug-free week). Thus, these may represent over-estimates of the rates of detachment. However, the fact that almost 1% of subjects discontinued prematurely (as discussed in Section 7.3) due to dissatisfaction with patch adhesion is concerning, and suggests that the adhesive properties of this patch may not be optimal.

7.4.7 Overall Assessment of Efficacy

The primary phase 3 Study 12, along with the supportive Study 13, does not demonstrate an acceptable Pearl Index to warrant approval for prevention of pregnancy. The Pearl Index and upper bound of the 95% confidence interval (7.50, 9.97 for Study 12 and 8.19, 16.19 for Study 13) are well in excess of those for any combined hormonal contraceptive ever approved by the Division. In addition, there were at least nine pregnancies (eight in Study 12, one in Study 13) in which the conception might plausibly have occurred on-treatment, but in which there was insufficient documentation of whether or not the subject was using the drug at the time of conception. There are also at least six cases in which the Applicant

concluded that a positive, but low level, HCG result represented a false positive. It is very unusual to see this number of questionable cases in a contraceptive trial. The Division typically uses a “worst case” scenario and counts ambiguous cases as on-treatment. We did not do so in all of these cases because there was too much missing data to make a plausible conjecture as to whether or not the conceptions occurred on-treatment, and because, even absent these additional possible pregnancies, the Pearl Indices are unacceptably high. However, the existence of this number of problematic cases illustrates the extremely poor quality of subject follow-up and data collection in this study.

The Applicant was alerted prior to the filing date that the Division was concerned about the high Pearl Index and responded on July 10, 2012 with its explanation that the trial subjects were “more representative of US women using hormonal contraception than those enrolled in earlier hormonal contraceptive trials.” According to the Applicant, relevant features of the trials included:

- No BMI restrictions
- High representation of new users (nearly 60%)
- Better minority representation (50% minorities) [note earlier trials are < 20%]
- Approved active comparator
- US-based study population

The Applicant’s assertion that the high Pearl Index is reflective of a broadly representative population does not provide appropriate justification for these results. While the Applicant did enroll Study 12 without regard to BMI, the efficacy population was restricted to women with BMI < 32 (and in Study 12, 72% of the women had BMI < 30), which resulted in an efficacy population very similar to (or even more restrictive than) that of most recent contraceptive trials. For example, NDA 22-501, a very low estrogen dose COC approved in 2010, indicates in its labeling that women with BMI > 35 were excluded (i.e., the efficacy population included all women with BMI ≤ 35) and demonstrated a Pearl Index of 2.92 with an upper bound of 4.21.

As previously noted, the population characterized by the Applicant as “new users” does not exclusively comprise women who are naïve to hormonal contraception use. It appears that women who had not used hormonal contraception in the six months prior to study enrollment were categorized as “new users” and the narratives provide a number of examples of “new users” who had prior use of hormonal contraception.

Although the study population did include slightly greater proportions of minority (Hispanic and African-American women) than other recent study populations, the overall proportion of Caucasian subjects ranged from 56-61% across the trials, so the claim of 50% minority representation is unfounded. Other recent trials have enrolled about 70-75% Caucasians, so it is true that the minority representation was slightly higher. However, the Applicant has not provided evidence that the fertility rate and/or the ability to comply with use of a weekly patch is substantially different in these populations. In addition, based on recent Census figures, whether the current demographics are “more representative” is debatable; while other trials may have over-represented Caucasians and under-represented Hispanics, Asians and “others,” this development program over-represented African-Americans and under-represented Caucasians, Asians and “others” compared to the general population.

The Division has never required contraceptive trials to provide comparative efficacy data against an approved product and does not consider such data, if provided, in its decision about approvability. For reasons that are not entirely clear, approved drugs, when used as comparators, frequently demonstrate higher Pearl Indices than observed in their registration trials. Additionally, demonstration of poor efficacy in both treatment arms raises concern about the rigor of the study conduct.

Finally, although some development programs have conducted both a US and a non-US contraception trial, the Division has always placed the greatest weight on US efficacy results and the US Pearl Index is typically presented in labeling.

Throughout the review of the NDA, numerous examples of poor study conduct and data recording were noted. In my opinion, these factors, along with possible concerns related to the patch's ability to delivery contraceptive hormones, as suggested by the CMC deficiencies, are far more likely to account for the poor efficacy results obtained in these studies.

8. Safety

The safety database comprised data from the two phase 3 studies, and included 1,220 women in the AG200-15 arm, 230 women who switched from a COC to the AG200-15 patch and 532 women in the COC arms. Exposure characterized as 28-day cycles and women-years (WY) is presented by study and treatment arm in Table 18. Overall, the Applicant provided data on just over 10,000 28-day treatment cycles for AG200-15; in addition, over 400 women completed a year of treatment.

Table 18 Exposure by Study and Treatment Arm

Study	Study 12			Study 13	
Arm	AG200-15, Cycles 1-13	OC20 →AG200-15, Cycles 7-13	OC20, Cycles 1-6	AG200-15	OC30
# of 28-day cycles					
Total	8,089	1,188	1,388	750	794
n (%) Completing Specified Cycles					
6 Cycles	633 (61%)	147 (64%)	171 (50%)	106 (60%)	124 (66%)
7 Cycles	613 (59%)	134 (58%)	--	--	--
13 Cycles	438 (34%)	--	--	--	--

Source: Based on Study 12 Report, Table 21, p 233 and Study 13 Report, Table 17, p 111

Team Leader Comments:

- The Applicant had agreed to the Division's request for at least 10,000 cycles of exposure to AG200-15, and intended to obtain this in Study 12. The protocol for this study stated "As the study proceeds, Agile will monitor discontinuation rates and, if necessary, increase the number of subjects enrolled to achieve the target number of cycles of exposure." However, in Study 12, they obtained data on only 9,277 cycles of exposure; by combining the two studies, they were able to obtain a total of 10,027 cycles. Clearly, the Applicant did not increase recruitment when the discontinuation rate rose above that anticipated and used in sample size calculations: 25% for six cycles and 40% for 13 cycles.
- The Applicant did obtain more than the requested 200 women who completed 13 cycles of patch use.

In most cases, this safety review will address the two studies separately because of their different durations. To the extent possible, the Study 12 subjects who crossed-over to the AG200-15 arm at Month 7 will be discussed separately (i.e., not merged in with the ongoing patch user cohort) because their risk of AEs may differ from that of women who have already tolerated the patch for six months.

8.1 DEATHS AND SERIOUS ADVERSE EVENTS

Deaths

There were no deaths among subjects using AG200-15 in the clinical development program. One COC subject in Study 12 died of a head injury incurred in a motor vehicle collision.

Serious Adverse Events

The Applicant reported that in Study 12, during the first six cycles, SAEs occurred in 14 (1.3%) patch subjects and four (1.2%) COC subjects, and that no additional SAEs were observed over all patch cycles.

Team Leader Comment:

Upon reviewing the SAE narratives, I identified several discrepancies. Although the Applicant reported 14 SAEs in Cycles 1-6 and none in Cycles 7-13 in patch subjects, review of the narratives indicated 16 SAEs in patch subjects, three of which occurred in Cycles 7-13. Upon request for clarification from the Division, the Applicant responded that

- **There were actually 16 SAEs in the patch arm; one attributed to a COC subject in the narrative actually occurred in a subject using the patch (Subject (b) (6)).**
- **There were 14 SAEs in Cycles 1-6 and two in Cycles 7-13 among patch subjects.**
- **Subject (b) (6)'s SAE date was incorrect by a year in the narrative; her SAE occurred in Cycle 2, not Cycle 12.**

No SAEs were reported in patch subjects in Study 13, two COC subjects (1.1%) in this study had SAEs. The corrected listing of SAEs for both studies by treatment arm and duration is shown in Table 19.

Table 19 SAEs in Phase 3 Studies

Study 12 – Cycles 1-6					
		00-15 1,043		OC20 N = 344	
		n	%	n	%
Total		16	1.5	4	1.2
Subject ID	Event				
(b) (6)	Suicidal ideation	1	0.1		
	Bilateral pneumonia	1	0.1		
	Head injury due to motor vehicle crash*#			1	0.3
	Diabetic ketoacidosis			1	0.3
	Subclavian venous thrombosis*	1	0.1		
	Asthma attack	1	0.1		
	Ovarian cyst*	1	0.1	1	0.3
	Vomiting*	1	0.1		
	Ankle fracture	1	0.1		
	Colonic dysmotility*	1	0.1		
	Appendicitis	1	0.1		
	Urinary calculus	1	0.1		
	Liver problem			1	0.3
	Ovarian cyst rupture*	1	0.1		
	Anaphylactic shock*	1	0.1		
	Drug overdose (benedryl)*	1	0.1		
	Gastroenteritis	1	0.1		
Study 12 – Cycles 7-13					
Total			Total N = 839±	NA	NA
(b) (6)	Compartment syndrome*	1	0.1	NA	NA
	Perforated appendicitis	1	0.1	NA	NA
Study 13 (6 Cycles)					
		AG200-15 N = 177		OC30 N = 188	
Total		0	0	2	1.1
(b) (6)	Murine typhus			1	0.5
	Convulsion			1	0.5

Bold = Applicant considered at least possibly drug-related

* subject discontinued due to SAE

subject died

± N based on 590 remaining from original patch cohort at Month 7 plus the 249 who switched from COC to patch at Month 7

Source: Applicant's Study Reports for Study 12 and Study 13, Applicant's Information Request

Response dated January 16, 2013

Team Leader Comments:

- Based on corrected information from the Applicant, the overall rate of SAEs in the two trials is 1.3% (16/1,220) in patch subjects and 1.1% (6/532) in COC subjects.
- Compared to some other recent contraception trials, the SAE rate appears similar and this comparison does not suggest significant under-reporting of SAEs in the current study. NDA 22-261, a six-month trial in 1,300 women, had an SAE rate of 0.8%; the 13-cycle studies in NDAs 22-252, 22-501 and 22-573 had SAE rates of 2-3%, 0.9% and 1.4%, respectively.
- At least five of the subjects with SAEs were lost to follow-up and have inadequate information about outcome.
- Subject (b) (6) is categorized as having completed the study, but the narrative describes her as lost to follow-up < 4 months after starting the study.
- Subject (b) (6) had her SAE categorized as vomiting, but her initial presentation to the ER was due to heavy vaginal bleeding of abrupt onset immediately upon starting the patch. She also reported nausea, vomiting, mild cramps and dysuria and was diagnosed with intractable vomiting and pyelonephritis.
- Subject (b) (6) had an unspecified "liver problem" that is categorized as "probably related" to COC use. She took her first pill on 10/15/10 and is reported as having called the site on 11/16/10 and stating she had stopped taking the COC due to having been hospitalized for a liver problem one month ago. Subject was then lost to follow-up. It seems unlikely that a "liver problem" that required hospitalization right around the initiation of a COC is drug-related.
- Dr. Davis' review includes detailed descriptions of the SAEs related to subclavian vein thrombosis, compartment syndrome, and anaphylactic shock.
- I believe that the following SAEs are at least possibly drug-related: suicidal ideation, Benedryl overdose (an apparent suicide attempt), subclavian venous thrombosis, "vomiting" (subject's chief complaint leading to ER visit was heavy vaginal bleeding), and compartment syndrome.
 - Depressive symptoms are not uncommonly associated with hormonal contraception. Subject (b) (6) does not appear to have a history of depression but experienced severe depression and suicidal ideation leading to hospitalization after about 3.5 months on the patch. She attributed her symptoms to the death of her father. Subject (b) (6) was diagnosed with depression and started on an antidepressant about a month before starting the patch. Her family discovered a suicide note after she had been on the patch for about 3 months and two days later she attempted suicide with 80 25 mg Benedryl tablets. She was treated and held in a behavioral unit for monitoring for almost a week.
 - The Applicant states that Subject (b) (6), who experienced the subclavian thrombosis after about 4 months on the patch, is physically active and lifts weights, and requested that she be evaluated for Paget-Schroetter syndrome (effort- or exercise-induced upper extremity VTE). Per Up to Date³, this condition occurs most commonly in males (2:1 ratio), and is considered a primary etiology, to distinguish it from other upper extremity VTEs that are associated with other risk factors, such as prothrombotic states. It is unclear how the diagnosis of Paget-Schroetter would be made in this young woman, who clearly has

³ http://www.uptodate.com/contents/primary-spontaneous-upper-extremity-deep-vein-thrombosis?source=search_result&search=Paget-Schroetter+syndrome&selectedTitle=1%7E5, accessed January 14, 2013

another risk factor (hormonal contraception) that could account for her event. If anatomic abnormalities that could lead to compression of venous structures, such as bone overgrowth following fracture or hypertrophied muscles related to repetitive lifting, were documented, that would lend support to such a diagnosis. No such evaluations were reported; in fact, a left arm angiogram reported no venous compression. Results of a planned vascular consult were not reported.

- O According to Up to Date⁴, acute compartment syndrome can occur in unconscious or obtunded patients who experience prolonged limb compression, perhaps following recreational drug abuse. Nontraumatic causes include thrombosis. The narrative history for Subject (b) (6) is insufficient to determine whether either of these causes might be relevant in this case; it is unclear whether she was evaluated for a deep vein thrombosis (DVT). According to additional information submitted in response to an Information Request from the Division, it is possible that she was pregnant (see Section 7.4.4), which could have predisposed her to a DVT.

8.2 OTHER ADVERSE EVENTS

8.2.1 AEs leading to Discontinuation

The study reports did not discuss AEs leading to discontinuation in the safety section, and for Study 12, the only presentation of these data was one table in the Appendix that provided comparative data over the first six cycles and one that provided information on the patch arm only, over all cycles. In both studies, discontinuations due to AEs occurred more frequently in the patch arm than the COC arm, but in Study 13, only menstrual bleeding complaints and application site reactions led to withdrawal in more than a single subject. In Study 12, these were also the most common AEs leading to discontinuation, but a number of other AEs common to hormonal contraceptives led to discontinuation, usually more frequently in the patch arm than the COC arm. Table 20 displays AEs that led to early withdrawal in more than one subject; data for Study 12 is only over the first six cycles in order to present comparative data. However, the majority of discontinuations due to AEs in the patch arm overall occurred in the initial six cycles.

⁴ http://www.uptodate.com/contents/acute-compartment-syndrome-of-the-extremities?source=search_result&search=acute+compartment+syndrome&selectedTitle=1%7E144, accessed January 9, 2013

Table 20 AEs leading to Premature Withdrawal in > 1 Subject, Phase 3 Studies

AE leading to withdrawal	AG200-15		COC	
	n	%	n	%
Study 12	N=1, 043		N=344	
Any Event	106	10.2	16	4.7
Application site complaint (dermatitis, discoloration, erythema, irritation, pain, pruritis, rash, reaction, vesicle)	46	4.4	0	
Menorrhagia/metrorrhagia/vaginal hemorrhage	13	1.2	3	0.9
Headache/migraine	9	0.9	1	0.3
Nausea/vomiting	9	0.9	1	0.3
Affect lability/mood swings	8	0.8	0	
Ovarian cyst/ovarian cyst ruptured	5	0.5	2	0.6
Depression	5	0.5	1	0.3
Dizziness	5	0.5	0	
Breast pain/tenderness	4	0.4	0	
Weight increased	4	0.4	1	0.3
Abdominal pain	3	0.3	0	
Abdominal distension	3	0.3	0	
Alopecia	3	0.3	0	
Hypertension	3	0.3	1	0.3
Irregular menstruation	3	0.3	1	0.3
Abnormal Pap/cervical dysplasia	2	0.2	0	
Acne	2	0.2	1	0.3
Fatigue	2	0.2	1	0.3
HPV test positive	2	0.2	0	
Irritability	2	0.2	1	0.3
Mood altered	2	0.2	0	
Study 13	N=177		N=188	
Any Event	13	7.3	3	1.6
Application site complaint (erythema, irritation, pruritis, reaction, vesicle)	7	4.0	0	
Bleeding complaints (menstrual irregularity, vaginal hemorrhage)	2	1.1	0	

Source: Based on Study Reports for Study 12, Table 14.3.2_1.1 and for Study 13, Table 14.3.2_1

Team Leader Comments:

- In general, the study reports are unclear as to whether subjects chose to discontinue due to the reported AE or were discontinued by the investigator. The narratives frequently use the passive “was discontinued from the study” but in a number of cases, the narrative notes that the AE was mild and had resolved by the day of discontinuation.
- In addition to the discontinuations due to bleeding seen above, an additional 1.4% of subjects discontinued due to bleeding but were not listed under AE discontinuations (see Section 7.3). Thus, it appears that 2.6% of subjects over the two trials discontinued due to bleeding.
- Application site complaints leading to discontinuation in Study 12 ranged from mild to severe, although they generally persisted for some time before the subject was discontinued. In addition to the terms listed above, three more patch subjects discontinued due to rash, pruritic rash and skin irritation, all of which were considered probably or definitely related to study drug. The rash was attributed to

patch adhesive. The narrative does not describe if the other two occurred at the application site.

- Most of the application site complaints in Study 13 were no greater than moderate in severity. One subject reported moderate itching all over her body. In addition to the subjects listed with application site complaints as the reason for withdrawal, an additional subject in Study 13 was noted to have a blister under the patch site at the time she was discontinued due to menstrual irregularity.
- In addition to the application site disorder AEs listed above, another 1% of subjects overall had their discontinuation attributed by the Applicant to “subject’s decision,” but were actually determined to have discontinued due to application site reactions. Thus, 5.3% of subjects over the two trials discontinued due to this AE. This is fairly similar to the rates reported in the labeling for the menopausal estrogen/progestin patch Climara Pro, which had discontinuations due to these disorders in 2-9% of subjects, depending on whether the trial was three or 12 months in duration.

8.2.2 Common AEs

The most common AEs for each study are reported in Table 21, based on AEs that occurred in at least 2% of subjects and were more common among subjects in the patch arm. For Study 12, AEs are reported only during the first six cycles in order to provide comparative data.

Table 21 Selected Common Adverse Events, Phase 3 Studies

Preferred Term	Study 12		Study 13	
	AG200-15 N=1,043 n (%)	COC N=344 n (%)	AG200-15 (N=177 n (%))	COC N=188 n (%)
At least one AE	495 (42.6)	163 (47.4)	85 (48.0)	88 (46.8)
Application site complaint (dermatitis, discoloration, erythema, irritation, pain, pruritis, rash, reaction, swelling, vesicle)	56 (5.4)	0	12 (6.8)	0
Headache/migraine	54 (5.2)	19 (5.5)	6 (3.4)	4 (2.1)
Abdominal pain	22 (2.1)	5 (1.5)		
Breast pain/tenderness	22 (2.1)	5 (1.5)	7 (4.0)	1 (0.5)
Menorrhagia/metrorrhagia/ vaginal hemorrhage	21 (2.0)	3 (0.9)		
Vulvovaginal mycotic + vaginal infection + vaginitis	20 (1.9)	9 (2.6)	11 (6.2)	5 (2.7)

Source: Based on Study Reports for Study 12, Table 14.3.1_2.2.1.1 and for Study 13, Table 14.3.1_2.2.1

Team Leader Comments:

- The rate of “any AE” is considerably lower than other contraceptive application; typical rates in a 12-month trial are 70-80%. While AEs are reported here only for the first six cycles, in Study 12, the AE rate in the 13-cycle patch cohort was only 54.7%, which suggests that most AEs occur initially in the first six cycles. In light of other indicators of poor quality of data collection in this NDA, this leads me to question whether AEs were under-reported in these trials.
- The rates of application site disorders in both studies are also lower than that reported in trials for other hormonal patches. The Climara Pro label reports rates of 34-40% in a one-year trial, and the Ortho Evra label reports a rate of 17% in data pooled over six and

13-cycle trials. Over the full 13 cycles in Study 12, the rate of application site disorders was only 6.3%.

- **Overall, there do not appear to be major differences in the rates of other common AEs between patch and COC subjects.**

8.2.3 Skin Irritation

Skin irritation was assessed by site personnel at each study visit, with irritation rated as none, mild, moderate or severe. Subjects also recorded skin irritation and itching daily. Data on skin irritation as assessed by investigators and by subjects is provided in Table 22. The data reflect the worst score for each subject. It is unclear if the subject assessments were defined, or whether it was left to the subjects to determine what each category meant to them.

Table 22 Summary of Investigator's Skin Irritation Scores, All Visits

Skin Irritation Score (n, %)	Study 12 N=1,273	Study 13 N=177
Investigators' Assessments		
None (no irritation or barely perceptible/spotty erythema)	677 (59%)	101 (64%)
Mild (mild erythema covering most of the application site)	379 (33%)	50 (31%)
Moderate (moderate erythema, possible mild edema)	83 (7%)	8 (5%)
Significant (severe erythema, possible edema, vesiculation, bullae and/or ulceration)	5 (0.4%)	0
Subjects' Assessments		
None	258 (21%)	44 (26%)
Mild	444 (36%)	73 (43%)
Moderate	351 (29%)	37 (22%)
Severe	170 (14%)	16 (9%)

Source: Study Report for Study 12, Table 43, p 398 and Table 14.3.7_5.1.1, Study Report for Study 13, Table 30, p 142 and Table 14.3.7_5.1.1

Team Leader Comment:

Based on worst scores over all assessments, subjects reported markedly more skin irritation than did investigators. This may reflect the fact that investigators evaluated the skin only at clinic visits, while subjects reported daily. Over both studies, slightly more than 5% of subjects discontinued due to application site complaints. However, only 0.6% reported unscheduled patch changes due to skin irritation.

8.3 LABORATORY TESTING AND VITAL SIGNS

Dr. Davis' review addresses the evaluation of laboratory parameters and vital signs in the phase 3 studies. There were no new safety signals of concern in either area. Patch subjects demonstrated slight alterations in lipids, a known effect of hormonal contraceptives. Using pooled data, there appears to be a slightly greater chance of clinically significant changes in blood pressure (defined as systolic ≥ 140 mm Hg and an increase of ≥ 20 from baseline, or diastolic ≥ 90 and an increase of ≥ 15 from baseline) for the patch (1-2%) compared to the COC comparators (generally $<1\%$), and increases were slightly more common when considering data over 13 cycles compared to six cycles. Hypertension is also described in class labeling for hormonal contraceptives.

8.4 POSTMARKETING SAFETY FINDINGS

The AG200-15 TCDS has not been approved for marketing anywhere in the world, so there are no postmarketing safety data on this product.

8.5 SAFETY UPDATE

A 120-day Safety Update was submitted on August 10, 2012, covering the period from NDA submission to July 23, 2012. There was no postmarketing safety information, as the TCDS has not been approved anywhere in the world subsequent to the NDA submission. There were also no new or ongoing clinical or nonclinical studies. The update provided recent literature search information and new or follow-up pregnancy forms collected since the original NDA submission. Many of the studies reviewed by the Applicant were epidemiologic studies related to arterial and venous thrombotic and thromboembolic risk of hormonal contraception, which have already been reviewed extensively by DRUP. The Applicant concluded that there was no new safety signal that would warrant revision of the proposed labeling.

Team Leader Comment:

I concur that there is no new safety concern based on the Safety Update.

8.6 OVERALL ASSESSMENT OF SAFETY FINDINGS

The clinical safety database for AG200-15 included 1,450 subjects who used the AG200-15 patch, for a total of just over 10,000 cycles of exposure. The single death occurred in a COC subject and appears unrelated to drug. In general, rates of SAEs were similar across treatment arms (1.3% in the patch arms vs. 1.1% in the COC arms). SAEs of concern in the patch arm include suicidal ideation/attempt (two cases), a VTE, and a case of compartment syndrome that was temporally associated with a possible pregnancy, and may therefore have been associated with an undiagnosed DVT. Overall, the SAE descriptions were sparse, and subjects were lost to follow-up in several cases. Discontinuations due to AEs occurred much more frequently in the patch arms than the COC arms, and were predominantly due to application site disorders and menstrual bleeding disorders. However, in Study 12, other AEs commonly associated with hormonal contraceptives also led to early withdrawal more frequently in the patch subjects. Common AE rates were generally similar across treatment arms, but appear lower than other contraceptive trial reports, raising the question of whether under-reporting occurred. Finally, application site reactions/skin irritation was reported very differently by investigators vs. subjects, with investigators reporting only 5-7% of subjects as experiencing moderate to severe skin irritation at a clinic visit, while subjects, reporting on a daily basis, reported moderate or severe skin irritation rates of 30-40%.

9. Advisory Committee Meeting

An Advisory Committee meeting was not requested for this application, as it does not utilize a novel combination of contraceptive hormones or dose regimen, and it is not the first transdermal contraceptive patch marketed.

10. Pediatrics

The Applicant requested a waiver of pediatric studies in premenarcheal females < 17 years of age because the indication is not relevant to this population. The Applicant also requested a

waiver of studies in postmenarcheal females < 17 years, with the justification that safety and efficacy data for this population can be extrapolated from the adult data. The Division concurred that a partial waiver and extrapolation was appropriate. The Pediatric Review Committee (PeRC), on January 16, 2013, agreed to a partial waiver for patients from birth to 11 years of age, and to extrapolate efficacy for patients from 12 to 16 years of age.

11. Other Relevant Regulatory Issues

The Applicant certified that it did not use any debarred investigators. The Applicant submitted financial disclosure information for investigators in Studies ATI-CL10 through ATI-CL16 and none had any disclosures.

The Division of Scientific Investigation (DSI) inspected three sites for Study 12. The sites were chosen based on considerations that included the number of subjects enrolled, unusually high numbers of pregnancies, and aberrant study discontinuation or AE rates.

Dr. Hazen's site (Study 12, Site 33) screened 180 subjects, enrolled 120 subjects, and 36 completed the study. Records of 20 subjects were reviewed by DSI. The site received a Form 483 due to failure to collect blood samples for SHBG and CBG in nine subjects at Visit 7 and PK samples for two subjects at Visit 3. Dr. Hazen provided an explanation that sampling kits had not been provided to the site for the hormone samples and acknowledged the oversight on the PK samples. DSI issued a No Action Indicated (NAI) evaluation and concluded that the study appeared to have been conducted adequately and that the data appear acceptable in support of the application.

Dr. Groom's site (Study 12, Site 31) screened 113 subjects, enrolled 73 subjects, and 22 completed the study. Records of nine subjects were reviewed by DSI. The site received a Form 483 due to multiple deficiencies, including failure to obtain consent from three subjects, failure to obtain blood samples from numerous subjects at protocol-specified visits, recruitment of at least one subject who met exclusion criteria, lack of protocol-required AE follow-up, inappropriate application of the patch to different sites in the same cycle, use of source documents lacking attribution and dates, presence of conflicting data regarding contraceptive history, and numerous discrepancies between subject diaries, CRFs and progress notes. Dr. Groom was asked to respond in writing as to how he will bring future studies into compliance with applicable regulations. DSI issued a Voluntary Action Indicated – Response Requested (VAI-RR) evaluation, but noted that, despite the number of discrepancies identified, the significance of the findings overall appears minimal with respect to the integrity of the efficacy data (pregnancy/non-pregnancy) or subject safety. Therefore, DSI concluded that the study appeared to have been conducted adequately and that the data appear acceptable in support of the application.

Dr. Eubank's site (Study 12, Site 23) screened 56 subjects, enrolled 47 subjects, and 22 completed the study. Records of 42 subjects were reviewed by DSI. The site received a Form 483 due to failure to collect PK samples for two subjects at Visit 5, discrepancies between source documents and CRFs with regard to study drug accountability, and additional discrepancies regarding concomitant medications and AEs. Discrepancies were noted for three pregnant subjects regarding pregnancy test dates and treatment cycles, date of conception, and AEs and pregnancy test dates. Dr. Eubank addressed each discrepancy, acknowledging some transcription errors and failure to correct source data when CRFs were

updated in response to interim queries. In other cases, he stated that CRF data was consistent with source data (e.g., laboratory reports) but did not provide the source data for review. He appears to have resolved discrepancies related to the pregnant subjects. DSI issued a Voluntary Action Indicated (VAI) evaluation and concluded that, aside from minor discrepancies, the study appeared to have been conducted adequately and that the data appear acceptable in support of the application.

Team Leader Comment:

Although Dr. Hazen's site (033) received an NAI, her site had eight pregnancies (per the Division's counting of on-treatment pregnancies) among 69 subjects. This is a far higher rate of pregnancy than even the other four sites that collectively accounted for about 40% of all on-treatment pregnancies. These other four sites enrolled < 40 subjects each, and had 2-3 pregnancies apiece; these relatively small numbers could indicate that the high pregnancy rates at the four sites were merely random outliers. However, Dr. Hazen's site had higher numbers of enrollees and pregnancies, which suggests to me that there is something aberrant at that site, possibly with respect to drug delivery by the patches, subject compliance, or other, unidentified, factors.

While DSI may be correct that the deficiencies identified, particularly at Drs. Eubank's and Groom's sites, may not impact the efficacy evaluation, the magnitude of missing and discrepant data is higher than typically observed in contraceptive trial inspections. These findings, along with the many questions about data accuracy and clarity in the NDA submission, lead me to view the submission overall with caution.

Roy Blay, Ph.D. from DSI made the following overall assessment and general recommendations in his review dated January 15, 2013:

Dr. Eubank's, Groom's and Hazen's clinical investigator sites were inspected in support of this NDA. Dr. Hazen was not issued a Form FDA 483, and the final classification of the inspection was NAI (No Action Indicated). Both Drs. Eubank and Groom were issued Form FDA 483s. The final classification for Dr. Eubank's site was VAI and the classification for Dr. Groom's site was VAI-RR (Voluntary Action Indicated – Response Requested).

Though numerous deficiencies were identified at Drs. Eubank's and Groom's sites as noted above, the deficiencies, overall, would not appear to seriously affect data integrity or the safety of study subjects; therefore, the data generated by these three clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

12. Labeling

The Applicant submitted the proposed proprietary name Twirla, which was found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

The label was submitted in the format prescribed by the Physician Labeling Rule (PLR). However, the labeling review was not completed due to the early recognition that the drug would not be approved in this review cycle. Labeling revisions were not discussed with the Applicant.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that this TCDS receive a Complete Response action on several grounds. In addition to CMC issues, there are significant issues with respect to the demonstration of efficacy in the two phase 3 trials. I have several concerns about the efficacy data submitted in this application.

As discussed in Section 7.4.7, I find the level of efficacy of the AG200-15 patch demonstrated in this development program to be unacceptable. Although the Applicant has proposed a number of justifications for the observed Pearl Index, suggesting that the population was “more representative” than that in other recent contraceptive trials, I do not find their explanation credible or to provide a rationale that would justify recommending approval of a product demonstrating this level of efficacy.

I have serious concerns about the validity of the data obtained in these two trials for two related reasons. First, the quality of study conduct and monitoring appears to have been very poor. For example, the Applicant did not follow its pre-specified plan to increase recruitment and sample size if the withdrawal rate were higher than that specified in the sample size calculations. This resulted in a lower than intended number of cycles of contraceptive exposure. The Applicant also failed to meet its own goal for recruitment of women of higher BMI, and did not provide sufficient information to allow us to determine if they had enrolled the proportion of truly naïve users the Division had requested be included in the study population. The very high discontinuation rate, particularly in the initial month of the study, indicates issues in study conduct that should have been addressed. The Applicant attributes this to “the possibility that a significant number of these subjects were primarily motivated to participate in the study for the benefits associated with the initial health care assessment, less so the full rigors of the entire trial” and “suggesting that these subjects never intended to be in the study. This may be a reflection of the bad economic times where many women have no health insurance.” It seems more likely that women with limited resources for healthcare would have appreciated a year’s worth of free medical care and contraception, and would have had a greater incentive to remain in the trial. However, if even if this explanation were pertinent, I would find it indicative of poor judgment on the part of investigators in their enrollment decisions.

It appears that a number of subjects were determined to be ineligible (e.g., already pregnant prior to study entry) after they had been enrolled. There was also a very high rate of loss to follow-up, particularly of concern in cases in which the subject had a significant AE or a possible pregnancy, for which the definitive evaluation was not conducted because of this loss to follow-up. Finally, the lack of accurate information about drug-taking (i.e., missing diary cards) and the apparent rate of non-compliance based on periodic sampling for EE and LNG levels suggests poor oversight of the subjects’ behavior in the trials. Suggestions of poor patch tolerability based on discontinuations due to application site reactions, problems with patch adhesion and “did not like the patch” warrant further exploration, as do the high rates of patch detachment reported by subjects.

Finally, it is noted that two of the three sites inspected received VAI classifications. Although OSI concluded that the deficiencies did not appear to impact data integrity, taken in

the context of all the other observations about the quality of these studies, I believe this is a signal of concern.

My second concern about the efficacy data arises because the accuracy and internal consistency of data reported in the two study reports appears to be questionable, and quality control measures appear to be lacking. Data were obscured in some cases, such as the recording of a number of AE- or patch-related discontinuations as “subject’s request.” The rate of reporting of common AEs and application site disorders is lower than that typically observed in other contraceptive trials. Several pregnancies that met the agreed-upon criteria for being considered “on-treatment” or which the investigator considered to have occurred on-treatment were categorized by the Applicant as “post-treatment.” In addition, despite having reviewed many contraceptive applications, I have never before found so many cases in which I disagreed with the Applicant’s determination of on-treatment pregnancies. I have also never seen so many instances of “false positive” pregnancy tests. As noted previously, it is concerning that 55% of the potential pregnancies not considered by the Applicant to have occurred on-treatment were either lost to follow-up or discontinued from the study without obtaining appropriate follow-up information.

Other examples of discrepancies in data reporting are noted throughout this review, including counts and treatment assignment in SAE reports. Numerous Information Requests were required to get comprehensible data from the Applicant, and even when responses were received, further clarification often had to be sought due to errors in the response. For example, in one case where the Applicant was asked to provide narratives for possible pregnancies that had not been included in the “Pregnancy Narrative” section of the study report, the Applicant submitted an identical narrative for two different subjects. When questioned about this, the Applicant responded

When drafting the narrative for subject [xx], the medical writer used the completed narrative for subject [yy] as a template. However, the narrative for subject [xx] was not completed and had information for both subjects on it when it was saved as a draft. After the medical writer completed the narrative for subject [xx], it was mistakenly saved with an additional keystroke in the filename. Therefore, when all the narratives were uploaded for the submission, the improper (draft) file was included.

Another example of poor data cleaning/report oversight was the attribution of one of the few SAEs to the COC arm, when, in fact, it occurred in a subject using the patch. In a final example, the Applicant was challenged over a statement that there were 14 SAEs in the patch arm in the first six cycles in Study 12, but that no additional SAEs were observed when all patch cycles [i.e., Cycles 7-13] were evaluated, because the reviewer had identified 13 SAEs in the first six cycles and three SAEs occurring in Cycles 7-13. The Applicant responded

The statement indicating “no additional AEs were observed when all patch cycles were evaluated” was in reference to a computer keyword search of the database for any adverse event that may fit the criteria for an SAE. No additional SAEs were found as a result of the database search.

There are two SAEs occurring after 6 months (subjects [xx and yy]). The SAE for subject [zz] occurred on 10/17/10 and not on 10/17/11 as stated in the narrative.

There are also numerous examples in the narratives where the subject's treatment arm is reported incorrectly, although this error does not appear to have occurred in the dataset coding.

I believe that if the Applicant desires to submit a Complete Response, it will need to make additional efforts to ensure that a subsequent preapproval trial is conducted rigorously, with appropriate site monitoring and quality control measures in place. The study report similarly needs to be carefully reviewed and the quality evaluated prior to submission to the Division. In addition, if the Applicant intends to rely on data from Study 12 for approval in a future review cycle, I would recommend that the Applicant obtain an external audit of the data from this study prior to submitting a Complete Response. I would be reluctant to rely upon the data from this study, even as supportive safety data, in the absence of such an evaluation.

13.2 Risk Benefit Assessment

The major concern in this application with respect to risk/benefit hinges on the unacceptable demonstration of efficacy in prevention of pregnancy. There is no signal of safety concerns that are unique to this application or different from the safety profile commonly observed with combination hormonal contraceptives. However, the data on AEs contained many inconsistencies and discrepancies, and is viewed with caution.

13.3 Recommendation for Postmarketing Risk Management Activities

The Applicant has proposed a postmarketing prospective cohort study to evaluate the risk of VTEs. The study would be conducted using one or more healthcare claims databases, and VTEs identified would be confirmed by blinded review of medical records. The study would compare patch users to users of other CHCs.

Given my recommendation against approval, no postmarketing risk management activities are recommended at this time. If the product were to be considered for approval in a future review cycle, the need for and design of a postmarketing safety study would be evaluated and discussed with the Division of Epidemiology in the Office of Surveillance and Epidemiology.

13.4 Recommendation for other Postmarketing Study Requirements and Commitments

I have no recommendations in this cycle for postmarketing studies.

13.5 Recommended Comments to Applicant

I believe that in order to address the deficiency of an unacceptable demonstration of efficacy for the requested indication, the Applicant will need to conduct another clinical trial in the US population. While enrollment of a diverse population that is representative of the US population of hormonal contraceptive users is valued, the Applicant will need to consider how to minimize poor compliance, early discontinuations and loss to follow-up. The study could be an open-label, single arm study; I do not see a need for further comparator-controlled data. The utility of assessing drug concentrations during the study is questionable, although it may be of value to individual investigators in counseling subjects.

The current trials raised questions about possible impact on efficacy of BMI, race/ethnicity and application site, and these factors should be explored further in the future trial. In

addition, in light of CMC concerns about possible impact of aging patches, an evaluation of efficacy by patch age should also be considered.

Any future trial needs to ensure rigorous conduct, excellent data collection, data cleaning and report preparation. In light of the poor data quality observed in the current studies, the Applicant may wish to consider external auditing of the data from any future trial prior to submission as a Complete Response. Data to be reported should include pregnancy outcomes, with appropriate follow-up until pregnancy termination or delivery. In addition, all suspected pregnancies need the appropriate work-up to determine whether a conception has occurred and the timing of conception with respect to drug use. SAEs should also be followed to resolution, and appropriate information should be obtained to clarify the nature and possible etiologies of the SAE.

Additional comments that should be conveyed to the Applicant are outlined in the reviews by the CMC, Biopharmaceutics and Clinical Pharmacology reviewers.

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/s/

LISA M SOULE

02/13/2013

HYLTON V JOFFE

02/13/2013

I concur with the recommendation for a Complete Response. See the Division Director Memorandum.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204017
Priority or Standard	Standard

Submit Date	April 12, 2012
Received Date	April 13, 2012
PDUFA Goal Date	February 13, 2013
Division / Office	DRUP/ODE 3/OND
Reviewer Name(s)	Daniel Davis, MD
Review Completion Date	January 21, 2013

Established Name	ethinyl estradiol/levonorgestrel
(Proposed) Trade Name	Twirla
Therapeutic Class	Hormonal contraception
Applicant	Agile Therapeutics
Formulation(s)	Transdermal patch
Dosing Regimen	1 patch/week for 3 consecutive weeks, then 1 patch-free week
Indication(s)	Prevention of pregnancy
Intended Population(s)	Women of reproductive age

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List of Abbreviations

Commonly Used Abbreviations and Acronyms in Medical Officer NDA Review	
AE	adverse event
AST	All-Subjects-Treated
ATE	Arterial thrombotic event
AUC	Area under the curve
BMI	Body mass index
CBG	Corticosteroid binding globulin
CDER	Center for Drug Evaluation and Research
CI	Confidence Interval
CHC	Combined hormonal contraceptive [estrogen + progestin]
CRF	case report form
DRUP	Division of Reproductive/Urologic Products
DSI	Division of Scientific Investigation
DVT	deep vein thrombophlebitis
EDC*	estimated date of conception*
EE	ethinyl estradiol
FDA	Food and Drug Administration
FPL	Final Printed Label
PK	pharmacokinetics
IND	Investigational New Drug
IRB	Institutional review board
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intent-to-treat
LMP	last menstrual period
LNG	levonorgestrel
MOR	medical officer review
NDA	New Drug Application
MF	Method failure
OCs	oral contraceptives
PE	pulmonary embolus
PI	principal investigator
PP	Per Protocol
SAE	serious adverse event
SHBG	Sex hormone binding globulin
STDs	sexually transmitted diseases
TCDS	Transdermal contraceptive delivery system
TEAE	Treatment-emergent adverse event
TLAD	Treatment-limiting adverse event
VTE	venous thromboembolism event

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I do not recommend approval for this NDA 204017 application for a 7-day combination hormonal transdermal patch for contraception. According to the FDA calculations based on 5 additional on-treatment pregnancies identified during the review, the Pearl Index for the prespecified primary efficacy dataset is 7.50 with an upper bound of the 95% confidence interval of 9.97. A total of 8 additional on-treatment pregnancies were identified, but only 5 were in the primary efficacy dataset. This is unacceptable for a combination hormonal contraceptive (CHC) product with all the known and expected safety issues associated with CHCs, especially thromboembolic events. The risk/benefit for this combination transdermal patch is not favorable compared to the other FDA-approved combination products currently on the market. Furthermore, there are significant unresolved chemistry and manufacturing (CMC) issues and several issues with the overall quality of the clinical trials and the data in the submission as commented on throughout this review.

1.2 Risk Benefit Assessment

The risk associated with the Agile transdermal patch does not appear to be significantly different from that seen with currently approved CHC products.

Although the Applicant did submit safety data for 10,027 cycles of exposure from the phase 3 studies, the unusually high discontinuation and lost to follow-up rates mean that safety and efficacy data are simply not available for a large number of subjects. There is no way to tell if these women in fact were pregnant or had a significant adverse event as the real reason for their stopping the trial or being lost to follow-up. The number of evaluable cycles for the determination of contraceptive efficacy was 6,070 (see Table 9). A larger safety and efficacy database is desirable, but not the primary reason for a non-approval recommendation.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At this time, it is premature to make a recommendation for or against a REMS. There has been a 7-day transdermal contraceptive patch on the US market since November 2001, so the Agile patch is not unique and the labeled instructions for use should be simple and clear if the product is eventually approved.

1.4 Recommendations for Postmarket Requirements and Commitments

At this time, it is premature to make a recommendation for or against postmarketing requirements or commitments. If this transdermal contraceptive patch is eventually approved, a prospective, long-term, preferably comparative study would likely be

required in order to better assess the safety of the patch, as the Division has required for most new CHCs. Especially important is to determine the risk of venous and arterial thromboembolic events, compliance, and, possibly, typical use contraceptive effectiveness. The design of the postmarketing study should be similar to the EURAS model used for the drospirenone products or the TASC study for NuvaRing; i.e., a comparative, non-interventional surveillance study in a large population of users.

2 Introduction and Regulatory Background

2.1 Product Information

Levonorgestrel (LNG) is the most widely used progestin in second-generation oral contraceptives and was first introduced to the US market in the 1980s. Since then, it has been one of the most popular and widely used progestins in the United States and globally. The LNG-containing oral contraceptives have an excellent safety profile. Epidemiological studies suggest that LNG may be a safer alternative to the third-and fourth generation progestins (desogestrel, etonogestrel, gestodene, and drospirenone) concerning the risk of venous thromboembolism (VTE).

The dose of ethinyl estradiol (EE) in combination oral contraceptives (OCs) has decreased over the years. The most widely prescribed oral contraceptives today contain 35 µg EE or less. Ortho Evra, the only transdermal contraceptive product currently on the market in the United States delivers an amount of EE that is 60% greater than an oral pill containing 35 µg of EE, based on area under the curve (AUC). The suspected association of EE dose with risk for VTEs has resulted in a specific warning in the Ortho Evra product labeling. Thus, there is a benefit to a transdermal contraceptive that delivers an EE dose with lower estrogen exposure, while still providing the theoretical convenience (still unproven) and reliability of a non-daily, non-oral, easily reversible administration of a contraceptive product.

Agile Therapeutics, Inc (Agile) has developed a 7-day transdermal contraceptive delivery system (TCDS) containing 2.60 mg LNG and 2.30 mg EE for the prevention of pregnancy. This transdermal drug delivery system (designated AG200-15) utilizes an active matrix core with an overlay peripheral adhesive system. The size of the active drug matrix is constant at 15 cm²; however, the overlay is flexible and can shrink or stretch after cutting and thus has an in-process specification of (b) (4). The overlay peripheral adhesive system was cut at 28 cm² for all patches used in clinical studies ATI-CL12, ATI-CL13, ATI-CL14, ATI-CL15 and ATI-CL16. The protocols for these studies describe the total size (active patch area plus overlay peripheral adhesive system) of the TCDS as (b) (4). The TCDS releases a quantity of EE and LNG that results in daily exposures (AUC) that are equivalent to an OC that contains 120 mcg LNG and 30 mcg EE over a 7-day period (see studies CL10 and 14 and the Clinical Pharmacology review for details). The patch is replaced every 7 days for 3 weeks, followed by a 1-week "patch-free" period.

2.2 Tables of Currently Available Treatments for Proposed Indications

The only available transdermal contraceptive product is the Ortho Evra patch that delivers norelgestromin as the progestin and EE as the estrogen. It was approved in November 2001. Since 1982, there have been several approved OCs that contain LNG and EE with varying doses of the two hormones: levonorgestrel ranging from 50 to 150 mcg, and EE ranging from 10 to 50 mcg. In the US, there is currently no approved transdermal contraceptive product that delivers LNG.

2.3 Availability of Proposed Active Ingredient in the United States

Levonorgestrel is a second-generation progestin and is the most widely prescribed contraceptive progestin worldwide. EE has been readily available in the US since the 1960s and LNG has been readily available in the US since the 1980's. Both active ingredients have a long history of use and acceptable safety.

2.4 Important Safety Issues with Consideration to Related Drugs

The most common and important safety issue with all combination hormonal contraception (CHC) is the risk of VTEs; of less concern is the arterial thromboembolic (ATE) risk (because these events are much rarer in young women). VTEs include deep vein thrombosis (DVT), pulmonary embolism (PE), and other thrombotic events such as retinal thrombosis and sagittal sinus thrombosis. ATEs include strokes (CVA), myocardial infarction (MI), and events such as a mesenteric artery thrombosis. Other less serious events such as headache, nausea, vomiting, breast symptoms, weight changes, mood changes may occur or be exacerbated with use of hormonal contraception.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On January 19, 1999, IND 57731 for prevention of pregnancy was opened in DRUP. The Sponsor proposed development of a combination transdermal patch containing LNG and EE for the prevention of pregnancy. The goal was to have a delivery of EE that was similar to an OC containing 30 mcg of EE.

On September 22, 2008, an End-of-Phase 2 meeting was held with the Sponsor to discuss the adequacy of the phase 1 and 2 studies already performed and data acquired thus far to proceed to the proposed phase 3 study and to support a future NDA for AG200-15. The proposed phase 3 development plan and a draft phase 3 study protocol were also discussed.

In August 2009, the Division sent a No Agreement letter to the Sponsor with comments following a Special Protocol Assessment (SPA) of their clinical Protocol ATI-CL12 for a large (N= 1,200) phase 3, open-label, randomized study of their transdermal patch in comparison to the oral contraceptive Levite® containing 100 mcg LNG and 20 mcg EE.

The Division did not reach agreement on the protocol design in the SPA response on the following issues:

1. The Division had requested that no restrictions on body mass index (BMI) be applied to the clinical studies, but agreed that the Sponsor could address women with a BMI $\geq 32 \text{ kg/m}^2$ in the proposed second phase 3 trial of 6 months duration, provided that the sample size was increased from the originally proposed 200 subjects/arm.
2. The Division recommended obtaining an ultrasound as early as possible to accurately assess the date of conception on all subjects who become pregnant.
3. How and what to record on the daily diary concerning cycle control data.
4. The Division recommended obtaining information regarding return to fertility in a subset of women who discontinue treatment and want to become pregnant.

In November 2009, Agile Therapeutics submitted a SPA for the smaller comparative study ATI-CL13.

On January 10, 2010, the Division sent a No Agreement letter to the Sponsor concerning the protocol for the phase 3 ATI-CL13 study. Several clinical, statistical, and pharmacology recommendations with regard to BMI, exclusion of women under the age of 35 who smoke, enrollment of younger women, bleeding parameters, patch wearability were included in the letter. The Division recommended conducting a pharmacokinetics study comparing plasma concentrations of LNG and EE with AG200-15 to an oral contraceptive product containing LNG 150 mcg and EE 30 mcg, and noted that "single blood draws during Cycles 3 and 6 are not likely to be useful for quantitative PK comparison of AG200-15 and oral contraceptive. Therefore, we continue to recommend that you conduct a relative bioavailability study comparing AG200-15 to an oral contraceptive product."

On March 9, 2010, a Type A meeting discussed the details of the CL12 phase 3 protocol and the Division made several recommendations on the revised protocol. At issue were several items:

- trial sample size to assure an overall total of 10,000 cycles of exposure to the patch,
- percentage of new users (who would potentially be at higher risk of thromboembolic events), including women under age 35 who smoke,
- use of ultrasound for accurate pregnancy dating,
- definition of bleeding and spotting,
- inclusion of adequate numbers of heavier women,
- additional clinical pharmacology and CMC issues

Another SPA for Study CL13 was submitted on April 21, 2010 and on June 3, 2010 the Division sent an agreement letter concerning the protocol for the smaller study with the following DRUP clinical comments:

Levonorgestrel/Ethinyl estradiol transdermal patch

1. We encourage the trial ATI-CL13 to enroll, if possible, women < age 17 years
2. As previously discussed, we strongly recommend that the Sponsor also enroll women with a BMI ≥ 32 kg/m² in at least one of the safety and efficacy trials. Failure to do so will likely result in a statement in labeling that safety and efficacy have not been evaluated in women with a BMI ≥ 32 kg/m², if the product is approved for marketing.

It would be acceptable to define the efficacy population so that it includes only women below a certain BMI (e.g., BMI < 32 kg/m²) and to include women above that BMI only in the safety population. In this case, we recommend that you perform a secondary analysis of efficacy in these heavier women. Exclusion of these subjects from the primary efficacy analysis, however, would be reflected in product labeling.

3. Exclusion of women under age 35 years who smoke more than 10 cigarettes per day will likely result in exclusionary labeling, if the product is approved.
4. The daily diary cards should include instructions to report skin irritation/itching experienced during any week of patch wear, not just "during last week of patch wear."
5. The daily diary cards should provide definitions of spotting, and light, normal, and heavy bleeding.
6. We request that you follow the Mishell et al. recommendations (Contraception Jan 2007, Vol. 75, Issue 1, pages 4-15) for your primary analysis of the bleeding profile, rather than using the 84-day reference period discussed in the protocol. For the various parameters of bleeding and/or spotting, provide the mean, median, and range of observed days of bleeding, spotting, and bleeding plus spotting within each 28-day reference period.

The Sponsor again requested a SPA of revised protocol ATL-CL12, titled "*An open-label, randomized, parallel group, Phase 3 study of the contraceptive efficacy and safety of Agile transdermal contraceptive delivery system (TCDS) in comparison to oral contraceptive (Levlite®).*" On July 13, 2010, the Division sent an Agreement letter to the Sponsor. Based on the information submitted, the Division agreed that the design and planned analysis of the larger phase 3 study adequately addressed the objectives necessary to support a regulatory submission.

A pre-NDA meeting scheduled for October 24, 2011 was cancelled based on the extensive preliminary responses that were conveyed from DRUP to the Sponsor on October 20, 2011. Some of the notable clinically relevant comments were the following:

1. Postmarketing requirements and commitments will be discussed as part of the approval process, if the NDA is approved.
2. The NDA submission needs to also include the narratives and CRFs for all pregnancies and all the Pregnancy Follow-up Forms. The Division also requests

that the Sponsor submit the Data Safety Monitoring Board (DSMB) meeting minutes, if applicable.

3. It would be helpful for the Sponsor to conduct and submit the results of a Standardized MedDRA Query (SMQ) for venous thromboembolism in the phase 3 database.
4. The Agency does not require submission in Study Data Tabulation Model (SDTM), but the Division strongly encourages the Sponsor to do so if possible.

The NDA was received on April 13, 2012 and has a PDUFA due date of February 13, 2013.

2.6 Other Relevant Background Information

On May 31, 2012, the Division had a teleconference with the Applicant concerning the high Pearl Index found in the two phase 3 clinical trials in the intent-to-treat (ITT) population. The Applicant was told that the acceptability of the risk/benefit profile of the LNG/EE transdermal delivery system would be a significant review issue. The Division requested that the following clinical information be submitted to the NDA:

1. Submit an integrated safety dataset for Studies ATI-CL12 and ATI-CL13.
2. The final study reports indicate that you have submitted narratives and case report forms (CRFs) for deaths, other serious adverse events and "certain other significant adverse events." Clarify whether you have provided narratives and CRFs for all subjects who withdrew due to adverse events, and submit these if you have not.

On June 26, 2012, other potential review issues (CMC, labeling, and promotional material) that were not discussed at the May teleconference were noted in a Filing Communication letter that was sent to the Applicant.

The Division concerns about the Pearl Index were repeated in the 10-25-12 DRUP Advice letter that stated the following:

1. We continue to find that the Pearl Index values demonstrated in the two phase 3 studies are well above the range the Division has generally determined to be acceptable for a hormonal contraceptive. The acceptability of the risk/benefit profile remains a significant review issue.
2. In addition to the 44 on-treatment pregnancies identified in the two study reports for the study drug arms, we have identified the following four additional pregnancies in Study CL-12 that we consider to be on-treatment pregnancies; inclusion of three of these pregnancies (the fourth had a body mass index $> 32 \text{ kg/m}^2$) results in a pooled 12-month Pearl Index of 7.07 (95% confidence interval 4.66-9.47) for the "ITT2" efficacy dataset that includes women aged 17 to 35 years with body mass index $< 32 \text{ kg/m}^2$.

3. We also have the following major quality concerns, which may have impacted product efficacy:
- We are concerned with the stability of the transdermal system with regard to the permeation enhancers, particularly given their importance in achieving proper therapeutic effect. A downward trend in excipient assay content is noted in long-term stability data provided in the application. *In vitro* drug release is not indicative of permeation characteristics and, therefore, cannot be used to justify the lower extremes of the acceptance criteria. We acknowledge receipt of your response to our Information Request letter dated September 24, 2012, in which you were requested to further justify the lower limits of the Excipient Assay; review of this response is ongoing.
 - Additionally, we note a downward trend in adhesion values as the product ages. Although we recognize that adhesion to steel is not indicative of adhesion to skin, a downward trend in quality adhesion values as a product ages may also translate to a downward trend in wearability, particularly given that this product requires seven-day wear and the use of an overlay to maintain adequate adhesion to the skin. We acknowledge receipt of your response to our Information Request letter dated September 24, 2012, in which you were requested to further assess the clinical impact of this finding by describing the age of transdermal systems used in your clinical trials and the impact of patch age on skin adhesion; review of this response is ongoing.

3 Ethics and Good Clinical Practices

IRB approval:

The protocol, informed consent form, and any materials such as subject information sheets, descriptions of the study used to obtain informed consent for the studies were reviewed and approved by an Institutional Review Board (IRB). The studies were performed in accordance with Good Clinical Practices (GCP) by qualified investigators. Each investigator who participated in the study provided a letter documenting IRB approval prior to initiation of the study. The amendments to the protocols were subject to the same requirements as the original protocols.

Study conduct and informed consents:

The studies were conducted in compliance with the Declaration of Helsinki (2004) guidelines for Good Clinical Practice E6 (R1). Each subject was provided with oral and written information describing the nature and duration of the individual study in a language they understood. All subjects who chose to participate in a study provided a signed informed consent form (ICF) before undergoing screening.

3.1 Submission Quality and Integrity

The submission integrity appears to be acceptable, but in my opinion **the quality is inferior to that seen in most NDA submissions for a hormonal contraceptive indication**. A few examples are the following:

1. The overall dosing compliance was poor.
2. The dropout and lost to follow-up rates were higher than usually seen.
3. Many subjects with multiple (4-6) medical problems and/or on multiple medications were enrolled.
4. In Study CL12 all sites had 3 specific scheduled times during Cycles 2, 6, and 13 to draw blood samples for LNG and EE levels. In a subset of 120 subjects, blood samples were drawn at three sites for serum levels of sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG). At one of these 3 sites, at least one of the 3 samples was not done for SHBG and CBG in 47% (27/57) of subjects, and at least one was not done for LNG and EE in 53% (30/57) of subjects.
5. Five subjects with positive pregnancy tests and “non-confirmed pregnancies” are discussed in the CL12 Study Report Section 11.4.1 (pages 147 to 164) but are not listed in the Clinical Statistical Report listing 16.2_6.2.3.4. This is clearly an omission by the Applicant.
6. In the CL12 Study Report Section 10.3 Protocol Violations (pg 72), the Applicant states there were “48 major protocol violations for randomized subjects” and makes reference to Listing 16.2._2.3. Listing 16.2._2.3 has 733 pages of violations for Study CL12 alone and several violations are listed on each page, so there were thousands of listed minor protocol violations. It is not clear which of these were the “major” protocol violations and the exact definition for major violations is not specified in the protocol.
7. There were many inconsistencies in the data reporting in several places throughout the study reports.
8. The Applicant notes that of the subjects who discontinued either of the phase 3 trials, 21% of them dropped out before Cycle 2 in the patch treatment arm and 18% in the OC treatment arm, “supporting the possibility that a significant number of these subjects were primarily motivated to participate in the study for the benefits associated with the initial health care assessment, less so the full rigors of the entire trial.” This reviewer would argue that it is the responsibility of the principal investigator (PI) at each site to enroll subjects who will stay in the trial for the stated duration, so the fact that 18-21% of the women dropped out before Cycle 2 indicates a lack of careful screening and discretion in enrollment at many of the study sites.

In summary, there were many omissions or errors discovered during the review process, as noted in most of the examples above. During the review process, the Division made several information requests to the Applicant to provide additional data important to the clinical or chemistry reviews.

As is common for registration trials, DSI inspected three clinical sites, which is a small fraction of the total sites. It is unknown if the poor performance and “numerous minor discrepancies” detected by the FDA field inspectors at the three sites is representative of the quality of data collection at the many other sites in the two phase 3 trials. **See Section 9.4 at the end of this review for further details.**

3.2 Compliance with Good Clinical Practices

The clinical trials needed for this NDA submission were reportedly conducted in compliance with the 2004 Declaration of Helsinki guideline for Good Clinical Practice.

3.3 Financial Disclosures

In Module 1.3.4 of the submission, Form 3454, statement (1), was signed by Marie Foegh, MD, Dr. Sc., the Chief Medical Officer and Vice-President, Clinical Research and Development. No financial disclosures (conflicts) were stated. Financial disclosures have not been independently audited by the FDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

On 9-24-12, Caroline Strasinger, Reviewing Chemist, the Division of New Drug Quality Assessment II, ONDQA II, made 21 comments and information requests to the Applicant. A prompt written response was requested for no later than October 17, 2012 in order to continue the CMC evaluation of the NDA.

On 9-24-12 a separate Methods Validation Request was made to the Applicant by Michael Trehy, MVP coordinator, Division of Pharmaceutical Analysis, Office of Pharmaceutical Science (OPS), CDER. The Applicant responded promptly on 9-26-12 and Michael completed his report on November 21, 2012.

Continuing CMC issues included the following, which were not resolved by 1/8/13:

- The US manufacturing site will not be “ready for inspection” until June 2013
- 12-month stability data has not been fully evaluated, especially with regard to the permeation enhancers
- Excipient assay content shows a downward trend, which is of concern for the long-term stability; the lower limits of the Excipient Assay must be adequately justified by the Applicant
- There is a downward trend in adhesion values as the product ages: patch adherence and potential loss of hormones has not been adequately analyzed by the Applicant and the FDA chemists; **if this is determined to be a significant issue, then it might help explain the unacceptable pregnancy (failure) rate.**

Reviewer’s comment:

These CMC issues alone are enough to warrant non-approval of the Agile transdermal contraceptive patch. It does not appear that there is any way that the Applicant can adequately address the above issues before the February PDUFA goal date for this NDA submission. Especially surprising was the statement that the Michigan manufacturing

site would not be ready for inspection until June 2013. It is unclear when this information became known to the Applicant.

4.2 Clinical Microbiology

It was determined that a microbiological review or inspection was not required.

4.3 Preclinical Pharmacology/Toxicology

Both of the active hormonal components are well known and their preclinical safety has been well established in the doses found in the proposed transdermal product. For further details, see the review by Krishan Raheja, DVM, PhD completed on 5-9-12. From the preclinical/toxicology perspective, Dr. Raheja recommended approval of NDA 204017 for the prevention of pregnancy.

4.4 Clinical Pharmacology

Data from several clinical pharmacology studies was reviewed by Hyunjin Kim, PhD. Table 1 lists the studies submitted in this NDA application that were either primarily a clinical pharmacology study or had a subset of subjects that were used for important clinical pharmacology data.

Table 1: Clinical Pharmacology Studies

Study ID	Design and Control Type Development Stage	Study and Control Drugs	Key PK/PD Study Objective(s)	# of subjects Mean: Age, BMI	Outcome Measures
ATI-CL15	Open-label, randomized, 3- period crossover Phase 1	AG200-15/TCDS 2.60 mg LNG/ 2.30 mg EE/15cm ² Subjects received study patch for 3 7-day periods; washout phase of at least 7 days patch	Assess the effect of the anatomic site of patch application on EE/LNG PK <u>Patch sites:</u> Lower abdomen Upper torso Buttock	24 enrolled 24 safety 32.2 years 24.7 kg/m ²	EE and LNG PK

Levonorgestrel/Ethinyl estradiol transdermal patch

Study ID	Design and Control Type Development Stage	Study and Control Drugs	Key PK/PD Study Objective(s)	# of subjects Mean: Age, BMI	Outcome Measures
ATI-CL16	Open-label, randomized, 3- period, incomplete block, crossover Phase 1	AG200-15/TCDS 2.60 mg LNG/2.30 mg EE/15 cm ² Subjects received study patch for 3 7-day periods; washout phase of at least 7 days	Assess the effects of extreme environmental conditions on EE/LNG PK/patch adhesion <u>Patch site:</u> Lower abdomen Four specified external conditions (dry sauna, whirlpool, treadmill exercise, and cold water immersion, vs normal conditions)	24 enrolled 24 safety 35.1 years 26.4 kg/m ²	EE and LNG PK, patch adhesion
ATI-CL10	Open-label, randomized comparative 2 period, crossover Phase 1/2	AG200/TCDS 2.17 mg LNG/1.92 mg EE/ 12.5 cm ² AG200LE/TCDS 2.17 mg LNG/1.28 mg EE/12.5 cm ² OC (Levlen®): 150 µg LNG / 30 µg EE daily Subjects underwent 7-day placebo screening period 2 followed by treatment periods of 21 days with washout period between each (at least 21 days).	PK profiles of LNG and EE; patch acceptability, cycle control, relative estrogenicity/ PD effects on synthesis of hepatic globulins <u>Patch site:</u> Lower abdomen	59 enrolled/38 safety 27.4 years 24.6 kg/m ²	EE and LNG PK; PD; bleeding; SHBG, CBG, CBG-BC levels; patch adhesion, skin irritation

Levonorgestrel/Ethinyl estradiol transdermal patch

Study ID	Design and Control Type Development Stage	Study and Control Drugs	Key PK/PD Study Objective(s)	# of subjects Mean: Age, BMI	Outcome Measures
ATI-CL11	Open-label, randomized, parallel group Phase 2	AG200-15/TCDS 2.60 mg LNG/ 2.30 mg EE / 15 cm ² AG200/TCDS 2.17 mg LNG/ 1.92 mg EE/ 12.5 cm ² AG200LE/TCDS 2.17 mg LNG/ 1.28 mg EE / 12.5 cm ² Subjects received study patch for 3 28-day cycles (3 weekly patches, 7 days patch- free)	Evaluate PK of TCDSs containing 2 different doses of LNG and 3 different doses of EE during 3 consecutive cycles of administration <u>Patch site:</u> Lower abdomen	AG200; 45 enrolled 44 safety 31.0 years 27.7 kg/m ² AG200-LE; 45 enrolled 43 safety 31.7 years 28.7 kg/m ² AG200-15; 33 enrolled 31 safety 32.1 years 27.5 kg/m ²	EE and LNG PK, progesterone and estradiol levels, SHBG levels, patch adhesion. Ovulation suppression.
ATI-CL12	Open-label, randomized, parallel group Phase 3	AG200-15/TCDS 2.60mg LNG/ 2.30mg EE / 15cm ² Subjects received study patch for 13, 28-day cycles (cycle = 3 weekly patches, 7 days patch-free) ----- Oral contraceptive 0.100 mg LNG/0.20 mg EE Subjects received once daily OC for 6 cycles then switched to AG200-15 for 7 28-day cycles	Effects of the patch on EE/LNG PK and on hepatic binding globulins compared to a low-dose OC, and patch wearability <u>Patch sites:</u> Abdomen, Buttock Upper torso (sites could be changed from cycle to cycle)	AG200-15; 1378 enrolled (includes 249 who switched to patch from OC at cycle 7) 1268 safety 26.48 yrs 27.54 kg/m ² ----- Oral Contraceptive 375 enrolled 344 safety 26.38 yrs 27.52 kg/m ² Note: 28.3% AG200-15 had BMI ≥ 30;	EE and LNG PK, SHBG and CBG levels, patch adhesion

Source: Applicant Clinical Overview, Table 2, page 10-12.

Reviewer's comment:

Study CL14 is not listed in the table above. Study CL10 has comparative PK information with 2 earlier formulations (AG200 and AG200LE), whereas Study 14 has the comparative PK information with the to-be-marketed formulation (same as the phase 3 formulation; AG200-15). Study 10 was not included in the Clinical Pharmacology review because it did not include the to-be-marketed formulation; but Study 14 was reviewed.

4.4.1 Mechanism of Action

The statement in the proposed label is the following:

Combination hormonal contraceptives lower the risk of becoming pregnant primarily by suppressing ovulation. (b) (4)

Reviewer's comment:

(b) (4)

Based on the results for ovulation suppression found in Study ATI-CL11, there is no reason to change the statement at this time for the Agile transdermal patch.

4.4.2 Pharmacodynamics

The phase 2 Ovulation Suppression study ATI-CL11 evaluated 3 different formulations (AG200-15, AG200, and AG200LE) at 13 centers for 3 cycles of use. Forty-five subjects used AG200, 45 used AG200LE, and 33 used the AG200-15 patch, so there were over 350 cycles with data to help determine ovulation rates. All of the formulations were similar with respect to the major components of the transdermal contraceptive delivery system (TCDS). The amounts of LNG and EE released differed between the formulations (see Table 2). AG200-15 had a higher load of LNG/EE and was expected to have a higher daily release than AG200, and had a 20% larger active drug area, namely, 15 cm² vs. 12.5 cm². Study ATI-CL11 demonstrated that a dose-response was observed between formulations.

The primary endpoint was the incidence of possible ovulation (defined as the proportion of cycles with progesterone level ≥ 4.7 ng/mL) in women with body mass index (BMI) ≤ 32 kg/m². This endpoint was evaluated on 4 different analysis datasets, representing various levels of treatment compliance. Secondary ovulation endpoints included using progesterone levels as markers for the following:

- Incidence of probable ovulation (2 successive progesterone levels ≥ 4.7 ng/ml)
- Incidence of luteal activity (cycles with progesterone levels > 3 and < 4.7 ng/ml)
- Incidence of likely ovulation (cycles with progesterone levels ≥ 9.0 ng/ml)
- Incidence of possible ovulation and/or luteal activity (the proportion of cycles with progesterone level ≥ 3.0 ng/ml)

The AG200-LE patch delivered less than the predicted levels of LNG/EE and was determined to be a non-effective dose (with respect to ovulation suppression) so further development was not pursued for this patch.

Table 2: Summary of Formulations in Efficacy Studies

Formulation	Study No.	Patch Active Drug Area Dimensions (cm ²)	Amount of LNG (mg)/ EE (mg)	Expected daily release LNG (µg)/EE (µg)
Final Formulation				
AG200-15	ATI-CL11	15.0	2.60/2.30	120/30
	ATI-CL12			
	ATI-CL13			
Prototype Formulations				
AG200	ATI-CL11	12.5	2.17/1.92	100/25
AG200LE	ATI-CL11	12.5	2.17/1.28	100/20

Abbreviations: LNG- levonorgestrel; EE- ethinyl estradiol.

Source: Sponsor Clinical Overview, pg 6.

AG200 and AG200-15 were both effective for ovulation suppression. However, AG200-15 exhibited a better cycle control than both AG200 and AG200-LE in the three 21/7 day treatment cycles. Therefore, AG200-15 was selected for further development.

Reviewer's comment:

Probable ovulation occurred in 25-27.2% of AG200LE cycles compared to 7.7-9.6% of AG200-15 cycles. The same trend was seen in the datasets for "possible" ovulation. I concur with the selection of the AG200-15 patch for further development in the phase 3 studies as ovulation suppression was effective and cycle control was better with this formulation as shown in Study ATI-CL11.

4.4.3 Pharmacokinetics (PK)

The Applicant did PK studies to compare the different Agile patches to two oral contraceptives (Levlen with LNG 150 mcg/EE 30 mcg and Ortho Cyclen with norgestimate 250 mcg/EE 35 mcg). The PK profiles for an OC and a transdermal patch are very different, but comparisons were made. The maximum EE concentration levels (C_{max}) were lower for the patch compared to the OCs. Based on steady-state concentration levels and AUC data, the Applicant's calculated in Study CL10 and CL14 that the daily dose of the AG200-15 patch was equivalent to approximately 30 mcg EE. The Applicant concluded that "levonorgestrel delivery after treatment with the AG200-15 patch was similar to the historical data for low-dose LNG/EE oral contraceptives."

Reviewer's comments:

Prior to submitting the NDA, the Applicant submitted summary PK data from Study CL10 (intense PK values for 2 different formulations: AG200 and AG200LE) and Study CL11 (trough PK values for 3 formulations: AG200, AG200LE and AG200-15 [the current formulation]). After Clinical Pharmacology reviewed these PK data, the Division requested the Applicant to conduct a relative BA study with AG200-15 and an OC (without defining the dose of EE to be studied). The Applicant conducted Study CL14 before conducting the two phase 3 studies.

The clinical pharmacology reviewer, Hyunjin Kim, has reviewed the PK data. His review states:

“EE exposures from AG200-15 and Ortho-Cyclen containing 0.035 mg EE and 0.25 mg norgestimate were compared in Weeks 1 and 3 during one cycle. There was approximately 13% increase of EE mean C_{max} from Week 1 to Week 3 in AG200-15, whereas there was no increase of EE mean C_{max} in Ortho-Cyclen. Overall, the EE mean C_{max} from AG200-15 was about 39% of EE mean C_{max} from Ortho-Cyclen based on PK data observed in Week 3. Overall, the AUC and C_{max} of EE from AG200-15 were about 10% and 61% lower than AUC and C_{max} of EE from Ortho-Cyclen based on the PK data observed in Week 3. However, due to the potential between cycle accumulation of EE, the study result may not be reliable.”

The actual PK profile of the transdermal patch is very different with lower C_{max} values and steady state concentrations that do not fluctuate daily. For a detailed analysis of the Applicant's studies and the FDA interpretation of the PK results, see the Clinical Pharmacology review by Hyunjin Kim, PhD.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 above provides a complete listing of clinical pharmacology and the larger of two phase 3 clinical trials, in which PK data were obtained. The phase 3 studies were conducted to evaluate the efficacy of AG200-15 to prevent pregnancy in women. Study ATI-CL12 was an open-label, randomized, active-controlled, multicenter (102 sites in the US), phase 3 study of the contraceptive efficacy and safety of AG200-15 in comparison to a low-dose oral contraceptive containing 20 mcg EE and 100 mcg LNG (OC20) in a 21-day regimen. Study ATI-CL13 was an open-label, randomized, active-controlled, 6-month, multicenter, phase 3 study at 21 US centers for the contraceptive efficacy and safety of Agile AG200-15 in comparison with an oral contraceptive containing 150 mcg LNG and 30 mcg EE (OC30).

Table 3: Phase 3 Clinical Trials

Study	Design	OC Comparator	Subjects (N)* Enrolled	Additional Information
ATI-CL12	Randomized 3:1, 13-cycle, open-label; OC arm: use for 6 months only	LNG 100 mcg EE 20 mcg	1129- patch 375- OC 249- change to patch at Cycle 7	102 US sites; Aug 2010 to Nov 2011 No BMI restriction
ATI-CL13	Randomized 1:1, 6-cycle, open-label	LNG 150 mcg EE 30 mcg	201- patch 206- OC Age 18-40	21 US sites; Oct 2010 to Jun 2011 BMI < 32

* N= the number enrolled; the N for efficacy and safety data will be smaller because of non-compliance and lost to follow-up.

Source: Reviewer table compiled from different sources.

Reviewer's comment:

Hereafter, these studies will be referred to by the last 4 digits of the full study ID number (for example, study ATI-CL12 will be referred to as study "CL12"). The table below outlines the schedule of visits and procedures that were done for the most important of the two phase 3 studies, namely the 13-cycle, large, comparative study CL12. The procedures were very similar for Study CL13, and there were visits

Table 4: Schedule of Visits and Procedures- Study CL12 (pivotal trial)

Procedure	Visit 1 (Screen)	Visit 2 (Randomi- zation)	Visit 3 (Cycle 2, Days 8-11)	Visit 4 ¹ (Cycle 4, Days 8-11)	Visit 5 (Cycle 6, Days 15-17)	Visit 6 (Cycle 9, Days 8-11)	Visit 7 (Cycle 13, Days 15-17)	Visit 8 (Final D/
Informed consent	X							
Relevant medical history	X							
Vital signs ²	X	X		X	X	X	X	X
Physical and Gynecological examination	X				X ³			X
Pap Smear	X ⁴							X
Routine laboratory evaluations ⁵	X ⁶				X ³			X
Serum (-hCG) pregnancy test	X			X	X	X	X	X
Urine pregnancy test ⁷		X						
Randomization (Enrollment)		X						
LNG/EE, SHBG/CBG blood			X		X		X	
Application site (skin)			X	X	X	X	X	
Subject satisfaction		X			X			X
Study drug, diary cards and urine pregnancy tests		X		X	X	X	X	
Adverse Event, Concomitant Medication, Compliance monitored			X	X	X	X	X	X

1 All visits during AG200-15 treatment should take place close to the patch change days (Cycle Days 8 and 15) if possible. Visit 8 should take place 14 days after last active dose.

2 Including body weight

3 For OC group only

4 Pap smear taken within 6 months prior to the screening will be acceptable if properly documented

5 Hematology, Clinical Chemistry, Lipid Panel, and Urinalysis. Subjects must be fasting 10-12 hours.

6 Other screening tests include HIV antibody test, HBsAg test, HCV antibody test, thyroxine (Free T4) test, chlamydia and gonorrhea screening tests

7 Urine pregnancy tests will be performed in the office prior to randomization and at home by subjects that experience no withdrawal bleeding before start of new treatment cycle.

8 LNG/EE and SHBG/CBG blood draws after application of the patch for that week (AG200-15 group) or 1-1.5 hours after the pill taken (OC group) if pill is taken in the morning. SHBG and CBG will be done at approximately 3 selected sites in a subgroup of approximately 120 subjects (60 patch/60 pill)

5.2 Review Strategy

The overall strategy was to look at the claims in the Applicant's proposed label and then focus on the overall typical use contraceptive efficacy from phase 3 trials CL12 and CL13. Review strategy also involved a review of the two Clinical Study Reports, previous meeting minutes, and agreements between the Division and Applicant. For the safety review, data from the total patch use in the several pharmacology studies and especially the two phase 3 clinical trials (data were pooled in the Integrated Summary of Safety) were used in the integrated safety analysis. The medical literature was not relied upon to support efficacy and safety for this product.

The Principal Investigators and the study sites were reviewed for total enrollments, pregnancies, serious adverse events and drop-outs. There was close collaboration with the FDA Statistician Kate Dwyer, PhD, regarding the Pearl Index (PI) calculations.

Consultations to the Office of Medication Error Prevention and Risk Management (DMEPA - tradename review), OPDP (former Division of Drug Marketing, Advertising, and Communications, DDMAC - package insert labeling review), and DMPP (former Division of Risk Management, DRISK - patient package insert review) were requested. After a review of the investigative sites (principal investigators, enrollments, study drop-outs, pregnancies, and adverse events) the Division elected to request DSI inspections of 3 specific sites.

5.2.1 Mid-cycle Meeting

The Division reached this major milestone of the NDA review and provided the Applicant with an update on the status of the review. On 10-25-12 the following clinical comments and recommendations were sent to the Applicant:

1. We continue to find that the Pearl Index values demonstrated in the two phase 3 studies are well above the range the Division has generally determined to be

Levonorgestrel/Ethinyl estradiol transdermal patch

acceptable for a hormonal contraceptive. The acceptability of the risk/benefit profile remains a significant review issue.

2. In addition to the 44 on-treatment pregnancies identified in the two study reports for the study drug arms, we have identified the following four additional pregnancies in Study CL-12 that we consider to be on-treatment pregnancies; inclusion of three of these pregnancies (the fourth had a body mass index $> 32 \text{ kg/m}^2$) results in a pooled 12-month Pearl Index of 7.07 (95% confidence interval 4.66-9.47) for the "ITT2" efficacy dataset that includes women aged 17 to 35 years with body mass index $< 32 \text{ kg/m}^2$.

- Subject (b) (6) used AG200-15 for two complete cycles starting August 21, 2010 and September 18, 2010; she had a negative hCG on August 5, 2010 and a positive serum hCG of 20,454 mIU/mL on October 15, 2010. No ultrasound or bimanual pelvic exams were performed. Her daily diary card shows no withdrawal bleeding following the two patch cycles, but the pregnancy form states that the first day of her last menstrual period (LMP) was September 7, 2010. The investigator (and the Division) believes her conception date is September 20, 2010, so this is considered an on-treatment pregnancy.
- Subject (b) (6) was treated for 11 cycles; her LMP started on June 7, 2011, the last active dose was June 28, 2011, and she was seen July 1, 2011 with a positive hCG of 251 mIU/mL. An ultrasound on July 7, 2011 confirmed the pregnancy (the photograph is unreadable) and she had a medical abortion that same day. The conception date was between June 9 - 17, 2011 as determined by the investigator, the hCG level and ultrasound. This is considered an on-treatment pregnancy.
- Subject (b) (6) was treated for 13 cycles; her LMP started on July 24, 2011, the last active dose was August 14, 2011, and she was seen on September 1, 2011 with a positive hCG of 236 mIU/mL. A pelvic exam that day was reported as "pregnant uterus." An ultrasound on September 13, 2011 showed a probable miscarriage and the hCG was 7 mIU/mL. Given the hCG of 236 mIU/mL, which corresponds to 1-2 weeks gestation, and the finding of a "pregnant" uterus on September 1, 2011, the Division considers that conception likely occurred around August 18-25, which includes the window of "last dose + 7 days," and therefore we consider this an on-treatment pregnancy under a "worst case" evaluation of a poorly dated pregnancy.
- Subject (b) (6) was treated for 13 cycles; her LMP started on September 15, 2011 with three days of spotting only. The last active dose was September 17, 2011, and she was seen on October 6, 2011, with a positive hCG of 68 mIU/mL. No ultrasound results or follow-up results are reported. The hCG of 68 mIU/mL corresponds to 1-2 weeks gestation, so the conception most likely occurred around September 22 - 29, 2011, which includes the window of "last dose + 7 days." Therefore, we consider this an on-treatment pregnancy under a "worst case" evaluation of poorly dated pregnancies. Other factors that

increase the likelihood that this is an on-treatment pregnancy are that the subject stopped active treatment on Day 18 (instead of Day 21) of the treatment cycle and that her LMP was three days of spotting only (i.e., compatible with an early pregnancy).

3. We also have the following major quality concerns, which may have impacted product efficacy:
- We are concerned with the stability of the transdermal system with regard to the permeation enhancers, particularly given their importance in achieving proper therapeutic effect. A downward trend in excipient assay content is noted in long-term stability data provided in the application. *In vitro* drug release is not indicative of permeation characteristics and, therefore, cannot be used to justify the lower extremes of the acceptance criteria. We acknowledge receipt of your response to our Information Request letter dated September 24, 2012, in which you were requested to further justify the lower limits of the Excipient Assay; review of this response is ongoing.
 - Additionally, we note a downward trend in adhesion values as the product ages. Although we recognize that adhesion to steel is not indicative of adhesion to skin, a downward trend in quality adhesion values as a product ages may also translate to a downward trend in wearability, particularly given that this product requires seven-day wear and the use of an overlay to maintain adequate adhesion to the skin. We acknowledge receipt of your response to our Information Request letter dated September 24, 2012, in which you were requested to further assess the clinical impact of this finding by describing the age of transdermal systems used in your clinical trials and the impact of patch age on skin adhesion; review of this response is ongoing.

Reviewer Comment:

From the clinical perspective, throughout the review process, including pre-submission, the Applicant has been warned about the Division's concerns about the high Pearl Index (PI), low trial completion rates, and the high dropout rates. The potential CMC issues were not known until the NDA chemistry data could be reviewed in detail. The issue of the overall study quality was discovered during the review process by this medical officer (clinical reviewer).

5.2.2 Applicant Response to DRUP Advice Letter dated 10-25-12

On 11-29-12 the Applicant responded to the Division letter with the following:

"We do not believe that the PIs in our pivotal studies are higher than would be expected in the populations studied and analyzed in the manner utilized. Nor do we believe that the study data or the product quality data support diminished product efficacy compared to the approved hormonal contraceptives used in our studies or to other previously approved hormonal contraceptives.

To respond fully to the clinical issues raised in the General Advice letter, especially in Comments 1 and 2, Agile is evaluating whether it would be helpful to the Division for us to prepare a submission providing detailed data and analyses. We are considering such a submission, targeted for January 2013, and would welcome your reaction to our providing such additional detailed data and analyses. We recognize, of course, that were we to make such a submission at that point in the process, it might entail your treating it as a major amendment and extending the PDUFA date.”

Reviewer’s comment:

The Division decided that additional data would not be helpful or necessary for an adequate evaluation of the NDA submission. While the Applicant is free to submit additional materials to the NDA application, the Division is not obligated to review them at such a late date in the review process, particularly where they are unlikely to change the review decision.

5.3 Discussion of Individual Studies/Clinical Trials

Although the two phase 3 trials were not identical in design, the efficacy results will be discussed in an integrated manner and conclusions made. A different OC comparator was used for the first 6 months in the two trials, but comparison to an OC is not critical for the approval of the Agile transdermal patch and no potential claims of superiority were agreed to with the Division during the development process. So the focus is on the performance of the Agile transdermal patch on its own merits and not on how it compares to the two OCs used in the trials.

6 Review of Efficacy

Efficacy Summary

Whether one looks at the Applicant’s results or the FDA calculations which include 5 additional pregnancies (8 total) not counted by the Applicant, the Pearl Index (PI) for the primary contraceptive efficacy dataset is unacceptable. Even in the population of all subjects without age restriction, which traditionally lowers the PI because women older than 36 are less fertile than younger women, the Applicant and FDA PI values of > 6.0 are unacceptable. The other notable finding here is the number of evaluable cycles for women age 17-35: the Division typically requests 10,000 cycles of exposure for efficacy and safety, but a lower number may be acceptable if the Pearl Index is lower (preferably < 3.0) and with a tight 95% confidence interval (and if the drug products have well-characterized safety profiles). In this NDA, the number of evaluable cycles for the primary efficacy endpoint in the ITT2 population is 6,070 (considerably less than 10,000), while the various Pearl Indices and the confidence intervals are all significantly higher/wider than the Division has previously found acceptable for approval of a combination hormonal contraceptive drug product.

The Applicant has several secondary analyses of subsets of subjects evaluating “compliant” subjects, subjects with a BMI < 32 and < 30, different racial groups, Cycle 1-6 use only, previous hormonal contraceptive users, etc. All of these analyses are not

part of the prespecified primary efficacy dataset, so they are not pertinent to the decision for approval of the NDA for contraception.

As noted throughout this NDA review, one of the most significant findings in the two phase 3 clinical trials is the high discontinuation rate and lost to follow-up rate. Data from these subjects is unknown/missing, and can only mean that the efficacy and safety findings may possibly be worse than those determined by review of the available data.

6.1 Indication

The Agile TCDS is indicated for the prevention of pregnancy in women who elect to use a transdermal patch for contraception.

6.1.1 Methods

The overall design of the two phase clinical trials is outlined in Table 3. The Applicant was told that a minimum of 10,000 cycles of exposure to the patch and at least 200 women completing 13 cycles of exposure would be needed for an NDA application.

Study CL12 was the large and key phase 3 contraceptive study. It was an open-label, randomized, comparative, parallel group, multi-center study. Up to 1,500 sexually active women requesting contraception were to be enrolled in this study. The subjects were randomized in 3:1 ratio, with 1,125 subjects assigned to use the AG200-15 patch and 375 subjects randomized to OC. Approximately 1125 subjects were to be enrolled in the AG200-15 group for a one-year (13-cycle) consecutive treatment and 375 subjects were to be enrolled in the OC group for a 6-cycle treatment. After completion of 6 OC treatment cycles, subjects in this group were to switch (crossover) to using the AG200-15 patch for the next seven (7) additional cycles of treatment. See Table 4 for a detailed outline of the study visits and procedures.

Safety was assessed by tracking adverse events, discontinuation information, vital signs and from physical and gynecological examinations and laboratory test results (including a lipid panel). Adequacy of dosing and compliance was further assessed by measurement of EE and LNG plasma concentration levels three times during the planned 13 cycles of treatment. Patch application information, reasons for patch change and skin irritation information (AG200-15 treatment group), as well as pill-taking information were recorded by the subjects on diary cards for each cycle. The percentage of patches with wearability problems (patches fallen off, patches accidentally pulled off, patches partly detached, patches changed due to skin reaction) were reported by each reason and for all reasons combined.

Study Cycle # 1: Subjects randomized to use the patch started on the morning of Cycle Day 1 (first day of menses) or any day if they were switching immediately from current use of another pill/patch/ring. Three consecutive 7-day patches were used, followed by Day 22-28 as a patch-free period. The patches were applied to the abdomen, buttock or upper torso (excluding the breasts) and each patch placement was recorded on the

daily diary. Per protocol, subjects were to use the same anatomical site for the 3 consecutive weeks but to place the patch on a different location from the previous patch, so it was a minor protocol violation if different anatomical sites (abdomen, buttock or upper torso) were used during the same treatment cycle. Pill users started on Cycle Day 1 or any day during the previous active interval, and no later than Day 3 of the pill/patch/ring-free interval. Backup contraception was not needed for Cycle 1 for either patch or pill users because of the starting method used for the study.

A diary card was provided for each 28-day treatment cycle. The subject was given instructions as to how to complete it and to bring the cards back at her clinic visits. The diary was a part of the eCRF. Subjects recorded study drug administration information (cycle days when patch was worn or active tablet was taken as well as number of active tablets taken during particular day of the cycle). Days of the patch application and removal were reported, as well as reasons for patch change. Additionally, presence of skin irritation and pruritus were also reported for each week of patch wear. Subjects recorded information regarding use of back-up contraception during the treatment cycles. They indicated whether back-up contraception was used for reasons other than missed days of drug-taking or not. Subjects also recorded whether they had sexual intercourse during the treatment cycle; if no intercourse occurred, then the cycle was not counted as evaluable.

Subjects were instructed that if a patch was partially or completely detached for less than 24 hours, she should try to re-apply it to the same place or replace it with a new patch immediately; no back-up contraception was needed. Backup contraception was recommended in the case of 2 consecutive missed OC pills and for missed or loose patches. Additional instructions were:

- “If the patch becomes partially or completely detached and remains detached for more than one day (24 hours or more) OR if you are not sure how long the patch has been detached, you may be at greater risk of pregnancy. You should immediately start a new cycle of three patches by applying a new patch. Use back-up contraception for one week.
- If you forget to change your patch during the cycle (at Day 8 or Day 15) for more than two days (more than 48 hours), you may be at greater risk of pregnancy. You should stop the current contraceptive cycle and start a new four-week cycle immediately by putting on a new patch. There is now a new ‘Patch Change Day’ and a new ‘Day 1.’ You must use back-up contraception for one week.”

Subjects recorded bleeding information. A response of “None,” “Spotting,” “Light,” “Normal” or “Heavy” was recorded for each cycle day. Bleeding was defined as any bloody discharge requiring at least one tampon or sanitary napkin per day. Spotting was defined as bloody discharge that requires only a panty liner.

Study CL13 was the smaller and shorter (6 cycles) of the two phase 3 studies. It was an open-label, randomized, comparative, parallel group, multi-center, contraceptive efficacy and safety study. Up to 400 sexually active women requesting contraception

were enrolled in this study. The subjects were randomized in a 1:1 ratio, with 200 subjects assigned to the AG200-15 patch and 200 subjects assigned to an OC containing 150 mcg of LNG and 30 mcg of EE. During the conduct of the study, 201 subjects were randomized to receive AG200-15, and 206 subjects were randomized to receive the OC. The subjects were treated for 6 cycles. Instructions for starting the product for Cycle 1, daily recording on the diary, use of backup contraception were basically the same as for Study CL12. The safety and efficacy parameters were also the same. The trial excluded women with a BMI ≥ 32 .

Inclusion/Exclusion:

Both phase 3 studies were conducted in generally healthy, sexually active women aged 18 to 40 requesting contraception. In Study CL12, the minimum age for eligibility was 17 (in states where the legal age of consent to receive contraceptives was 17). Exclusion criteria in both studies were similar except that in the smaller and shorter Study CL13, eligibility was restricted to subjects with a BMI $< 32 \text{ kg/m}^2$.

The exact inclusion/exclusion criteria for Study CL12 follow here. Subjects must have met ALL of the following inclusion and exclusion criteria to be enrolled in the study:

Inclusion Criteria

1. Sexually active women requesting contraception;
2. 17 to 40 years old;
3. Regular menses every 24 - 35 days; if current continuous use of hormonal birth control, historical data will be used to determine qualification;
4. In good general health, confirmed by medical history, physical (including gynecologic) examination and screening laboratory values;
5. Willing to sign the informed consent form to participate in the study and refrain from using condoms on a regular basis and any other steroid hormonal therapy (other than topical corticosteroids) for the duration of the study.

Exclusion Criteria:

Subjects were excluded if ANY of the following exclusion criteria apply:

1. Known or suspected pregnancy;
2. Lactating women;
3. Breast-feeding within 42 days prior to the start of study medication;
4. Abnormal Papanicolaou (Pap) smear (Pap smear results within last 6 months were acceptable if properly documented and met the criteria specified in the protocol);
5. Women who smoked and were ≥ 35 years old or turned 35 anytime during the study;
6. Uncontrolled hypertension (blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) in women with BMI $< 32 \text{ kg/m}^2$;
7. History or presence of hypertension (blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) in women with BMI $\geq 32 \text{ kg/m}^2$;
8. Valvular heart disease with complications;

9. Diabetes Mellitus with vascular disease in women with BMI $<32 \text{ kg/m}^2$;
10. Diabetes Mellitus type I and II in women with BMI $\geq 32 \text{ kg/m}^2$;
11. History of headaches with focal neurological symptoms;
12. Uncontrolled thyroid disorder;
13. Sickle cell anemia;
14. Current or history of clinically significant depression in the last year;
15. Known disturbance of lipid metabolism (triglycerides >300);
16. Acute or chronic hepatocellular disease with abnormal liver function;
17. Hepatic adenoma or carcinoma;
18. Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use;
19. Positive human immunodeficiency virus (HIV) and/or hepatitis at screening
20. Plans for major surgery with anticipated prolonged immobilization;
21. History of or existing thromboembolic disorder, vascular disease, cerebral vascular or coronary artery disease;
22. Undiagnosed abnormal genital bleeding;
23. Known or suspected breast carcinoma, endometrial carcinoma, or estrogen-dependent neoplasia;
24. History or presence of dermal hypersensitivity in response to topical applications (bandages, surgical tape, etc.) or known hypersensitivity to any components of this product;
25. Use of an injectable hormonal contraceptive within the past 6 months prior to the screening visit;
26. Used a contraceptive implant or hormone-medicated intrauterine device (IUD) within the 2 months prior to the screening visit;
27. Other contraceptive methods such as sterilization, tubal ligation or IUD (must be removed prior to randomization);
28. Status post-partum or post-abortion within a period of 42 days prior to the start of study medication;
29. Chronic use of any medication that might interfere with the efficacy of hormone contraceptives (including barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's Wort, topiramate, and HIV protease inhibitors);
30. Administration of any investigational drug and/or experimental device within 30 days prior to the screening visit, or current participation in any observational studies;
31. A recent history (within prior 12 months) of drug or alcohol abuse;
32. Deemed by the investigator to have questionable ability to comply with the protocol and provide accurate information;
33. Positive for chlamydia and gonorrhea;
34. Same sex relationship.

Reviewer's comments:

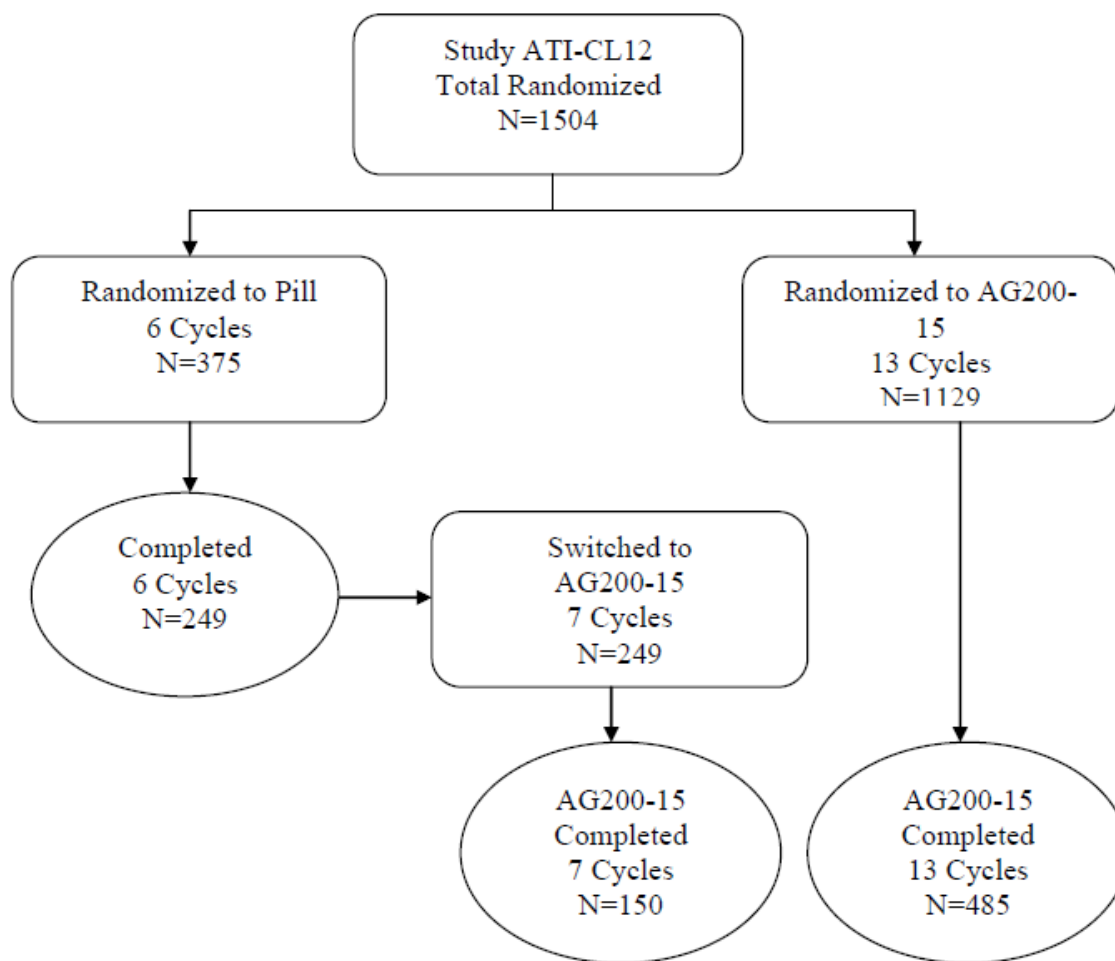
I concur with the above inclusion/exclusion criteria. The BMI restriction in Study CL13 was discussed with the Applicant. Prohibited medications include recent hormonal exposure and any medication that might interfere with the efficacy of hormonal contraceptives. However, it is unclear how Inclusion criterion #4 was interpreted by investigators. Several subjects were taking multiple medications for different significant medical conditions (including asthma, GERD, IBS, migraines, psychiatric conditions and renal stents), so it is difficult to know if the reported adverse events are due to the patch, the multiple medications or one of the medical conditions. It is also possible, although speculative, that the medications might interfere with the efficacy of the transdermal patch.

Even more problematic is exclusion # 32. It is apparent that some of the investigators were not very strict or careful in assessing the ability of many subjects to comply with the study protocol and provide accurate or reliable information. This fact led to a high drop-out rate, high lost to follow-up rate, and many subjects whose diary and visit data are hard to interpret, which complicates the accuracy of the assessment of safety and efficacy.

6.1.2 Demographics for Study CL12 and CL13

To better understand some of the difficult interpreting the data from the two phase 3 studies, especially Study CL12, Figure 1 displays a Flow Diagram of Study CL12 provided by the Applicant upon request by the Division. Study 12 had one arm in which subjects switched to patch use after completing 6 cycles of OC use. So there is a set of subjects who used the patch for 7 cycles, directly following use of the designated study OC for 6 cycles. This group of subjects is not equivalent to the subjects who used only the patch for 6 cycles in Study CL13 and then completed the study.

Figure 1
Flow Diagram



Source: Applicant diagram.

The table below shows the overall characteristics of the safety population in the larger 13-cycle Study CL12 by age, weight, height, and BMI. The lower portion of the table shows subsets of subjects by ethnicity, age, BMI, and hormonal contraceptive use.

Table 5: Demographic Characteristics- Safety Population CL12

Parameter	Statistic	Cycle 1-6 OC users	Cycle 7-13 Switchers (Subset of OC users)	Total AG200-15 N=1273
Subjects	n	344	230	1273
Age (years)	Mean	26.4	26.9	26.5
	Median	25.0	26.0	26.0
	SD, CV (%)	5.7, 21.8	5.7, 21.4	5.7, 21.5
	Min, Max	(17.0, 40.0)	(17.0, 40.0)	(17.0, 40.0)
Weight (kg)	n	344	230	1273
	Mean	73.7	72.8	73.9
	Median	68.4	67.6	69.0
	SD, CV (%)	19.6, 26.6	18.6, 25.6	19.9, 26.9
Height (cm)	Min, Max	(34.8, 149.7)	(45.5, 147.2)	(41.1, 172.3)
	n	344	230	1273
	Mean	163.5	163.2	163.8
	Median	163.2	163.2	163.5
BMI (kg/m2)	SD, CV (%)	7.2, 4.4	7.2, 4.4	7.0, 4.3
	Min, Max	(143.0, 185.4)	(143.0, 185.4)	(134.6, 188.0)
	n	344	230	1273
	Mean	27.5	27.3	27.5
	Median	26.4	26.2	26.0
	SD, CV (%)	6.8, 24.6	6.6, 24.2	7.1, 25.7
	Min, Max	(15.6, 56.6)	(17.6, 52.4)	(16.5, 59.8)
Subsets by Ethnicity, Age, BMI, and CHC use				
White (Not Hispanic)	n (%)	191 (55.5%)	140 (60.9%)	733 (57.6%)
Hispanic	n (%)	61 (17.7%)	37 (16.1%)	191 (15.0%)
Black	n (%)	71 (20.6%)	36 (15.7%)	275 (21.6%)
Asian	n (%)	12 (3.5%)	9 (3.9%)	44 (3.5%)
Other ethnicity	n (%)	9 (2.6%)	8 (3.5%)	30 (2.4%)
≤ 35 years	n (%)	313 (91.0%)	208 (90.4%)	1163 (91.4%)
> 35 years	n (%)	31 (9.0%)	22 (9.6%)	110 (8.6%)
BMI < 30	n (%)	245 (71.2)	168 (73.0)	912 (71.6)
BMI ≥30	n (%)	99 (28.8)	62 (27.0)	361 (28.4)
New CHC user	n (%)	198 (57.6)	116 (50.4)	710 (55.8)
Current CHC user	n (%)	57 (16.6)	45 (19.6)	228 (17.9)
Recent CHC user	n (%)	89 (25.9)	69 (30.0)	335 (26.3)

SD=standard deviation; CV=coefficient of variation; BMI=body mass index

Total AG200-15: Subjects randomized to AG200-15 + subjects in the OC/AG200-15 cohort.

OC/AG200-15 Switchers: Smaller set of subjects randomized to OC who switched to AG200-15 after 6 cycles.

Applicant Source: Table 14.1_2.1

Reviewer Source: Clinical Study ATI-CL12 Report, Applicant Table 6 on pg 76-77 of 423/

Reviewer's comments:

Data on women who used OCs in the first six months of the trial and then crossed-over to the patch are included in all three columns. The Applicant has been asked to provide clearer information about numbers of subjects in each arm of the study without duplicating information for this group that crossed-over to the patch at Month 7.

The flow diagram in Figure 1 does help show the number of subject who switched from OC use to patch use. Here again we see a discrepancy in the data provided by the Applicant; the flow diagram above has 249 subjects switching while the column in Table 5 above has 230.

As would be expected in a randomized trial, subjects in the treatment groups were comparable with respect to age, weight, height, BMI, race/ethnicity, categorical age, and previous contraceptive use status. The percentage of African Americans is higher than the 13-14% estimates for the 2011 US population, but in general, the trial population presents the diversity seen in the US. The treatment groups were also comparable with respect to highest level of education, smoking status, and current alcohol use. For their gynecological history, they were comparable with respect to age at menarche, typical length of menstrual cycle, and typical duration of menses; approximately half of the subjects in each group had never been pregnant; the majority of remaining subjects in each group reported 1 or 2 pregnancies and deliveries.

The Applicant's data for current contraceptive use prior to study CL12 enrollment are confusing and somewhat contradictory, and the Applicant was requested to provide clarification.* For the subjects in the Total AG200-15 cohort, the data in Applicant Table 6 above has 17.9% of subjects as current users of hormonal contraception and 26.3% as having used hormonal contraception within the last 6 months for a total of 44.2%. Using data from Applicant Table 8, pg 80 of the CL12 Study Report for current methods used in the prior 6 months, for the subjects in the Total AG200-15 cohort, 35.7% were utilizing an oral contraceptive method, 10.6% using a patch or vaginal ring, and 0.5% other hormonal methods for a total of 46.8% which does not agree with the 44.2% reported in Table 6. The highest proportion of subjects utilized a male condom with or without spermicide (50.4%) in the prior 6 months.

*On 1-9-13, in response to the DRUP Information Request, the Applicant provided the following explanation. For Table 6, the subject classification was based on the use of at least one hormonal contraceptive used over the prior 6 months; for Table 8, if a subject used more than one hormonal contraceptive over the prior 6 months, then > 1 was counted, therefore creating a higher % of hormonal contraceptive use in the prior 6 months. The percentages in both tables are correct, although they were initially confusing to this reviewer.

Demographic data for Study CL13

Table 6: Demographic Characteristics- Safety Population CL13

Parameter	Category	Statistic	OC N=188	AG200-15 N=177
Age (years)		n	188	177
		Mean	26.7	25.9
		Median	26.0	25.0
		SD	5.7	5.4
		CV (%)	21.5	21.0
		Min, Max	(18.0, 40.0)	(18.0, 40.0)
Weight (kg)		n	188	177
		Mean	66.2	65.9
		Median	65.0	65.9
		SD	10.9	11.1
		CV (%)	16.4	16.8
		Min, Max	(46.0, 99.0)	(43.2, 94.1)
Height (cm)		n	188	177
		Mean	163.0	163.7
		Median	162.6	163.8
		SD	6.2	6.8
		CV (%)	3.8	4.1
		Min, Max	(149.0, 180.3)	(147.3, 182.8)
BMI (kg/m ²)		n	188	177
		Mean	24.8	24.6
		Median	24.6	24.5
		SD	3.6	4.0
		CV (%)	14.4	16.1
		Min, Max	(17.0, 32.0)	(17.2, 31.9)
Race/Ethnicity	White (Not Hispanic)	n (%)	111 (59.0%)	106 (59.9%)
	Hispanic (White)	n (%)	37 (19.7%)	28 (15.8%)
	Black	n (%)	30 (16.0%)	34 (19.2%)
	Asian	n (%)	2 (1.1%)	6 (3.4%)
	Other	n (%)	8 (4.3%)	3 (1.7%)
Age Category (years)	≤ 35 years	n (%)	172 (91.5%)	164 (92.7%)
	> 35 years	n (%)	16 (8.5%)	13 (7.3%)
Previous Contraceptive Use Status	New User	n (%)	100 (53.2%)	107 (60.5%)
	Current User	n (%)	65 (34.6%)	44 (24.9%)
	Recent User	n (%)	23 (12.2%)	26 (14.7%)

SD=standard deviation; CV=coefficient of variation; BMI=body mass index

OC=oral contraceptive (150 µg Levonorgestrel/30 µg Ethinyl Estradiol)

Source: Table 14.1_2.2

Reviewer Source: CL13 Clinical Study Report, pg 60 of 163.

Reviewer's comments:

Subjects in the treatment groups were comparable with respect to age, weight, height, BMI, race/ethnicity, categorical age, and previous contraceptive use status. The treatment groups were also comparable with respect to highest level of education, smoking status, and current alcohol use. For their gynecological history, they were comparable with respect to age at menarche, typical length of menstrual cycle, and typical duration of menses; approximately half of the subjects in each group had never

been pregnant; the majority of remaining subjects in each group reported 1 or 2 pregnancies and deliveries.

For hormonal contraceptive use within 6 months prior to study enrollment, similar proportions of the subjects in each treatment group were utilizing an hormonal contraceptive method (approximately 47% [assigned to the patch] and 40% [OC]), with the same proportion of subjects in each group utilizing a male condom with or without spermicide (41%) at the time of study enrollment [condom data from Applicant Table 8, pg 63, CL13 Study Report].

6.1.3 Subject Disposition

The subject disposition for Study CL12 is shown in Table 7 below.

Table 7: Subject Disposition Study CL12

Screened (total)	2198	OC Use Cycle 1-6	Switch to Patch Use Cycle 7-13	Patch Use Cycles 1-13
Randomized	1504= Total	375	249	1129
Safety Population*		344 (91.7%)	*230	1,043 (92.4%)
Contraceptive Efficacy (ITT1)		330 (88.0%)	228 (91.6%)	998 (88.4%)
Cycle Control		324 (86.4%)	216 (86.7%)	918 (81.3%)
PK Population		326 (86.9%)	144 (57.8%)	933 (82.6%)
Completed Study		249 (66.4%)	150 (60.2%)	485 (43.0%)
Did not Complete		126 (33.6%)	99 (39.8%)	644 (57.0%)
Reasons for Premature Discontinuation				
Any Reason		126 (33.6%)	99 (39.8%)	644 (57.0%)
Adverse events		15 (4.0%)	16 (6.4%)	123 (10.9%)
Death		1 (0.3%)	0	0
Non-Compliance		9 (2.4%)	6 (2.4%)	42 (3.7%)
Lost to FU		61 (16.3%)	37 (14.9%)	229 (20.3%)
Subject's Decision		30 (8.0%)	28 (11.2%)	183 (16.2%)
Pregnancy ^a		4 (1.1%)	8 (3.2%)	34 (3.0%)
Protocol Violation		4 (1.1%)	0	11 (1.0%)
Investigator's Decision		1 (0.3%)	2 (0.8%)	13 (1.2%)
Sponsor's Decision		0	0	0
Other		1 (0.3%)	2 (0.8%)	9 (0.8%)

The denominator for percentages is the number randomized.

^aSubjects with in-treatment pregnancy detected before the end of the study. Source: [Table 14.1_1.1.1](#)

Source: Table revised by Applicant, submitted January 9, 2013, from the CL12 Study Report, pg 70 of 423.

Reviewer's comments:

Because of the different designs for Study CL12 and CL13, the subject disposition data is kept separate. In the table above for Study CL12, women who used OCs for six months, OC users who crossed-over to the patch at Month 7, and women who used the patch for 13 cycles are presented in 3 separate columns.

“Lost to Follow-up” was the listing for 266 (229+37) subjects (19.3% of the total patch population) as the reason for premature discontinuation; this was carefully examined. It is possible that a pregnancy, a significant adverse event, or patch intolerance might be the reason some of these 266 women were lost to follow-up despite attempts by the clinical sites to contact them.

“Subject’s Decision” was the listing for 211 (183+28) subjects (15.3% of the patch population) as their reason for premature discontinuation; this was also carefully examined. There are no CRFs for these subjects, but at least a brief reason is listed for each one in the Table of Listings. The reasons listed in descending frequency (the % of the 211) are the following:

- 29.0%- Consent withdrawal (no reason given)- 61 subjects
- 20.5%- Moving out of the site area- 43 subjects
- 19.6%- Patch problems (reactions, poor adhesion, patch dislike)- 41 subjects
- 10.2%- Miscellaneous (major surgery, IUD insertion desired, weight gain, hormonal side effects, no reason)- 22 subjects
- 7.4%- Pregnancy desired by subject- 16 subjects
- 7.4%- Bleeding unacceptable- 16 subjects
- 6.4%- Work schedule, too busy, want to stop- 12 subjects

In the “Other” category in the Subject Disposition Table 7 above, all 11 of the women were either determined (8) or suspected (3) to be pregnant before treatment. All potential subjects had a serum β -hCG pregnancy test done at the screening visit. Because of this fact, the reviewer is not sure why they were randomized, as one common reason for screen failure was a determination at Visit 1 (screening) that a potential subject was pregnant.

The low completion rate for patch users and the number of premature discontinuations is problematic, especially noting the high cumulative percent of women (34.6%) who were either lost to follow-up or decided to prematurely stop their participation in the clinical trial. The 139 subjects (10.1%) who were discontinued early because of an adverse event is understandable and acceptable and is consistent with the percentage seen in most contraceptive trials for an NDA application.

6.1.3.1 Reasons For Screen Failure- Study CL12

In Study CL12, a total of 2198 subjects were screened and 1504 (68.4%) were randomized. Among the 694 screen failures, 270 (38.9%) had an abnormal Pap smear,

74 (10.7%) withdrew consent, 57 (8.2%) were not in good general health, enrollment closed for 43 (6.2%), and 40 (5.8%) were lost to follow-up. Fewer than 5% of the screen failures were accounted for in any other category.

Reviewer's comment:

There were a large number of potential subjects who had abnormal Pap smears, consent withdrawal, or did not show for the randomization visit. It is difficult to interpret the meaning/significance of the finding that 31.6% of the 2,198 screened women were not eligible to be enrolled in the clinical trial, but this is in the range seen with some other recent NDA applications.

Women were excluded from enrollment if their Pap smear was read as "class III or greater or a Bethesda System report of low grade squamous intraepithelial lesions (SIL) or greater". The protocol Amendment 1 (dated 8-31-10) further states that women were excluded if a Pap was read as ASCUS (atypical squamous cells of undetermined significance) + they were positive for human papilloma virus (HPV) or the Pap smear was AGC (atypical glandular cells, favor endocervical type) + they were positive for HPV. All women with low grade (LGSIL), high grade (HGSIL), and LGSIL-H (LGSIL, cannot exclude high-grade squamous intraepithelial lesion) squamous intraepithelial lesions were excluded. The protocol does not state, however, that all subjects had to be tested for HPV.

Overall, 12.3% of the 2,198 women screened had an abnormal Pap smear that excluded them from enrollment; this finding is indicative of an "at risk" population by most gynecological clinical standards. Applicants are asked to screen and enroll a target population that is representative of the US population of reproductive-age women, but there is no guideline that a specific percentage should be at a higher risk for safety or efficacy. The Applicant does emphasize that the large enrollment of high-risk subjects is one explanation for the overall poor compliance and high rate of lost to follow-up.

6.1.3.2 Reasons For Protocol Violations- Study CL12

The Study Report for CL12 states: "Forty-eight major protocol violations were recorded for randomized subjects. Of these violations, 4 were for subjects who became pregnant prior to the start of study drug, 15 were related to inclusion/exclusion criteria violations, 15 were related to taking excluded medications, 9 subjects did not have sexual intercourse during one or more cycles in which they took study drug, 4 subjects took antibiotics without using backup contraception, and one subject was non-compliant with taking study drug (see Listing 16.2._2.3)."

Reviewer's comment:

The Applicant's Listing 16.2_2.3 is 733 pages of violations for Study CL12 alone and several violations are listed on each page; so there are several hundreds of protocol violations. I would not consider the following as major protocol violations: pregnancy prior to start of study drug, no sexual intercourse during treatment cycles [the analysis plan excludes these cycles from the evaluable cycles], and taking antibiotics without using backup contraception.

The subject disposition for Study CL13 is shown in Table 8.

Table 8: Subject Disposition Study CL13

Disposition Status	Category	Total	OC	AG200-15
Screened (total)		626	---	---
Randomized		407	206	201
Safety Population			188 (91.3%)	177 (88.1%)
Contraceptive Efficacy Population (ITT1)			186 (90.3%)	170 (84.6%)
Cycle Control Population			182 (88.3%)	162 (80.6%)
PK Population			147 (71.4%)	117 (58.2%)
Completed Study			145 (70.4%)	112 (55.7%)
Did not Complete Study			61 (29.6%)	89 (44.3%)
Reason for Premature Discontinuation	Any Reason		61 (29.6%)	89 (44.3%)
	Adverse Event(s)		4 (1.9%)	14 (7.0%)*
	Death		0	0
	Non-Compliance		5 (2.4%)	2 (1.0%)
	Lost to Follow-up		32 (15.5%)	44 (21.9%)
	Subject's Decision		13 (6.3%)	21 (10.4%)
	Pregnancy ^a		1 (0.5%)	4 (2.0%)
	Protocol Violation		3 (1.5%)	2 (1.0%)
	Investigator's Decision		1 (0.5%)	1 (0.5%)
	Applicant's Decision		0	0
	Other		2 (1.0%)	1 (0.5%)

OC=Oral Contraception (150 mcg Levonorgestrel/30 mcg Ethinyl Estradiol); Denominator for percentages is number randomized.

^aIncludes subjects with on-treatment pregnancy detected before the end of the study. For other subjects, on-treatment pregnancy was detected after study completion.

* Applicant's error corrected

Applicant Source: Table 14.1_1.1.1

Reviewer Source: CL13 Clinical Study Report, Table 4, pg 56 of 163.

Reviewer's comments:

The listing was examined for the 44 subjects using the patch (21.9% of the total patch population) who had "Lost to Follow-up" as the reason for premature discontinuation. This means it is possible that a pregnancy, a significant adverse event, or patch intolerance might be the reason why some of these 44 women were lost to follow-up despite attempts by the clinical sites to contact them. For the "Subject's Decision" category, the distribution of reasons is similar to that found in the larger CL12 study.

With an equal number of subjects randomized to either an OC or the Agile patch, it is noted that 2% of the OC subjects and 7% of the patch subjects were prematurely discontinued because of an adverse event. This finding is compatible with the difference of 4% and 10% found in the larger Study CL12.

6.1.3.3 Reasons for Screen Failure- Study CL13

A total of 626 subjects were screened prior to randomization of 407 subjects into the two treatment groups. Among the 219 screen failures, 24 (11.0%) failed inclusion criteria, 151 (68.9%) failed exclusion criteria, 17 (7.8%) withdrew consent, 7 (3.2%) were lost to follow-up, enrollment closed for 16 (7.3%), and 3 (1.4%) failed for other reasons.

Reviewer's comment:

There was a large percentage of potential subjects who failed either inclusion or exclusion criteria, or withdrew their consent. It is difficult to interpret the meaning/significance of the finding that 79.9% of the screened women who failed enrollment did not meet the inclusion or exclusion criteria to be enrolled in the clinical trial as compared to 47% of the screen failures in the larger CL12 study.

6.1.3.4 Applicant's Explanation for the Discontinuation Rate

The Applicant offers this explanation on page 195 of their ISE:

"Nearly 50% of discontinuations in Study ATI-CL13, and a somewhat lower percentage in Study ATI-CL12, occurred in first cycle, suggesting that these subjects never intended to be in the study. This may be a reflection of the bad economic times where many women have no health insurance. This is also reflected in the unexpectedly high lack of compliance in both studies."

An additional explanation is found in the ISS (page 14); the Applicant notes that of the subjects that discontinued either of the phase 3 trials, 21% of those in the patch group and 18% in the OC group dropped out before Cycle 2,

"supporting the possibility that a significant number of these subjects were primarily motivated to participate in the study for the benefits associated with the initial health care assessment, less so the full rigors of the entire trial."

Reviewer's comments:

The two Applicant statements above concerning the percentage of discontinuations during the first cycle of use do not agree with each other; "nearly 50%" is nowhere near the 18-21% claimed in the second statement. This is another example of the confusing data presented by the Applicant, which required an information request (IR) for clarification by the Division. In any case, the discontinuation rate was unusually high during the first cycle of product use. [NOTE: in their 1-9-13 response to the IR, the Applicant stated that the percentages differ because they refer to discontinuations "before the 2nd cycle" in the ISE rather than "in the first cycle" in the ISS.]

It is difficult to compare NDA applications for contraceptive indications because the trial designs, subject enrollment, and length of treatment differ. However, upon review of some other recent hormonal contraceptive NDAs (NDAs 22-252, 22-501 and 22-573) that submitted studies lasting at least 13 cycles, study completion rates ranged from 50-78%, loss to follow-up rates of 2-16%, discontinuations due to AEs of 9-15%, subject-determined withdrawal of 2-10% and "other" reasons for discontinuation ranging from 5-8%. Thus, the study completion rate in the 13-cycle Agile patch arm was well below that

typically observed for contraception trials, and discontinuations due to loss to follow-up and subject's decision were higher than usually seen. Discontinuations due to "other" were less common, but the Applicant provided more explanatory categories than did other NDAs, which likely resulted in fewer attributed to this non-specific reason.

This is a major problem because it 1) reduces the total cycles of drug exposure available for the analysis of drug safety and efficacy and 2) may say something about the quality of the trial and perhaps the intentions of the enrolled subjects. In a clinical contraceptive trial for an NDA approval, a higher completion rate is desirable.

Furthermore, if, as the Applicant opines, "bad economic times and/or no health insurance" were a key factor, this reviewer would argue that the free medical care and free contraception for 6 or 12 months would be a strong incentive to stay in the study (not to prematurely discontinue it). It is the responsibility of the principal investigator (PI) at each site to enroll subjects who will stay in the trial, so the fact that 18-21% of the enrolled women dropped out before Cycle 2 does not indicate careful screening and discrimination at many of the study sites.

The Division has to look at the trial data as it is recorded and cannot accept unproven speculations from the Applicant. It is concerning that the overall discontinuation rates were so high irrespective of the reasons. For an additional comparison, I compared the original Ortho Evra NDA data, as this is the only approved transdermal patch for contraception: in the three phase 3 Ortho Evra clinical trials (N= 3,330), only 26% of the subjects failed to complete their 6 or 12-month trial, with discontinuations for the following reasons: 4% lost to follow-up, 7% for subject's choice, and 12% for adverse events. If only the US women are counted, the discontinuation rate was slightly higher at 30%, which is still considerably lower than the 52.7% rate in the two Agile phase 3 trials, which were strictly US- and Canada-based.

6.1.4 Analysis of Primary Endpoint(s)

The prespecified primary efficacy dataset was based on the ITT2 population, defined as women age 17-35 with a BMI < 32, and included only cycles with intercourse and with no use of backup contraception. This population is a subset of ITT1, which included all women age 17-35, with a BMI < 32, and all complete or incomplete on-therapy cycles.

What was problematic for Study CL12 (pages 116 and 117) were the 7 subjects listed in Table 16 Subjects with Positive hCG Result and No Pregnancy Report and the 9 subjects in Table 17 Subjects With Form A Pregnancy Report Not Deemed Pregnant by Investigator. Each of these 15 subjects was carefully reviewed and led to the conclusion that 3 were added as on-treatment pregnancies [REDACTED] (b) (6)] and two would be added in a worst-case scenario analysis [REDACTED] (b) (6)]. During the entire review cycle, the Division identified a total of eight additional on-treatment pregnancies, five of which were included in the primary efficacy results for the Division's analysis and calculations. The Applicant was initially notified of the following 5 subjects from Study CL12; 4 of the subjects are in the primary efficacy dataset with a BMI < 32.

1. Subject [REDACTED] (b) (6) (age 27, BMI 21, G4P2) was treated for 11 cycles; her LMP started 6-7-11, last active dose was 6-28 (Day 14), and she was seen 7-1-11 with a positive hCG of

251. An ultrasound on 7-7 confirms pregnancy (the photo is unfortunately unreadable) and she had a medical abortion that same day. The conception date was between June 9-17 as determined by the investigator, this reviewer, the hCG and ultrasound. This pregnancy was considered on-treatment by the Division.

2. Subject (b) (6) (age 29, BMI 29, G2P1) was treated for 13 cycles; her LMP started 7-24-11; last active dose was 8-14-11, and she was seen on 9-1-11 with a positive hCG of 236. A pelvic exam that day was reported as “pregnant uterus.” An ultrasound on 9-13-11 showed a probable miscarriage and the hCG was 7. Given the positive hCG and “pregnant” uterus on 9-1-11, this reviewer believes the conception date was definitely prior to her 8-14 last active dose and therefore this pregnancy was considered on-treatment.
3. Subject (b) (6) (age 30, BMI 24, G3P3) was treated for 13 cycles; her LMP started 9-15-11 with 3 days of spotting only; last active dose was 9-17 on Day 18, and she was seen on 10-06 with a positive hCG of 68. No ultrasound results or follow-up results are reported. The hCG of 68 has a range of 10-14 days from conception, so the conception was probably around 9-23 to 26, which is within the 7 day window after the last recorded active dose. It is unfortunate that there is no repeat hCG or ultrasound data. The study did a poor job of follow-up [no repeat hCG and no sonogram]. Other factors are that she stopped active treatment on Day 18 (instead of Day 21) and her LMP was 3 days of only spotting (i.e., compatible with an early pregnancy). This will be counted as an on-treatment pregnancy.
4. Subject (b) (6) (age 30, BMI 36.9, G2P1) used AG200-15 for two complete cycles starting 8-21-10 and 9-18-10; serum hormone levels on 9-29-10 showed she had been using the patch. She had a negative hCG on 8-5-10 and a positive hCG of 20,454 on 10-15 following her last patch use on 10-09. No ultrasound or bimanual pelvic exams were performed. Her daily diary card shows no withdrawal bleeding following the two patch cycles, but the pregnancy form states her LMP as 9-7-10. The investigator believed her conception date is 9-20-10 and this reviewer agrees, so this will be counted as a pregnancy on-treatment. The Applicant offered no explanation why they disagreed with the investigator’s conclusion.
Note: because her BMI was 36.9, this pregnancy is not counted in the primary efficacy analysis.
5. Subject (b) (6) (age 25, BMI 22.1, G3P2 Ab1, applied her first patch on 2-17-11. She was a compliant subject, last seen on 6-23-11 when she had a serum hCG level 5,567; an ultrasound on 6-27 showed a 9x6 mm hyperechoic focus in the lower uterine segment. The Applicant discontinued her for a “suspected but unconfirmed pregnancy.” An hCG as high as 5,567 indicates that this compliant subject should be counted as a pregnancy on treatment. It is of note that she did not have any expected withdrawal bleeding while on the OC for 6 cycles or during the first 4 patch cycles. She used the patch for only 14 days of her last cycle (6-9 to 6-23), stopped the patch on 6-23 because of the positive pregnancy test, and had bleeding on Days 12-17 of the last cycle. A repeat hCG was not performed so there is no way to tell if the positive one on 6-23 was a lab error or was increasing or decreasing. This will be counted as an on-treatment pregnancy and included in the final FDA calculation for the primary efficacy Pearl Index.

On 12-31-12 the Division sent an additional information request to the Applicant requesting clarification for 8 subjects with positive pregnancy tests and “non-confirmed pregnancies.” Further analysis by this reviewer after receiving the Applicant’s response on 1-9-13 resulted in the addition of 3 more pregnancies on-treatment and 2 more that were not added but would be added in the truly “worst case scenario”. This included the following 3 subjects from Study CL12.

Subject (b) (6): 23 year old, G0P0, BMI 25.3, male condom user. Last patch was on 5-12-11.

1. The hCG was negative on 5-13 at the study visit and then 9,191 on 6-23 [lab results are in the Pregnancy Follow-up Form A (PFF)]. The sonogram on 6-23 showed a sac, but no pregnancy.
2. Table 17 (pg 117 of the CL12 Study report) states the hCG was 191 on 6-23 [this is an error]. The Narrative Summary and the PPF do have the correct value.
3. **From the CRF and PFF the hCG was 9,191 on 6-23-11. The hCG value corresponds to ~5.5 weeks from a conception/ovulation date of 5-15-11 which is within the 7-day window after her last patch use on 5-12-11. Assuming the 6-23 sonogram is also correct, then the subject must have had a spontaneous complete abortion by 6-23 (as shown on the ultrasound) and the hCG level was decreasing. A repeat hCG value would have been very helpful in this case. This pregnancy was considered on-treatment.**

Subject (b) (6): 37 year old, G8P8, BMI 43.2, no birth control. Last patch 1-20-11.

1. LMP dates all differ by a couple of days using the Narrative Summary, CRF, and PFF
2. Narrative Summary states serum hCG results on 1-13, 1-21, and 1-28, respectively, were 44, 11, and 0, but the results are not in the CRF or the PFF. At the site visit on 1-28-11, the CFR states NO for any positive serum pregnancy test during the study, yet the narrative summary states 3 results.
3. The PFF states “pregnancy ended in early spontaneous abortion;” Narrative Summary states “there is no confirmation subject was pregnant and according to the site subject was lost to follow-up.”
4. **Reviewer conclusion: subject was pregnant on treatment, had a positive hCG, and did have an early spontaneous abortion, as stated by the investigator on the PFF.**

Subject (b) (6): 29 year old, G5P5, BMI 33.2, male condom user. Last patch removed 7-14-11.

1. **There is no CRF submitted with the NDA**, yet the PFF is submitted.
2. Narrative Summary says hCG results on 8-16 were 140 and 132, yet makes no reference to the earlier hCG values. The PFF has copies of the lab reports for an hCG 2,118 on 7-27; repeat on 7-29 was 1,415; both tests were within 2 weeks of the last patch use date. There is no record of an ultrasound.

3. Investigator states on the PFF “hCG levels were decreasing; therefore subject was not de***ed.” The handwriting is very difficult to read.
4. **Conclusion: subject conceived while on the patch given the hCG results on 7-27 and 7-29 with the last patch removed on 7-14.**

Reviewer’s comment:

Missing data, conflicting data, and illegible data make it difficult to accurately determine the date of conception and the date of last patch use in many of these cases. Moreover, for Subject (b) (6) it is hard to reconcile the omission of the hCG values of 2,118 and 1,415 within 2 weeks of the last patch use. On 1-11-13, the FDA statistician was asked to add these 3 pregnancies to her analysis. Because of the BMI values for these three subjects, only one is added to the primary efficacy dataset.

It is of further note that under a “worst case scenario” several additional pregnancies would be added as on-treatment. Here are three such examples out of several:

Subject (b) (6): 27 year old, G4P2, BMI 23.8, patch and condom user. Last Agile patch on 12-28-10.

1. Serum test during Cycle 2 (11-1-10) showed hormone levels EE < 2.0 and LNG < 50 which were below the lower levels of quantification.
2. LMP, last patch date, and daily diary are not available after her Cycle 4 visit on 12-28-10; however, she was dispensed patches for 2 cycles + 3 reserve patches at the 12-28-10 visit.
3. The PFF states that on 2-28-11 she called to say she had a positive urine pregnancy test; she failed to keep her follow-up appointment; no serum hCG or ultrasound results are available.
4. If she used the patches from the 12-28 10 visit, then she would be counted as an on-treatment pregnancy.

Subject (b) (6): 26 year old, G2P1, BMI 24.5, OC user. Last patch date uncertain.

1. LMP, last patch date, and daily diary are not available; however, she was dispensed patches at the 12-10-10 visit (Cycle 4).
2. The PFF is very difficult to read (poor FAX resolution and handwriting); it states she had an 8-week pregnancy terminated on 2-18-11 which means the conception date would be 1-7-11. This conception date is within 28 days of the last patches she was given at the 12-10-10 clinic visit.
3. This is a good example of someone who was lost to follow-up who was definitely pregnant and not counted as an on-treatment pregnancy by the Applicant. She will not be counted as an on-treatment pregnancy because we do not definitively know her LMP and her last patch use.

Subject (b) (6): 24 year old, G0P0, BMI 22, was treated for 3 cycles; she did not return her diary cards for Cycles 2 and 3 and was lost to follow-up.

1. Her CRF states her last active patch was 11-15-10; she was seen on 12-16-10 with a positive hCG of 102.
2. There is no diary data after Cycle #1, no stated LMP, and no diary confirmation of her last active dose.
3. An ultrasound on 1-4-11 showed a 6.5 week gestation with a conception date of 12-02. Given the limited (poor) data, this pregnancy probably occurred post-treatment, and

the subject is not counted as an on-treatment pregnancy. In a true “worst case scenario” she would be counted as on-treatment.

There were no additional pregnancies in the smaller clinical trial CL13 that the reviewer added as “on-treatment” pregnancies.

Calculations from FDA statistician Kate Dwyer, PhD, (1-14-13) that included these additional pregnancies showed the following for the two phase 3 studies:

Table 9: Applicant and FDA Pearl Index- ITT2 Population (Study CL12)

	Population	N	# of On-Treatment Pregnancies	Number of Evaluable Cycles	Pearl Index	95% Confidence Interval
Applicant	Age 17-35 years	1,060	38	7,685	6.43	(4.39, 8.47)
	*BMI < 32 kg/m²	827	30	6,070	6.43	(4.13, 8.27)
	BMI < 30 kg/m ²	767	27	5,645	6.22	(3.88, 8.56)
	All Subjects	1,158	40	8,446	6.16	(4.25, 8.06)
Reviewer (FDA)	Age 17-35 years	1,060	45	7,685	7.61	(5.39, 9.83)
	*BMI < 32 kg/m²	827	35	6,070	7.50	(5.02, 9.97)
	BMI < 30 kg/m ²	767	32	5,645	7.37	(4.82, 9.92)
	All Subjects	1,158	48	8,446	7.39	(5.30, 9.47)

*The primary efficacy dataset is shaded gray.

Source: FDA Statistician Kate Dwyer, PhD

The Division had concerns that the 7-month data from the cross-over subjects was not equivalent to the data for that same interval in women who were on the patch throughout the study (e.g., women with poor compliance or other risk factors for pregnancy likely already became pregnant during the OC phase, so women who “survived” to enter the cross-over period may have been at lower risk of pregnancy). To evaluate this, the FDA Statistician also did a sensitivity analysis excluding the women in Study CL12 who switched from OC use to patch use for Cycles 7-13.

Table 10: Study CL12 Sensitivity Analysis Excluding Switchers from OC to Patch Use

	Population	N	# of On-Treatment Pregnancies	Number Evaluable Cycles	Pearl Index	95% Confidence Interval
Using Applicant Reported Pregnancies	Age 17-35 years	863	32	6,673	6.23	(4.08, 8.39)
	BMI < 32 kg/m²	675	25	5,278	6.16	(3.75, 8.57)
	BMI < 30 kg/m ²	621	22	4,885	5.85	(3.41, 8.30)
	All Subjects	940	33	7,320	5.86	(3.87, 7.86)

Using FDA Identified Pregnancies	Age 17-35 years	863	37	6,673	7.21	(4.89, 9.52)
	BMI < 32 kg/m²	675	29	5,278	7.14	(4.55, 9.74)
	BMI < 30 kg/m ²	621	26	4,885	6.92	(4.27, 9.57)
	All Subjects	940	39	7,320	6.93	(4.76, 9.09)

*The primary efficacy dataset is shaded gray.

Source: FDA Statistician Kate Dwyer, PhD

Because there were no added on-treatment pregnancies from the FDA evaluation, the efficacy data for Study CL13 is the same for the Applicant and the FDA. The primary efficacy findings are shown in the next table.

Table 11: Applicant and FDA Pearl Index- Study CL13 ITT2 Population Patch Users

	Population	N	# of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Applicant and FDA	Age 17-35 years	147	4	635	8.19	(0.19, 16.19)
	All Subjects	158	4	673	7.73	(0.18, 15.28)

*The primary efficacy dataset is shaded gray

Source: FDA Statistician Kate Dwyer, PhD

Reviewer's comments:

It is commonly observed in contraception trials that shorter trials (e.g., 6 months) demonstrate higher Pearl Indices, because pregnancies tend to be front-loaded in the initial months of a trial. It is not surprising that the Pearl Index in Study CL13 is higher than that for Study CL12.

Whether considering the Applicant's results or the FDA calculations, the Pearl Index for the primary contraceptive efficacy dataset is unacceptable. The range for the FDA Pearl Indices for the four groups in the ITT2 population is from 7.37 to 7.61. Even in the population of all subjects without any age restriction (which typically provides a lower Pearl Index because women older than 36 are less fertile than younger women), the Applicant (6.16) and FDA Pearl Index (7.39) values of > 6.0 are unacceptably high.

The other notable value here is the number of evaluable cycles for women age 17-35: the Division requested 10,000 cycles of exposure for efficacy and safety, but a lower number may be acceptable for efficacy if the Pearl Index is lower (preferably < 3.0) and with a tight 95% confidence interval. In this NDA, the number of evaluable cycles (6,705) is obviously less than 10,000, while the various Pearl Indices and the confidence intervals are all considerably higher/wider than the Division has ever found acceptable for approval of a combination hormonal contraceptive drug product.

6.1.5 Analysis of Secondary Endpoints(s)

Calculations were also made for subjects aged 17 to 35 with BMI < 30 kg/m² (i.e., non-obese subjects), and for all subjects (no age restriction) in subsets of the ITT2 population. Further populations (datasets) included the following:

- MF1 (Method Failure): All complete or incomplete on-therapy cycles with intercourse excluding two cohorts: (1) cycles in which another birth control method was used; (2) cycles during which the subject missed more than one day of active drug-taking and the immediately following cycle for each given subject. In-treatment pregnancies with an estimated date of conception attributed to the cycles from the first and second cohorts were not included in the calculation of the pregnancy rates.
- MF2: All complete or incomplete on-therapy cycles with intercourse excluding two cohorts: (1) cycles in which another birth control method was used for reasons other than missed days of drug-taking, unless pregnancy occurred; and (2) cycles during which the subject missed one or more days of active drug-taking and did not adhere to the procedures recommended for the missed days of drug taking, as well as the immediately following cycle for each given subject. In-treatment pregnancies with an estimated date of conception attributed to the cycles from the first and second cohorts were not included in the calculation of the pregnancy rates.
- Due to the high number of laboratory verified non-compliant subjects (10%-14%) the above datasets were extended to exclude those subjects. The expanded datasets are named MF1_E and MF2_E.

Pregnancy rates were also stratified by race/ethnicity for the intent-to-treat, method failure, and safety populations (ITT1, ITT2, MF1, MF2, and S).

Reviewer's comments:

It is unclear why the Applicant had cycles immediately following a cycle with one or more missed days of active drug excluded from the evaluable cycles.

The method failure datasets are only exploratory and were not carefully reviewed by the Division because they are not the prespecified primary efficacy dataset. For all previous NDA approvals for combination hormonal contraceptive products, the primary efficacy has been determined based on the ITT population, as this will be closer to the actual efficacy of the product if the product is approved. In reality, many studies have shown that the "actual use" contraceptive effectiveness of approved combination hormonal products is considerably worse than the Pearl Index found in the original clinical trials. There is no reason to believe this would be different if the Agile patch were approved, which is another reason non-approval is recommended by this reviewer.

The expanded datasets, named MF1_E and MF2_E, contain 1,166 fewer cycles of exposure because of the excluded subjects who had at least one lab value showing undetected or very low blood levels of LNG and/or EE. The FDA Pearl Index values in this secondary analysis dataset were much lower [range 3.18 to 3.41] than found in the primary efficacy dataset, but the confidence intervals were rather wide [1.38, 4.98 and 1.56, 5.26].

Levonorgestrel/Ethinyl estradiol transdermal patch

The Applicant also did a secondary analysis for use of the patch by Cycles 1-6 and 1-13 for the ITT2 dataset and the ITT2-BMI < 30 subset. The results are shown in the table below and then shown in a different way for the ITT2 dataset in the FDA table that follows.

Table 12: Applicant Pearl Index for Patch by Cycle groups and BMI, Pooled Data

Population Variable	Cycles	Category	N = 1158
Age 17-35; BMI <32 ITT2 (primary dataset)	1-6	Subjects (N)	675*
		Cycles (N)	2885*
		Pregnancies	12
		Pearl Index (95% CI)	5.41 (2.35, 8.46)
	1-13	Subjects (N)	827**
		Cycles (N)	6070
		Pregnancies	30
		Pearl Index (95% CI)	6.43 (4.13, 8.72)
Age 17-35; BMI <30 (ITT2 BMI subset)	1-6	Subjects (N)	621
		Cycles (N)	2673
		Pregnancies	12
		Pearl Index (95% CI)	5.84 (2.54, 9.13)
	1-13	Subjects (N)	767
		Cycles (N)	5654
		Pregnancies	27
		Pearl Index (95% CI)	6.22 (3.88, 8.56)

* This includes patch users from CL13 + Cycle 1-6 patch users from CL12 + cross-over patch users in CL12.

** This includes patch users from CL13 only.

Source: Adapted from Integrated Summary of Efficacy, Table 4-28, pg 104 of 195.

The following is another way to look at the ITT2 dataset for women using the patch. The women in CL12 who crossed-over to using the patch after 6 cycles of OC use are not the same as the women who were randomized to patch use for only 6 cycles in CL13 and then stopped the study.

Table 13: FDA Pearl Index for Agile Patch by Cycle groups- ITT2, Pooled Data

Study	Number Enrolled ITT1	Number 28 day cycles	Cycles with back-up birth control	Cycles with no inter-course	Number evaluable Cycles ITT2	Number of pregnancies	Pearl Index	Upper 95% CI
CL12: 13-cycle Patch users	719	6,319	440	601	5,278	29	7.14	9.74
CL12: Cycle 7-13 Patch users	159	951	67	92	792	6	9.85	21.34
CL13: Cycle 1-6 Patch users	158	777	73	69	635	4	8.19	16.19
Totals	1,036	8,047	580	762	6,705	39	NA	NA

Source: Table from FDA statistician Kate Dwyer, PhD.

Reviewer's comments:

The ITT2 population is women age 17-35 with a BMI < 32. It is interesting that inclusion of subjects in the cross-over group results in 6 pregnancies and a higher Pearl Index (9.85) for this group.

It is of note that backup contraception was used in 7.2% (580/8047) of the recorded cycles and that in 9.5% (762/8047) of the 28-day cycles the subjects did not have intercourse. The 9.5% finding is perhaps another marker of the poor quality of the enrollment for the two phase 3 trials.

The Division's standard for evaluating contraceptive efficacy is not based on comparative efficacy, so this review does not focus on how the Agile patch compares to the two oral contraceptive.

There are two unexpected findings in the Applicant's efficacy analysis. In both of the Applicant's population sets in Table 12 above (BMI < 32 and < 30), the Pearl Index is higher in the 1-13 Cycle group than in the 1-6 Cycle group. Second is that the efficacy is slightly better (5.41 compared to 5.84) in the heavier (BMI < 32) group for Cycles 1-6. The difference is small and not of clinical significance, but both of these findings are discrepant from what is usually observed in contraceptive trials (i.e., Pearl Indices tend to be higher in shorter trials and in heavier subgroups).

In hormonal contraceptive trials we typically see that the Pearl Index decreases or improves with duration of use. This is because the more fertile and less compliant subjects will have a pregnancy (failure) sooner or drop out of the study and thus be eliminated from the trial, while the less fertile and/or more compliant subjects will make up a greater proportion of the study population, leading to a relatively lower rate of pregnancies as time goes by. Yet we see the opposite here and this is unusual and unexpected. The Applicant does not offer an explanation.

It is speculative that it could be related to the stability of the patch; i.e., as time goes by, each subject might be using an older transdermal patch and, if it is chemically unstable, it may be less effective. It could be by chance or for some other reasons. It is difficult to know with certainty why this occurred in the phase 3 Agile trials, but this finding is not typical of contraceptive trials previously submitted for an NDA approval.

Concerning the lower Pearl Index in the higher BMI group (< 32) with only 1 to 6 Cycles of exposure, this would not generally be expected, but it is not statistically significant and is most likely due to chance. It is noted that the two BMI subsets had almost the same number of average cycles of exposure, 4.30 for the BMI < 30 group and 4.27 for the BMI < 32 group, so this is not a contributing factor.

6.1.6 Other Endpoints

Other endpoints were examined by the Applicant and data submitted to the NDA. This includes patch adherence, patches fallen off by application site, reasons for patch change, and unscheduled patch changes. The Pearl Index and Life Table analysis was calculated by age groups, BMI values, and several compliance subgroups.

Reviewer's comment:

The Applicant did several analyses for these other efficacy subsets. Patch adherence and tolerability are discussed elsewhere in this review and did not appear to be a reason for the poor efficacy results. Analysis of efficacy for women with a BMI < 32 and < 30 did not show a significant difference. Analysis of efficacy for all ages also did not show a noticeable difference. What did significantly improve the contraceptive efficacy (Pearl Index) was to add back all cycles with no intercourse, use of backup contraception, and non-compliance; these important factors were not included in the primary efficacy dataset.

6.1.7 Subpopulations

Because the study results had high Pearl Indices, the Applicant analyzed subpopulations based on BMI criteria, age, patch data, and compliance. See brief comments in Section 6.1.6.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the results of the clinical pharmacology studies using 3 different patches and evaluating ovulation rates and hormone levels, this reviewer agrees that the patch chosen by the Applicant was the correct one. The dosing regimen of three consecutive 7-day patches followed by a patch-free week is also acceptable and compatible with the 21/7 dosing used for many other CHC products over the past 40+ years.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

It is clear from many years of experience with oral, vaginal, and transdermal hormonal contraception that persistence of efficacy is not expected or proven beyond 7 days after the product is stopped. This is why all hormonal regimens have no more than a 7-day product-free interval before the next dosing cycle is started. Several more recent

regimens have only 2-4 days without estrogens/progestins, and some have added estrogen-only days instead of any drug-free interval. Tolerance or dependence on hormonal contraceptive products has not been demonstrated. Some hormonal or other minor side effects are often experienced during the drug-free interval or upon stopping the product altogether.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Patch application sites and adherence

Data regarding the application sites used over Cycles 1-13 in Study CL12 is shown in Table 14.

Table 14: Distribution of Application Site- Study CL12

All Cycle Combined (1-13)	% of Total Cycles N= 10,180	% of Total Number of Patches N= 32,508
Buttock	47.4	47.7
Abdomen	40.3	38.8
Upper torso	11.7	11.8
No data	0.6	1.7
TOTAL	100%	100%

Source: Summary Clinical Safety, Table 25, pg 69.

Reviewer's comment:

The buttock area was the most common site of patch application, followed by the abdomen. This finding was also true for the smaller Study CL13 [buttock 51.2%, abdomen 32.2%, torso 15.7%, no data 0.9%]. The reason the percentages are not identical is that data was missing for the application site for one or two of the 3 patches in a given cycle. The number of total patches is more than 3 times the number of cycles because when a patch was completely detached or partially detached and could not be reapplied successfully, the woman was instructed to apply a new patch in that cycle.

Data from the daily diaries for the number and percentage of patches that fell off throughout the clinical trials is shown in Table 15.

Table 15: Number and Percentage of Patches that Fell Off – Pooled Data

	Cycles 1-6 (N=1220)		Cycles 1-13 (N=1450)	
	Number of Subjects with Patches Off	Number of Patches Off	Number of Subjects with Patches Off	Number of Patches Off
Abdomen	37/528 (7.0%)	46/1372 (3.4%)	40/629 (6.4%)	50/1632 (3.1%)
Buttock	72/706 (10.2%)	91/1911 (4.8%)	86/840 (10.2%)	109/2303 (4.7%)
Upper Torso	25/209 (12.0%)	27/479 (5.6%)	30/259 (11.6%)	32/594 (5.4%)

Source: Modified from Applicant Table 31, pg 77 of the Summary of Clinical Safety.

Patch adhesion scores (reported by the study site personnel on a 5-point scale ranging from 0, meaning $\geq 90\%$ of the patch surface adhered [no lift] to 4, meaning the patch completely detached) were recorded at each scheduled visit (see Table 16). Patch adhesion, as assessed by the investigators, was evaluated for Cycles 1-6 in the two phase 3 studies, for Cycles 1-13 in Study CL12, and by the 3 application sites. The patches were applied to the abdomen, buttock or upper torso (excluding the breasts) and each patch placement was recorded by the subject on the daily diary. Per protocol, subjects were to use the same anatomical site for the 3 consecutive weeks but on a different location from the previous patch, so it was a minor protocol violation if different anatomical sites (abdominal, buttock or upper torso) were used during the same treatment cycle. If a patch was partially or completely detached for less than 24 hours, the subject was instructed to re-apply it to the same place or replace it with a new patch immediately; no back-up contraception was needed. If the patch became partially or completely detached and remained detached for more than one day (24 hours or more) OR if the subject was not sure how long the patch had been detached, subjects were instructed to start a new cycle immediately by applying a new patch and to use back-up contraception for one week.

Table 16: Patch Adherence Scoring System

Score	Description
0	$\geq 90\%$ adhered (no lift)
1	$\geq 75\%$ but $< 90\%$ adhered (some edges showing lift)
2	$\geq 50\%$ but $< 75\%$ adhered (half of system lifts off)
3	$< 50\%$ ($>$ half of system lifts off, but undetached)
4	patches completely detached or no patch was present

Source: FDA modified table.

Reviewer's comments:

95.5% (Cycles 1-6) to 97.1% (Cycles 1-13) of the patches had a score of 0-1. There were $< 1\%$ of subjects for whom a patch was substantially lifted or partially detached (score 2 or 3). For the entire trial durations, 8.0% of subjects experienced a patch that fell off, but this accounted for $< 1\%$ of the total patches used.

It is important to note that there was a major flaw in the scoring system: the patch adherence score was determined by the site personnel at the site visits, so the data for patch adherence is not complete because each subject used at least 3 patches per cycle. For visits where a subject came during the non-patch week or where the subject was non-compliant, an accurate determination could not be made. Given the combined data for the overall scores of 0-3, it is apparent to me that patch adherence was acceptable because at least 96-98% of the patches did not fall off. Moreover, a partially detached patch could be reapplied (or a new one applied) and a completely detached patch was replaced with a new one. The instructions to the subject were clear and straight forward. However, in any future trial a better scoring system for patch adherence should be devised and data should not be dependent on only observation at site visits.

6.1.10.2 Cycle Control

The cycle control population included all subjects who took study medication and provided diary cards with relevant bleeding and drug-taking information. There was no weight restriction for this population. Bleeding was defined as any bloody discharge requiring at least one tampon or sanitary pad per day. Spotting was defined as bloody discharge that required only panty liners. An episode included any recorded data of bleeding or spotting with no minimum length of time, but preceded and followed by at least 2 bleeding free days. Per protocol for the phase 3 trials, for each treatment cycle, a number of cycle control parameters were evaluated and reported by treatment group (OC or patch). The subject incidence of unscheduled bleeding episodes, i.e., breakthrough bleeding/spotting (BTB/S), during all cycles was the primary endpoint for the cycle control analysis. The incidence at cycles 3, 5 and 12 were considered by the Applicant as the most important evaluations.

Data for scheduled and unscheduled bleeding only, spotting only, and bleeding/spotting days were collected and analyzed. All cycle control parameters were summarized by giving the proportion of subjects who experienced the event by cycle, by mean number of days of such event and by the frequency distribution of the number of days of such event. Summaries were provided for each treatment cycle and for all treatment cycles combined. Comparisons to the OC subjects' cycle control data were made.

Table 17: Incidence of Unscheduled Bleeding and/or Spotting- Patch Users, by Study

Cycle	Study ATI-CL13	Study ATI-CL12
	(N = 162) n/N (%)	(N = 715) n/N (%)
Cycle 1	46/148 (31.1%)	168/649 (25.9%)
Cycle 2	33/127 (26.0)	155/566 (27.4)
Cycle 3	28/119 (23.5)	147/574 (25.6)
Cycle 4	23/118 (19.5)	101/517 (19.5)
Cycle 5	25/114 (21.9)	110/512 (21.5)
Cycle 6	24/105 (22.9)	109/481 (22.7)
Cycles 1-6	179/731 (24.5)	790/3299 (23.9)
Cycle 12	N/A	63/356 (17.7)

Note: N = number of subjects in the cycle control population.

Numerator (n) is number of subjects with unscheduled bleeding (breakthrough bleeding and/or spotting).

Denominator is number of subjects with relevant bleeding and drug-taking information for the cycle(s).

Breakthrough Bleeding and/or Spotting Episodes = any number of days with bleeding/spotting preceded and followed by at least 2 bleeding free days.

Source: Applicant Table 5-5, pg 192 of the ISE and Table 18 in CL12 Study Report .

Reviewer's comments:

It is of note that at the 3-9-10 meeting with the Applicant the Division did not agree with the proposal to evaluate bleeding in Cycles 3, 5, and 12 only, and indicated it would consider the bleeding profile at all cycles. For the purposes of cycle control evaluation, bleeding was defined as any bloody discharge requiring at least one tampon or sanitary pad per day. Spotting was defined as bloody discharge that required only panty liners.

For subjects randomized to patch use in Study CL12, in Cycles 2-13, the incidence of unscheduled bleeding between cycles ranged from 17.7% to 27.4%, compared with 17.5% to 26.6% for subjects randomized to the OC group for 6 cycles. In Cycle 1, a much higher proportion of subjects in the patch treatment group (25.9%) experienced unscheduled bleeding, compared to 17.5% of subjects in the OC treatment group. For patch users, the incidence of unscheduled bleeding generally decreased in Cycles 7-13 compared with Cycles 1-6 [data not shown in table above].

In summary, for the subset of 877 women with BMI < 32 using the Agile patch, the range of unscheduled bleeding (breakthrough bleeding and/or spotting episodes) during Cycles 2-6 was from 19.5% to 27.4% with an average of 24.1% for the 5 cycles. From Cycles 7-13 the range was lower from 17.7% to 22.8% with an average of 19.4%. Although the range here appears to be high, if a subject experienced one day of unscheduled bleeding or spotting, then the cycle was counted as having unscheduled bleeding. These percentages are far from ideal, but it is important to note that in Study CL12, of the 211 women who withdrew from the study because of "Subject's Decision" only 16 (7.4%) listed unacceptable bleeding as the primary reason [see discussion in Section 6.1.3], so it does not appear that this was a bothersome finding for most of the subjects. There were no subjects who discontinued because of a serious adverse event due to hemorrhage.

Over the course of Cycles 1-6, 323/4221 (7.7%) of the total cycles in the patch treatment group and 181/1423 (12.7%) of the total cycles in the OC treatment group were associated with an absence of scheduled, or withdrawal, bleeding. Comparing individual Cycles 1-6, the range for no scheduled bleeding was from 6.6 to 9.2% for patch users and from 8.6 to 24.4% [Cycle 6] for OC users.

Reviewer's comment:

Clearly there was a lower percentage of cycles with no withdrawal bleeding in the patch users compared to the OC users. For a comparison, in the Ortho Evra NDA trials on average 2.2% of patch users experienced amenorrhea each cycle with the range from 1-4% per cycle. The findings for the Agile patch are higher, but did not appear to be a significant factor in study discontinuations.

7 Review of Safety

Safety Summary

The safety profile for the Agile transdermal contraceptive patch is acceptable. It should be noted, however, that the high percentage of study discontinuations and subjects lost to follow-up makes it difficult to determine the true safety profile. There were no deaths. There was one confirmed venous thrombosis (subclavian) in a healthy young woman using the patch. There were other SAEs that occurred but were probably not related to the use of the patch. Patch adherence was acceptable, and accounted for only 41 (19.4%) of the 211 women in Study CL12 who stopped the trial early because of "subject decision."

It is notable that a larger percentage of the subjects enrolled in the two phase 3 trials were, in my opinion, "at risk" than has been seen in previous NDA applications for hormonal contraception. This population appeared to be at higher risk for premature discontinuations, loss to follow-up, worse drug compliance, and poor/inaccurate medical histories and record keeping. These factors do impact the ability to ascertain the overall safety of the contraceptive patch.

Overall, the adverse reactions (ARs) that were recorded as leading to study discontinuation were those commonly seen in contraceptive trials and do not raise a safety signal. The common AEs were also those expected in a hormonal contraceptive trial. For blood pressure changes, ~2% of subjects had a clinically significant increase in either systolic nor diastolic BP at one point in the 13-cycle Study CL12, but in most cases, these changes were transient and returned to normal at a subsequent visit. Data for the two 6-cycle OC user cohorts showed that a range of 0.6-2.3% of subjects had a similar increase in BP changes.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical program associated using the AG200-15 patch involved 19 clinical studies. Of these studies, 6 assessed the AG200-15 patch at one or more of the anatomical sites (b) (4). The Applicant's summary of clinical safety from these 6 studies provides safety information associated with the AG200-15 patch (b) (4) and use of the final product, if approved. The 6 studies include the following (see Table 1 and Table 3):

- Three phase 1 studies (CL-14, 15, and 16) with safety data that is not pooled with the other studies because the studies were relatively short with a small number of enrollees. [Note: there were a total of 176 subjects, of whom 140 used a patch for one week only; 36 subjects used patches for only 3 weeks.]
- One phase 2 pharmacodynamic study CL-11 included 33 subjects using the patch for a total of 88 completed cycles (< 3 cycles on average per subject)
- Two large phase 3 studies (13-cycle Study CL-12 and 6-cycle Study CL-13)

Reviewer comment:

With the assistance of Vaishali Popat, MD, the new MAED system was used for a high-level overview of the safety of the Agile patch. The Agile data was assessed alone and in comparison to the two oral contraceptives that were used in the phase 3 clinical trials. No obvious safety signals were identified using the MAED system and looking for unexpected and expected serious adverse events that might be related to the hormonal contraceptive product. There were two reports of seizures, one in an OC user and one in a transdermal patch user. One DVT event was found in a patch user and this is discussed later in this review.

7.1.2 Categorization of Adverse Events

In the NDA submission, the Applicant used the following format for the categorization of adverse events (AEs): "Adverse events have been coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 13.1. All adverse events with an onset date on Day 1 (after the first dose of study drug) are considered 'treatment emergent'."

Treatment-emergent AEs are presented by treatment group and treatment period. The treatment periods are (1) Treatment Cycles 1-6 for all treatment groups, and (2) All AG200-15 Treatment Cycles combined (this includes 13 cycles for subjects who were randomized to use the patch in Study CL12 + 7 cycles for subjects who were randomized to use the OC and switched to patch use after 6 cycles in Study CL12 + 6 cycles for subjects who were randomized to patch use in the shorter Study CL13). The standard categorization used is for AEs and adverse reactions (ARs- relationship of possibly related, probably related, or definitely related to the drug) serious, adverse events (SAEs), AEs resulting in study discontinuation, and AEs resulting in death.

Incidence of treatment-emergent adverse events during Cycles 1-6 was summarized separately for (a) New Users, (b) Current and Recent Users, and by (c) BMI category. A New User was defined as anyone who had no exposure to hormonal contraceptives

within 6 months prior to the start of study medication; Current Users stopped their previous hormonal contraception on the first day of study medication or were on hormonal contraception and started study medication during the 7-day hormone-free interval; Recent Users used a hormonal contraceptive within the 6 months prior to starting study medication but were not Current Users.

Reviewer's comment:

In the two phase 3 trials, the incidence rates of treatment Emergent Adverse Events (TEAEs), drug-related TEAEs, severe TEAEs, TEAEs resulting in study discontinuation, Serious Adverse Events (SAEs), drug-related SAEs and deaths were analyzed. Causality (related or not related to treatment) was determined primarily by the investigator at the site where the subject was enrolled. Adverse events by Body System and Preferred terms are summarized and the most common AEs are listed. All adverse events are categorized by severity from mild to moderate to severe, according to standard criteria. The Applicant did compare the Agile safety profile to that of the two comparator OCs, but that will not be the focus of this safety review.

7.1.3 Pooling of Data Across Studies to Compare AE Incidence

As noted above in Section 7.1.1, safety data for the Agile patch were pooled from the three combined phase 2 and 3 studies, but will not be formally compared to the two oral contraceptives (OC20 and OC30). The Applicant added the OC arms to the trials so there would be some general data for efficacy, significant safety events, and common side effects for the OC products and the transdermal patch.

Reviewer's comment:

Throughout the Applicant's ISS it is often difficult to tell whether the Applicant is pooling the six studies listed above, only the three combined phase 2 and 3 studies, or the two phase 3 studies. The key studies are clearly the two phase 3 studies as they have the most data for safety.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses; Study Demographics

Drug Exposure in the Clinical Trials in the safety review

There were 10,454 cycles completed with the AG200-15 patch in the six studies included in the Applicant's safety review. The safety data are derived from the All Treated Population, which consisted of 1,660 subjects who received at least one dose of study drug during the clinical trial. The meaningful safety data, however, come from the two phase 3 trials with 6-13 cycles of planned exposure per protocol.

Table 18: Drug Exposure with AG200-15 in the Phase 3 Safety Population

Parameter	ATI-CL13	ATI-CL12 ^A		Total
	Patch use Cycle 1-6	Patch Use Cycle 1-13	Patch Use Cycle 7-12	
Total number of subjects	177	1,043	230	1,450
Total number of safety cycles	750	8,089	1,188	10,027
Number of subjects completing 13 cycles		438		438

Abbreviations: OC20, oral contraceptive (100 mcg LNG/20 mcg ethinyl estradiol)

^AStudy CL12: subjects randomized to AG200-15 only for 13 cycles or OC20/AG200-15 subjects randomized to OC20 for 6 cycles and then switched to AG200-15 (cycle 1 of AG200-15 followed cycle 6 of OC20).

Source: Applicant Clinical Overview, Table 4, pg 15.

Reviewer's comment:

The Division considers the Applicant's sample size and length of drug exposure to be reasonably adequate for the evaluation of the safety of this transdermal contraceptive product. There were 771 women-years of exposure. In the NDA submission for Ortho Evra, a new molecular entity progestin (norelgestromin) and a new delivery system, there were 3,300 subjects, over 22,150 cycles of use, and 1,704 women-years of exposure. If this NDA were to be approved in opposition to my recommendation, because there is limited exposure data, there should be a postmarketing requirement (PMR) for a large long-term prospective study to carefully evaluate safety and efficacy.

7.2.2 Explorations for Dose Response

This was done in the early stages of the development for the Agile patch. As noted earlier in this review, the choice of the specific patch that was chosen for the phase 3 trials was reasonable.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was indicated or required.

7.2.4 Routine Clinical Testing

The routine clinical testing obtained in this NDA was adequate and typical for the evaluation of a CHC product. The two active components, LNG and EE, have been widely used for many years. A listing of the routine tests follows.

Table 19: Clinical Laboratory Tests- Phase 3 Trials

CLINICAL CHEMISTRY	HEMATOLOGY
<i>The following clinical chemistry test, including Lipid Panel s will be performed at the Screening Visit (Visit 1) and the Final Visit</i>	<i>The following hematology tests will be performed at the Screening Visit (Visit 1) and the Final Visit (Visit 8)</i>
Calcium	Hemoglobin
Chloride	Hematocrit
Creatinine	RBC count
Glucose	WBC count with differential
Alkaline Phosphatase	Platelet count
Potassium	URINALYSIS
Sodium	<i>The following urinalysis tests will be performed at the Screening Visit (Visit 1) and the Final Visit</i>
Aspartate aminotransferase (AST)	pH
Alanine aminotransferase (ALT)	Specific gravity
Blood urea nitrogen (BUN)	Glucose
Phosphorus	Protein
Protein total	RBC
Albumin	WBC
Bilirubin total	
LIPID PANEL	
Cholesterol	
Triglycerides	
LDL	
HDL	
<i>The following tests will be performed at the Screening Visit (Visit 1)</i>	<i>The following test will be performed at Screening Visit (Visit 1), Visits 3-7 and Final Visit (Visit 8)</i>
HIV antibody test	Serum pregnancy (β -hCG) test
HBsAg (hepatitis B surface antigen)	
HCV antibody test (hepatitis C virus)	<i>The following test will be performed at Admission Visit (Visit 2) and before start of any new treatment cycle (at home)</i>
Thyroxine (Free T4) test	Urine pregnancy test
Chlamydia and gonorrhea screening tests	

Source: Appendix E in Study CL12 Protocol.

7.2.5 Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance or interaction studies were performed for this NDA. If approved, this will be reflected in the final labeling.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events associated with hormonal contraception are well known and were evaluated by both the Applicant and this clinical review.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in subjects using the Agile patch in any of the trials.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

No SAEs occurred in the phase 2 and 1 trials. There were 17 SAEs in 12 patch subjects from Study CL12; there were no SAEs in Study CL13. The Table 20 below lists the serious adverse events for patch and OC users.

Table 20: SAEs in Phase 3 Trials- Patch and OC users

	AG200-15	OC Cycles 1-6	
System Organ Class/PT	All Cycles N=1268	OC20 N=344	OC30 N=188
Any Serious Adverse Events	17 (1.3%)	3 (0.9%)	2 (1.1%)
Gastrointestinal disorders	2 (0.16%)	0	0
Vomiting	1 (0.08%)	0	0
Gastrointestinal motility disorder	1 (0.08%)	0	0
Hepatobiliary disorders	1 (0.08%)	0	0
Liver disorder	0 (0.00%)	1 (0.3%)	0
Immune system Disorders	1 (0.08%)	0	0
Anaphylactic shock	1 (0.08%)	0	0
Infections and Infestation	4 (0.3%)	0	1 (0.5%)
Pneumonia	1 (0.08%)	0	0
Appendicitis	1 (0.08%)	0	0
Perforated appendicitis	1 (0.08%)	0	0
Gastroenteritis	1 (0.08%)	0	0
Murine typhus	0	0	1 (0.5%)
Injury, poisoning and Procedural complications	2 (0.16%)	1 (0.3%)	0
Head injury	0	1 (0.3%)	0
Ankle fracture	1 (0.08%)	0	0
Drug overdose	1 (0.08%)	0	0
Metabolism and nutrition disorders	0	1 (0.3%)	0

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	AG200-15	OC Cycles 1-6	
System Organ Class/PT	All Cycles N=1268	OC20 N=344	OC30 N=188
Diabetic ketoacidosis	0	1 (0.3%)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.08%)	0	0
Compartment syndrome	1 (0.08%)	0	0
Nervous System Disorders	0	0	1 (0.5%)
Seizure	0	0	1 (0.5%)
Psychiatric disorders	1 (0.08%)	0	0
Suicidal ideation	1 (0.08%)	0	0
Renal and urinary Disorders	1 (0.08%)	0	0
Calculus urinary	1 (0.08%)	0	0
Reproductive Disorders	2 (0.16%)	1 (0.3%)	0
Ovarian cyst	1 (0.08%)	1 (0.3%)	0
Ovarian cyst rupture	1 (0.08%)	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.08%)	0	0
Asthma	1 (0.08%)	0	0
Vascular Disorders	1 (0.08%)	0	0
Thrombosis left subclavian vein	1 (0.08%)	0	0

Source: Applicant Table 11 in the ISS, page 34.

Reviewer's comment:

The three SAEs that the Applicant believed may possibly be related to use of the Agile patch were a drug overdose with 80 Benadryl tablets, vomiting, and left subclavian venous thrombosis. I do not believe the Benadryl overdose was related to use of the contraceptive patch. The 26 year old woman was on a CHC prior to study enrollment and was being treated for depression with Zoloft 50 mg TID and had finished 3 cycles on the patch when she took the overdose. Final diagnosis after discharge from the behavioral unit was drug overdose and bipolar disorder, type 2.

All of the SAE cases were reviewed and the ones that I believe might be associated with the use of the patch are discussed in detail below. In some cases there were no diary cards returned to the study site; information was gathered verbally from the subject or from hospital records.

Subject (b) (6): vomiting. The subject was age 35, Caucasian, G0P0, BMI 20.4 with use of condoms for contraception. Past history includes intolerance to CHCs, UTI, endometriosis, peptic ulcer, and migraines. The first patch was applied on 9-2-10. On (b) (6) she went to the ER with complaints of heavy vaginal bleeding, vomiting, mild cramps, dysuria and frequency. She was discharged the next day on 9-5 with a

diagnosis of intractable vomiting, pyelonephritis, and medication reaction. Study medication was discontinued.

Reviewer's comment:

This is a woman who had a history of intolerance to hormonal birth control medications, peptic ulcer and migraines, yet was enrolled in the trial. Within 48 hours of her first patch application she was admitted to the hospital; the specific treatment is not reported and she was discharged the next day. Given her medical history, it is certainly plausible that the use of the patch contributed to her symptoms.

Subject (b) (6): ovarian cysts. This woman was age 20, Black, G0P0, BMI 26.1 (weight 166 pounds), with use of the rhythm method for contraception. She was randomized on 8-31-10 and applied her first patch on 9-3-10. No diary cards were returned to the study site. She was seen in the ER on (b) (6) when an ultrasound showed a cystic left ovary measuring 19x18x12 cm and a 4.4 cm right ovarian cyst. The CRF also states she had a right kidney stone on 10-09.

Reviewer's comment:

The large ovarian cyst requiring surgery was probably not related to using the patch. What is significant is that at her screening visit on 8-24-10 a Pap smear and pelvic exam were performed and reported as normal. It is very doubtful that such a large cyst was not present at the screening visit (6 weeks before the actual diagnosis); had it been diagnosed at the screening visit, she would have been treated sooner.

Subject (b) (6): kidney stone with partial obstruction. This 28 year old Black subject, G6P6, BMI 31.0, was using condoms for birth control. Her medical history includes cocaine abuse, renal insufficiency, nephrolithiasis, hypertension and anemia (all with unknown start dates), Hodgkin's lymphoma in 1997, ureteral stone and ureteral stent placement in 2008, allergy to Bactrim, and bacterial vaginosis. Subject was not taking any medication at the time of Screening and her laboratory evaluations, physical exam and vital signs were within normal limits. The subject met all of the inclusion and exclusion criteria and she applied the first patch on 8-24-10. On (b) (6) she was admitted to the hospital with left flank pain and a UTI. On (b) (6) a stent replacement was performed at another hospital and shock wave lithotripsy was planned. She was continued in the study for a total of 4 cycles of patch use, although she did not return her diary cards for Cycles 2-4.

Reviewer's comment:

It is difficult to say if the adverse event was related to using the patch for 2 cycles. What is of note is that she was enrolled in the first place given her past medical history and significant kidney problems, but "she met all the inclusion and exclusion criteria." I am also surprised that she was continued in the study for a total of 4 cycles (she did return the used patches to the site for all 4 cycles despite not having the diary card for the last 3 cycles. While on treatment, she had the stent replacement and was a candidate for lithotripsy which, in my opinion, are not benign procedures.

Subject (b) (6): left subclavian venous thrombosis case. This is a significant thromboembolic event. Information from the subject's narrative shows she is a 26 year old, G0PO Caucasian female, non-smoker, with a BMI of 19.9 who was screened for the study on 9-20-10. She has a no prior pregnancies and a regular menstrual cycle. Seasonal allergies, tonsillitis, viral meningitis, breast augmentation and Chlamydia are noted in the subject's medical history. Her concomitant medication included Z-pak for Chlamydia, multivitamins, and Claritin. The subject also began taking Spirolactone for acne on 12-3-10. The subject's laboratory evaluations, physical exam and vital signs were within normal limits.

The subject was randomized to the Agile treatment group on 9-24-10 and applied the first patch on 10-7-10. Diaries for Cycle 1-3 are unremarkable with the exception of a patch replacement on Day 18 in Cycle 1. Cycle 4 diary information is not available.

On (b) (6) (the beginning of Cycle (b) (6)) the subject presented to the emergency room with dull pain in her left arm for 6 days. The subject noticed swelling on (b) (6) that got progressively worse throughout the evening. The subject reported discontinuing the patch on 1-19-11 due to increased acne. Physical exam was within normal limits. The subject's platelet count at the time of the ER admission was 222 and her BUN was slightly elevated at 33.3; all other labs on (b) (6) were within normal limits. A venous Doppler revealed a deep vein thrombosis with partial occlusion in the left subclavian vein proximally. The subject was admitted to the hospital and a heparin drip was started.

Laboratory testing during hospitalization included an anticoagulant panel, Factor II, Antithrombin III, Protein C, Protein S and Factor V Leiden. All results were within normal limits or negative. A CT angiography was performed on (b) (6), however, this test was considered non-diagnostic, perhaps because she had been anticoagulated for 48 hours. On (b) (6) the pain and swelling had decreased and the heparin was discontinued and she was placed on Coumadin. On (b) (6) (Day 5), the subject was discharged on Coumadin and told to follow up with an ultrasound in 2 weeks and with her primary care doctor for PT/INR checks every two weeks. She had a study visit 1-5-11 and final study visit on 2-16-11: normal vital signs, physical exam, and lab tests.

The subject is active and she lifts weights and participates in kick boxing. She reported that she has been very physically active since age 6 secondary to being involved in soccer. For the past 4-5 years she has not changed her exercise activity level. Her

workouts involve multiple repetitions with the use of weights that are 8-10 pounds. The Applicant requested the subject be evaluated for possible Paget-Schroetter syndrome, a form of spontaneous effort-related or exercise-induced upper extremity deep vein thrombosis (DVT), especially with vigorous repetitive upper arm motions. The subject's great aunt also had a similar clot. No other significant family history is noted. Final diagnosis is left subclavian thrombosis.

Follow-up on 6-17-11: the PI noted that the subject has recently completed a left arm angiogram which showed development of collaterals but thrombosis still blocking the left subclavian vein. No compression was noted. Following the discussion the PI agreed to refer the subject for a vascular consultation for follow-up on the thromboembolic event as well as to rule out Paget-Schroetter syndrome.

Reviewer's comment:

This is an interesting venous thrombosis case and one that I have not seen in previous NDA reviews of hormonal contraceptive products. The subject was discontinued from the study and the Applicant stated that the event was possibly related to study drug. Her coagulation profile was normal and she does fit the profile for Paget-Schroetter syndrome because of her repetitive weight lifting. She was using male condoms prior to the study and the record unfortunately does not state whether she had ever previously used hormonal contraception. It is difficult to say if this thromboembolic event is definitely related to the contraceptive patch. It is a significant signal, however, that cannot be ignored. Because contraceptive trials are never large enough to characterize the VTE risk prior to approval, if the Agile patch is approved, then it will be important to have a large long-term prospective study to evaluate the safety of the transdermal patch, particularly with respect to relatively infrequent but serious ARs like VTEs and ATEs.

Subject (b) (6): lower leg Compartment Syndrome leading to bilateral AK amputations. This 25 year old G3P1 smoker (1.5 packs a day) had a past history of migraine since 2008, surgical removal of right ovarian cyst in 2007 and low back pain since February 2010. Subject was taking Percocet prn for low back pain at the time she was screened for the study and denied any substance abuse. The first patch was applied on 9-12-10. She was last seen at the study site on 2-16-11 when she returned all patches and stated her LMP as 2-5-11. She was discontinued from the study on 3-28-11 due to a positive home pregnancy test according to information received by phone from the subject. She reported that her last patch was applied on 3-28-11. It should be noted that her LNG and EE levels on 2-16 were not detectable when she said she was using the patch.

During the course of the study subject was diagnosed in November 2010 with fibromyalgia, for which she was prescribed Neurontin (gabapentin) 100 mg bid and Savella (milnacipran) 1 tablet bid, and depression with anxiety disorder, for which she was prescribed Clonapine (benzodiazepine) 1 mg prn. On admission to the hospital on (b) (6) the subject reported as current medications: Trazodone, Percocet and Celexa (citalopram), which was not reported to the study site.

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On (b) (6) she had difficulty walking and standing and needed assistance. On (b) (6) the symptoms continued and her legs had become purple and she could not walk at all. On (b) (6) subject was admitted to the hospital with a history of 12-18 hours of vaginal bleeding and abdominal pain more than 48 hours prior to admission. On admission she reported loss of sensation from both feet up to both calves with severe, unrelenting, unremitting pain, which was agonizing; she also reported anuria for 48 hours. She was diagnosed with Compartment Syndrome with non-viable muscle in four compartments, bilateral lower extremities. Subsequently rhabdomyolysis caused her to go into acute renal failure and she also developed acute blood loss anemia for which she received 2 units of blood. She was placed on dialysis. She was taken to the OR for emergency bilateral lower extremity fasciotomies which included a long lateral calf fasciotomy all the way to the ankle. Incisions were made to expose the superficial, posterior and then deep posterior compartments. She was also diagnosed with mild-to-moderate thrombocytopenia of unknown origin with a possibility of being induced by heparin, as she was placed on DVT prophylaxis after surgery.

During consultation with an Ob-Gyn at the hospital, the subject's beta HCG was over 900 but a bedside ultrasound revealed no intrauterine pregnancy. The Applicant's conclusion was that the subject was not pregnant and the serum HCG level was considered false-positive due to her condition and treatment.

Subject was transferred to another hospital and the last information received by the study coordinator was 5-13-11 when she was informed that the subject had above knee amputations (AKAs) for both legs. A report from a third hospital where the subject was admitted for rehabilitation states that the AKA was performed on (b) (6). The hospital records also state that the surgical procedure was complicated by blood loss anemia which required 18 units of blood and a right pneumothorax requiring chest tube placement.

During her stay at the rehabilitation hospital, more information became available, which had not been disclosed when she was screened for the study or during her admittance to the ER. Subject has a significant substance abuse history (heroin, cocaine, benzodiazepine abuse and opiate dependence) and during her hospital stay required significantly higher than usual doses of pain medication to control her pain, and she exhibited drug-seeking behavior. She also reported significant spousal abuse and a history of a motor vehicle accident with back injury. While at this hospital a psychiatry evaluation revealed the subject to be an unreliable historian with respect to substance misuse, having a problem with impulse control and decision making with substance-seeking behavior.

Reviewer's comment:

This tragic case in an unreliable subject is possibly related to the use of the Agile patch. It could plausibly be related either to her substance abuse or potentially to the patch if she had a DVT. It is not certain that a DVT was ruled out during the initial hospital evaluation. It is not possible to accurately know when she used the patch and when was her last patch application. With the undetectable hormone levels on 2-16 and the more accurate medical history that was revealed with time, it is plausible that the subject was not using the patch in March and April. Whether she was ever pregnant or not is also unresolved, but early pregnancy (as opposed to an advanced pregnancy) is not associated with compartment syndrome. The factors contributing to her compartment syndrome are not clear from the information provided.

Subject (b) (6): Anaphylactic shock. This 20 year old subject, BMI 26.8, condom user, with a history of GERD started the patch on 9-30-10. On (b) (6) she experienced lower abdominal pain, nausea and vomiting and went to the local ER. A week prior to this episode she was seen at another ER with the same complaints and given a prescription for antiemetics. In the current ER admission, she was given IV morphine 4 mg and had a severe reaction with respiratory failure and cardiopulmonary arrest; she developed anoxic encephalopathy and was left with residual amnesia; she was discharged on (b) (6) and lost to follow-up.

Reviewer's comment:

This unfortunate severe reaction to a relatively low dose of IV morphine was probably not related to the patch which she had used for only 3 days. According to the narrative summary she was treated for GERD since November 2005 (age 15) and experienced similar episodes of abdominal pain with nausea and vomiting multiple times in the past.

7.3.3 Dropouts and/or Discontinuations

See Section 6.1.3 of this review for the analysis and comments on the data for subjects who did not complete the studies as designed. There were a total of 52 subjects who discontinued therapy due to application site reactions; the Applicant split the reactions into 9 different subcategories in one analysis and 6 in another [6 are listed in Table 21].

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Table 21: Subjects with AEs Leading to Discontinuation, Pooled Data

Body System	Patch Cycle 1-6 No switchers are included here	Patch Cycle 1-13	OC20	OC30
	n=1220*	n=1450	n=344	n=188
	n (%N)	n (%N)	n (%N)	n (%N)
*Any AE: the preferred terms listed below refer to Cycle 1-6 patch users only (CL13 + CL12 Cycle 1-13 subjects); switchers in CL12 are not included.	119 (9.8%)	151 (10.4%)	16 (4.7%)	3 (1.6%)
Cardiac Disorders: tachycardia	2 (0.2)	2 (0.1)	0	0
Gastrointestinal Disorders: nausea- 8; distension- 3; pain- 3	14 (1.1)	18 (1.2)	1 (0.3)	0
Application Site Conditions: irritation- 21; pruritis- 17; erythema- 6; rash- 4; vesicles- 2; discoloration or pain- 2	52 (4.0)	65 (4.5)	0	0
General Disorders: fatigue- 2; irritable-2; pain-2; chest pain-1; asthenia- 1; flu with fever-1	9 (0.7)			
Hepatobiliary Disorders: cholecystitis	1 (0.1)	1 (0.1)	1 (0.3)	0
Immune System Disorders: acute morphine reaction	1 (0.1)	1 (0.1)	0	0
Infections and Infestations	0	0	1 (0.3)	0
Injury/Poisoning: Benadryl overdose	1 (0.1)	1 (0.1)	1 (0.3)	1 (0.5)
Investigations: Pap test- 2; weight ↑- 4;	6 (0.5)	6 (0.4)	1 (0.3)	0
Metabolism & Nutrition Disorders: decreased appetite	1 (0.1)	1 (0.1)	0	0
Musculoskeletal and Connective Tissue: pain/spasms- 3	3 (0.2)	5 (0.3)	0	0
Neoplasms benign, malignant, and unspecified: fibroid	1 (0.1)	1 (0.1)	0	0
Nervous System Disorders: headache- 7; migraine- 3; dizzy- 6	16 (1.3)	18 (1.2)	1 (0.3)	0
Psychiatric Disorders: mood change- 11; depression-5; anxiety-2; bipolar-1; suicidal- 1; decreased libido- 1	21 (1.7)	22 (1.5)	2 (0.6)	0
Reproductive System and Breast: menometrorrhagia-14; irregular bleeding- 4; ovarian cyst-5; breast tender-5; breast mass- 1; pelvic pain- 2; PMS- 1	32 (2.6)	35 (2.4)	6 (1.7)	1 (0.5)
Skin-Subcutaneous Tissue: alopecia- 4; acne-2; rash-2; irritation-3	11 (0.9)	12 (1.0)	2 (0.6)	1 (0.5)
Vascular Disorders: hypertension- 3; embolism-1	4 (0.3)	5 (0.3)	1 (0.3)	0

Source: FDA analysis using (b) (4) and Applicant Table 14, pg 44 of Summary of Clinical Safety.

Reviewer's comments:

The table above provides a summary by Body System (and preferred term for Cycles 1-6 for patch users only) of the TEAEs that resulted in subjects discontinuing in either Study CL12 or CL13. Some subjects are listed more than once, as there are 175 events listed for the 119 subjects in the patch Cycle 1-6 column and 193 events for the 151 subjects who are listed in the patch Cycle 1-13 column.

First, the data indicate that there was a higher probability of discontinuation because of an AE in women using the Agile patch for 6 cycles as compared to women using the two OC products for 6 cycles (9.8% for patch users versus 3.6% for the two OC groups combined).

The most commonly reported preferred terms leading to study discontinuations after 6 cycles of patch treatment were: patch application symptoms (52), menometrorrhagia/irregular bleeding (18), mood changes (11), headache and migraine (10), nausea (8), and dizziness (6). Breast symptoms, depression, and ovarian cyst each had 5 entries. It is notable that of the women in Study CL12 who discontinued due to bleeding problems, all 13 stopped the trial within the first 6 cycles; there were no discontinuations for bleeding during cycles 7-13. The sample size for the two OCs is small and OCs were used for only 6 cycles so it is not possible to compare 13-cycle data between the patch and the OCs.

Concerning the commonly reported individual adverse events associated with treatment discontinuation, these side effects are common with hormonal contraception and are expected. It is interesting that analysis of the data from the larger phase 3 trial fails to support that breakthrough or abnormal bleeding problems were a common cause of study discontinuation, in contrast to what has often been seen as the reason for study discontinuation with other hormonal contraceptives. Patch-related irritation and itching were more prominent in this regard. However, symptoms of local irritation and pruritus are to be expected with a transdermal drug-delivery product.

7.3.4 Significant Adverse Events

No additional significant adverse events were reported in the clinical trials.

7.3.5 Submission Specific Primary Safety Concerns

As discussed earlier, the subclavian thrombosis is of concern and occurred in a compliant subject who was otherwise young and healthy and had no obvious risk factors except for her regular vigorous workout routine (which had not changed since she began using the patch, according to the Narrative Summary).

7.4 Supportive Safety Results**7.4.1 Common Adverse Events**

The Applicant had a summary of all treatment-emergent adverse events for the two phase 3 studies.

Table 22: Treatment-emergent Adverse Events- Phase 3 Studies

	Patch Cycles		OC Cycles 1-6	
	1-13* Study CL12 (N=1450)	1-6 CL12 + CL13 (N=1220) No switchers are included here	OC20 CL12 (N=344)	OC30 CL13 (N=188)
All Subjects with TEAEs	781 (53.9%)	580 (47.5%)	163 (47.4%)	88 (46.8%)
Subjects with severe TEAEs	73 (5.0%)	50 (4.1%)	9 (2.6%)	3 (1.6%)
Subjects with serious TEAEs (SAE)	16 (1.1%)	14 (1.1%)	4 (1.2%)	2 (1.1%)
Drug-related TEAEs All Subjects	338 (23.3%)	261 (21.4%)	55 (16.0%)	24 (12.8%)
Subjects with TEAEs resulting in study drug discontinuation	151 (10.4%)	119 (9.8%)	16 (4.7%)	3 (1.6%)
Subjects with drug-related & serious TEAEs (SAEs)	3 (0.2%)	3 (0.2%)	1 (0.3%)	0
Subjects who died	0	0	1 (0.3%)	0

*This column does not include subjects from Study CL13.

Source: Reviewer modified Applicant Table 6, ISS page 27.

Reviewer's comment:

It is true that the women in Study CL12 who switched to patch use were different from the OC users because all of the switchers had been on 6 cycles of the same OC containing 20 mcg EE immediately prior to starting the patch. Certain AE risk factors, compliance, and hormonal exposure were already tested during the first 6 cycles on the OC. However, the most meaningful comparison for TEAEs is to look at the data for only Cycles 1-6 of use [the 3 columns on the right]. The total percentage of subjects with TEAEs is essentially the same (47%), but there was a higher percentage of patch users who had severe TEAEs, drug-related AEs, and discontinuations due to an adverse event. Of the SAEs that were believed to be drug-related (a very small number), there is basically no difference (0.2% and 0.18%) between the patch users and the OC users.

Treatment-emergent adverse events by preferred terms occurring in $\geq 3\%$ of subjects are shown in FDA Table 23 below. For Cycles 1-6, no severe adverse events occurred in $\geq 1\%$ of subjects in any treatment group.

Table 23: All AEs ≥ 3% by Patient- Combined Patch and OC Data for Cycles 1-6

Body System	Preferred Term Adverse Event	Patch Users Cycle 1-6 N=1235				OC Users Combined N=511			
		All Grades		Severe		All Grades		Severe	
		Number	%	Number	%	Number	%	Number	%
Gastrointestinal disorders	Nausea	50	4.05	1	0.08	26	5.09	2	0.39
Gastrointestinal disorders	Vomiting	17	1.38	1	0.08	16	3.13	1	0.20
Infections and infestations	Nasopharyngitis	64	5.18	1	0.08	20	3.91	0	0.00
Infections and infestations	Upper respiratory tract infection	43	3.48	2	0.16	15	2.94	0	0.00
Nervous system disorders	Headache	42	3.40	6	0.49	18	3.52	1	0.20
Reproductive system and breast disorders	Cervical dysplasia	28	2.27	0	0.00	28	5.48	0	0.00
General disorders and administration site conditions	Application site reaction	68*	5.51	7	0.57	0	0	0	0

* Applicant data has 74 (6.0% of 1235).

Source: FDA table based on (b) (4) analysis of NDA dataset.

Reviewer's comments:

The table above uses a ≥ 3% cutoff. If ≥ 2% cutoff is used, then the following preferred terms were added: Breast tenderness, HPV test positive, UTI, and sinusitis.

It is a more direct comparison to use AE data only for Cycles 1-6 for patch and OC users. In Cycles 1-13 for patch users, the incidence and the pattern of individual adverse events varied by only 0.0 to 0.4% when compared to Cycle 1-6 patch users.

The AEs associated with the patch are consistent with what is usually seen for common treatment-related AEs for a hormonal contraceptive patch or OC. Although there were 7 subjects that were considered to have a severe patch reaction, none were considered to be a serious adverse event. There were 52 subjects during Cycle 1-6 patch use who discontinued from their study because of a patch reaction; if patch use is extended for Cycle 1-13 use, then the total becomes 65 subjects (see Table 21).

The application site data is a bundling of the Applicant's 10 possible subcategories depending on which table the Applicant created: dermatitis, discoloration, erythema, irritation, pain, pruritus, rash, reaction, swelling, and vesicles. In summary, for Cycles 1-6 (N= 1,235), 5.5% of subjects reported an application site reaction and for Cycles 1-13 (N= 1,450), 7.4% of subjects reported an application site reaction. In the large phase 3 13-cycle Ortho Evra trials (N= 3,330), there were 581 subjects (17.4%) who reported an application site reaction during the trials. In the Ortho Evra trials an application reaction (adverse event) led to discontinuation from the trial for 62 (1.9%) of the subjects,

compared to 4.0% in the Agile patch users.

By comparison to the Ortho Evra 13-cycle patch data, the Agile patch had a higher percentage of discontinuations and a lower percentage of total application site patch reactions. It is important to remember that in the case of an application site reaction, a patch can easily be removed and another placed at a different location to maintain contraceptive efficacy.

7.4.2 Laboratory Findings

Clinical laboratory tests: were performed at the Screening Visit and at study completion in both studies and included the following (see Table 19):

- Serum Chemistry: Sodium, potassium, calcium, chloride, glucose, uric acid, creatinine, blood urea nitrogen, ALT, AST, total protein, albumin, lipid panel, alkaline phosphatase, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), and inorganic phosphorus.
- Hematology: Hemoglobin, hematocrit, red blood cell count, platelets, white blood cell count and differential.
- Urinalysis: pH, ketones, protein, occult blood, and glucose.
- Other screening tests include HIV antibody test, HBsAg test, HCV antibody test, thyroxine (Free T4) test, chlamydia and gonorrhea screening
- In a subset of ~120 subjects, SHBG and corticosteroid-binding globulin (CBG) levels were drawn in Study CL12 at Cycles 2, 6, and 13

Clinical chemistry findings in the 13-cycle Study CL12 (with the EE 20 mcg OC comparator for only 6 cycles) did not provide any evidence of a significant safety signal for the Agile patch. The clinical chemistry laboratory parameters showed some variability with respect to the distribution of subjects in the below normal, normal, and above normal groups. However, these changes in distribution generally represented no more than 5% of the subjects, and there were no consistent shifts with respect to a single treatment group across multiple chemistry tests or consistent changes with respect to a single analyte across treatment groups.

In Study CL12 (N= 777), there were small increases in mean cholesterol (1.3 mg/dL; 175 to 176.3) and triglycerides (5.6 mg/dL) for the patch group from baseline to end of treatment; mean low-density lipoprotein (LDL) cholesterol decreased by 3.8 mg/dL and high-density lipoprotein (HDL) cholesterol increased by 4.1 mg/dL. For the 20 mcg EE OC users (N= 291), mean cholesterol dropped 5.9 mg/dL, triglycerides dropped 2.9, LDL cholesterol dropped 0.7, and HDL dropped 4.7 mg/dL.

For the 6-cycle Study CL13 there were increases in mean cholesterol (7.0 mg/dL; 171 to 178) and triglycerides (10.8 mg/dL; 95.3 to 106.1) for the patch group from baseline to end of study; mean LDL cholesterol remained stable over the course of the study (94.4 to 94.7), and HDL cholesterol increased 4.6 mg/dL (57.7 to 62.3). For the 30 mcg EE OC users, mean cholesterol dropped by approximately 4 mg/dL, while triglycerides

rose by approximately 3 mg/dL, LDL cholesterol dropped by approximately 3 mg/dL, and HDL cholesterol dropped slightly. The shift tables failed to provide evidence of a clinically significant effect of the patch or the OC on the clinical chemistry findings.

Reviewer's Comment:

For the combined phase 3 data there is a trend that the changes seen for the lipid values in the patch users were slightly greater when comparing the Study CL13 values to the Study CL12 values. When comparing women with a BMI < 30 with a BMI ≥ 30 the changes were smaller in the lower BMI group. There were, however, no changes that were of major concern. For the non-lipid chemistry parameters, there was no evidence of any significant safety findings for the Agile patch group; the mean changes were small and not clinically significant. The shift tables did not show a significant systemic effect of the patch or the OCs on clinical chemistry.

Hematology

In Study CL12, the mean decrease in hematocrit from baseline for the Cycle 1-13 users was -0.54% [baseline 42.51% to 41.97] with a median change of -0.50%. For the 344 OC users, the corresponding mean decrease was -1.32% (median -1.3%). In Study CL13, the mean increase in hematocrit from baseline for the Cycle 1-6 users was 0.58% [baseline 42.5% to 43.08] with a median increase of 0.70%. For the 188 OC users, the corresponding increases were mean 1.72% and median 1.6%. The small changes in hemoglobin values were in the same direction as those for hematocrit.

Reviewer's comment:

There were no transfusions in either study. Although there were some shifts to lower values for basophils and monocytes, significant infections or anemia were not prominent and do not appear to be a safety concern. My overall impression is that the hematology data for both phase 3 studies acceptable and does not show any safety signals.

7.4.3 Vital Signs

Vital signs measured during the Phase 3 trials included blood pressure (BP), heart rate, and weight, both at Screening/Baseline and at End of Study. Table 25 below for all subjects indicates that use of the Agile patch was more likely (1.2% compared to 0.6% of OC users) to result in an elevation of systolic blood pressure (SBP). For the same 6 cycles, this was not true for diastolic blood pressure (DBP) as compared to the OCs (1.2% compared to a combined OC rate of 1.3%). For the longer period of observation for patch users (Cycles 1-13) compared to use in only Cycles 1-6, there is an increase in the incidence of clinically significant changes in SBP and DBP (see Table 25).

When comparing BP data for subjects Cycles 1-6 with BMI < 30 kg/m² to those with BMI ≥ 30, the incidence rates for increased SBP and DBP change from 1.2% to 1.4%, which is of no clinical significance. However, when the highest subgroup of BMI (>35 kg/m²) is compared to the lower BMI groups, there appears to be a linear trend of increasing incidence across increasing BMI values, which is not an unexpected finding (obesity is one known risk factor for hypertension).

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The changes in BP were often transient. In several cases, the elevation in SBP and DBP were observed for only one assessment and the BP returned to baseline levels at the last recorded visit. For 5 subjects in the OC group with elevated BP, the BP dropped after switching from the OC to the patch.

Data for the use of antihypertensive drugs during Cycles 1-6 is shown in the next table.

Table 24: Concomitant Use of Antihypertensives- Cycles 1-6

Antihypertensive Medication	Patch Users Cycles 1-6 N = 1220	Combined OC Users Cycles 1-6 N =532	Comment
ACE inhibitor	6 (0.49% of N)	2 (0.38% of N)	Rx can be used for other indications
Beta blocker	7 (0.57%)	3 (0.56%)	Rx can be used for other indications
Angiotensin II	2	1	Rx can be used for other indications
Totals →	13 (1.07%)	6 (1.13%)	

Source: Reviewer data extracted from ISS Table 7.1 Concomitant Meds for Cycles 1-6.

Reviewer's comment:

The table for concomitant medications used between Day 1 of treatment and last day of treatment for Cycles 1-6 shows that 13 patch subjects were on antihypertensive drugs with an almost identical percentage for the patch and OC users. The data is for the number of medications and not necessarily the number of subjects; furthermore, the data does not reflect when the medication was started or ended or the exact indication for the use of the antihypertensive drug. As alluded to in the comment column, these antihypertensive drugs may also be used for migraine prevention, mitral valve prolapse, congestive heart failure, arrhythmias, etc.

Table 25: Clinically Significant Changes in Vital Signs- Phase 3 Trials- All Subjects

		Patch Cycles -----		OC Cycles 1-6	
Parameter	Criterion	Cycle 1-6 N=1220	Cycle 1-13 N=1450	OC20 N=344	OC30 N=188
Systolic Blood Pressure	Value $\geq$ 140 mmHg and increased $\geq$ 20 mmHg from Baseline	n= 14 (1.2% of N)	n= 25 (1.7% of N)	n= 2 (0.6% of N)	n= 1 (0.5% of N)
Diastolic Blood Pressure	Value $\geq$ 90 mmHg and increased $\geq$ 15 mmHg from Baseline	n= 14 (1.2% of N)	n= 31 (2.1% of N)	n= 6 (1.7% of N)	n= 1 (0.5% of N)
Heart Rate	Value $\geq$ 120 bpm and increased $\geq$ 20 bpm from Baseline	n= 1 (0.1% of N)	n= 2 (0.1% of N)	n= 1 (0.3% of N)	n= 0 (0% of N)
Weight	Value increased $\geq$ 4.54 kg (10 lb) from Baseline	117/1131 (10.3%)	206/1357 (15.2%)	22/310 (7.1%)	20/184 (10.9%)
	Value decreased $\geq$ 4.54 kg (10 lb) from Baseline	64/1131 (5.7%)	163/1357 (12.0%)	19/310 (6.1%)	15/184 (8.2%)

Source: Applicant Summary of Clinical Safety, Table 20.

Patch Cycles 1-6 = Cycles 1-6 for subjects randomized to patch use in study CL13 and cycles 7-13 in CL12.

Patch Cycles 1-13 = All cycles for subjects randomized to patch use in studies CL13 and ATI-CL12(Cycles 1-13).

Source: Table modified by Reviewer.

Reviewer's comments:

There were no significant changes in heart rate for any of the 3 arms over time.

Overall, for Cycles 1-6, the percentage of patch subjects who had a significant change in systolic BP is 1.2% compared to 0.6% (3/532) for the combined OC users. For 6-cycle data, a significant change in diastolic BP was seen in 1.2% of patch users and 1.3 % (7/532) of the combined OC users. The number of patch users is greater than the number of OC users, as the CL12 trial was designed this way. It is not possible to make any 13-cycle comparison because there are no OC users with more than 6 cycles of exposure.

A JMP analysis of the weight changes on treatment showed that there was no difference in weight gain for non-obese versus obese women. In the larger Study CL12 at Cycle 6, there was a difference comparing patch and OC users: the mean change for patch users was +0.92 kg (median 0.90 kg) and the mean change for OC users was +0.38 kg (median 0.25 kg), which amounts to a weight gain difference of approximately 1.2 pounds (0.54 kg). For Cycle 1-6 data, 10.3% of patch users and 8.5% (42/494) of OC users had a 10 pound increase; for a 10 pound decrease, there were 5.7% of patch users and 6.9% (34/494) of OC users. Change in weight is seen with all hormonal contraceptive trials and the percentages shown here are in the range seen in other trials. My opinion is that

these weight increases and decreases do not show a significant difference between the patch and OC users.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed during the phase 3 clinical trial. No significant ECG changes were noted in the phase 1 studies.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed.

7.4.6 Immunogenicity

No immunogenicity studies were performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This product delivers lower EE blood levels than found with the Ortho Evra transdermal patch. It is not possible to directly compare serum levels of LNG with those of norelgestromin from the Ortho Evra patch because they are different progestins and have different progestational properties. Although the Applicant has not proposed any labeling claim, in their summary report they claim that their product has fewer of the common side effects seen with the OE patch. No direct clinical trial comparison has been made and no such claim will be allowed in final labeling if the product is approved.

Reviewer's Comments:

The Agile transdermal patch is loaded with more EE than is found with the Ortho Evra transdermal patch (2.3 mg vs 0.75 mg), but the serum level delivered by the Agile patch is considered to be lower.

To some extent, minimizing exposure to estrogen and progestin reduces the risk of thrombotic events. For any particular estrogen/progestin combination, the recommended dose regimen is that which contains the least amount of estrogen and progestin that is compatible with a low pregnancy rate, an acceptable bleeding profile, and the medical needs of the individual patient. From the clinical trial data for the Agile patch with an unacceptable high Pearl Index, it is not possible to tell if the Applicant has selected the optimal dose. As noted earlier, the poor contraceptive efficacy is most likely due to poor compliance, but some of the chemistry factors (stability, enhancers, uneven hormonal delivery, patch adherence) for the patch may also have a role in contraceptive failures.

7.5.2 Time Dependency for Adverse Events

Aside from characterizing AEs in the 13-cycle trial and the 6-cycle trial, exploration for time dependency of adverse events was not performed.

7.5.3 Drug-Demographic Interactions

This product is indicated for use only in women of childbearing age. No other special populations were studied. There is no evidence in the current medical literature that the safety or efficacy of CHCs is significantly affected by race or ethnicity. The results in the Agile trials did show worse contraceptive efficacy in the African-American group. There are, however, many other factors that may impact contraceptive efficacy that may be more significant than race/ethnicity, such as income level, education level, compliance, stress, motivation to have no more pregnancies, etc.

Reviewer's Comments:

For the ITT2 population, the Applicant's pregnancy rates (Pearl Index) for subjects using the patch were highest for Black women (10.83; CI 3.36, 18.31), followed by Hispanic white women (9.85; CI 2.58, 17.12), and non-Hispanic white women (4.16; CI 1.81, 6.51). The FDA analysis showed a Pearl Index of 14.90 for Black women and 11.26 for Hispanic white women. The pregnancy rates for the OC users were 41.60 (CI 1.49, 81.71) for Black women and 8.28 (CI 0.0, 24.46) for Hispanic white women. No pregnancies were reported for non-Hispanic white women on the OC, but the number of subjects is small.

In non-Hispanic white women, the Pearl Indices were similar across all populations. In Black and Hispanic white women, the Pearl Indices were generally highest in the ITT2 population and lowest in the MF2 population.

In addition, based on the laboratory evaluation of serum levels at 3 points in the study, 11-14% appeared to be noncompliant. Specifically, in the patch arm, 12-14% had EE levels below the LLOQ and 11-13% had LNG levels below the LLOQ. They report by race (presumably aggregating over visits and treatment arms) that black women had 17-32% noncompliance, Hispanics had 11-20% and white women 6-12% [p 143 of Study 12 report].

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed for this NDA application. Class labeling for combination hormonal contraception includes a section on drug-drug interactions, which would be included in the final label if the product were to be approved.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity trials were indicated or performed. Class labeling for combination hormonal contraception discusses potential associations with malignancies (breast, cervix).

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction or pregnancy data was required for this NDA. No fetal or maternal toxicity has been attributed to the LNG/EE combination found in oral contraceptives and there is no biological plausibility that this would be different for a transdermal patch containing LNG and EE.

7.6.3 Pediatrics and Assessment of Effects on Growth

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant has requested a full waiver of the requirement for pediatric studies associated with this NDA because the Applicant believes that the safety and efficacy of the LNG/EE combination have been established in all women of reproductive age. Similarly, the efficacy profile of the Agile patch is expected to be the same for post-menarcheal adolescent females less than 18 years of age as it is for females older than 18 years of age.

Reviewer's Comments:

- **A partial waiver for premenarchal girls is recommended.**
- **The pediatric study requirement may be able to be met by extrapolation from the trial data obtained on adult women in this development program.**
- **The Division's recommendations regarding the partial waiver for premenarchal girls and data extrapolation from adult to postmenarchal females is scheduled to be discussed by the Pediatric Review Committee on January 16, 2013.**

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no issues with combination hormonal contraception (oral, transdermal, or vaginal) and drug abuse potential, withdrawal, or rebound. The issue of overdose is covered in the approved labels for hormonal contraceptives. The potential for either intentional or accidental overdose with a transdermal patch is viewed as unlikely, and probably would not cause serious effects even if it occurred. Correct disposal of the transdermal patch would also be specifically mentioned in final labeling, if the product were approved.

7.7 Additional Submissions / Safety Issues

Annual Report: stamp date 6-29-12, was submitted to IND 057731. The data cut-off date was 4-12-12, the day of the NDA submission. No additional clinical work with the Agile combination hormonal transdermal system was anticipated at the time of the submission. The annual report contained the integrated safety data from the two phase 3 studies that were submitted with the NDA, so there was no new safety data in the annual report.

120-day Safety Report: this was submitted on 8-10-12. The nonclinical data provided in the NDA was mainly literature-based and covered the period ending February 2012. The literature review of clinical safety data (2.7.4 Summary of Clinical Safety), covered the period ending March 2012. This safety update covers the period from original NDA submission up until July 23, 2012. The report includes the following information:

- Results from nonclinical and clinical literature searches conducted from February 1, 2012 until July 23, 2012.
- Information from initial and/or follow-up pregnancy forms collected since submission of original NDA

The safety information gathered over this reporting period from pregnancy forms of subjects who had participated in Studies ATI-CL12 and ATI-CL13 and from a review of the nonclinical and clinical published literature does not raise any new safety signals that would mandate a change to this current NDA review or the Applicant's proposed prescribing information for Twirla.

Worldwide experience on the safety of this drug product is not available, as Twirla has not yet been marketed in any country. In addition, there have been no ongoing or new nonclinical or clinical studies with the Agile contraceptive patch since the original NDA submission, so there is no new findings or changes in the safety profile of the drug.

8 Postmarket Experience

There are no postmarketing data because there is no transdermal contraceptive patch containing levonorgestrel and ethinyl estradiol approved anywhere in the US or globally.

9 Appendices

9.1 Literature Review/References

Several references (23) were submitted with the NDA application. Some of these were reviewed when appropriate to the clinical review process.

9.2 Labeling Recommendations

DMEPA (Division of Medication Error Prevention and Analysis)

Alison Park, Safety Evaluator in DMEPA, reviewed the proposed product name Twirla. Her 7-05-12 review concluded that the proprietary name is acceptable from both a promotional and safety perspective.

Reviewer's Comment:

The Division concurs.

DMPP (Division of Medical Policy Programs)

The Patient Labeling Team (PLT) is located in the new Office of Medical Policy Initiatives (OMPI), Division of Medical Policy Programs. The goal of the PLT is to promote the safe and effective use of prescription medications by providing accurate and easily understood patient medication information. The PLT collaborates with and responds to consult requests from CDER review divisions on patient labeling and is responsible for the review of Medication Guides (MG), Patient Package Inserts (PPI), and Instructions for Use (IFU). For this NDA it was determined that a Medication Guide was not necessary.

Because the Division does not recommend approval of this product, labeling negotiations were not initiated. If approved in the future, then labeling negotiations and a label will need to be finalized. The trade name Twirla was found to be acceptable but this will need to be re-visited if the application moves forward.

9.3 Advisory Committee Meeting

During the 6-6-12 teleconference, when the Division conveyed its concerns about the high Pearl Index, the Applicant asked whether this NDA could be presented to an Advisory Committee meeting. The Division indicated that it did not plan an Advisory Committee meeting for this application, and that the review issues were not of the type typically requiring Advisory Committee input. In addition, the product is not first in class [there is an approved transdermal product for hormonal contraception for women], and the two active steroid hormones are not unique [levonorgestrel and ethinyl estradiol have been in approved contraceptive products for many years], so there is currently not an unmet medical need for this product.

9.4 Division of Scientific Investigation (DSI) Inspections

Three sites from Study CL12 were selected to have DSI inspections. They are shown in the following Table 26. There were no international sites.

The main factors that were relied on for choosing these sites are listed below:

- Sites with large enrollment numbers (# 33 and 31)
- Sites with large numbers of pregnancies or a high Pearl Index, which represents more contraceptive failures than would usually be expected (# 23 and 33)
- Sites with unusually high or low study discontinuations rates (# 31 and 33)
- Sites with high or low adverse event rates (# 23 and 31)

Table 26: DSI Inspection Sites- Study CL12

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
33 Hazan, Lydie 5800 Wilshire Blvd Los Angeles, CA 90036 US United States phone:310-289-8242 fax:310-289-8248 email:drhazan@impactla.org	ATI-CL12	121	An Open-Label, Randomized, Parallel Group, Phase 3 Study of The Contraceptive Efficacy and Safety of Agile Transdermal Contraceptive Delivery System (TCDS) in Comparison to a Low-Dose Oral Contraception
23 Eubank, Jr., Charles 5920 Saratoga Blvd., Suite 100 Corpus Christi, TX 78414 US United States phone:361-906-9178 fax:361-906-0309 email:eubank@araresearch.com	ATI-CL12	47	An Open-Label, Randomized, Parallel Group, Phase 3 Study of The Contraceptive Efficacy and Safety of Agile Transdermal Contraceptive Delivery System (TCDS) in Comparison to a Low-Dose Oral Contraception
31 Groom, Richard 1001 South Rancho Drive Las Vegas, NV 89106 US United States phone:702-889-0061 fax:702-889-0062 email:RMGroom1@gmail.com	ATI-CL12	73	An Open-Label, Randomized, Parallel Group, Phase 3 Study of The Contraceptive Efficacy and Safety of Agile Transdermal Contraceptive Delivery System (TCDS) in Comparison to a Low-Dose Oral Contraception

Source: DRUP consult request to DSI.

Hazen site report:

At this site for Study CL12, 180 subjects were screened, 120 subjects were enrolled (one subject duplicated), 75 subjects withdrew from the study, and 36 subjects completed the study.

An audit of the study records of 20 of the subjects in the study was conducted. Signed informed consent forms were present for all subjects. Other records reviewed included, but were not limited to, source documents, drug accountability, laboratory reports, progress notes, test records, and concomitant medications. Efficacy endpoint and adverse event reporting was reviewed for all subjects completing the study. Of the 75

subjects withdrawing from the study, nine became pregnant. There was no evidence observed of inaccurate data capture or of under-reporting of adverse events.

A Form FDA 483 with a single two-part observation was issued at the conclusion of the inspection for: the failure to collect blood samples for nine subjects for SHBG/CBG at Visit 7 and PK samples for another two subjects at Visit 3. Dr. Hazen responded in writing noting that the central laboratory (PRL) failed to send SHBG/CBG sampling kits to the site. PRL, according to Dr. Hazen, acknowledged that it shipped the kits to the wrong address. In the case of the missed PK samples, Dr. Hazen acknowledged that it was the site's oversight in failing to collect the two samples. According to Dr. Hazen, there were a total of 360 samples to be collected with only two failing to be collected for an error rate of 0.005%. No significant regulatory violations were noted for the study overall. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Reviewer's comment:

The Field Classification for this inspection was VAI (Voluntary Action Indicted). The Headquarter's Classification, however, was NAI (No Action Indicated). The reason for the different classification from headquarters follows:

"SHBG/CBG samples were not collected because sampling kits were not provided by the testing laboratory despite repeated requests for such kits. Failure to collect required samples was not the responsibility of the clinical investigator in this case. Two PK samples from a total of 360 were not collected; this minimal percentage of missed samples would not support a VAI classification."

Groom site report:

There were initial concerns at the site in Las Vegas. Richard Groom, MD, Principal Investigator at Site 031 had several errors in their data collection and reporting according to the Division of Scientific Investigation (DSI) FDA field inspector Anthony Keller. Here are some excerpts of his preliminary findings that demonstrate errors and lack of follow-up to comply with the protocol for scheduled visits that included important blood drawings. The Field Classification for this site was OAI: Official Action Indicated.

"c) According to the protocol, the randomization will be stratified according to BMI and history of hormonal contraception. The protocol defines "new user" as no hormonal contraception within the previous six months and "current user" as having a history of hormonal contraception within the previous six months. Seven (10%) of 67 patients' user status were inappropriately redefined through the query process:

i) Three patients were correctly stratified, but their registration data was subsequently changed to an incorrect value through the query process:

- Patient (b) (6) was a "current user" (having discontinued oral contraceptives one month prior to screening on 8/12/10). The designation was changed to "new user" on 5/27/11.

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- Patient (b) (6) was a "current user" (having discontinued using a vaginal ring four months prior to screening on 8/12/10). The designation was changed to "new user" on 6/7/11.
- Patient (b) (6) was a "current user" (having discontinued oral contraceptives several days prior to screening on 9/1/10). The designation was changed to "new user" on 6/8/11.

ii) There are conflicting records for four patients related to the history of hormonal contraception. The registration data was changed for these patients through the query process but the conflicting documentation was not clarified.

Patient (b) (6):

- screening worksheet (pg #1) dated 8/17/10 lists the last date of contraceptive use as July 2010;
- screening worksheet (pg #6) indicates the "current contraceptive methods" is male condom;
- screening worksheet (pg #10) indicates "not currently using hormonal contraceptives";
- the randomization day worksheet dated 8/24/10 indicates "n/a" for "date of last dose of hormonal contraception";
- the concomitant medication log (undated) indicates the only medication within six months of screening is (b) (4);
- the patient's user designation was changed from current user to new user on 6/15/11.

Patient (b) (6):

- screening worksheet (pg #1) dated 8/18/10 lists the last date of contraceptive use as March 2010;
- screening worksheet (pg #6) indicates the "current contraceptive methods" is "NONE";
- screening worksheet (pg #10) indicates "not currently using hormonal contraceptives";
- the randomization day worksheet dated 9/2/10 indicates both "n/a" and "March 2010" for "date of last dose of hormonal contraception";
- the randomization day satisfaction questionnaire indicates "no contraceptive method used before"
- the concomitant medication log states: "Pt denies any cc meds @ screening or in the last 6 mo"
- the patient's user designation was changed from current user to new user on 5/27/11.

Patient (b) (6):

- screening worksheet (pg #1) dated 9/3/10 lists the last date of contraceptive use as May 2010;
- screening worksheet (pg #6) indicates the "current contraceptive methods" is male condom;
- screening worksheet (pg #10) indicates "not currently using hormonal contraceptives";
- the randomization day worksheet dated 9/13/10 indicates "n/a" for "date of last

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dose of hormonal contraception";

- the concomitant medication log states: "9/3/10 Pt denies any current cc meds for past 3 mo"
- the patient's user designation was changed from current user to new user on 5/27/11.

Patient (b) (6):

- screening worksheet (pg #1) dated 9/15/10 lists the last date of contraceptive use as May 2010;
- screening worksheet (pg #6) indicates the "current contraceptive methods" is "none";
- screening worksheet (pg #10) indicates "not currently using hormonal contraceptives";
- the randomization day worksheet dated 9/13/10 lists "May 2010" for "date of last dose of hormonal contraception";
- the randomization day satisfaction questionnaire dated 9/23/10 indicates "no contraceptive method used before"
- the concomitant medication log (undated) indicates the patient discontinued oral contraception in May 2009;
- the patient's user designation was changed from current user to new user on 5/27/11."

Reviewer's comment:

The Field Classification for this inspection was OAI. The Headquarter's Classification, however, was VAI-RR (Voluntary Action Indicated- Response Requested). The reason for the different classification from headquarters follows:

"Inspection revealed numerous deficiencies including failure to obtain consent from three subjects involved in a PK sampling sub-study; failure to obtain blood samples from multiple subjects at protocol- specified visits; the recruitment of at least one subject who met an exclusion criteria; incorrect stratification of multiple subjects; a lack of protocol-required follow up for three subjects complaining of headache; inconsistencies in subject diaries with regards to dates of placement of the test article; the inappropriate placement of the test article in different anatomical areas within one cycle by at least two subjects; the lack of completion of Subject Satisfaction Questionnaires by five subjects at various visits; the use of source documents lacking attribution and dates; the presence of conflicting data with regards to contraceptive histories for at least four subjects; and numerous discrepancies between subject diaries, Case Report Forms (CRFs), and/or progress notes. Despite the number of discrepancies revealed by this inspection, the significance of the findings overall appears minimal with respect to the integrity of the endpoint data (pregnancy/non- pregnancy) or the safety of the study subjects. Therefore, this inspection is classified VAI-RR. The letter to the investigator requests that he respond with a corrective action plan to address the deficiencies noted above."

Eubank site report:

At this site, 56 subjects were screened, 47 were enrolled, and 22 completed the study. Numerous minor discrepancies were noted. Dr. Eubank responded to the inspection findings and addressed each discrepancy; his written response was determined to be

adequate. The Field Classification was RTC (Return to Center) and the Headquarter's Classification was VAI, which was completed by Dr. Eubank to the satisfaction of the main DSI office.

Reviewer's comment:

The above findings from the 3 sites speak for themselves. The level of discrepancy in the patient records, documentation, and stratification at the Groom site is concerning despite the Headquarter's Classification of VAI-RR. Only 3 sites out of >100 in Study CL12 were inspected, so there is no way to know how many other errors exist in the CRFs and database submitted with this NDA application; several have been noted in this review.

Throughout this review, there are comments on the poor quality of 1) the clinical trials and 2) the NDA submission, especially the presentation of conflicting or erroneous data. Such comments are found especially in the following sections:

1. Section 3.1 Submission Quality and Integrity: 8 examples are listed.
2. Section 6.1.4 Analysis of Primary Endpoint(s): several pregnancies on-treatment were missed by the Applicant.
3. Section 7.3.2 Nonfatal Serious Adverse Events: comments on individual subjects, their enrollment, the delay in diagnosis, and causality relative to study product (patch use).

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/s/

DANIEL DAVIS

01/22/2013

LISA M SOULE

01/23/2013

I concur with Dr. Davis' conclusions and recommendation that NDA 204-017 receive a Complete Response action for the indication of prevention of pregnancy.