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*APPLICATION NUMBER:*

**204017Orig1s000**

**SUMMARY REVIEW**

## Deputy Director Summary Review

NDA: 204017 / SN58

Drug Name: Twirla® (levonorgestrel/ethinyl estradiol 120/30 mcg/day) t  
transdermal contraceptive system (TDS)

Indication: Prevention of Pregnancy

Applicant: Agile Therapeutics, Inc.

Application Type: 505(b)(2)

Submission Date: 05/16/2019

Original PDUFA Goal: 11/16/2019

Extended PDUFA Goal: 02/16/2020

Memo Date: 02/14/2020

Review Priority: Class II Resubmission (third cycle)

### **Brief Background:**

This memo serves as my assessment of the approvability of NDA 204017. NDA 204017 proposes a levonorgestrel (LNG) and ethinyl estradiol (EE) transdermal system (TDS) at doses of 120 mcg and 30 mcg, respectively. The Applicant, Agile Therapeutics, Inc. seeks approval of this LNG/EE TDS (hereafter referred to by the tradename, Twirla) for prevention of pregnancy in women of reproductive age. Twirla, like the majority of approved combined hormonal contraceptives (CHCs) in the US, contains an estrogen component and a progestin component. Throughout the development process for Twirla, the LNG/EE formulation has remained the same.

Multiple CHC contraceptive options have been approved for the prevention of pregnancy (see Appendix – Figure 1). In the registration trials, these products all had a mean Pearl Index (PI) and associated 95% Confidence Interval (CI) upper bound below 5, reflecting an estimated pregnancy rate in the trials of less than 5 pregnancies per 100 women years. One CHC TDS has been approved in the US to date, Ortho Evra (approved in 2001). Although the efficacy of Ortho Evra in the submitted clinical trials was comparable to that of other approved CHCs, 5 of 15 women weighing more than 198 pounds (lbs) became pregnant in the trial. This reduced efficacy in women > 198 lbs led to a Limitation of Use in the drug label. Ortho Evra is now withdrawn in the Federal Register but is available as an approved generic under the tradename Xulane.

A brief overview of the regulatory history for Twirla is outlined below:

- January 19, 1999 – the Applicant (Agile) opened IND 57731

- September 22, 2008 - End of Phase 2 meeting to discuss pivotal phase 3 trials
- April 13, 2012 - Agile Therapeutics submitted NDA 204017 containing effectiveness and safety data from phase 3 trials. These trials included: Study ATI-CL12 (hereafter referred to as Study 12) and Study ATI-CL13 (hereafter referred to as Study 13)
- February 13, 2013 - FDA issued a Complete Response Letter (CRL) citing numerous product quality and clinical trial conduct deficiencies. FDA recommended that the Applicant conduct another clinical trial once the outlined CMC deficiencies were addressed.
- June 24, 2013 - NDA resubmission addressing CMC deficiencies
- July 17, 2013 - FDA issued an Incomplete Response letter after review of the Applicant's NDA resubmission and deemed the Applicant's responses to the product quality deficiencies were inadequate
- June 7, 2014 - Applicant submitted a new phase 3 protocol for Study ATI-CL23 (hereafter referred to as Study 23) to their IND
- June 26, 2017 - Applicant's Complete Response received containing effectiveness and safety data from trial 23
- December 21, 2017 - FDA issued a second CRL to Applicant related to Product Quality, specifically citing concerns with adhesion properties
- April 16, 2018 - Type A meeting with the Applicant to discuss the second CRL. The FDA relayed their concern that the in-vivo adhesion data provided in the NDA were insufficient to address the concerns with Twirla's adhering capacity for a TDS.
- June 6, 2018 - Formal Dispute Resolution requested by Agile appealing the December 21, 2017 Complete Response letter that the Applicant had not demonstrated that the drug product has the in vivo adhesion properties requisite for its safe and effective use.
- July 19, 2018 – The ODE 3 Director denied the dispute appeal. The basis for the denial was the lack of clinical data that demonstrates acceptable adhesion properties of the TDS.
- August 10, 2018 – Formal Dispute Resolution requested by Agile appealing the denial decision by the ODE 3 Director that acceptable adhesion properties were not adequately demonstrated.
- October 4, 2018 – The OND Director denied the dispute appeal. The OND Director recommended that to resolve the issue of acceptable adhesion properties, a clinical wear study should be conducted.

The Complete Response for this third review cycle was received on May 16, 2019. The original PDUFA goal date was November 16, 2019. The Division convened a meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC, hereafter referred to as the AC) on October 19, 2020, to discuss the effectiveness and safety of Twirla. After the AC meeting, additional data and

analyses were requested by the Division. The Applicant responded to this information request on November 12, 2019. The November 12, 2019 submission was determined to be a major amendment and the PDUFA goal date was extended to February 16, 2020.

Twirla was reviewed by the PeRC and it was determined that PREA was not triggered, so no iPSP or waiver was required for this Complete Response.

**Effectiveness Overview:**

The primary efficacy endpoint in trial 23 was the pregnancy rate measured by the Pearl Index (PI) in women who were ≤ 35 years of age at study entry irrespective of BMI. The PI is defined as the pregnancy rate per 100 women-years of drug exposure and is calculated as follows:

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

The PI is dependent on the number of cycles; We generally recommend at least 10,000 cycles for the primary efficacy analysis to obtain a reasonable estimate of contraceptive effectiveness. The Division also assesses the width of the 95% confidence interval (CI) surrounding the point estimate for the PI. The Division has consistently informed Applicants of hormonal products, including Agile, to show a PI upper bound of 5 in the primary efficacy analysis given the associated risks of these CHC therapies.

The Applicant submitted Study 23 to support the effectiveness and safety of Twirla in 2017. Study 23 was a U.S.-only, single-arm, open-label, one year (thirteen 28-day cycles), multicenter phase 3 study of the contraceptive efficacy, safety, and tolerability of Twirla with no restriction on BMI. The primary efficacy endpoint was the pregnancy rate described by the PI in subjects aged ≤35 years (at study entry), irrespective of BMIs. Life table estimates of the probability of pregnancy were also provided as a supportive analysis.

The primary analysis population for effectiveness included 1,736 women aged ≤35 years who wore at least one Twirla system, had a negative enrollment serum pregnancy test and had at least one evaluable cycle. An evaluable cycle was defined as a treatment cycle in a woman in which there was sexual activity and no back-up or emergency contraception used. In 15,165 evaluable cycles, we identified 68 on-treatment pregnancies.

The overall PI based on the primary efficacy analysis was 5.83 (95% CI 4.45, 7.21). A subgroup analysis by BMI was conducted and is presented in Table 1:

**Table 1 –Subgroup analyses by BMI in subjects ≤ 35 years of age at baseline (Study 23\*)**

Population	N	# On-Treatment Pregnancies	# Evaluable Cycles	Pearl Index (95% CI)
<b>BMI (kg/m<sup>2</sup>)</b>				
<30 (Non-obese)	1,123	33	9,888	4.34 (2.86, 5.82)
<25 (Normal)	684	16	6,007	3.46 (1.77, 5.16)
≥25 to <30 (Overweight)	439	17	3,881	5.69 (2.99, 8.40)
≥30 (Obese)	612	35	5,264	8.64 (5.79, 11.50)

\*Adapted from Table 10 of the Statistical Review dated 2/11/2020.

The Applicant asserted that Study 23 is a “real world study” and that this accounts for the higher PI than that seen in other CHC trials. The Division does not agree that this study represents a “real world study”. Real-world includes women using contraceptives under routine clinical care, with few exclusions and follow-up per community standards. In contrast, Study 23 had strict enrollment criteria, including exclusion of subjects who were <90% compliant with e-diary use during the run-in period (note: study medication was not provided during run-in). Run-in period data revealed that 625 women screened (16% of the screened population) were screen failures based on non-compliance with the e-Diary. Compliance was assessed at every study visit and poor compliance was a reason for study discontinuation in 116 subjects. The higher pregnancy rates for Study 23 occurred despite an enriched population for compliance and closely monitored environment intrinsic to a clinical trial. I do acknowledge, however, that the study included a more racially diverse and heavier patient population than have been enrolled in other CHC programs.

***Comment: Pregnancy rates in the “real-world” postmarketing setting will likely be higher than that reported in Study 23. Higher postmarketing rates could approach those of progestin only daily tablets and non-hormonal contraceptives that do not carry a significant thromboembolism risk. I have carefully considered the AC members approval recommendation but also that there was recognition that there was reduced effectiveness with increasing BMI.***

***I concur that effectiveness is sufficient in normal weight women (<25 kg/m<sup>2</sup>) because the mean PI was acceptable (3.5) and the upper bound of 5.16 is very close to 5.0. I believe that there are sufficient cycles to make this determination for this sub-population (>5,000) as we have accepted 5,000 cycles in certain circumstances for the primary efficacy analysis of a non-novel, non-NME CHC product. If there were 10,000 cycles in this application in normal women, the 95%***

***upper CI likely would have been tighter and it is reasonable to assume the upper bound would be less than 5 but I do not believe the mean PI would have been significantly different.***

The remaining concerns with Twirla from my perspective are:

- the PI and upper bound of the 95% CI in overweight women ( $\geq 25$  to  $< 30$  kg/m<sup>2</sup>) demonstrates reduced effectiveness when compared to clinical trial results from previously approved CHCs. The concept of reduced effectiveness was acknowledged by the AC committee members.
- the PI and upper bound of the 95% CI in obese women ( $\geq 30$  kg/m<sup>2</sup>) for a combined hormonal contraceptive (CHC) approaches that of a progestin only tablet and non-hormonal products that do not carry a thromboembolic risk.
- Assessment of comparative adhesion studies (ATI-CL25 and ATI-CL26) to determine whether Twirla has acceptable adhesive properties for approval

***Comment: My considerations and recommendations on the effectiveness and benefit/risk in these subpopulations is discussed in more detail below. The adhesion studies were reviewed by the Division of Biometrics VI, Office of Biostatistics and CMC review team. Their findings are summarized later in this memorandum.***

#### **Safety Overview:**

All CHCs contain estrogen. As a class, CHCs are associated with arterial and venous thrombotic risks, including venous thromboembolism (VTE), myocardial infarction (MI) and stroke. This risk increases with smoking, age, prior thromboembolic event, hypercoagulopathies, estrogen dosage, and obesity. The Division's past experience with CHCs is that one or two VTE events are usually reported in the integrated safety dataset of 10,000 cycles in NDA submissions for non-NME products. In current labeling, the Division's estimated risk of VTE with use of non-oral CHCs is 3-12 per 10,000 women and this is based on postmarketing data.

The safety database for Ortho Evra included 17 combined studies with a total of 1,870 women-years of exposure. There were two subjects identified with a pulmonary embolism, one of whom discontinued her transdermal system one day before major elective cosmetic surgery (breast augmentation, abdominoplasty and liposuction). This translated to a rate of 10.7 VTEs per 10,000 women-years.

The risk of VTEs were further evaluated for Ortho Evra after postmarketing reporting (stimulated by litigation) indicated that there may be an increased thromboembolic risk. The concerns of an increased VTE risk for Ortho Evra resulted in an Advisory Committee meeting in 2011 to discuss whether Ortho Evra should be removed from the market. Although the Advisory Committee did not recommend removal of Ortho Evra, prominent labeling changes were made to the product, including a boxed warning different from all other CHC products. Current labeling for Ortho Evra acknowledges

that the EE at steady state is in the 50 mcg range (equivalent to a high-dose CHC contraceptive) and contains 5 epidemiologic studies with a risk ratio for VTE varying from 1.2-2.2 with one study reaching statistical significance.

**Comment: As noted previously, a relationship between increasing weight and decreasing efficacy was observed, albeit with more limited data, in the contraceptive TDS approved in 2001 (Ortho Evra), which has a limitation of use for women weighing > 198 lbs. However, at the time of approval of Ortho Evra, the number of obese women who chose to use contraception in the US was not as prevalent as it is in current timeframe. Ortho Evra is not the only CHC product that contains labeling text suggesting a concerning risk of increased thromboembolism. The progestins desogestrel and drospirenone also have labeling language suggesting the possibility of increased fatal and non-fatal VTE risk compared to other hormonal contraceptives. However:**

- **It is not possible to reliably compare risks of VTE identified in a clinical trial population, whom are generally healthy to that of a postmarketing population.**
- **comparing risks across CHC products using postmarketing epidemiologic studies is exceeding difficult as the selected populations, methodologies and study designs vary. In general, epidemiologic data on thromboembolism, when available, is provided in prescribing information (PI) for consideration and no comparative statements on safety with regard to thromboembolism are provided.**

The clinical team identified venous thromboembolism and pulmonary embolism cases in a total of six cases in the Twirla development program. In this third review cycle, the statistical team was asked to assist with the assessment of this safety signal. A table of the cases is outlined in Table 2 below:

**Table 2: Summary of Subjects with VTEs in Studies 12, 13, and 23**

<b>Subjects</b>	<b>Age</b>	<b>BMI (kg/m<sup>2</sup>)</b>	<b>VTE Event(s)</b>	<b>Relatedness to Drug</b>
<b>Study 12</b>				
Subject (b) (6)	26	19.9	DVT	Probably related
<b>Study 23</b>				
Subject (b) (6)	25	31.8	PE	Probably related
Subject (b) (6)	26	34.3	PE	Probably related
Subject (b) (6)	24	35.7	DVT	Not related
Subject (b) (6)	33	36.3	DVT/PE	Probably related
Subject (b) (6)	35	39.0	DVT	Probably related

\*Adapted from the Statistical Review dated February 11, 2020 and the Applicant’s Briefing Document for the 2019 BRUDAC Meeting / Clinical Review of NDA 017 SN0000

The Applicant stated that their Twirla related VTE incidence rate was 22 per 10,000 woman-years by pooling safety data from Studies 12, 13, and 23. The Division did not agree with the Applicant's pooling of safety data from all three phase 3 studies because the Division had concerns about the quality of data collection in Studies 12 and 13 and that the VTE rate could have been artifactually lowered by the addition of cycles that did not have adequate safety data collection. There was one normal weight woman who had a VTE in Study 12. It is not unusual to have a single VTE in a clinical trial for a CHC.

In the third cycle with the assistance of the statistical review team, we calculated the Twirla VTE incidence rate as 28 (95% CI: 8 to 71) per 10,000 woman-years based solely on Study 23. This is greater than the Division has seen in any other recent registration trial. Perhaps of most concern is that all of the VTEs in Study 23 were in obese women.

***Comment: Although there are uncertainties (e.g., whether the VTEs in Study 23 reflects the higher background risk in the obese population vs. an increased risk due to Twirla), I agree with the clinical review team that the VTE signal is of significant concern. I also agree that adding cycles from Studies 12 and 13 with inadequate collection of safety data could potentially artifactually lower the VTE rate. To resolve the issue related to VTE rate, I conclude that a large epidemiologic safety study is needed for more reliable VTE incidence estimates. The finding of these VTE events, especially those in a single study that are solely in obese women is a strong safety signal that cannot be ignored. I believe that until the interim data from the epidemiologic study is provided from normal and overweight women, obese women should not use Twirla, particularly in the context of its reduced benefits in that population.***

#### **Brief Advisory Committee Meeting Summary**

The Division and the Applicant presented their views of the benefit/risk assessment of Twirla. The Applicant included data from Studies 12 and 13 which were poorly conducted and were not considered by the Division to be acceptable as evidence of the effectiveness and safety of Twirla.

**Comment: I believe that Study 12 and 13 data from the comparator products were too limited and collection of pregnancy data was so inadequate that no comparative interpretation is possible.**

The focus of the Division's presentation provided a historical perspective on development of CHCs and an overview of the CHC's approved by the Division in the last 10 years. As Study 23 was the only adequately conducted study, the Division focused on effectiveness and safety data from Study 23. The Division presented:

- An effectiveness assessment of the PI and 95% confidence interval in the overall group as well as subgroup analyses by body mass index (BMI) which is provided in Table 1 of this document.
- An assessment of the safety information, primarily related to the venous thromboembolism cases identified in Study 23

After discussion questions, the Division provided a single voting question to the committee:

**Do the benefits of [Twirla] outweigh its risks and support approval for the prevention of pregnancy?**

- The AC committee voted 14-1 in favor of approval.
- The review team and I believe the committee members voted for approval in order to provide another transdermal option for women.
- Many committee members voiced different levels of concern about the use of the product in heavier weight women.
- The one dissenting vote came from a practicing Ob-Gyn in the Pacific Northwest who stated that her patients would not accept a product with this extent of efficacy.

Additional details of the regulatory history of Twirla are captured in the clinical and CDTL reviews. My summary review will focus on the third cycle reviews. These reviews primarily considered approvability based on the benefit/risk assessment and labeling. In addition, the CMC group evaluated data from one comparator clinical study (ATI-CL25) to address the outstanding issues related to the adhesion properties of the product in response to the OND dispute resolution appeal recommendation.

***Comment: The Division did not discuss specifics of labeling of the product at the Advisory Committee. Providing a detailed background on labeling and whether a risk mitigation and evaluation strategy (REMS) was necessary was outside the scope of the Division's objective of the AC.***

CMC Overview:

In the previous review cycle, the CMC review team determined that the product did not demonstrate adequate in-vivo adhesion performance in ATI-CL23 (11.3% of TDS applications resulted in less than 75% adherence, and 14.7% of all cycles used 4 or more TDS during the cycle). This led to the 2017 CR letter with the following deficiencies summarized below:

- Inadequate in-process adhesion and tack tests for ensuring the quality and the in vivo adhesion of the commercial-scale product.
- The finished drug product specification was not adequate to ensure the quality, tack and adhesion of the drug product at release and on stability.

The current in vitro adhesion test does not ensure adequate in vivo adhesion properties requisite for the safe and efficacious use of the drug product.

- Objectionable conditions at a manufacturing facility
- The clinical trial data on adhesion raised clinical concerns that Twirla did not have in vivo adhesion properties requisite for its safe and effective use.

The comparative study (Study ATI-CL25) was conducted by the Applicant in response to the OND Appeal Denied Letter which set the following path to determine the acceptability of adhesion of this product to the Applicant:

*“...if AG200-15 can demonstrate generally similar adhesion performance to Xulane, this would support the conclusion of adequate adhesion of AG200-15 and suggest that the results of the ATI-CL23 are those that might be seen with an adequately performing patch in the context of a clinical trial.”*

The CMC review team asked the Division of Biometrics 7 to evaluate the submitted clinical studies (ATI-CL25 and 26) containing data on the adhesive properties of Twirla to assess whether non-inferiority to another approved transdermal product was met and acceptability of adhesion had been met as directed in the OND Appeal denied letter.

Study ATI-CL25 was a randomized, open-label, single-dose, two-treatment, comparative crossover adhesion study of AG200-15 and Xulane (an approved CHC transdermal system) in healthy female volunteers with a total of 83 subjects randomized in the study. The Biometrics review team assessed the design and conduct of this critical study to assess the adequacy of the adhesive properties of Twirla and determined that these were acceptable for review purposes. The primary outcome was the adhesion score measured on a 5 point scale. The Applicant's data demonstrated that the difference between the means of the paired mean adhesion score between the Twirla TDS and Xulane was -0.24, and the 95% upper confidence limit for the mean difference was -0.16, which was less than the predefined non-inferiority margin, 0.15.

Study ATI-CL26 was a single-dose, open-label, non-comparative adhesion study of the Twirla TDS in healthy female volunteers. This study assessed the probability that a randomly selected Twirla TDS maintains at least 75% adhesion throughout its entire wear period is estimated to be 0.93 and its 95% lower confidence limit is 0.83. Study 26 was similar in design and conduct to Study 25, but no comparator was included in the assessment.

As Study 25 data was critical for approval, an inspection of the clinical site was conducted. In the CMC review dated 8/14/19, the CMC reviewer stated that, “An inspection of the clinical site was conducted to verify the integrity of the trial; no 483 was issued.”

The Biometrics team (Chao Wang, Meiyu Shen and Yi Tsong in DBVI) evaluated the adhesion data and completed their analyses of the adhesive data from Studies 25 and 26. In the biometrics review dated August 14, 2019, the reviewers’ conclusion and recommendation stated, “In conclusion, my independent evaluation showed that the data in the controlled study ATI-CL25 support the non-inferiority of AG200-15 to Xulane in terms of in vivo adhesion. In addition, a standalone evaluation of the data for AG200-15 showed that the probability that a randomly selected AG200-15 maintains at least 75% adhesion throughout its entire wear period in the controlled setting is estimated to be 0.99 and the 95% lower confidence limit is 0.95. Using the data in the single-arm, noncomparative study ATI-CL26, the probability is estimated to be 0.98 and the 95% lower confidence limit is 0.83, where the smaller 95% lower confidence limit is likely due to the smaller sample size.”

The CMC review team also evaluated the adhesive properties of Twirla using the data from Study 25 and concluded that, “Therefore, because AG200-15 (Twirla) demonstrated non-inferiority to Xulane and because AG200-15 (under the study conditions of ATI-CL25) demonstrated that a randomly selected TDS could maintain 70% surface area adhesion at the 95% Lower Confidence Limit, OPQ recommends APPROVAL to the Office of New Drugs for adhesion of AG200-15 (i.e. Twirla”).

A second outstanding issue was the manufacturing facility deficiency identified on the prior (2017) review cycle. The facility was inspected during this cycle and no 483 was issued.

The final outstanding issue was related to residual drug release. The CMC reviewers identified that the only available residual drug data for Twirla are from in vitro assessments or theoretical calculations, and expression of strength was based on comparisons to oral formulations. The CMC review believes that although this is sufficient for initial approval, the delivery rate of active drugs (LNG and EE) released from Twirla needs to be further characterized. These data can then be compared to control (i.e. unused) Twirla to ensure that the maximal drug released from Twirla can be accurately determined. This information is important to assure correct labeling and also to ensure that there is no unusual pattern of release, including unforeseen excessive release of drugs, that could result in serious safety outcomes, such as venous thromboembolism.

The CMC review team also evaluated relevant sections of the prescribing information including the Dosage Forms section. The summary CMC review team dated 2/12/2020 concluded that, "This NDA is now recommended for Approval from the OPQ perspective".

**Comments:**

- ***Studies 26 and 25 were conducted to resolve the deficiency related to adhesive properties identified in 2017 using TDS replacement rates from Study 23. The replacement rates (10-20%) raised clinical concern regarding the adequacy of the adhesive properties of Twirla. The new submitted clinical adhesion data demonstrates that the adhesive properties of Twirla using the scoring data from Study 26 are non-inferior to another approved contraceptive TDS (Xulane), and therefore, are acceptable from a CMC perspective. I concur with the CMC reviewer that demonstration of non-inferiority to another approved TDS product resolves the outstanding deficiency on adhesive properties from 2017. In addition, the Applicant has also included a program for patients to obtain a replacement TDS in their labeling. Although it can be inconvenient for a patient to need a replacement TDS, the replacement program will be sufficient to address patient needs. Finally, the Applicant will also provide ongoing information regarding the replacement program through additional reporting requirements, and this will allow further assessment of postmarketing issues with TDS replacement on an ongoing basis.***
- ***The manufacturing facility issue and CMC labeling issues are also resolved.***
- ***I concur with the CMC review team that there should be a residual drug assessment. The need for this study was communicated with the Applicant and the Applicant agreed to a postmarketing commitment to complete this study (See Postmarketing Studies and Additional Reporting Requirements section)***
- ***I concur with the CMC reviewer that there are no other outstanding CMC issues that would prevent approval.***

**Pharmacology/Toxicology (nonclinical) Overview:**

No new nonclinical data was included in this resubmission. The nonclinical reviewer primarily provided edits to the nonclinical sections of the Applicant's proposed label. After review, the nonclinical reviewer (Mukesh Summan) concluded, "There are no nonclinical safety issues which would preclude approval of this NDA." (refer to Pharmacology/Toxicology review dated 01/29/2020). On February 13, 2020, the Pharmacology/Toxicology Supervisory provided an additional memo regarding revisions to nonclinical labeling sections 8.1, 8.2 and 13.1. The Pharmacology supervisor's review concluded that Agile's proposed revisions were acceptable.

***Comment: I concur that there are no outstanding nonclinical issues.***

Clinical Pharmacology Overview:

No new clinical pharmacology data was included in this resubmission. The Clinical Pharmacology review team primarily reviewed and provided edits to the Applicant's proposed label. After review, the Clinical Pharmacology review team (Peng Zou, Fang Li, Yanhui Lu and Jingyu Yu) concluded, "The Office of Clinical Pharmacology has reviewed the information contained in NDA 204017 and finds this NDA acceptable from a clinical pharmacology perspective, provided that the EE/LNG strength issue is addressed through a postmarketing requirement (PMR) study." (refer to Clinical Pharmacology review dated 2/4/2020)

***Comment: I concur that there are no outstanding approvability issues related to clinical pharmacology concerns. I concur with the recommendation for a postmarketing study to evaluate EE/LNG strength through residual TDS evaluation. This will be conducted as a postmarketing commitment (PMC). This study was determined to be a PMC as the benefit/risk profile of Twirla appears favorable in normal and overweight women; however, there are uncertainties about the delivery rate of active drugs (LNG and EE) from the Twirla TDS. The PMC and milestones to characterize the pattern of release of hormones from Twirla were agreed to by Agile on February 6, 2020 (see section on Postmarketing Studies and Additional Reporting Requirements)***

Statistical Review Overview:

No new effectiveness or safety data was included in this resubmission. The Statistical review team provided input on the October 2019 AC background package and presented the Agency's view on efficacy focusing on the data from Study 23. The statistical team evaluated the effectiveness data using BMI cutoffs and also assessed the VTE incidence. These evaluations were incorporated into the Applicant's proposed label primarily for the Clinical Studies section (Section 14 of the PI).

At the AC meeting, several committee members recommended that the label display effectiveness information in a continuous manner by BMI to clearly communicate to providers how BMI affects effectiveness. To address this recommendation, the Statistical review team provided input on a model using continuous BMI that was developed for the prescribing information to assist providers in determining whether the product would have sufficient effectiveness for their patient. The Statistical team subsequently reviewed and provided labeling guidance on the effectiveness sections of the prescribing information (PI).

After review, the Statistical reviewer (Yun Tang) concluded in her review dated February 10, 2020, "At this time in the review cycle, a remaining key issue is whether AG200-15 can be approved for a subgroup of women based on subgroup analyses by BMI in Study 23 when overall effectiveness was considered deficient in both the previous and current review cycle. We recommend that AG200-15 is studied further to reduce the

uncertainty around the effectiveness and safety. Therefore, we do not recommend approval based on the lack of new clinical efficacy data.”

**Comment: I disagree with the statistical reviewer’s conclusions on effectiveness. This is the first Applicant to have enrolled a large proportion of overweight and obese women, more closely reflecting US demographics. In the past, the majority of effectiveness data submitted to the Division came from normal weight women or normal weight women and a proportion of overweight women. I believe it is reasonable to evaluate the sub-population of normal weight women where we have approximately 6,000 cycles. I believe that if the Applicant had presented only this data to us, given that the upper bound can still round off to 5, this would have been approvable.**

**Regarding overweight women, I acknowledge that the statistical review team is correct that there is clear demonstration of reduced effectiveness, although the number of cycles is limited. It is possible that with additional cycles, the PI might have been closer to an acceptable result. However, given the Advisory Committee recommendation to approve and the lack of a safety signal in this population, I believe that these results could be described in labeling. I agree that the mean PI of 5.7 and upper 95% CI of 8.4 reflect reduced efficacy in overweight women, but I also believe that labeling can adequately describe this. For this category, I believe that providers can adequately counsel patients and decide as to whether they should use this product.**

**Regarding obese women, I do not believe the benefit/risk is acceptable. The PI and upper bound are approaching that of progestin only and non-hormonal products that do not have the venous thromboembolism risk seen with CHCs. Given that obese patients already have predisposition to venous thromboembolism and that we already have a safety signal of VTEs in that population from Study 23, use in obese women will be CONTRAINDICATED.**

Clinical Review Overview:

The Primary Clinical Reviewer (Nneka Mc-Neal-Jackson) contributed to writing the safety section in the advisory committee briefing book and also made a presentation on the Division’s assessment of the safety of Twirla at the 2019 advisory committee. As previously stated, no new clinical effectiveness or safety data was included in this resubmission. The sole new clinical studies (ATI-CL25 and ATI-CL26) presented data on adhesive properties to demonstrate acceptability were reviewed by the biometrics and CMC review teams.

The clinical reviewer concluded that she could not recommend approval. In her review dated February 14, 2020, she stated, “ 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.”

**Comment: I disagree with the clinical reviewer’s recommendation to not approve Twirla. I have considered her concerns and outline my considerations and determinations as follows:**

**Efficacy Concerns:**

*The Primary Clinical Review statement:*

“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.”

*The CDTL statement (which disagreed with the clinical reviewer’s efficacy concern):*

“The clinical reviewer raises concerns about the phase 3 trial (Study 23) and the resulting mean PI and upper bound of the 95% CI. Although I agree that the results from Study 23 were obtained from a refined population because of the methodology used to enroll women, I do not agree that the Pearl Indices and 95% CI for normal weight women is significantly different than those from trials previously reviewed by the Division. In overweight women, it is clear there is reduced effectiveness, but as previously stated, I believe that this issue can be addressed in labeling. My recommendations on normal and overweight women are consistent with the guidance received at the 2019 Advisory Committee meeting. For obese women, I concur with Dr. McNeal-Jackson that there is insufficient evidence of benefit in these women. Based on this, I concur that a CONTRAINDICATION is necessary.”

**Comment (Efficacy):** My opinion on the effectiveness of Twirla was influenced by the 2019 Advisory Committee meeting and I concur with the CDTL that Study 23 was adequately conducted and is acceptable to serve as the basis for an effectiveness determination for a hormonal contraceptive product that is not a new molecular entity or represents a novel product. Although I agree that the population in Study 23 may have been somewhat enriched by trial design, I do not interpret the mean PI and upper bound of the 95% CI from this trial (which is at the upper limit of 5) as demonstrating a clinically unacceptable finding in normal weight women. The results in the normal weight population are sufficient for clinical interpretation (>5,000 treatment cycles) and important to consider as is the population evaluated in the majority of phase 3 trials presented to the Division for review. Based on my interpretation of the results in normal weight women, I believe that these results can be labeled for provider and patient interpretation. In overweight women, I concur with the CDTL that reduced effectiveness has been identified. The CDTL and I agree that reduced effectiveness can be addressed in labeling. For obese women, I concur with the CDTL that the reduced effectiveness is unacceptable as it approaches that of other types of contraceptives that do not incur a thromboembolism risk.

**Safety Concerns:**

*The Primary Clinical Review statement:*

“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 remain 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  $\geq 30$  kg/m<sup>2</sup>. 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.”

*The CDTL statement (disagreeing with the clinical reviewer’s recommendation for additional pre-approval safety data):*

“The clinical reviewer raises concerns about the insufficient collection of adverse events in Study 12 and 13. It is clear from the Division’s previous review that these studies were inadequately conducted and collection of safety information was not acceptable. I conclude that the data from these trials is not necessary to support approvability as the Applicant subsequently conducted an adequately designed phase 3 trial (Study 23) that was acceptable for clinical review. As

mentioned by Dr. McNeal-Jackson, the key finding from Study 23 was identification of 4 VTEs in obese women resulting in an incidence of 28 per 10,000. This is the highest VTE rate reported in a trial submitted for approval. The clinical reviewer recommends requiring more safety information before approval. All of the VTE reports from Study 23 were in obese women (BMI > 30kg/m<sup>2</sup>). I believe that by CONTRAINDICATING it in obese women we are sufficiently mitigating the safety concern. Further information to evaluate the risk in normal and overweight women can be obtained from a postmarketing requirement.”

**Comment (Safety Concern related to VTE): Regarding the VTE issue, I agree with the CDTL that there is a strong safety signal in obese women. This is sufficiently mitigated by contraindicating use in this population. For normal and overweight women, the data from Study 23 do not demonstrate this risk, but it is difficult to rule out an increased VTE risk without results from a large epidemiologic study. I believe that labeling the available safety data from Study 23 is sufficient to provide the available risk information until we have the postmarketing study results to provide more clarity on the signal.**

#### **Adhesion Concerns:**

*The Primary Clinical Review statement:*

“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.”

*The CDTL statement (disagreeing with the clinical reviewer’s concern regarding the adhesion properties of Twirla):*

*“The clinical reviewer raised a concern regarding the adhesive properties of Twirla. Her determination was based on subject data from Study 23 where between 10 and 20% of women required 4 or more TDS per cycle. Although it is possible that more frequent TDS application during a cycle could result in somewhat higher exposure to EE than directed use, the clinical reviewer did not*

*present any information in her summary review that supports that this additional EE exposure is directly linked to thromboembolic adverse events.*

*The question of whether Twirla had acceptable adhesion properties was discussed during this review cycle. For this application, the OND Director recommended in his 2018 Dispute resolution that acceptable adhesion properties could be demonstrated in a clinical study that evaluated whether Twirla had comparable adhesive properties to another approved product (Xulane). The Applicant conducted this study (ATI-CL25). The CMC reviewer evaluated the comparative adhesion study (ATI-CL25) and determined that the adhesive properties were non-inferior and therefore acceptable from their perspective. I concur with the CMC assessment that ATI-CL25 demonstrates that Twirla is no worse than another approved TDS contraceptive product (Xulane). Although I agree it may be inconvenient for a patient to obtain a replacement TDS, the Applicant has provided a replacement program that is described in labeling.”*

**Comment (Adhesion): It is of clinical concern that 10-20% of women required more than 4 TDS products to complete a treatment cycle in Study 23. As mentioned by the CDTL in his February 2020 review, this issue was discussed and the OND Director recommended that the Applicant demonstrate acceptable adhesion properties of Twirla by demonstrating that adhesion was non-inferior to an approved TDS product (Xulane). The Applicant conducted this comparative clinical study (ATI-CL25) as well as a supportive clinical study (ATI-CL26) and submitted these studies for review in this resubmission. The Biometrics groups assessment was that Twirla demonstrated non-inferiority of in vivo adhesion to an approved comparator (Xulane) and also an ability to maintain at least 75% adhesion throughout its entire wear period (Refer to Biometrics review dated August 14, 2019). The CMC reviewer also reviewed the adhesion data from Studies ATI-25 and ATI-26 and concluded that, “From a quality perspective, the formulation and product design of the drug product used in clinical study ATI-CL25 have demonstrated adequate in-vivo adhesion for the prescribed 7-day wear period. From the OPQ perspective, recommendation of APPROVAL is made to the Office of New Drugs for adhesion of AG200-15 (i.e. Twirla).”**

**The CDTL also evaluated the adhesion scoring data from studies ATI-25 and ATI-26. In his February 2020 review, he stated that, “Although Studies 26 and 25 did not show any difference with the marketed generic Xulane, the performance in the real world can really only be judged by clinical studies done outside of in-house study centers and to a lesser degree by voluntary postmarketing reports.”**

**I conclude that Twirla has demonstrated similar adhesion properties to an approved TDS and has acceptable clinical adhesion performance in a dedicated wear study to meet current requirements. Also important is that we have no data**

to indicate that TDS replacement impacts the effectiveness or safety of Twirla. Based on this, I conclude that the Applicant has demonstrated acceptable adherence properties and this issue is resolved from an approvability issue. I agree that from a clinical perspective, the replacement program and additional reporting requirements will not only assist patients with compliance if a TDS does not adhere but will also allow the Agency to collect more postmarketing information on adherence.

**Unfavorable benefit risk:**

*The Primary Clinical Review statement:*

“Based on aforementioned factors regarding reduced efficacy, VTE incidence, and adherence 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 noninvasive, 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.”

*The CDTL statement in response to the primary clinical reviewer’s benefit-risk conclusion:*

“I have reviewed the clinical reviewer’s concerns regarding the benefit/risk of Twirla and I do not agree that the current standard for approval of contraceptive products is comparative effectiveness. The Division bases approvability for an individual product based on the benefits and risks provided in the application. For Twirla, I believe that the benefit/risk in normal and overweight women has been adequately evaluated and labeled.”

**Comment (benefit-risk):** I do not agree with the clinical reviewer that the benefit-risk in normal and overweight women is unacceptable. The Division has long accepted single-arm, open-label trials without a comparator as a basis for approval and proof of comparative effectiveness is not necessary. Although the overall study population demonstrated an unacceptable mean PI and upper bound of the 95% CI, I believe that there are sufficient treatment cycles in the BMI categories to conclude that normal and overweight women may have benefit with use of Twirla. There is no evidence in Study 23 that these normal and overweight women would have a different VTE risk from that with use of other combined hormonal contraceptives. Based on these considerations along with a recognition that choice of contraceptives is important, I concur with the CDTL that the issue of reduced effectiveness in overweight women is adequately addressed in labeling.

Other Discipline Reviews:

A review of Patient Package Insert (PPI) labeling and the Instructions for Use (IFU) of the TDS was conducted by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP). Their review of the patient labeling and IFU was completed on 2/7/2020. The Labeling Development Team (LDT) was also asked to assist the Division with the formatting and content of the Prescribing Information. Their proposals and recommendations were accepted and incorporated into labeling that was conveyed to Agile. The Agency's key labeling recommendations are provided in the section entitled, "Labeling Considerations".

Cross Discipline Team Lead (CDTL) Summary Review (Overview):

The CDTL review provides a more detailed review of the regulatory history and clinical background. The CDTL review also provides a more detailed summary of the Division's perspective on the AC committee meeting. After evaluation of the benefit/risk of Twirla, the CDTL concluded, "I recommend approval of Twirla contingent on labeling that contraindicates its use in obese patients with a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> and provides adequate caution in prescribing Twirla to overweight patients based on its reduced effectiveness in the overweight sub-population. The contraindication for obese patients is based on both effectiveness and safety concerns. A Pearl Index (PI) of 8.64 (95% Confidence interval or CI = 5.79, 11.50) was calculated for the obese sub-population in Study 23. The lower bound (5.79) exceeds the upper bound of every combination hormonal contraceptive (CHC) ever approved by the Division. This reviewer considers this pregnancy rate and 95% CI in the obese subjects in Study 23 to be clearly unacceptable and the upper bound approaches that of a non-hormonal contraceptive with no inherent risk of VTE when used. The principal safety concern in Study 23 relates to the venous thromboembolic events (VTEs) identified. All 4 subjects with treatment-emergent VTEs were in obese subjects. It is difficult to assess at this juncture whether the etiology for this finding is primarily related to the increased percentage of obese subjects in Study 23 or whether non-oral CHC mechanisms play a role. This reviewer considers that this safety finding in obese subjects plus the very high pregnancy rate requires a label contraindication. The "convenience" of using a transdermal system does not outweigh these concerns." (Refer to CDTL review dated 2/14/2020)

***Comment: Given the significant impact of unintended pregnancy on a woman's health and the recommendations from the 2019 Advisory Committee members, I concur with the CDTL reviewer's recommendation to approve Twirla. Also, both the CDTL and I have reviewed the prescription label, patient package insert and instructions for use and agree these labels are acceptable for approval.***

**Decisional Summary Regarding Benefit/Risk**

Given the significant impact of unintended pregnancy on a woman's health, it is critical to ensure hormonal contraceptives are effective and also have an acceptable benefit/risk profile. It is clear to me that the AC members consider contraceptive choice important. Although the upper bound of the 95% CI for the PI in normal weight women was slightly over 5, the members did not see that as a barrier to approval, provided the reduced effectiveness in heavier weight women is appropriately labeled.

After considering all available data and the AC recommendations, I conclude that Twirla can be approved if labeling can be agreed to that allows effective and safe use in some reproductive women who may consider using a TDS for contraception.

- In normal weight women, the upper bound of the PI slightly exceeded 5 (5.2) and is the highest rate in a CHC product submitted for approval. Based on the AC discussion, I believe that the benefit/risk in this group is acceptable. The PI for normal weight women in Study 23 was added to labeling in section 14 (Clinical Studies).
- In overweight women, the mean PI was 5.7 and the upper bound of the associated 95% CI was 8.4. This demonstrates reduced effectiveness as compared to other approved oral CHCs. It is still unclear to me whether the reduced effectiveness is a result of weight, body mass index or other combinations of factors such as compliance with dosing regimen. It is important for providers and women who would fall into this category to understand this as it is significantly higher than identified in any other product to date.
- For obese women, the mean PI is 8.6 and the upper bound of the 95% CI was 11.5. This effectiveness approaches that of a non-hormonal contraceptive. Given the significantly high upper bound and the fact that the 4 VTEs identified in the clinical trial were in obese women, I do not believe that Twirla has an acceptable benefit/risk in this population. I concur with the CDTL's conclusions that use in this population be CONTRAINDICATED. For additional discussion, refer to my effectiveness overview.

## **Next Steps and Outstanding Issues**

### **Labeling Considerations**

The Agency and Agile (the Applicant) worked on a number of labeling revisions. The Applicant provided extensive materials and discussion to support their labeling positions on sections including the Division's proposed Indication and Usage Statement, Limitation of Use Statement and Contraindication for women with a BMI > 30 kg/m<sup>2</sup>. The issues that the Applicant raised (based on the most recent email communication on 2/8/2020) are summarized below:

- A 2017 Complete Response letter stated, "The 2017 CRL notes that the VTE risks with Twirla appears to be similar to that of other CHCs and makes no distinction regarding women with obesity."

- None of the 16 advisory committee members at the October 30 BRUDAC meeting supported a contraindication for this population. In their expert view, the risks of Twirla do not clearly outweigh the benefits in this population. The risks and benefits can be communicated in labeling without a Contraindication.
- The Advisory Committee members (unanimously) did not want a CONTRAINDICATION statement in labeling
- Epidemiologic data supports that the VTE rate seen in the studies is consistent with VTE rates in published literature. Agile also provided an expert opinion by Dr. Greg Piazza to support Agile's position.

***Comment: I will address each of these points separately:***

- ***As previously mentioned the Division recalculated the VTE rate during this review cycle based solely on Study 23 data and it was rechecked by the statistical review team. The Applicant did not dispute that the recalculated rate was incorrect, rather they stated that they did not believe that this rate was of significant concern as well as pointing to other approved labels for CHCs. I do not agree with the Applicant - I think it is concerning that all of these events in Study 23 were in obese women. It is possible that the Applicant is correct and that all CHC products that contain a certain level of estradiol result in a somewhat higher thromboembolism risk in obese women but we do not have reliable data to resolve this issue for Twirla. I believe that the safety signal from Twirla is sufficient to support the need for a large postmarketing study to further assess the thromboembolism risks as CHC trials for approval contain inadequate data to assess the actual risk (Refer to the Postmarketing Studies and Additional Reporting Requirements section). This data will assist the Division in determining whether we can revisit the CONTRAINDICATION at some point in the future.***
- ***I do not concur that none of the 16 AC members supported a CONTRAINDICATION. That was not asked of the members. In fact, one member abstained from the approval vote and one voted not to approve. I do not believe it is possible to use an approval vote to determine what the individual members would have thought had there been a more detailed discussion of labeling.***
- ***In order to support a labeling discussion at the AC, detailed background on what constitutes a CONTRAINDICATION, WARNING and PRECAUTION and Limitation of Use LOU) would have to have been provided in the background package and a discussion of a Risk Evaluation and Mitigation Strategy would have been required as well. This was not the objective of the meeting. In addition, neither the Division nor Agile provided this detailed type of background to allow this detail in discussion.***
- ***As stated in our background package, it is not possible to use published literature rates of VTE to provide context to rates seen in clinical trials. The rate for Ortho Evra was 10.7/10,000 and it is clear that the risk of this***

***transdermal product was sufficiently concerning that labeling reflected additional detailed text in the boxed warning.***

***In summary, I continue to believe that the proposed Indication and LOU needs to describe the decreased effectiveness in overweight women. I also believe that there is significantly decreased effectiveness in obese women and the VTE safety signal identified in obese women makes the benefit/risk in those women unacceptable. I am not swayed by the Applicant's contentions.***

***If the Applicant determines that they would like to have discussions regarding removal of the CONTRAINDICATION in this sub-population, a required part of the data will be thromboembolism epidemiologic data to ensure that there is no increased risk in the normal and overweight populations. Additional discussions with the Applicant to determine what data could be provided are needed and are outside the scope of this approval determination.***

***None of the information Agile has provided in their submission or communications has changed my determination that the benefit/risk in the obese population is unacceptable.***

The Division has now finalized labeling discussions with the Applicant and the Labeling Development Team. The following are the final agreed upon labeling on the Indication and Usage Statement, Limitation of Use and Contraindication related to BMI:

Key labeling agreements:

*Labeling for the Full Prescribing Information:*

**1 INDICATIONS AND USAGE**

*TWIRLA is indicated as a method of contraception for use in women of reproductive potential with a BMI < 30 kg/m<sup>2</sup> for whom a combined hormonal contraceptive is appropriate.*

*Limitations of Use*

*Consider TWIRLA's reduced effectiveness in women with a BMI  $\geq$  25 to < 30 kg/m<sup>2</sup> before prescribing Twirla [see Use in Specific Populations (8.9) and Clinical Studies (14)]. TWIRLA is contraindicated in women with a BMI  $\geq$  30 kg/m<sup>2</sup> [see Contraindications (4)].*

**CONTRAINDICATION**

*TWIRLA is contraindicated in women with a BMI  $\geq$  30 kg/m<sup>2</sup>. Compared to women with a lower BMI, women with a BMI  $\geq$  30 kg/m<sup>2</sup> had reduced effectiveness and may have a higher risk for VTEs (venous thromboembolisms) [see Contraindications (4) and Warnings and Precautions (5.1)].*

***Comment: I concur that the CONTRAINDICATION for women with a BMI  $\geq$  30 kg/m<sup>2</sup> is necessary for safe and effective use. A PMR study to further evaluate the thromboembolic safety in the approved population will be required and conducted in the postmarketing period. An interim assessment will provide data in 2026. At that time, an assessment can be made as to whether the benefit/risk of Twirla would be acceptable in the obese population and adjustment to the labeling can be requested by the Applicant.***

## **Postmarketing Studies/Additional Reporting Requirements:**

1. *Given the strength of the VTE safety signal, the Applicant is required to conduct the following epidemiologic study as a postmarketing requirement (PMR):*
  - *PMR-3785-1: A controlled, non-interventional, prospective, observational cohort study comparing the risks for fatal and non-fatal venous thromboembolism (VTE) and arterial thromboembolism (ATE) in new users of Twirla to new users of oral combined hormonal contraceptives (CHCs) (primary comparator) and new users of Xulane (secondary comparator) in U.S. women of reproductive age using CHCs primarily for contraceptive reasons. The study should be designed to detect a 1.5 to 2-fold increased risk for VTE in new users of Twirla and adequately measure and control for possible confounders, especially age, BMI, and smoking status, among others.*

*The following milestones were agreed to by email on 02/06/2020:*

<i>Draft Protocol Submission:</i>	<i>11/2020</i>
<i>Final Protocol Submission:</i>	<i>11/2021</i>
<i>Interim Safety Analysis Report:</i>	<i>11/2026</i>
<i>Study Completion:</i>	<i>11/2031</i>
<i>Final Report Submission:</i>	<i>11/2032</i>

2. *Given the lack of information on residual drug content of LNG and EE and the potential that this information may have clinical importance, the Applicant was asked to conduct a postmarketing study to assess the residual drug content and strength of Twirla after clinical wear. The Applicant agreed to conduct the following postmarketing commitment (PMC) by email on 2/6/2020:*
  - *PMC-3785-2: A clinical study in a minimum of 25 women to accurately assess the residual drug content and strength of Twirla. This study will evaluate Twirla worn by study subjects and analyze the ethinyl estradiol (EE) and levonorgestrel (LNG) content after the prescribed wear and monitor adhesion over the entire wear period.*

<i>Draft Protocol Submission:</i>	<i>06/2020</i>
<i>Final Protocol Submission:</i>	<i>09/2020</i>
<i>Study Completion:</i>	<i>06/2021</i>
<i>Final Report Submission:</i>	<i>09/2021</i>

*The study and milestones for this PMC were agreed to by email //on 02/06/2020.*

***Comment: I concur that the PMR and PMC are necessary and that the milestones are acceptable.***

*Reporting Requirements*

The Applicant will include a section in their quarterly safety reports on transdermal system related events. This section will capture the number of TDS replacements and reason(s) for the replacement (if provided by the patient).

**Comment: Although the Applicant demonstrated adequate adherence in clinical studies, it is notable that 10-20% of all users in the year-long phase 3 study required four or more TDS per cycle to maintain therapy per labeled instructions. As this product will be packaged in cartons of three, obtaining replacement TDS may be a significant inconvenience in the postmarketing setting. It is possible that there will be a significant number of users that may need replacement product in order to maintain prescribed wear and subsequently contraception. I believe it is important to monitor the need for replacement TDS in the postmarketing setting as compliance with the regimen is critical to maintaining contraceptive effectiveness in the real-world setting. In order to better understand the replacement information reported in Study 23 I have asked the Applicant to have an additional reporting requirement to ensure that the Division can gain a better understanding of how often and what reasons are driving replacement requests in the postmarketing setting.**

## APPENDIX

Figure 1 – List of recently approved CHC contraceptives

### PI of AG200-15 compared with approved contraceptives in last 10 years

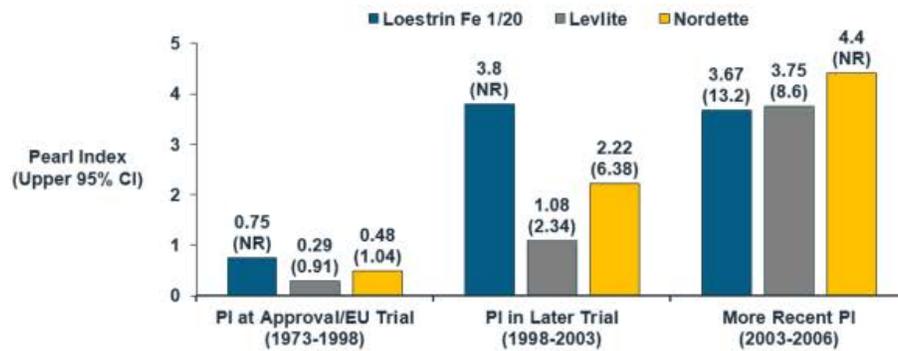


Drug/Study	Year Approved	PI	95% CI	BMI(kg/m <sup>2</sup> )
AG200-15 Study 12	NA	7.50	(5.02, 9.97)	No restriction
AG200-15 Study 13	NA	8.19	(0.19, 16.19)	BMI <32
AG200-15 Study 23	NA	5.83	(4.45, 7.21)	No restriction
Quartette	2013	3.19	(2.49, 4.03)	No restriction
Lo LoEstrin Fe	2010	2.92	(1.94, 4.21)	BMI ≤35
Natazia	2010	1.64	(NA, 3.82)	BMI ≤35
Generess	2010	2.01	(1.21, 3.14)	BMI ≤35
Lo Seasonique	2008	2.74	(1.93, 3.78)	BMI ≤35
Annovera	2018	2.98	(2.13, 4.06)	BMI <29
*pre NDA Estetrol/DRSP	NA	2.65	(1.73, 3.88)	No restriction

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## Pearl Indices of Approved CHCs



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**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.**  
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/s/  
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AUDREY L GASSMAN  
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