CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204017Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	February 13, 2020
From	Gerald Willett, M.D. (CDTL)
Through	Audrey Gassman, MD (Deputy Division Director)
NDA#	204017 (Second Resubmission)
Applicant	Agile Therapeutics, Inc.
Date of Resubmission	May 14, 2019
Original PDUFA Goal Date	November 14, 2019
Extended PDUFA Goal Date	February 14, 2020
Proprietary Name	Twirla (AG200-15)
Established or Proper Name	Levonorgestrel/ethinyl estradiol
Dosage Form	Transdermal system
Applicant Proposed Indication(s)/Population(s)	Indicated for use by females of reproductive potential to prevent pregnancy
Applicant Proposed Dosing Regimen(s)	New system each week for three weeks (abdomen, buttock or upper torso) then one system-free week
Recommendation on Regulatory Action	Approval (with labeling restrictions)
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the prevention of pregnancy in women who have a BMI < 30 kg/m^2 and for whom a transdermal system is appropriate
Recommended Dosing Regimen(s) (if applicable)	Same as Applicant's

Overview

Agile Therapeutics, Inc. (Applicant) is seeking approval of AG200-15 (referred to by the proprietary name "Twirla" in this review), a new contraceptive transdermal delivery system (TDS) containing levonorgestrel (LNG) and ethinyl estradiol (EE) for the prevention of pregnancy.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Agile's contraceptive transdermal delivery system (TDS), AG200-15 (Proprietary name Twirla) is being submitted for approval under NDA 204017 for the indication of prevention of pregnancy. This TDS contains two commonly used contraceptive hormones, ethinyl estradiol (EE, 30 mcg/day) and levonorgestrel (LNG, 120 mcg/day). The dosing regimen per 28-day cycle employs once-weekly applications of a 7-day system for three weeks followed by a one-week system-free interval. The application sites include abdomen, buttock and upper torso.

This is the third review cycle for this NDA. Approval was not granted in the previous submissions for a number of clinical and product quality issues. Clinical deficiencies were noted in data collection and reporting in the first submission and reduced effectiveness manifested by high pregnancy rates in submissions accepted for FDA review. System adhesion issues noted in study subjects by the Division in the first two submissions were subsequently brought to the agency via dispute resolution and eventually addressed through a comparative in-house study with Xulane (the generic of Ortho Evra). This comparative study (Study 25) and a pilot wear study (Study 26) represent the only additional clinical data in this submission to resolve one of the outstanding deficiencies from the previous 2017 CR letter related to demonstration of adequate adhesion. The Applicant found and FDA biostatistics concurred that Twirla was non-inferior to Xulane in the comparative study. There were no new safety signals identified in Studies 25 and 26. Most of the review decisions regarding approvability and labeling are based on Study 23, a large safety and efficacy study that was included in the submission by the Applicant in 2017. The other CMC deficiencies outlined in the second CR letter and the manufacturing inspection issue are resolved.

I recommend approval of Twirla contingent on agreed to labeling that contraindicates its use in obese patients with a body mass index (BMI) ≥ 30 kg/m^2 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. Obese patients have much better options in regard to efficacy with other hormonal contraceptive products. 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 of a lack of efficacy and serious VTE risk in this subpopulation.

A postmarketing requirement was recommended for the Applicant to study fatal and nonfatal thromboembolism events in a large prospective epidemiology study in women using Twirla. A postmarketing commitment will be set for the Applicant to study residual drug content and strength of Twirla to ensure that there are no safety issues related to residual drug content in the TDS. Additional reporting requirements will assist the clinical and CMC staff in early identification of tolerability and/or product quality issues based on information on replacement TDS.

This reviewer notes that not all members of the review team favor approval of Twirla at this time and I will briefly summarize their considerations and conclusions.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Although there may be secondary benefits, the principle objective of hormonal contraception used by reproductive age women is to prevent unintended pregnancy. • Unintended pregnancy has immense personal, societal and health consequences for women and their families. • Since the 1960s women have come to expect highly effective contraception (especially from combined estrogen/progestin products) • Development of new oral and non-oral CHCs provides options for women.	CHCs have played a leading role in women's health in reducing unintended pregnancy since the 1960s.
Current Treatment Options	• Many types of hormonal and non-hormonal contraceptives are on the US market • Only one contraceptive transdermal delivery system (TDS) is currently available (Xulane, generic of Ortho Evra®) • Ortho Evra® was withdrawn from market for commercial reasons (not for safety or efficacy) • CHC formulations available in the U.S. include a large number of oral products, 2 intravaginal rings and 1 TDS. • Progestin-only formulations include oral, injections (intramuscular and subcutaneous), dermal implant and intrauterine systems	Although there are a large number of CHCs overall, most of these products are oral requiring 21 to 24 days of daily intake per cycle. Non-oral products that require application weekly x 3 (transdermal) or insertion every three weeks (intravaginal ring) may provide an attractive option for women seeking to avoid daily dosing regimens.
Benefit	• The benefit of this product in regard to protection against pregnancy is limited and therefore this reviewer recommends that the contraceptive indication for Twirla be for women with BMI < 30 kg/m^2. Labeling should include a limitation of use for overweight women (BMI ≥ 25 – < 30 kg/m2) and the product should be contraindicated in obese women (BMI ≥ 30 kg/m^2). • The evaluable cycles, PI and 95% confidence intervals (CI) by BMI in Study 23 (Age ≤ 35 years) are the following:	From an effectiveness standpoint the PI and the 95% CI for the obese sub-population are clearly unacceptable. The lower bound (5.79) exceeds the upper bound of every CHC ever approved by the Division. Although this reviewer finds an indicated BMI population of less the 30 kg/m^2 acceptable for

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><th>BMI (kg/m2)</th><th>Cycles</th><th>PI</th><th>95% CI</th></tr>
<tr><td>< 25</td><td>6,007</td><td>3.5</td><td>1.8, 5.2</td></tr>
<tr><td>≥ 25 - < 30</td><td>3,881</td><td>5.7</td><td>3.0, 8.4</td></tr>
<tr><td>≥ 30</td><td>5,264</td><td>8.64</td><td>5.79, 11.50</td></tr>
<tr><td>All</td><td>15,165</td><td>5.83</td><td>4.5, 7.2</td></tr>
</table>
Although convenience of use may represent a benefit to some women, the Applicant did not analyzed this as a co-primary or key secondary endpoint. It is unclear that the Division would have accepted this type of analyses for a claim regarding benefit for convenience
</td><td>approval:
Reduced effectiveness text for the overweight population warrants a limitation of use (LOU) statement in the label.
No LOU is required for the normal weight population as the PI and upper 95% CI were sufficiently close to previous approvals?</td></tr>
<tr><td>Risk and Risk Management</td><td>Safety findings in Study 23 were significant for the finding of 5 VTEs, 4 of which were considered related to treatment. These treatment-emergent cases all arose in obese subjects. The fifth VTE also occurred in an obese subject but the event occurred 2 months after stopping treatment and appeared to be related to gallstone-induced pancreatitis and pancreatic surgery which is likely not related to Twirla since she had stopped her medication before the VTE event occurred.</td><td>This safety concern also contributes to the recommendation of a contraindication of Twirla to obese patients. A postmarketing requirement will be set for the Applicant to study thromboembolism adverse events in women with BMIs in the normal to overweight range.</td></tr>
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2. Background

This is the third NDA review cycle for Twirla. The same formulation (system configuration and hormonal doses) has been used in all three of the phase 3 clinical trials and in a recent comparative wear trial.

First Review Cycle

The initial submission for Twirla occurred in April 2012, which included two phase 3 studies. Study ATI-CL12 (hereafter referred to as Study 12) was a multicenter, open-label randomized study that was comparative for 6 cycles against a 100 mcg LNG/20 mcg EE oral product (Lessina) and then extended to 13 cycles that included both Twirla users and switchers from the oral product. Study ATI-CL13 (hereafter referred to as Study 13) was a multicenter, open-label, randomized study that compared Twirla to a 150 mcg LNG/30 mcg EE oral product (Levora).

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

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

In the Complete Response letter the Division recommended that a new pre-approval 13 cycle phase 3 study be conducted. There were also a number of recommendations related to product quality. At an end-of-review meeting in October 2013 the Division met with the Applicant to discuss the unacceptable evidence of effectiveness and the steps required before the application could be approved. The Applicant was informed that the Division had never approved a CHC for which the upper bound of the 95% CI around the PI exceeded 5,

CDTL Comments:
The Applicant did not prespecify Studies 12 & 13 trials as non-inferiority trials (not powered as such, no margin set). Only the Twirla arm in Study 12 had enough evaluable cycles (6,070) to properly assess contraceptive efficacy. The number of cycles for each of the comparators did not exceed 1,000. The Division only analyzed the Twirla arms of Studies 12 & 13 for the

number of on-treatment pregnancies. The Applicant's analysis of the on-treatment pregnancies in Study 12 was concerning. The Division identified 5 additional on-treatment pregnancies that resulted in a Pearl Index of 7.50 (95% CI 5.02, 9.97) for a population age 17-35 years with BMI < 32 kg/m^2. Of even more concern was the Division's identification of 9 additional pregnancies (not included in the PI) where the collection of pregnancy and also safety data was so inadequate that no determination could be made about the on-treatment status or whether the safety database was sufficient. Thus I believe were data adequately collected on pregnancy, the PI and VTE rates could have been even higher in Study 12.

Second Review Cycle

The Applicant submitted a complete response in June 2017 with data from a new phase 3 study (Study 23) that is discussed in greater detail in Sections 8 and 9 of this review. The FDA notified the Applicant in December 2017 that the application still could not be approved. There were product quality issues and deficiencies identified at a manufacturing facility. The FDA also had concerns related to product adhesion, high subject withdrawal rates and the high PI. It was unclear to what extent adhesion problems affected efficacy, unscheduled bleeding and high discontinuation rates.

Formal Dispute Resolution Requests

In June 2018 and again in August 2018, the Applicant submitted Formal Dispute Resolution Requests to FDA's Office of Drug Evaluation III and the Office of New Drugs, respectively. The Applicant asked that FDA consider the existing in vivo adhesion data for Twirla, along with planned risk management activities, to be adequate for approval. In both cases the FDA denied these appeals. In the OND Director appeal, a path forward was provided to allow resolution of the concerns related to demonstration of adequate adhesion properties. The Applicant was asked to provide a non-inferiority study to demonstrate that their clinical adhesion properties of Twirla were sufficiently similar to an approved comparator TDS product.

Third Review Cycle

The Applicant submitted a complete response in May 2019 which included additional study information to address the adhesion-related concerns of the December 2017 Complete Response Letter. This additional study (Study 25) was an in-house comparative wear study for Twirla versus Xulane. No other clinical data were submitted.

3. Product Quality

Mark Seggel, Ph.D. (Acting CMC Lead) noted in the Integrated Quality Review that the following quality assessments were adequate:

- Drug substance
- Drug product
- Environmental assessment
- Manufacturing
- Facilities
- Biopharmaceutics
- CDRH requirements

The following attributes were deemed acceptable:

- System appearance
- Assay
- Content uniformity
- Degradation products
- Drug release / Skin permeation l Dose dumping
- Residual solvents
- Permeation enhancer assay
- Adhesion, Shear, Tack and Cold flow

At the time of the quality review submission in DARRTS there was no agreement on the content and format of the final product labeling.

Caroline Strasinger, Ph.D., Chao Wang, Ph.D. and Meiyu Shen, Ph.D. reviewed the Applicant's non-inferiority comparative wear study versus Xulane, an approved TDS for contraception (Study 25, see section 7 of this review for further details)

Drs. Wang and Shen (from the Biometrics group) found that data in the controlled Study 25 supported the non-inferiority of Twirla to Xulane in terms of in vivo adhesion. In addition stand-alone evaluations of Twirla (Study 25 & 26) showed that the probability that a randomly selected Twirla maintains at least 75% adhesion throughout the entire wear period in the controlled setting.

Dr. Strasinger concluded from a quality perspective, that the formulation and product design of the drug product used in Study 25 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 Twirla. Dr. Seggel completed the final review from all OPQ disciplines and concluded that the submission and labeling are acceptable for approval from OPQ's perspective.

4. Nonclinical Pharmacology/Toxicology

Mukesh Summan, PhD, DABT noted in his Pharmacology/Toxicology Supervisor review that there are a large number of CHCs that contain LNG and EE. He stated that there are no nonclinical issues which would preclude approval of this NDA and in an addendum that the labeling changes proposed were accepted by the Sponsor.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (Yanhui Lu, PhD signatory) finds this NDA to be acceptable from a clinical pharmacology perspective, provided that the EE/LNG residual strength issue is addressed through a postmarketing study. (See their review and also Section 13 of this review for more information on the postmarketing study.

6. Clinical Microbiology

Mark Seggel, Ph.D. (Acting CMC Lead) noted in the Integrated Quality Review that the risk for microbial contamination of this non-aqueous formulation is low and that testing indicates that the formulation inhibits microbial growth. Microbial limits testing is not required for batch release and stability testing. The facility inspection issue that was outlined in the 2017 Complete Response was also resolved.

7. Clinical/Statistical- Efficacy

This review section includes the following:

- Summary of efficacy from Study 23
- Study 26 – Pilot study for Twirla adhesion
- Study 25 – Comparative adhesion study between Twirla and Xulane
- Study 11 – Reanalysis of ovulation inhibition data
- Executive summary (biostatistics)
- Memorandum (summary review (clinical)

Summary of Efficacy from Study 23

The reader is referred to the division's clinical and statistical reviews of efficacy in Study 23 (2017 submissions) for full details regarding assessment of on-treatment pregnancies and pregnancy rate determinations (PI and life table). A summary of the number of subjects, number of on-treatment pregnancies, evaluable cycles, mean PIs and 95% confidence intervals (CI) are shown in the following table:

Pregnancy Rates (Pearl Indices) for Study 23 (≤ 35 years) - FDA

Population	N	# On-Treatment Pregnancies	# Evaluable Cycles	Pearl Index (95% CI)
Overall	1,736	68	15,165	5.8 (4.5, 7.2)
BMI (kg/m²)				
Normal (< 25)	684	16	6,007	3.5 (1.8, 5.2)
Non-obese (< 30)	1,123	33	9,888	4.3 (2.9, 5.8)
Overweight (≥ 25 < 30)	439	17	3,881	5.7 (3.0, 8.4)
Obese (≥ 30)	612	35	5,264	8.6 (5.8, 11.5)
Race				
White	1,159	46	10,281	5.8 (4.1, 7.5)
Black	418	17	3,454	6.4 (3.4, 9.4
Other	159	5	1,430	4.6 (0.6, 8.5)
Ethinicity				
Hispanic/Latino	330	12	2,851	5.5 (2.4,8.6)
Not Hispanic/Latino	1,406	56	12,314	5.9 (4.4,7.5)

BMI = body mass index; CI = confidence interval
Evaluable cycles were those with at least one episode of vaginal intercourse and no back-up contraception
Source: FDA Biostatistician (2017)

Life Table analyses by subgroup for Study 23 were provided by Dr. Tang in both the intent-to-treat population (ITT) and contraceptive efficacy population (CEP -- i.e. no exclusion of cycles for lack of vaginal intercourse and use of back-up contraception). These analyses are shown in the following 2 tables.

Cumulative Pregnancy Rates in Subjects ≤ 35 Years by Subgroup (ITT): Study 23

Population	N	# On-Treatment Pregnancies	# Cycles	Cumulative Pregnancy Rate (95% CI)
BMI[1] (kg/m²)				
Normal (< 25)	684	16	6,007	3.06 (1.87, 5.00)
Non-obese (< 30)	1,123	33	9,888	4.08 (2.89, 5.74)
Overweight (≥ 25 < 30)	439	17	3,881	5.59 (3.47, 8.94)
Obese (≥ 30)	612	35	5,264	8.08 (5.82, 11.17)
Race				
White	1,159	46	10,281	5.36 (4.02, 7.14)
Black	418	17	3,454	6.24 (3.85, 10.02
Other	159	5	1,430	4.65 (1.91, 11.07)
Ethinicity				
Hispanic/Latino	330	12	2,851	5.77 (3.27, 10.07)
Not Hispanic/Latino	1,406	56	12,314	5.42 (4.17, 7.03)

ITT = intent-to-treat; BMI = body mass index; CI = confidence interval
[1]BMI subpopulations (Normal, Overweight and Obese) add up to N = 1,735: Subject (b) (6) had no BMI information.
Source: FDA Statistical Reviewer's Analysis (2020)

Cumulative Pregnancy Rates in Subjects ≤ 35 Years by Subgroup (CEP): Study 23

Population	N	# On-Treatment Pregnancies	# Cycles	Cumulative Pregnancy Rate (95% CI)
BMI[1] (kg/m²)				
Normal (< 25)	721	16	6,464	3.01 (1.83, 4.91)
Non-obese (< 30)	1,177	33	10,619	3.98 (2.82, 5.60)
Overweight (≥ 25 < 30)	456	17	4,155	5.45 (3.38, 8.70)
Obese (≥ 30)	638	35	5,698	7.79 (5.62, 10.77)
Race				
White	1,212	46	11,014	5.21 (3.91, 6.94)
Black	436	17	3,757	6.06 (3.75, 9.73
Other	168	5	1,559	4.44 (1.84, 10.50)
Ethinicity				
Hispanic/Latino	350	12	3,083	5.61 (319, 9.79)
Not Hispanic/Latino	1,466	56	13,247	5.27 (4.05, 6.83)

[1]BMI subpopulations (Normal, Overweight and Obese) add up to N = 1,815: Subject (b) (6) had no BMI information.
CEP = contraceptive efficacy population (i.e. no exclusion of cycles for lack of vaginal intercourse and use of back-up contraception)
Source: FDA Statistical Reviewer's Analysis (2020)

CDTL Comments:

- ***It can be seen from all 3 preceding tables that the upper bound of the 95% CI is very close to 5.00 for the normal BMI subgroup (for the PI and both determinations of the cumulative). This supports the decision to indicate Twirla for women with BMIs < 25 without limitation or contraindication. All 3 tables also support the decision to include a***

limitation of use for overweight women and a contraindication for obese women.

- ***One of the points made by the Applicant at the Advisory Committee Meeting was that the Division's definition of evaluable cycles (at least one episode of vaginal intercourse and no back-up contraception) was a reason why pregnancy rates have been increasing in clinical trials. However, in the 2 life table analyses shown above the difference in pregnancy rates between the ITT and CEP is small. This reviewer feels that the "evaluable cycle" argument proposed by the Applicant is not a major reason that the phase 3 trial for Twirla's reported high pregnancy rates compared to other recently approved CHCs.***

Study 26

Study 26 was a phase 1, single-dose, open-label, non-comparative in-house adhesion study. The Applicant enrolled 30 subjects and all completed the study. The demographics are shown in the following table. The Study enrolled healthy women, age 18-35 years. Subjects with a BMI < 19 and ≥ 35 kg/m^2 were excluded from the study. Six subjects (20%) had a BMI ≥ 30 kg/m^2.

Demographics for Study 26

Parameter	Category	Statistic	Twirla N=30
Age (years)		Median (Min, Max)	28.0 (18,35)
BMI (kg/m^2)		Median (Min, Max)	26.4 (20.3, 34.4)
Race	• White • Black or African American • Other	n(%) n(%) n(%)	10 (33.3%) 18 (60.0%) 2 (6.7%)
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino	n(%) n(%)	13 (43.3%) 17 (56.7%

Source: Study ATI-CL26; Table 14.1.2 (linked to page 20/32 in report)

Scoring of transdermal system adhesion was based on the following 5-point scale:

0 = ≥ 90% adhered (essentially no lift off the skin)
1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
2 = ≥ 50% to < 75% adhered (< ½ of the patch lifting off the skin)
3 = > 0% to < 50% adhered (not detached, but > ½ of the patch lifting off the skin without falling off)
4 = 0% adhered (patch detached; completely off the skin)

In this 7 day study adhesion was assessed by study personnel at the following time periods (0 hr, 24 hr, 48 hr, 72 hr, 96 hr, 120 hr, 144 hr, and 168 hr). Adhesion measurements were made independently, with the assessor blinded to the patch adhesion score from the previous day.

The Applicant's summary of results indicated the following:
The overall mean adhesion score was 0.08 [standard deviation (SD) = 0.35]. There were no individual scores of 3 or 4 in the study. 96.7% of subjects had a mean adhesion score < 1 (i.e., ≥ 90% adhesion) and 100% of subjects had mean adhesion scores < 2 (i.e., ≥ 75% adhesion).

CDTL Comments:
Study 26 was basically a pilot study done before the comparative in-house Study 25 in which Twirla was compared to Xulane (generic of Ortho Evra). All transdermal systems were placed by study site personnel using the lower abdomen as the sole anatomic site. Although the study allowed subjects to conduct "normal activities of daily living", one would expect an in-house environment to be more restrictive. In fact, prolonged water exposure (>10 minutes at a time), strenuous exercise and sexual activity were not permitted during the wear period. Therefore this reviewer was not surprised at the good adhesion score results. All of the 6 obese subjects enrolled scored 0 throughout the 7 days. Only 2 subjects ([redacted] (b) (6)) had scores of 2 at any point.

Study 25

Study 25 was a randomized, single-dose, open-label, two-treatment, two-period crossover comparative in-house adhesion study between Twirla and Xulane. The Applicant enrolled 83 subjects and 79 completed the study. The demographics are shown in the following table. The Study enrolled healthy women, age 18-35 years. Subjects with a BMI < 19 and ≥ 35 kg/m^2 were excluded from the study. Fourteen subjects (17%) had a BMI ≥ 30 kg/m^2.

Demographics for Study 25 (N=83)

Parameter	Category	Statistic	Twirla
Age (years)		Median (Min, Max)	28.0 (19,35)
BMI (kg/m^2)		Median (Min, Max)	25.5 (19,35)
Race	• White • Black/African American • Asian • American Indian or Alaska Native • Native Hawaiian/Pacific Islander • Multiracial	n(%) n(%) n(%) n(%) n(%) n(%)	26 (31.3%) 52 (62.7%) 1 (1.2%) 1 (1.2%) 1 (1.2%) 2 (2.4%)
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino	n(%) n(%)	22 (26.5%) 61 (73.5%

Source: Study ATI-CL25; Table 3; page 26 of 41

The Applicant's summary of results found that Twirla demonstrated non-inferiority to Xulane. The mean adhesion score of 0.39 for Xulane was worse than the mean score of 0.14 for Twirla. This produced a negative mean difference and the test for non-inferiority demonstrated a p value < 0.0001.

CDTL Comments:
Study 25 was designed in a similar fashion to the pilot Study 26 in regard to study personnel application of the system to the abdomen and the activity restrictions. Study 25 had a 2-period crossover comparing Twirla with Xulane. The study was open-label. The transdermal system size is different with Xulane at 20 cm^2 and Twirla at 28 cm^2.

This reviewer evaluated the data listing # 16.2.5.2 which provided all the adhesion assessments. There was no evidence of grade 3 or grade 4 adhesion scores for any of the subjects using either Xulane or Twirla. The number of subjects by treatment and the highest adhesion score assigned during the seven day system exposure for each treatment is shown in the following table:

Number of Subjects by Treatment and Highest Adhesion Score in Study 25

Transdermal system	Adhesion Score				
	0	1	2	3	4
Twirla (subjects)	59	19	1	0	0
Xulane (subjects)	30	38	12	0	0

Source: Data Listing 16.2.5.2 Adhesion Assessments

Of the 83 subjects in the ITT population 14 were obese (17%). All 14 of these subjects completed both periods with placement of both Twirla and Xulane. The number of obese subjects by treatment and the highest adhesion score assigned during the seven day system exposure for each treatment is shown in the following table:

Number of Obese Subjects by Treatment and Highest Adhesion Score in Study 25

Transdermal system	Adhesion Score				
	0	1	2	3	4
Twirla (subjects)	10	3	1	0	0
Xulane (subjects)	5	7	2	0	0

Source: Data Listing 16.2.5.2 Adhesion Assessments and Data Listing 16.2.4.1 Demographics and Baseline Characteristics

The number of subjects in the two previous tables correlates with the adhesion mean scores listed above in the paragraph that discusses non-inferiority.

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. Dr. Sewell in her CDTL review for Study 23 noted "that over 11% of TDS 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 TDS detachment in the first cycle of use. 14.7% of patients required more than 4 patches per cycle."

Though it is difficult to make cross-study comparisons the medical officer review of Ortho Evra in 2001 included study data on the integrated percentage of "patches that fell off" in 3 different clinical trials. The overall percentage for 70,552 patches was 1.8% and the percentage in the first cycle for 11059 patches was 2.1%

Study 11 Reanalysis

The Applicant was asked to reanalyze the progesterone levels used in Study 11 for evidence of ovulation inhibition. Specifically they were asked to evaluate the data by BMI subgroup (Normal, overweight and obese) rather than "all BMI" and "≤ 32 kg/m^2". The Applicant's table for this reanalysis is shown below:

Incidence and Proportion of Cycles with Likely, Probable, or Possible Ovulation by BMI Categories for Twirla, Study ATI-CL11

BMI Subgroup	Number of Cycles with Ovulation Probability		
	Likely	Probable	Possible
Normal	2/32 (6.25%)	4/32 (12.5%)	6/32 (18.75%)
Overweight	1/31 (3.23%)	2/31 (6.45%)	2/31 (6.45%)
Obese	1/20 (5%)	2/20 (10%)	8/20 (40%)

Likely = greatest progesterone level ≥ 9.0 ng/mL; Probable = 2 successive progesterone levels ≥ 4.7 ng/mL; Possible = greatest progesterone level ≥ 4.7 ng/mL; Normal = BMI < 25 kg/m^2; Overweight = BMI ≥ 25 kg/m^2 and <30 kg/m2; Obese = BMI ≥ 30 kg/m^2

CDTL Comments:
The Division has typically utilized the Hoogland Score for pharmacodynamic evaluation of ovulation inhibition in contraceptive development trials. The Hoogland Score incorporates follicular activity, follicle size, estradiol and progesterone measurements rather than just progesterone alone. Thus, this reviewer finds it difficult to assess the role of BMI with these progesterone measurements because in the "likely" and "probable" columns the percentage in normal BMI is slightly greater than that in the obese category. In the "possible" column the obese group is much higher than normal but there does not appear to be any elevation of the overweight category to suggest a continuum. Since ovulation inhibition

is not the only mechanism of contraceptive action for a CHC, the most important findings in regard to this review are the pregnancy rates for Study 23.

Although this information will not be placed in labeling, it suggests one potential reason for the reduced effectiveness with increasing BMI/weight.

Executive Summary – Biostatistics

Yun Tang, Ph.D., the primary statistical reviewer concluded the following:

"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."

CDTL comment: I do not agree with the recommendations and conclusion of the statistical review team. Although the BMI was not prespecified as a primary analyses, the division has based approval decisions on a totality of 5,000 treatment cycles in previous CHC applications. I conclude the following:

- ***There is sufficient data in normal weight women to make an approvability determination. For those women, the mean PI is acceptable and the upper bound of the 95% CI rounds off to 5. Therefore, the benefit/risk is acceptable in this population and no additional advisory labeling is needed.***
- ***For overweight women, although there are less than 5,000 cycles, there is a clear indication from the ovulation data, mean PI and upper bound of the 95% CI that there is reduced effectiveness. The AC members also acknowledged that there was reduced effectiveness. I believe that this can be addressed through labeling, specifically through a LOU statement.***
- ***For obese women, the reduced effectiveness is unacceptable as it approaches that of a progestin only and non-hormonal contraceptive products where there is no thromboembolism risk. I will provide further discussion in my Safety review.***

Memorandum (summary review (clinical)

Nneka Mc-Neal Jackson, the primary clinical reviewer concluded the following: "From a clinical perspective, this clinical reviewer recommends that AG200-15, the to-bemarketed 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."

CDTL comment: I do not agree with the recommendations and conclusion of the clinical reviewer. I address each of her concerns separately as follows:

- ***Efficacy Concerns: 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.***
- ***Safety Concerns: 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^2). 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 the postmarketing requirement.
- ***Adhesion Concern: 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.

- ***Unfavorable benefit/risk: 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.***
- ***Postmarketing requirement/postmarketing commitment: The clinical reviewer did not disagree with the need for these two studies.***

8. Safety

This review section includes the following:

- Summary of safety from Study 23 (for greater detail see Division clinical reviews in 2017)
- Summary of safety from Studies 26 & 25
- Summary of thromboembolism in Study 23

Summary of Safety from Studies 23

- There were no deaths
- There were 40 serious adverse events (SAEs); the following possibly/probably related (cholecystitis - 2, cholelithiasis-4, depression-3, suicidal ideation-1, suicidal attempt-1, thromboembolism – see below)
- There were 224 subjects with treatment-emergent adverse events (TEAEs) resulting in study drug discontinuation

CDTL comment:
The safety database for Study 23 and for the pooled safety database (Studies 12, 13 and 23) was reviewed. After review, the clinical team and CDTL identified a serious safety signal of thromboembolism (VTE). The adverse event profile and VTE signal were discussed at the Advisory Committee meeting and I will now expand on my considerations and conclusions.

Summary of Thromboembolism in Study 23

Although they are rare the most critical safety concerns with CHCs are cardiovascular. These include VTEs, myocardial infarction and stroke.

In Study 23, there were 3 events of pulmonary emboli and 3 events of deep vein thromboses occurring in 5 subjects as shown in the following table:

VTE Cases in Study 23

Subject #	Age (yrs)	BMI kg/m^2	PE	DVT	Probably related
(b) (6)	25	31.8	X		yes
	26	34.3	X		yes
	35	37.1	X	X	yes
	33	36.3		X	yes
	24	35.7		X	no

* subject with a prolonged hospital course (beginning 2 months after study drug discontinuation) for gallstone-induced pancreatitis and [1]complicated by pancreatectomy, sepsis and ARDS.

One additional probably-related DVT case reported by the Applicant occurred in a 26-year-old subject with a BMI of 19.9 kg/m^2 in Study 12.

[1] The highest VTE risk the Division has identified in a clinical trial development program was seen in ANNOVERA (a vaginal ring) which had a VTE rate from their phase 3 clinical trials of 24/10,000. However, the benefit/risk profile of this product is different from the TDS under consideration.

CDTL Comments:
Based on the number of safety cycles in Study 23 (18,841) the incidence rate of drug-related VTEs (4) based solely on Study 23 is approximately 28/10,000 women-years. During this cycle, I recalculated the VTE incidence prior to the AC and had my calculations confirmed by the statistical review team (See also statistical review dated 2/10/2020).

The Applicant and the Division agree that a larger safety study is needed to provide a more reliable VTE incidence estimate. However, I am very concerned that Study 23 identified 4 events in obese women in a single study – this is a strong safety concern that we have never seen in previous trials conducted for approval.

In a recent safety profile for a CHC vaginal system (Annovera), the VTE incidence rate was somewhat lower (22/10,000). Although there were also 4 VTEs identified, these were not from a single clinical trial and distributed across BMI range…For that labeling, the PI and upper bound were acceptable and a large epidemiologic study will be performed to assess whether there is a concerning VTE safety signal.

The fact that the VTEs were solely in obese women coupled with an unacceptable pregnancy rate in obese women is the reason that a contraindication is sought for this product in obese patients and why a postmarketing safety study is required.

Summary of Safety from Studies 26 & 25

In Study 26 there were no deaths, no serious or severe treatment-emergent adverse events (AE), and no AEs leading to discontinuation from study medication or the study. There were no significant safety findings in the lab evaluations, vital signs and physical exams.

In Study 25 there were no deaths or serious treatment-emergent AEs.
There were 2 severe AEs in the Twirla arm (one subject with nausea, the other subject with abdominal cramps) Both of these events resolved with medication. There were no subjects in either treatment arm with any AEs leading to discontinuation from study medication or the study. In regard to mild and moderate common AEs the actual number of cases was small and the percentages between the two products appeared similar. There were no significant safety findings in the lab evaluations, vital signs and physical exams.

CDTL Comment:
No other safety issues or signals were identified in these small clinical studies.

9. Advisory Committee (AC) Meeting

The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) reviewed the Twirla NDA on October 30, 2019. The Applicant's key points from their briefing document and their slide presentation supporting approval of Twirla (called the "Agile Patch" at the meeting) include the following Applicant bulleted items:

Applicant

- Need for more contraceptive options to fit individual lifestyles and evolving needs
- Only 3 non-daily CHC methods available
- Another transdermal system could provide women a new, non-invasive method
- Only available system delivers approximately 56 mcg of ethinyl estradiol
- Twirla delivers approximately 30 mcg of ethinyl estradiol daily

CDTL Comments:
The Division concurs that new, non-oral contraceptives with less dependence on daily dosing would be a welcome option for some women.

In regard to the ethinyl estradiol delivery, the Division feels that Twirla data indicates an estrogen level closer to 35 mcg but concurs it has a lower estrogen delivery than the approved system (Xulane, the generic of Ortho Evra). However, Twirla is not a "low dose" CHC product as there are CHC products that contain 10-20 mcg of EE. The progestin component differs between the two systems. Twirla has levonorgestrel, whereas, Xulane has norelgestromin.

Applicant

- Phase 3 studies 12 & 13 showed similar efficacy and safety to two approved oral contraceptives (this statement was reiterated multiple times to the AC)

CDTL Comments:
The Division disagrees with the Applicant's statement about Studies 12 &13. These studies were very poorly conducted that the Division recommended repeating the phase 3 program with a new clinical trial to demonstrate effectiveness and safety. Because of this, for this review cycle, the Division decided to focus only on Study 23 during its AC presentations.

Additionally, comparison statements regarding studies 12 & 13 are not appropriate because the Applicant did not prespecify, power appropriately or set a margin for these studies to qualify as non-inferiority trials. Only the

Twirla arm in Study 12 had enough evaluable cycles (6,070) to properly assess contraceptive efficacy. The number of cycles for each of the comparators did not exceed 1,000.

Comparative studies with an oral contraceptive also present difficulties because of different metabolic pathways and potentially differences in tolerability that could result in different dropout rates. The dropout rate for Twirla was around 50% and if the comparator arm had a significantly different dropout rate, factoring in the tolerability data into the effectiveness and safety calculations would be clinically difficult to assess.

Applicant:

- Arguments presented that Study 23 was an inclusive, contemporary trial reflective of and generalizable to the current US population
- Study 23 integrated more elements of FDA guidance than prior historical CHC trials
- Twirla's high PIs are a result of a "creeping pearl" and contemporary trial design that more closely resembles real world use

CDTL Comments:
This reviewer acknowledges that the demographics of Study 23 better reflect the US population in regard to BMI than previously conducted trials. Because of this enrollment goal the Division was able to properly identify the risks for this population in regard to effectiveness and safety.

This reviewer acknowledges that the mean PI has been rising over the last 20 years. This increase is probably related to a number of factors including:

- ***More sensitive and frequent pregnancy testing***
- ***Improved imaging techniques to assess conception***
- ***Focus on the overall pregnancy rate rather than separation into method and user failure results***
- ***Exclusion of cycles in which the subject is not sexually active***

I do not agree with the Applicant regarding the aspect of Study 23 more closely resembling a "real world" trial. The overall study monitoring and entry criteria were comparable to a typical phase 3 open label contraceptive trial. In distinction to other contraceptive trials the Applicant incorporated a run-in compliance test regarding eDiary use. The number of subjects not admitted to the trial based on eDiary use was 625. It was not clear from the report why the Applicant felt a need to institute this run-in. One possibility is that they were concerned about the compliance issues in Studies 12 & 13 and felt that it negatively affected the effectiveness results. The PIs for the women ≤ 35 years in Study 23 (overall and sub-populations) are included in Section 6 of this review. I believe that the PIs and 95% CIs

probably were improved by enrichment for compliance in Study 23 and are likely to be worse in postmarketing (real world).

There was just one voting question for the committee namely "Do the benefits of AG200-15 outweigh its risks to support the drug's approval for the prevention of pregnancy?"

CDTL Comments:
The results of the committee voting were 14 YES, 1 NO and 1 ABSTENTION. After listening to the committee members after their vote and reviewing the transcript it appeared to this reviewer that they were voting in favor of providing another option for women and taking into consideration the fact that the transdermal presently on the market delivers a greater amount of estrogen. The committee member who voted No was concerned about the high PI and felt her patients would expect better effectiveness. I am not sure why the AC committee member abstained, but it appeared to be based on his disagreement with the trial design and not the results.

A number of committee members mentioned the need to convey the pregnancy rates and safety issues (especially in light of the BMI subpopulation data) as a continuum in the label. There were no voting questions related to labeling per se but a few committee members after their vote stated that they did not feel the product should be excluded from obese patients. Others seem to raise concerns with use in the obese population.

This reviewer disagrees with allowing use in obese patients. Twirla's very high pregnancy rate and VTE safety concerns that were specifically identified in obese patients make the use in women with BMI ≥ 30 kg/m^2 unacceptable. From my clinical perspective, until the VTE risk is better understood, obese women should seek contraceptive alternatives that are likely to provide benefit with a lower VTE risk such as progestin only products, IUS or non-hormonal alternatives.

10. Pediatrics

The Applicant provided the following information regarding pediatric assessment requirements:

> "Pediatric studies are not applicable in pediatric females <17 years of age because, as acknowledged by the Agency at the Type A End of Review Meeting [End of Review Meeting Minutes], none of the criteria set forth in 21 U.S.C 355c(a)(l)(A)(i) apply at this time to the current application. Accordingly, Agile Therapeutics, Inc. is exempt from the requirement to conduct pediatric studies."

CDTL Comments:
I concur with the Applicant's statement and that PREA is not triggered.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) inspected TLK Research, Inc. for this application. This was the study center that conducted the pilot (Study ATI-CL26) and comparative (Study ATI-CL25) in-house transdermal system wear studies. The OSI field classification for this inspection was – No Action Indicated (NAI) OSI sent a letter to TLK Research that included the following statement:
"We have reviewed the FDA Establishment Inspection Report and the documents submitted with that report, and we did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance."

The Applicant filed OMB form No. 0910-0616 (Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank) with this submission.

The Applicant filed a Debarment Certification with this submission.

Financial Certification and Disclosure for the new Studies 25 & 26 was included in this submission along with resubmissions of previous studies evaluated on the first two review cycles..

CDTL comments:
There are no clinical review concerns related to any of the above noted inspections or certification submissions (OSI, ClinicalTrials.gov, Debarment and Financial)

12. Labeling

After reviewing the Applicant's proposed labeling, I am going to provide comments on key sections

Prescribing Information

Although labeling is a critical component of any NDA approval process it is particularly true for this application. This will be the first hormonal contraceptive label that includes BMI as a major component in a Black Box Warning, in the indication, in a limitation of use, and a contraindication.

Boxed Warning

> "WARNING: CIGARETTE SMOKING AND
> SERIOUS CARDIOVASCULAR EVENTS and

CONTRAINDICATED IN WOMEN WITH A BMI ≥ 30 KG/M^2"

Contraindicated in Women with a BMI ≥ 30 kg/m^2
TWIRLA is contraindicated in women with a BMI ≥ 30 kg/m^2. Compared to women with a lower BMI, women with a BMI ≥ 30 kg/m^2 had reduced effectiveness and may have a higher risk for venous thromboembolism events (VTEs).

Indication

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

Limitations of Use

Consider TWIRLA's reduced effectiveness in women with a BMI ≥ 25 to < 30 kg/m^2 before prescribing TWIRLA. TWIRLA is contraindicated in women with a BMI ≥ 30 kg/m^2.

Contraindication

- BMI ≥ 30 kg/m^2. Compared to women with a lower BMI, women with a BMI ≥ 30 kg/m^2 had reduced effectiveness and may have a higher risk for VTEs

Dosage, Administration and Instructions for Use

These sections are all acceptable in the PI submitted by the Applicant on 2/12/2020. Warnings related to prolonged exposure to water and advice about concomitant use of topical products applied to the skin are noted in the label

5.9 Unscheduled and Scheduled Bleeding and Spotting

Uterine bleeding irregularities are commonly seen with many combination and progestin-only hormonal contraceptives and are problematic in regard to patient's continuing a contraceptive method. An adequate level of endogenous and/or exogenous estrogen is crucial to towards maintaining endometrial stability and less unscheduled bleeding/spotting. This section of the label reports on the unscheduled bleeding/spotting on Twirla (60.4% at cycle 1 and 42.3% at cycle 13). No claims were allowed based on the bleeding/spotting patterns

6.1 Clinical Trial Experience

In addition to the usual safety information in this section, the 4 VTEs considered to be related to treatment in obese subjects from Study 23 are included in labeling as well as the common adverse event profile.

14.0 Clinical Studies

Pregnancy rates and 95% Cis are listed in a table and a figure by BMI categories (normal, overweight and obese) and BMI continuum respectively as recommended by the AC members. The pregnancy rate and 95% CI calculations as well as the model used for the BMI continuum was checked by the statistical review team and found to be correct.

There was discussion of how far in the BMI continuum to present data. The Applicant had PI data up to a BMI of 60. However, given that Twirla is contraindicated for women with a BMI > 30 kg.m2, I believe that using a cutoff of 40 kg/m^2 in the model allows providers a better visual representation of patients who are likely to use Twirla.

13. Postmarketing Recommendations

The Division is issuing 1 postmarketing requirement (PMR) and asked the Applicant to conduct 1 postmarketing commitment (PMC) to the Applicant for NDA 204017. The PMR is designed to assess the risk for cardiovascular (CV) adverse events (VTE is the primary outcome) and the PMC is designed to accurately assess the residual drug content and strength of Twirla.

PMR – VTE and Other CV Adverse Events

As previously discussed, the Division has concerns about the thromboembolism risk with use of Twirla. To address this risk, the following PMR was required:

Title: 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.

Study design/conduct elements include:

(b) (4)

(b) (4)

PMR Schedule Milestones

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

The milestones for the PMR, including an interim analyses were agreed to by email on February 6, 2020.

CDTL comments:
BMI and smoking status are important variables to assess in this study. Although one would not anticipate any obese patients registering for this trial due to the labeling contraindication it will be important to assess normal versus overweight BMI patients. Many claims-based epidemiologic

studies of hormonal contraception in the past have been deficient in not being able to obtain smoking and BMI information.

PMC – Residual Drug Content & Strength of Twirla

Given the outstanding question as to whether there is a clinically significant amount of residual drug in Twirla, the following PMC was recommended.

Title: 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 prescribed wear and patch adhesion over the entire wear period.

Study Design/Conduct: (b) (4)

(b) (4)

PMC Schedule Milestones

Draft Protocol Submission,:	06/2020
Final Protocol Submission:	09/2020
Study Completion:	06/2021
Final Report Submission:	09/2021

The PMC and milestones were agreed to by the Applicant on February 6, 2020.

CDTL Comment:
I concur that the residual drug study is necessary. If there are significant amounts of residual drug in the TDS after wear, it could indicate not only a manufacturing issue, but a clinically-related safety issue and could potentially indicate one reason for the VTE occurrences.

Reporting Requirements

The Applicant was informed that they would have additional reporting requirements in the postmarketing period. In Study 23, between 10-20% of women required 4 or more TDS. It is important to understand whether women in the postmarketing period will have significant need of replacement TDS and why. The information from these reporting requirements will be used to determine if future assessments of the TDS are needed.

The reporting requirements were agreed to by the Applicant on February 11, 2020.

14. Recommended Comments to the Applicant

Not applicable

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/

GERALD D WILLETT
02/14/2020 01:54:57 PM

AUDREY L GASSMAN
02/14/2020 01:57:09 PM
I concur with the CDTL's conclusions and recommendations