

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204017Orig1s000

OTHER REVIEW(S)



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology
(OSE)
Epidemiology: ARIA Sufficiency
Version: 2018-01-24

Date: 1/13/2020

Reviewer(s): Adebola Ajao, PhD, Epidemiology Reviewer
Division of Epidemiology II

Team Leader: Jie (Jenni) Li, PhD, Epidemiology Team Leader
Division of Epidemiology II

Division Director: CAPT David Moeny, MPH, RPh, USPHS
Division of Epidemiology II

Subject: ARIA Insufficiency Memo

Drug Name(s): Levonorgestrel and Ethinyl Estradiol Transdermal System

Application Type/Number: NDA 204017

Applicant/sponsor: Agile Therapeutics

OSE RCM #: 2017-1315; 2019-1099



EXECUTIVE SUMMARY (place "X" in appropriate boxes)

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	
-Outcome(s) of Interest	
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	X

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Agile Therapeutics (the sponsor) is seeking FDA approval of a new transdermal system (TDS), Twirla, containing levonorgestrel (LNG) and ethinyl estradiol (EE) for the prevention of pregnancy in women of reproductive age. The product is a 28 cm² matrix TDS designed to deliver approximately 120 mcg of LNG and 30 mcg EE per day. The proposed dosing regimen is one TDS to be applied to either the abdomen, buttock, or upper torso every 7 days for three consecutive weeks followed by one TDS-free week. The primary efficacy evaluation was a pivotal single-arm, open-label, one-year, multi-center US phase 3 study with no restriction on BMI. The study included 1,736 women aged 18 – 35 years with 15,165 evaluable cycles and identified 68 on-treatment pregnancies. This resulted in a high pearl index (PI) (pregnancy rate per 100 women-years of drug exposure) of 5.8 (95% confidence interval (CI): 4.5, 7.2) when FDA generally accepts 5 or less for the upper bound CI of the PI. Twirla's pearl index was higher in women with BMI \geq 30 at 8.6 (95% CI: 5.8, 11.5). In this pivotal study, five venous thromboembolisms (VTEs) occurred; all five cases had BMI \geq 30. Four of the five VTEs were considered drug-related, resulting in a VTE incidence rate of 28/10,000 women-years.

Ortho Evra (now discontinued from marketing) and its generic, Xulane, are the only transdermal Combined Hormonal Contraceptives (CHCs) that have been approved in the US for prevention of pregnancy in women of reproductive age. VTE is a known dose dependent adverse effect of combined hormonal contraceptives, primarily due to the estrogen component of the products.¹ The dosage form and strength section of Xulane label describes the EE dose as 35 mcg/day, but the pharmacokinetic profile states that the average concentration of EE at steady state is approximately 60% higher in women using the TDS compared to women using oral contraceptives of 35 mcg of EE.^a The most recent approved labeling for Xulane also states that there may be an increased risk of VTE among women who use Xulane compared to women who use certain oral contraceptives.^b However, it is unclear how the pharmacokinetic profile of Twirla compares to that of Xulane or other CHCs and how this may translate to VTE risk. To this end, the sponsor will also be issued a PMR for a dose delivery study for Twirla, to better characterize the delivery of EE.

FDA previously conducted a study in Sentinel Distributed Database comparing VTE risk in users of continuous and extended COCs to users of traditional cyclic COCs. This

^a ORTHO EVRA Label Assessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021180s048lbl.pdf

^b XULANE Label Assessed at [file:///C:/Users/Adebola.Ajao/Downloads/20181205_f7848550-086a-43d8-8ae5-047f4b9e4382%20\(1\).pdf](file:///C:/Users/Adebola.Ajao/Downloads/20181205_f7848550-086a-43d8-8ae5-047f4b9e4382%20(1).pdf)



study was initiated when the sponsor of Lybrel, a non-cyclic/continuous COC approved in 2007 withdrew their NDA due to marketing concerns. The sponsor also terminated their ongoing post-marketing study issued due to the concerns that VTE risk for non-cyclic/continuous COCs may be elevated compared to cyclic COCs. After the NDA withdrawal, although FDA had concerns about residual confounding from using administrative claims data, DEPI undertook a sentinel analysis to evaluate if a grossly elevated VTE risk exist that would outweigh any residual confounding concerns. The study used propensity score matching to balance covariates across study groups and reported a slight elevated VTE risk associated with continuous COCs compared to cyclic COCs.² The study found a statistically significant increased VTE risk for continuous COCs vs cyclic COCs (HR 1.32 (1.07, 1.64)). However, this study used obesity/overweight ICD9 codes rather than BMI to adjust for obesity in the propensity score model. The agency concluded that the observed increase in risk was likely due to residual confounding. This conclusion was supported by an unexpected inverse association with EE dose (VTE incidence rate per 1000 person-years was 1.70 for 20mcg and 1.51 for 30mcg continuous COCs). Furthermore, the finding that women on continuous COCs were more likely to be older, have more cardiovascular and metabolic conditions, more pre-existing gynecological conditions, greater number of medical service utilization, and higher utilization of drug products at study baseline further substantiated FDA conclusion. The agency also concluded that incomplete information on smoking, obesity, lifestyle factors, and inability to reliably capture comorbidities and indication(s) for use were limitations of this analysis.

FDA is currently performing active surveillance using Sentinel's sequential monitoring tool to assess VTE risk for [REDACTED] (b) (4). This tool is useful for assessing risk of signals that arise from pre-licensure trials and obtaining safety data early, but the tool is unable to evaluate important risk factors for VTE such as BMI and smoking. For the [REDACTED] (b) (4), FDA issued a PMR in addition to active surveillance to evaluate VTE risk following [REDACTED] (b) (4).

Furthermore, in Twirla's pivotal phase 3 trial, there was suggested reduced efficacy in the overweight and obese populations and a high VTE incidence rate in the obese population. The question of risk/benefit was posed to the Bone, Reproductive, and Urologic Drug Advisory Committee (BRUDAC) on October 30, 2019. Fourteen of 15 BRUDAC members recommended that FDA approve Twirla despite the reduced efficacy to increase contraceptive choices available to women but were concerned about Twirla's VTE risk in obese women. Thus, the committee recommended a post-marketing safety study to compare VTE risk in new users of Twirla to new users of other prescribed CHCs.

Based on BRUDAC's approval vote, the division of bone, reproductive and urologic products (DBRUP) held a post-AC debrief. At this meeting, the division undertook discussion of the recommendations from BRUDAC, including the need for a post marketing study. This discussion pre-empted the typical SAM process for discussion of a potential PMR and suitability of Sentinel. The Division discussed that for transdermal



CHCs, there is some evidence of potentially 2-fold increased risk of VTE compared to oral CHCs with similar EE content. Given the relatively small anticipated effect estimate, the review team was concerned that residual confounding would be an issue, and this would necessitate the need for a confirmatory study with adequate measure and control for important covariates such as age, BMI, and smoking status.

DBRUP sought further advice from the medical policy and program review council (MPPRC) on January 15, 2020. The MPPRC supported DBRUP’s decision to contraindicate in obese women (BMI>30 kg/m²) due to reduced efficacy and high VTE incidence rate. Thus, BMI is an important covariate to both define the indicated population and conduct a well-adjusted study. Since BMI and other important covariates are not adequately captured in administrative claims data, there is need for primary data collection using a prospective cohort design.

Finally, on February 10, 2020, DBRUP held a meeting with the sponsor to discuss the contraindication of use for women > 30 BMI. DBRUP indicated that upon submission of the sponsor’s interim safety analysis, they would consider whether the contraindication was still warranted, considering all safety data available at that time. DBRUP therefore is relying on obtaining high quality BMI data in post-marketing analysis.

1.2. Describe the Safety Concern

Although COC use is associated with a 3 - 4 fold increased risk of VTE compared to non-use,^{3,4,5} there is concern that transdermal CHCs may be associated with slightly higher VTE risk compared to COCs.⁶ The EE pharmacokinetic profile of transdermal CHCs differs from that of COCs containing the same amount of EE in that transdermal CHCs have higher systemic and steady state EE concentrations, but lower EE peak concentrations. Therefore, the overall higher exposure to estrogen with transdermal CHCs could potentially translate into a higher VTE risk compared to women using COCs.⁷ Five epidemiologic studies conducted in the US have examined VTE risk among users of a transdermal CHC compared to COC users and reported relative risk estimates ranging from 1.2 to 2.2^{6,8} although these studies did not adjust for BMI and used a potentially higher dose transdermal system than TWIRLA.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an “X” in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	



1.4. Statement of Purpose

The purpose of the post marketing study is to conduct a prospective cohort study to quantify fatal and nonfatal VTE/ATE risk in women of reproductive age who use the new LNG/EE transdermal system for contraceptive purpose compared to women who use other commonly prescribed COCs or the currently marketed transdermal CHC, Xulane.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The purpose of the study is to quantitatively assess fatal and nonfatal VTE/ATE risk in women using the new LNG/EE transdermal system compared to all prescribed COCs. FDA requires that the post-marketing study be designed to detect a 1.5 – 2-fold increased risk for VTE in new users of the new transdermal system with adequate control for possible confounders especially age, BMI, and smoking status among other covariates. (b) (4)

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population should include the indicated population of women of reproductive age who newly initiate the LNG/EE transdermal system or a control CHC. The study population should be incident CHC users with no previous exposure to hormonal contraception in a defined baseline period.

(b) (6)

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is the new LNG/EE transdermal system. Exposure should be incident, i.e. no previous exposure to hormonal contraception of any form.



3.2 Comparator Exposure(s)

Both fatal and nonfatal VTE and ATE events are established serious adverse effects of CHC use.¹ The question of interest is whether the new LNG/EE transdermal system confers a higher fatal and nonfatal VTE/ATE risk than all prescribed COCs or the currently marketed transdermal system, Xulane in US women. Therefore, the primary control group are new users of all prescribed COCs, while the secondary control group are new users of Xulane.

(b) (6)

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest are fatal and nonfatal VTE (i.e. DVT and PE) and fatal and nonfatal ATE (i.e. AMI and stroke)

(b) (4)

(b) (6)



5 COVARIATES

5.1 Covariates of Interest

Confounders are covariates that are associated with the exposure of interest (i.e. factors that influence physician treatment decision and patient medication use) and are also associated with the health outcome of interest. Covariates of interest typically include demographic variables, comorbidities, concomitant medications, and indicators of healthcare utilization. Specific covariates of interest for the proposed study are noted below.¹⁴

1. Demographic variables: age, calendar year
2. Typical cardiovascular risk factors: hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, chronic kidney disease, obesity or overweight, smoking.



(b) (6)





(b) (6)

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

We request that the sponsor conduct a prospective cohort safety study with sufficient confounding control for known confounders such as age, BMI, smoking, (b) (4) among other covariates.

(b) (6)





The current proposed PMR language is as follows:

A controlled, prospective, observational cohort study comparing the risks for fatal and non-fatal venous thromboembolism (VTE) and arterial thromboembolism (ATE) in new users of Twirla compared to new users of oral combined hormonal contraceptives (CHC) (primary comparator) and new users of Xulane (secondary comparator) in US 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, among others.

8 REFERENCES

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 7, 2020

To: Jeannie Roule
Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Elvy Varghese
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (established name): TWIRLA (levonorgestrel and ethinyl estradiol)

Dosage Form and Route: transdermal system

Application Type/Number: NDA 204017

Applicant: Agile Therapeutics Inc.

1 INTRODUCTION

On May 14, 2019, Agile Therapeutics Inc. submitted for the Agency's review a Class 2 Resubmission regarding the Complete Response Letter (CRL) issued by the agency on December 21, 2017. This resubmission of the NDA provides Agile's complete response to all deficiencies identified in the CRL and initiates a new review cycle for the NDA.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on May 20, 2019 and February 3, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TWIRLA (levonorgestrel and ethinyl estradiol) transdermal system.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft TWIRLA (levonorgestrel and ethinyl estradiol) PPI and IFU received on May 14, 2019 and received by DMPP and OPDP on February 3, 2020.
- Draft TWIRLA (levonorgestrel and ethinyl estradiol) Prescribing Information (PI) received on May 14, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 6, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 10, 2020

Requesting Office or Division: Division of Bone, Reproductive and Urologic Products (DBRUP)

Application Type and Number: NDA 204017

Product Name and Strength: Twirla^a (levonorgestrel and ethinyl estradiol) transdermal system,
120 mcg/30 mcg/day

Applicant/Sponsor Name: AGILE THERAPEUTICS

OSE RCM #: 2019-1101-2

DMEPA Safety Evaluator: Ebony Whaley, PharmD, BCPPS

DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

On January 8, 2020, the Applicant submitted a response to our carton labeling recommendation for Twirla that we made during a previous label and labeling review.^b The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the response to determine if it is acceptable from a medication error perspective.

In our previous review, we recommended that the Applicant revise the NDC numbers for the carton labeling and overpack carton labeling such that they use different NDC package codes (last 2 digits of the NDC) in alignment with 21 CFR 207.33. In their response to our recommendation, the Applicant indicates that they no longer intend to market overpack cartons for Twirla. As such, the Applicant states that there is no longer a concern regarding the NDC codes.

^a The proposed proprietary name Twirla was found conditionally acceptable on July 25, 2019.

^b Whaley E. Label and Labeling Memo for Twirla (NDA 204017). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 29. RCM No.: 2019-1101-1.

2 CONCLUSION

The Applicant's response to our labeling recommendation is acceptable. We have no further recommendations for the container label and carton labeling at this time.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 29, 2019

Requesting Office or Division: Division of Bone, Reproductive and Urologic Products (DBRUP)

Application Type and Number: NDA 204017

Product Name and Strength: Twirla^a (levonorgestrel and ethinyl estradiol) transdermal system,
120 mcg/30 mcg/day

Applicant/Sponsor Name: AGILE THERAPEUTICS

OSE RCM #: 2019-1101-1

DMEPA Safety Evaluator: Ebony Whaley, PharmD, BCPPS

DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 15, 2019 for Twirla. The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised container labels and carton labeling for Twirla (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b We note the Applicant proposes to provide the change recommended to the patch application instructions in the Guide for Using Twirla (package insert) in conjunction with other changes anticipated during labeling negotiations with the Agency. In addition, the Applicant ^{(b) (4)}  ^{(b) (4)}  use the trade pouch for both trade (3-pack) and replacement (1-pack) products. These products will be packaged in distinct cartons.

^a The proposed proprietary name Twirla was found conditionally acceptable on July 25, 2019.

^b Whaley E. Label and Labeling Review for Twirla (NDA 204017). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 27. RCM No.: 2019-1101 and 2019-1752.

2 CONCLUSION

The revised container labels are acceptable from a medication error perspective. However, the revised carton labeling is unacceptable from a medication error perspective. We note the Applicant did not implement our recommendation to use a different package code for the NDC numbers for the carton labeling, replacement carton labeling, overpack carton labeling, and replacement carton labeling.

3 RECOMMENDATIONS FOR AGILE THERAPEUTICS

We recommend the following be implemented prior to the approval of this NDA 204017:

A. Carton labeling

- i. We note the NDC package codes on the trade and replacement carton labeling and the trade and replacement overpack carton labeling are not in alignment with 21 CFR 207.33. Specifically, the carton (trade) contains 3 transdermal systems and overpack carton (trade) contains 18 transdermal systems; however, they share the same NDC number (i.e. NDC 71671-100-03). In addition, the replacement carton contains 1 transdermal system and the replacement overpack carton contains 6 transdermal systems; however, they share the same NDC number (i.e. NDC 71671-100-01). Revise the NDC numbers so that the trade and replacement carton labeling and the trade and replacement overpack carton labeling use a different NDC package code (last 2 digits of the NDC) in alignment with 21 CFR 207.33.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Memo: Division of Epidemiology's Responses in Preparation for Advisory Committee (AC)
Meeting and Action for AG200-15

Date: October 9, 2019

Reviewers: Adebola Ajao, PhD, Epidemiologist
Division of Epidemiology II

Jie Li, PhD, Lead Epidemiologist
Division of Epidemiology II

Team Leader: Jie Li, PhD, Lead Epidemiologist
Division of Epidemiology II

Division Associate Director: Rita Ouellet-Hellstrom PhD, MPH
Division of Epidemiology II

Subject: VTE risk by progestin type in hormonal contraceptive use
AC Backgrounder for AG200-15

Application Number: NDA 204017

Applicant/Sponsor: Agile Therapeutics

OSE RCM #: 2019-1371

The Division of Bone Reproductive and Urology Products (DBRUP) consulted the Division of Epidemiology (DEPI) to assist with preparing for an Advisory Committee (AC) Meeting and Action for AG200-15 (NDA 204017) scheduled for October 2019. This memo is to provide responses to the four questions provided by DBRUP and listed below in preparation for the AC.

- Question 1: Do Combined oral contraceptives containing levonorgestrel show a lower risk for venous thromboembolism than combined oral contraceptives containing other progestin types?
- Question 2: Is there a distinct cut-off in body mass index associated with a consistent increased risk in venous thromboembolism with combined hormonal contraceptive use?
- Question 3: Describe the limitations of comparing venous thromboembolism risks based on population-based data to venous thromboembolism risks identified in controlled clinical trial(s) with AG200-15.
- Question 4: Describe the types of studies and study elements, including study design and ascertainment methods, that would best inform venous thromboembolism risks in a post marketing setting with a contraceptive product.

Background

AG200-15 is a weekly transdermal system designed to theoretically deliver 120 mcg of levonorgestrel and 30 mcg of ethinyl estradiol (EE) daily developed by Agile Therapeutics. The Division of Bone, Reproductive and Urology product (DBRUP) have concerns about the potential risk for venous thromboembolism (VTE) [includes pulmonary embolism (PE) and deep vein thrombosis (DVT)] with use of this transdermal system. In the combined phase 3 development program, five subjects developed VTE four of which were observed in obese women with a body mass index (BMI) of >30 kg/m². BMI is calculated using a person's weight in kilograms divided by the square of their height in meters. In adults 20 years and older, underweight is defined as having a BMI <18.5 kg/m², normal weight is BMI 18.5 – 24.9 kg/m², overweight is BMI 25 – 29.9 kg/m², and obese is BMI >30 kg/m².^a The sponsor claimed that AG200-15 was safe because it contains levonorgestrel (LNG), a progestin that has been reported to have a lower VTE risk when compared to specific other progestin types in combined hormonal contraceptives (CHCs) especially in combined oral contraceptives (COCs). Furthermore, the sponsor believed that the higher-than-expected VTE cases observed in their development program were due to the inclusion of overweight and obese women in their clinical trial. They proposed to limit the indication of use to women with BMI ≤ 29 kg/m².

DEPI's Response to Q1: Do COCs containing levonorgestrel show a lower risk for VTE than COCs containing other progestin types?

Combined hormonal contraceptive (CHC) use is associated with a higher risk of VTE compared to non-use.¹ The incidence rate of VTE in non-users of COC/CHCs is estimated to be between 1

^ahttps://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

and 5 events per 10,000 woman-years, and 3 to 9 events per 10,000 woman-years among COC/CHC users.^b Although, most of these studies were conducted using COCs, transdermal combined hormonal patches may be associated with a slightly higher risk for VTE, compared to oral tablets.²

VTE risk may vary by dose of estrogen and potentially by type of progestin in COC/CHCs.³ There are a large number of epidemiology studies examining the risk of VTE associated with use of COC/CHCs containing newer generations (third or fourth) progestins, compared to levonorgestrel-containing products (second generation). (Appendix Table 1) The research hypothesis in these studies was that the newer progestins, such as drospirenone (DRSP)-containing products might be associated with a higher VTE risk than levonorgestrel-containing products. The observational study results are inconsistent, with some studies reporting up to a three-fold increase in VTE risk while other studies reported no difference in VTE risk between products. The crude incident VTE rate for levonorgestrel-containing COC/CHCs with 30 – 40 ug EE reported by these studies ranged from 0.9 to 7.2 per 10,000 women years for idiopathic VTEs^c and 1.6 to 10.9 per 10,000 women years for fatal and non-fatal VTEs. (Appendix Table 1) We noted significant heterogeneity in these published studies and concluded that the slight increased risk in VTE observed by progestin types could be explained in part by study design issues and uncontrolled biases (detailed discussion below).

We conclude that there is some evidence supporting a slightly lower VTE risk with use of levonorgestrel-containing COC/CHCs compared to products containing newer generation progestins. Results from observational studies that support the safety of levonorgestrel-containing products are not entirely consistent and are subjected to various limitations in study design, data sources, and the number and type of other progestin-containing comparators used. Furthermore, the absolute risk difference between progestin types in COCs/CHCs appears to be small. Therefore, we call for caution in drawing conclusion that levonorgestrel-containing products are safer than COC/CHCs containing newer generation progestins. There is also potential for channeling bias if levonorgestrel-containing products are deemed safer. Other risk factors (such as BMI, family history, smoking, and genetic factors), rather than progestin type alone, should be considered in advising women to choose a certain type of CHC for use.

Limitations of observational studies that may contribute to the conflicting results on COC/CHC use and VTE risk by progestin type

- a. New users vs. Prior user designs:** Current evidence suggests that women with prior history of COC/CHC use may be at a lower baseline risk for VTE than new or first time naïve users as these women are deemed to be survivors.⁴ Furthermore, prior users could be switchers (users who switched from one COC/CHC to another without a break or with a break of less than 4 week) or restarters (users who restarted COC/CHC use after a break of more than 4 weeks). There is also evidence that switchers and restarters may have different VTE risk profiles.⁵ Recent studies show that VTE risk is highest in the first

^b https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021676s019lbl.pdf

^c Idiopathic VTE are unprovoked venous thromboembolism occurring in the absence of any apparent provoking or triggering personal or environmental risk factors, such as cancer, pregnancy, surgery, trauma, and immobilization.

three months of COC/CHC use, with the risk decreasing after the first three months.^{4,6,7} Many studies compared current users of COC/CHCs containing third generation progestins to levonorgestrel-containing products without considering their prior COC/CHC use.^{8,9} These studies appear to compare experienced current users of COC/CHCs containing older progestins to new current users of COC/CHCs containing newer progestins which could over-estimate the true relative risk for VTE.

- b. Residual confounding:** Measurement of and control for potential confounders varied across studies and may result in different risk estimates across VTE studies. Although most studies, many conducted outside the U.S. adjusted for age, other established risk factors for VTE, such as BMI, personal or family history of VTE, and smoking, are frequently missing from U.S. claims database studies^{6,10,11} or noted only if clinicians believe them to be a concern. These variables are mostly collected through patient interview and lack of adjustment for these variables would likely bias the observed estimate in either direction.
- c. Selective prescribing or channeling bias:** There is evidence that physicians prescribed third-generation COC/CHCs as their first-choice formulation to higher risk women with obesity, family history of VTE, and pre-existing arrhythmia⁵ as these progestins were considered safer when they were first approved for use. This practice of selective prescribing may result in channeling higher risk women to COC/CHCs containing newer generation progestins and over-estimate the true relative risk for VTE associated with these products. Furthermore, publication of various observational study results may change the way that susceptible patients are channeled, from newer products (initially believed to be safer) to older products (later reported to be safer). Drug utilization prescription data showed that in 2009, COC/CHCs containing drospirenone were the second most commonly dispensed COC/CHCs from U.S. retail pharmacies but their prescription has since decreased. By 2018, most prescriptions were dispensed for COC/CHCs containing the progestins norethindrone, norgestimate, levonorgestrel, followed by drospirenone.^d Therefore, timing of channeling bias may also vary by the publications of different study results. There may also be differences in VTE relative risks when comparing COC/CHCs containing newer-generation progestins to those containing levonorgestrel alone or to all products containing other progestins.¹²
- d. Misclassification of exposure:** Method of ascertaining COC/CHC exposure also varied across studies. In studies where patients were asked to recall contraceptive use history, exposure data such as type, dose, and duration of contraceptive products used may be self-reported but possibly reported inaccurately. In studies where prescription data were used to capture contraceptive exposure, prior contraceptive use may not be captured in the databases due to left truncation of prescription data. In addition, these databases only provide information on prescriptions filled and not necessarily medication taken. Furthermore, many studies did not differentiate type of COC/CHC exposure (new users versus prior users) as previously discussed. Possible misclassification of COC/CHC exposure could bias the observed risk estimate in either direction.

^d Reference ID 4501827: 2019-1371 Contraceptive Drug Utilization Review OCT 19

- e. **Misclassification of outcome:** Type of VTE captured and definition of VTE used varied across studies. Many studies limited evaluation to idiopathic VTE^{13,14} or non-fatal VTE.^{10,11,15} Fatal VTE cases are not always captured leading to underestimation of VTE cases. Although hospitalized VTE has been validated with hospital medical records when identified in U.S. claims data,¹⁶ some women diagnosed with only DVT are treated as outpatients in the U.S. and algorithms in the outpatient setting are not easily validated.¹⁷ VTE cases that are not captured will likely be misclassified as non-cases, while non-VTE cases documented as VTE in claims data may be misclassified as cases. Both types of outcome misclassification could bias the observed estimate in either direction.

DEPI's Response to Q2: Is there a distinct cut-off in BMI associated with a consistent increased risk in VTE with COC/CHC use?

We are unaware of any distinct cut-off value in BMI below which there is no increased risk for VTE with COC/CHC use. Even among normal-weight women (BMI < 25 kg/m²), COC/CHC use appears to be associated with 3 - 4 fold increased risk of VTE compared to non-use.^{18,19,20}

Overweight (BMI between 25 and 29 kg/m²) and obesity (BMI of 30 kg/m² or higher) are known risk factors for cardiovascular events including VTE. Many studies reported that the VTE risk with COC/CHC use was substantially higher among overweight and obese women than among women with normal BMI.²¹ For example, a case control study reported that, among women with BMI < 30 kg/m², the VTE risk tripled for current COC (only oral products) use compared to non-use, while the risk was six-fold higher among women with BMI > 30 kg/m².²⁰ Current COC use showed a statistically significant interaction with BMI as a continuous variable (p=0.01); however, the regression coefficient for BMI was not reported in the publication. Another case control study¹⁹ reported that among women with normal BMI, COC use was associated with a 4.6-fold increase in DVT risk than non-use. While among overweight and obese women, the risk was 10-fold higher for COC use vs. non-use. A third case-control study¹⁸ reported that, using a common reference group of normal weight women without COC use, COC use was associated with an odds ratio (OR) of 4.15, 11.63, and 23.78 for VTE among normal BMI, overweight, and obese women, respectively.

In conclusion, the current literature shows that COC/CHC use is a known risk factor for VTE in women with normal weight and the risk is substantially higher among overweight and obese women. We are unaware of any BMI cut off value below which there is no VTE risk with COC/CHC use.

DEPI's Response to Q3: Describe the limitations of comparing VTE risks based on population-based data with risks identified in controlled clinical trial (s) with AG200-15.

Differences in incidence rate and relative risk estimates are expected between open label clinical trials and population-based observational studies owing to the following reasons.

- Clinical trials generally employ strict inclusion criteria and are more likely to exclude women with known risk factors for VTE such as older age, obesity, family history of VTE, smoking, and immobility, limiting the generalizability of their study results. While, observational studies generally employ less strict inclusion criteria, and more likely to include women with multiple risk factors for VTE especially since not all risk factors may be recorded in the data sources utilized.²² Therefore, observational studies more likely reflect real-world use and safety profile of COC/CHCs and produce more generalizable study results.
- Women enrolled in clinical trials are more likely to be new users of the hormonal contraceptive being studied, although enrolled women may have previously used other CHCs, while many population-based observational studies enroll both new and experienced users of the hormonal contraceptive being studied. Since naïve and experienced COC/CHC users have different baseline risks for VTE,⁴ observational studies that include more experienced COC/CHC users will likely report a lower VTE incidence rate as these women are considered VTE survivors.
- Clinical trials (even non-randomized) are often specifically designed to examine efficacy, rather than safety of hormonal contraceptives; therefore, the collection of safety data is secondary to the study objectives. In contrast, observational studies could be safety specific, but data availability may be limited by missing key baseline risk factors, such as BMI, smoking, and family history of VTE, that are not always available in retrospective data sources such as claims unless personal interviews are completed but then the participants may be highly selected.
- Monitoring of baseline data and adverse events during non-randomized clinical trials tend to be more systematic and comprehensive than in population-based retrospective studies. This may lead to more complete capture of VTE cases in open labeled clinical trials than in population-based retrospective studies.

While it is difficult to determine which of these reasons could explain observed differences in VTE risk in open label clinical trials and population-based observational studies, differences in patient characteristics and the quality of data collected in clinical trials compared to observational studies make it inappropriate to compare VTE risks from these two different types of study.

DEPI’s Response to Q4: Describe the types of studies and study elements, including study design and ascertainment methods, that would best inform VTE risks in a post marketing setting with a contraceptive product.

A desired study that would best inform VTE risks in a post marketing setting with a hormonal contraceptive product would adopt a study design such as prospective cohort design or case control study nested in an exposed population of new COC/CHC users that excludes prior COC/CHC users. These study designs may allow for better capture of baseline risk factors and risk factors that vary over time. Risk factors such as BMI, personal and family history of VTE, and smoking status are not usually captured in U.S. claims databases typically used for retrospective cohort designs but can be obtained by supplementing exposure cohort analyses with personal interviews of consenting women.

Important Study Elements

Selection of comparison group: Observed risk estimates may vary by type of comparison group selected. A study that will best inform VTE risks for AG200-15 in a post-market setting will likely include multiple comparators. An oral hormonal contraceptive containing levonorgestrel with similar EE dose as AG200-15 may provide the advantage of a comparator with the same progestin and estrogen exposures as AG200-15. The currently marketed contraceptive patch (Xulane, delivers a daily dose of 150 mcg of norelgestromin and 35 mcg EE) would provide the advantage of a comparator with similar (continuous) hormone delivery system. Since none of these two comparators are ideal, AG200-15 could also be compared to all other COC/CHCs as a group with new users of AG200-15 propensity-score matched to new users of any other CHCs.

COC/CHC Exposure Capture

Adequate measure of COC/CHC exposure: Data on COC/CHC exposure are usually obtained from prescription data or self-reported through patient interviews. Self-reported COC/CHC exposure maybe prone to recall bias and dispensed prescriptions do not always reflect actual exposure. Furthermore, history of COC/CHC use are not adequately captured in database studies. Supplementing self-reported COC/CHC exposure with prescription data may better capture COC/CHC exposure when assessing VTE risk but these studies may be prone to selection bias.

Adequate classification of COC/CHC exposure: Studies that stratify by type of current COC/CHC exposure (i.e. new use versus prior use) reported different adjusted relative risk for VTE. It is important to differentiate COC/CHC exposure type, define the criteria for establishing new use, and account for COC/CHC exposure history in studies of COC/CHC and VTE risk to reduce bias due to exposure misclassification. Studies that ignore previous COC/CHC experience may underestimate the person time at risk and over-estimate the VTE incidence rate in women with prior history of COC/CHC since women especially older women were pre-screened. Larivee et al. conducted a retrospective cohort study in CPRD and reported a higher adjusted hazard ratio (aHR) for VTE in current COC users who were also first time users (HR:3.2, 95% CI: 1.1, 9.1) compared to current COC users with prior history of COC/CHC use (HR: 2.0, 95% CI: 1.1, 3.4), when comparing COC-containing drospirenone to COC-containing levonorgestrel.⁴ Dinger et al. also reported that in the first three months of COC use, restarters and switchers with a break of greater than 4 weeks had higher VTE incidence rate than starters (first-time users) or switchers with no break.⁵ Although, the overlapping confidence intervals indicate that the reported adjusted hazard ratios (HR) or incidence rates may not be statistically significantly different.

VTE Outcome Capture

Type of study outcome: Studies of COC/CHC and VTE risk capture different types of VTE. Some studies limited to idiopathic (with known risk factors excluded) VTE,¹³ and non-fatal VTE (the more common DVT, PE or both),^{10,15} while other studies included both fatal and non-fatal VTEs.^{6,7} To reduce both outcome misclassification and competing outcome bias, a comprehensive cardiovascular study would capture VTE including both fatal and non-fatal VTEs

(DVT and PE), and arterial thrombotic events (ATE) including fatal and non-fatal stroke and acute myocardial infarction, although ATEs are rarer.

Definition of study outcome: Definition of VTE also vary across COC/CHC and VTE studies and these definitions vary by country. Studies that limited to confirmed VTE cases based on hospitalization or ER visit, objective diagnostic and imaging test results, and anticoagulation treatment are more likely to include true VTE cases and reduce outcome misclassification.^{15,23} Blinded adjudication and validation of cases also increase case validity and reduce outcome misclassification.⁶ Validating DVT cases treated in the outpatient setting in the U.S. however is very challenging because of poor medical record retrieval rates from private providers but this may not a problem in other countries like Denmark.²⁴

Risk factors for VTE: Established risk factors for VTE such as age, personal history of VTE, pregnancy and postpartum, BMI, family history of VTE, long term immobility, and smoking must be adequately captured and appropriately controlled. Other risk factors for VTE such as surgery (major, orthopedic), hospital immobilization based on length of stay, trauma, chronic diseases (cerebrovascular disease, cardiovascular disease, hypertension, hyperlipidemia, diabetes, coagulation disorder, cancer, asthma), gynecologic disorders (polycystic ovary syndrome, fibroids, endometriosis, oophorectomy, hysterectomy, sterilization), concurrent medication (statin, angiotensin converting enzyme inhibitors, diabetes medication, antidepressant), history of other COC/CHC use, and length of COC/CHC use should also be measured and adjusted for in a multivariable analysis or summarized into a propensity score (frequently used for confounding control if the number of risk factors exceed the number of cases). Adequate capture of risk factors depends on the data source used. Risk factors may also be highly correlated as believed by some investigators²² and aggregated in few women at higher VTE risk. The correlation of risk factors should also be assessed in future studies

Statistical methods for confounding control: Risk factors for VTE can be controlled in multiple ways including restriction, matching, stratification, weighting, and modeling. Risk factor information collected at study baseline could be adjusted for directly in a multivariable analysis or used to develop a propensity score, a technique commonly used to adjust for a large number of measured covariates without loss of statistical precision. Since age is such an important risk factor for VTE,^{13,22} many studies matched on age/year of birth^{10,25,26} or controlled for age in a multivariable model,^{5,27,28} or in a propensity score adjustment.^{4,11,29} Even when matching on age if a data source has a large number of older women, the risk estimates may be higher than studies of younger women. So, despite matching on or adjusting for age, studies should also assess adjusted relative risk, odds ratio, or hazard ratio by stratifying on smaller age categories to ensure that all age categories are well represented and to check if the adjusted risk estimates differ by age groups.

Sensitivity and subgroup analyses: Sensitivity analyses are conducted to understand the impact of various study elements including data source on the observed study results. Studies conduct sensitivity analyses to assess impact of data source and study design elements such as exposure definition, exposure period, exposure dose, outcome definition, covariate selection, and choice of comparator on the robustness of their study results.^{4,5}

In summary, an observational study that would best inform VTE risk in post-marketing setting with a contraceptive product would encompass the identified study elements such as appropriate choice of comparators, adequate definition and classification of exposure, adequate definition and validation of study outcome, adequate capture of relevant risk factors, appropriate statistical adjustment of relevant risk factors, and age stratification to increase the likelihood of obtaining an unbiased risk estimate for VTE.

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Appendix

Table 1: Table of Studies Assessing VTE Risk for Different Progestins and Levonorgestrel											
Study	Database, Country	Design	Study Period	Age range	Exclusion	Exposure	Outcome	Adjustment/ Matching	Incidence rate/10,000 Women-years	3 rd or 4 th gen vs. Levonorgestrel OR/RR/HR	95% CI
Farley et al. WHO. Lancet. 1995 ⁸	10 countries (Brazil, Chile, Colombia, Germany, Hong Kong, Hungary, Jamaica, Thailand, UK), 9 centers	Case Control	1989, 1993	15 - 49	Death within 24 hours of admission, history of stroke, DVT, PE, acute MI, natural or surgical menopause, recent history of pregnancy, Prolonged bed-rest, and surgery.	Current use of COC containing desogestrel (20/30 ug EE), gestodene, norgestimate, levonorgestrel (EE < 35 ug)	Definite, probable, and possible Idiopathic VTE based on signs, symptoms, investigations (venography, duplex scanning, radioisotope studies)	BMI, live births, alcohol consumption, smoking, history of hypertension, hypertension in pregnancy, diabetes, varicose veins.	NR	Desogestrel 2.4	1.3, 4.6
									NR	Gestodene 3.1	1.6, 5.9
									NR	Levonorgestrel 1	
Jick H. 1995 ²³	GPRD U.K.	Nested Case Control	1991 - 1994	<40	History of VTE, stroke, acute MI, cancer, epilepsy, diabetes, treated hypertension, hyperlipidemia and cystic fibrosis. Potential cases with no hospitalization no anticoagulation, negative VTE test, pregnant or 3-months postpartum, recent trauma or surgery.	Current COCs containing levonorgestrel desogestrel, or gestodene with <35 ug EE	Nonfatal VTE (DVT/PE) Include confirmed VTE (Signs/symptoms, clinical diagnosis, hospitalized and anticoagulated, objective diagnostic test) and Possible VTE	Matched by age, practice, and index date, Adjusted for Smoking and BMI	Desogestrel 2.9/10,000	Desogestrel 2.2	1.1, 4.4
									Gestodene 2.8/10,000	Gestodene 2.1	1.0, 4.7
									Levonorgestrel 1.6/10,000	1	
Bloemenkamp KW. 1995 ³⁰	Netherlands	Case Control	1988, 1992	15 - 49	Pregnancy, puerperium, recent miscarriage, previous	Current use of COC containing desogestrel, levonorgestrel (30 ug EE)	First episode of DVT	Age, factor V Leiden mutation, family history of VTE,	NR	Desogestrel 2.2	0.9, 5.4
									NR	Levonorgestrel 1	

					injectable progestogen	from interview and hospital discharge letter		pregnancy history			
Farmer R.1997 ³¹	MediPlus UK	Nested Case Control Study	1991, 1995	15 - 49	Personal history of VTE, recent trauma or surgery, pregnancy, postpartum, post abortion, use of EC (marker for prescription COC non-use)	Current use of desogestrel (30 ug EE), desogestrel (20 ug EE), gestoden, levonorgestrel	Fatal and non-Fatal VTE diagnoses (DVT/PE) treated with anticoagulation reviewed independently by two MD	Matched by year of birth, practice site current use of COC (Matching) BMI change in type of COC prescribed within 3 months if event, number of prescribed cycles previous pregnancy, concurrent disease, previous use of morning after pill	Desogestrel (30 ug EE)	Desogestrel (30 ug EE)	Desogestrel (30 ug EE)
									3.99/10,000	0.64	0.29, 1.45
									Desogestrel (20 ug EE)	Desogestrel (20 ug EE)	Desogestrel (20 ug EE)
									11.53/10,000	2.93	0.86, 10
Gestodene 4.41/10,000	Gestodene 0.95	Gestodene 0.43, 2.11									
Levonorgestrel 3.62/10,000	1										
Bloemenkamp 1999 ⁹	Amsterdam	Case Control	Sept 1982, Oct 1995	15 - 49	VTE at other sites than leg, personal/family history of VTE, cancer, pregnancy, pos-partum, known inherited clotting defects, incomplete OC information, no objective diagnosis, real time B mode ultrasound, or miscellaneous reasons	Current use of levonorgestrel (30 ug, 30 - 40 ug EE) desogestrel (20 ug, 30 ug EE), gestodene (30 ug EE)	Confirmed DVT	Age, family history of VTE, calendar time, center, surgery, trauma, immobilization	NR	Desogestrel /Gestodene 1.9	Desogestrel /Gestodene 0.8, 4.5
									NR	Levonorgestrel 1	
Herings 1999 ³²	PHARMO Netherlands	Retrospective Cohort	1986, 1995	15 - 49	History of VTE, anticoagulation use, depot hormone	First use of COC with desogestrel	VTE (identified by diagnostic codes from	Adjusted for year and age	Desogestrel 30 ug EE 3.5/10,000	Desogestrel 4.2	Desogestrel 1.7, 10.6
									Desogestrel 20 ug EE	Desogestrel 4.5	Desogestrel 1.1, 18.2

					drugs, cardiovascular medication morning after pill' recent hospitalization within 2 months prior to COC	(20ug EE, 30 ug EE), gestodene (30ug EE), levonorgestrel (30 ug EE) from drug dispensing data	hospital discharge)		4.7/10,000		
									Gestodene (30 ug EE) 4.2/10,000	Gestodene 3.9	Gestodene 1.2, 12.9
									Levonorgestrel (30 ug EE)	1	
Todd JC. 1999 ¹³	MediPlus UK	Case Control	1992, 1997	15 – 49	Prior VTE event, pregnancy or post-partum, abortion, surgery requiring general anesthetic, major trauma to the lower limb, concurrent use of other sex hormones, malignant disease within 6 weeks of VTE.	Current users of COCs with Levonorgestrel, Desogestrel, Gestodene	Fatal and non-fatal Idiopathic VTE (DVT, PE) with anticoagulation verified by medical record	Year of birth, practice (matching) BMI, smoking, diastolic blood pressure, non-oral contraceptive preparation	Desogestrel (30 ug EE) 5.8/10,000	1.5	0.7, 2.6
									Gestodene (30ug EE) 5.0/10,000	1.1	0.5, 2.3
									Desogestrel (20 ug EE) 8.6/10,000	1.3	0.4, 3.4
									Levonorgestrel (30 ug EE) 4.4/10,000	1	
Farmer 2000 ³³	GPRD UK	Nested case control	1992, 1997	15 – 49	< 6-month data, pregnancy, surgery, trauma, cancer, other sex hormones, congenital heart disease, drug overdose	Current users of COCs with Levonorgestrel (30 ug EE) Desogestrel (30 ug EE, 20 ug EE) Gestodene (30 ug EE)	Fata and non-fatal idiopathic VTE and anticoagulation	Year of birth, practice, (matching), BMI, DBP, asthma, smoking, duration of use of any OC, chronic disease, non-asthma prescription	Desogestrel 30 ug EE 4.3/10,000	Desogestrel 30 ug EE 1.0	Desogestrel 30 ug EE 0.7, 1.7
									Gestodene 4.4/10,000	Gestodene 1.3	Gestodene 0.8, 2.1
									Desogestrel 20 ug EE 4.8/10,000	Desogestrel 20 ug EE 0.8	Desogestrel 20 ug EE 0.4, 1.6
									Levonorgestrel 3.4/10,000	Levonorgestrel 1	
Jick H. 2000 ³⁴	GPRD UK	Cohort	1993, 1999	15 - 39	<1 year of information, injury, pregnancy, surgery, trauma, arthroscopic procedure,	Current users of COCs with Levonorgestrel, Desogestrel, Gestodene	Idiopathic VTE (DVT/PE)	Year of birth, practice, diagnoses date (matching), BMI, Smoking, duration of use of any OC, switch for CC	Desogestrel /Gestodene 3.7 – 4.1/10,000	Desogestrel /Gestodene 1.9	Desogestrel /Gestodene 1.3, 3.9
		Case Control							Desogestrel /Gestodene NR	Desogestrel /Gestodene 2.3	Desogestrel /Gestodene 1.3, 3.9

					cancer & benign tumor						
Jick SS. 2006 ²⁵	Pharmetrics USA	Nested Case Control	Jan 2000, March 2005	15 - 39	Documented clinical risk factors for VTE (recent history of VTE, lower limb injury, invasive surgery, severe trauma, pregnancy), history of cancer, renal failure, inflammatory, auto-immune conditions, prescription of estrogen-containing COC after index date.	Current users of CHCs with norgestimate (35 ug EE), desogestrel (30 ug EE) levonorgestrel (30 ug EE)	Incident non-fatal idiopathic VTE followed by long term coagulation by blinded exposure assessment	Age, index date (matching) fibroids, endometriosis, menstrual disorders, hypertension, hyperlipidemia, CVD, diabetes, asthma, back pain, recent emergency room and physician visit	Desogestrel 5.34/10,000	Desogestrel: 1.7	1.2, 2.4
									Norgestimate 3.1/10,000	Norgestimate: 1.1	0.8, 1.5
									Levonorgestrel 2.7/10,000	Levonorgestrel: 1	
Dinger JC 2007 ¹²	Seven European countries Austria, Belgium Denmark, France Germany Netherlands U.K.	Cohort	2000, 2005	17 - 35	None	First time users or switchers of drospirenone, levonorgestrel (30 ug EE)	VTE, ATE, Sudden death	Age, BMI, history of VTE, duration of OC use	Drospirenone 9.1/10,000	0.8	0.5, 1.5
									Levonorgestrel 10.2/10,000	1	
Jick SS. 2010 ³⁵	Pharmetrics Database USA	Nested case control	2002, 2007	15 - 44	Recent (within 90 days) major surgery, trauma, epilepsy, pregnancy, previous anticoagulation Cancer coronary artery, ulcerative colitis	Current use of ORTHO EVRA Patch, or first use of levonorgestrel with 30 ug EE	Incident non-fatal Idiopathic VTE (DVT, PE) with hospitalization, ER visit, or diagnostic test results with subsequent anticoagulation therapy	Year of birth, index date (matching)	Patch: 5.6/10,000	Patch: 2.0	0.9, 4.1
	Market Scan, USA								Levonorgestrel: 3.8/10,000		
Dinger J. 2010 ¹⁵	Germany	Community Case	January 2002,	15 - 49	Women without		Non-Fatal VTE (DVT and PE)	Year of birth, Neighborhood	NR	Dienogestrel 1.0	0.6, 1.8

		Control	February 2008		informed consent or women who could not speak German	Current use of COCs containing dienogestrel, levonorgestrel, drospirenone (30 ug EE) by self-administered questionnaire	diagnosed clinically confirmed by imaging or anticoagulatory treatment	(matching), VTE history, BMI, duration of current CHC use, parity, chronic disease, concurrent medication use, smoking collected by questionnaire		Drospirenone 1.0 Levonorgestrel 1	0.5, 1.8
Parkin L. 2011 ¹⁴	GPRD UK	Nested Case Control	May 2000 Sept 2009	15 - 44	History of risk factors for VTE, such as pregnancy, surgery, major injury, prolonged immobilization, surgery, previous VTE, cancer, chronic renal disease, myocardial infarction, stroke, other cardiovascular disease	New and current episode of COC (new users and restarters, excluding continuous use) containing Drospirenone or levonorgestrel	Idiopathic VTE with evidence of anticoagulant treatment	BMI, smoking, varicose veins, use of antidepressant, duration of current use	Drospirenone: 2.3/10,000	Drospirenone: 3.2	1.3, 7.6
									Levonorgestrel 0.9/10,000	Levonorgestrel 1	
Jick S. 2011 ¹⁰	Pharmetrics Database USA	Nested Case Control	2002 - 2008	15 - 44	History of cancer, renal failure, chronic cardiovascular disease, inflammatory, auto-immune conditions, Severe lower limb injury, major surgery, severe trauma, pregnancy	Current or new use of COC containing drospirenone or levonorgestrel with 20 or 30 ug EE	Incident Non-Fatal VTE (DVT or PE) clinically diagnosed with a hospital admission, visit to ER, with subsequent prolonged anticoagulation	Age, index calendar year (matching) duration of OC use, OC switching, obesity (ICD 9 code), comorbidities, number of visits to a physician or ER in the 6-month baseline period.	Drospirenone 3.1/10,000	Drospirenone 2.8	1.5, 5.2
									Levonorgestrel 1.3/10,000	Levonorgestrel (20/30 ug EE) 1	
Lidegaard, O 2011 ⁷	National Registries Denmark	Retrospective cohort	2001, 2009	15 - 49	History of thrombotic events, cancer, coagulation disorder, oophorectomy	Current use of COCs containing norethisterone, levonorgestrel, norgestimate,	Incident Fatal and non-fatal VTE with at least 4 week of anticoagulation therapy	Age, calendar year, length of schooling and education, length of	Drospirenone (30 ug EE) 9.3/10,000	Drospirenone (30 ug EE) 2.09	1.55, 2.82
									Desogestrel (30 ug EE) 11.8/10,000	Desogestrel (30 ug EE) 2.24	1.65, 3.02

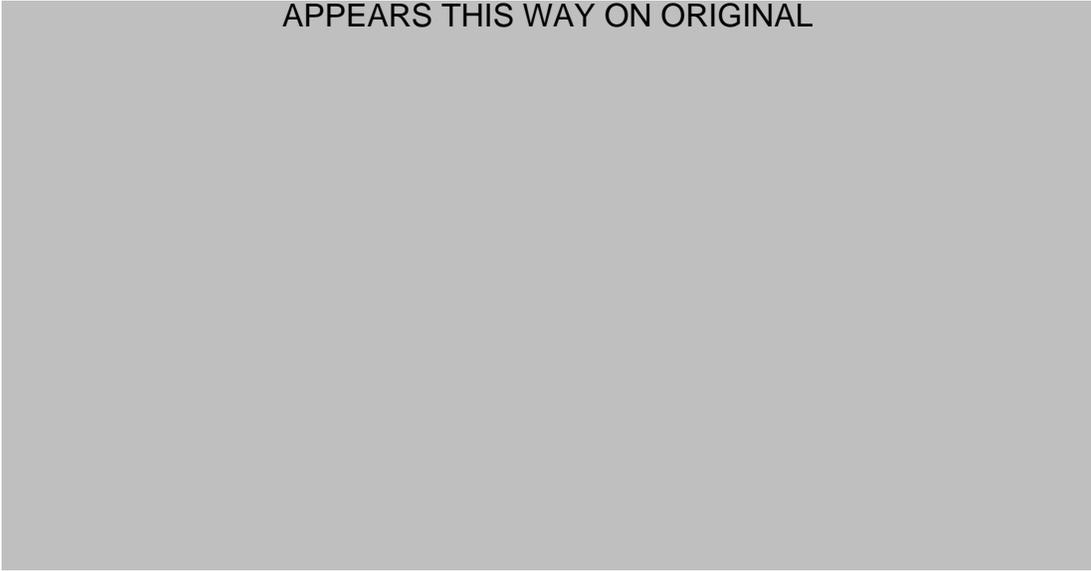
					, hysterectomy, sterilization, pregnancy	desogestrel, gestodene, drospirenone	Blinded validation of random sample of cases	contraceptive use	Norgestimate (30 ug EE) 6.2/10,000	Norgestimate (30 ug EE) 1.18	0.86, 1.62
									Levonorgestrel 30 – 40 ug EE 7.5/10,000	1	
Lidegaard, O. 2012 ¹	National Registries Denmark	Retrospective cohort	2001, 2010	15 - 49	History of thrombotic events, cancer, oophorectomy hysterectomy, sterilization, pregnancy, coagulation disorder	Current use of non-oral contraceptive: transdermal patch containing norelgestromin and EE, vaginal ring containing etonogestrel and EE, subcutaneous implant containing etonogestrel only	Incident Fatal and Non-Fatal VTE with anticoagulation therapy	Age, calendar year, length of schooling and education, length of contraceptive use	Norgestimate 4.54/10,000	Norgestimate 1.09	0.86, 1.38
									Patch norelgestromin 9.71/10,000	Patch 2.31	1.92, 5.23
									Vaginal Ring (etonogestrel) 7.75/10,000	Ring 1.90	1.33, 2.71
									Implant (etonogestrel) 1.7/10,000	Implant 0.43	0.18, 1.05
									Levonorgestrel (IUS) 1.38/10,000	0.18	0.12, 0.26
								Levonorgestrel OC (30 – 40 ug EE): 6.22/10,000	1		
Bird S. 2013 ¹¹	IMS Database USA	Retrospective cohort	2001, 2009	18 - 46	< 1 year of enrollment, History of cancer, cerebrovascular disease, cardiovascular disease, VTE, and prior anti-coagulation,	Current/New use of COC containing levonorgestrel, or drospirenone with 20 or 30ug EE	Non-Fatal VTE (PE or DVT) with anticoagulant treatment	Age, smoking, calendar year, cancer, asthma, COPD, hirsutism, acne, PCOS, hypertension, use of ACEI/ARE, statin, diabetes medication, prior time on OCs, prior number of OCs, obesity	Drospirenone (All EE doses) 18.0/10,000	Drospirenone (All EE doses) 1.90	1.51, 2.39
									Levonorgestrel (All EE doses) 8.9/10,000		
									Drospirenone (30 ug EE) 15.7/10,000	Drospirenone (30 ug EE) 1.82	1.34, 2.49
								Levonorgestrel (30ug EE) 9.6/10,000			
								Drospirenone (20 ug EE) 24.3/10,000	Drospirenone (20 ug EE) 2.38	1.55, 3.65	
								Levonorgestrel (20 ug EE) 10.4/10,000			
Sidney S. 2013 ⁶	Kaiser Integrated health plans data and State Medicaid programs	Retrospective cohort	2001, 2007	10 - 55	Severe life-threatening disease (sickle cell, cystic fibrosis, cerebral palsy, cancer, HIV, organ	New use of drospironone-containing pill (DRSP 30ug EE), norelgestromine containing patch (NGMN),	Fatal and Non-Fatal VTE (DVT and PE) with blinded assessment and adjudication	Age, site, calendar year of entry	Drospirenone 13.7 (10, 18.6)	Drospirenone 1.57	1.13, 2.18
									NR	Levonorgestrel (30 ug EE) 1	

					transplant, liver failure, severe congestive heart failure, renal failure, respiratory failure), pregnancy	etonogestrel vaginal ring					
Ziller M. 2014 ²⁸	IMS-Health Germany	Retrospective cohort	2005, 2010	16 - 45	History of thrombotic events, prior history of anticoagulation therapy, prior use of a study COC	Current use of COCs containing norgestimate, dienogest, chlormadinone desogestrel, drospironone and levonorgestrel)	Non-Fatal VTE identified by diagnostic code	Age, BMI, history of hormonal contraceptive use, cardiovascular disease, history of pregnancy, childbirth, or puerperium, pulmonary disease.	NR	Norgestimate 3.24	0.59, 17.75
									NR	Desogestrel: 1.95	0.52, 7.29
									NR	Drospironone 1.57	0.46, 5.38
									NR	Levonorgestrel 1	
Bergendal A. 2014 ³⁶	Sweden	Case Control	2003 - 2009	18 - 54	Previous VTE, Pregnancy, Malignancy	Contraceptive patch and vaginal ring use obtained from telephone interview	VTE confirmed by review of radiologic anticoagulant treatment	BMI, immobilization smoking	NR	Patch 1.0	0.1, 11.0
									NR	Ring 1.5	0.4, 5.9
Dinger J. 2014 ²⁷	INAS-OC Prospective cohort USA Europe (Austria, Croatia, Germany, Italy, Poland, Sweden)	Prospective cohort Active Surveillance	2005, 2012	11 - 65	No specific inclusion and exclusion criteria	Starters, Switchers, restarters of COCs containing levonorgestrel, drospironone With 20ug EE by questionnaire	Fatal and non-Fatal VTE assessed via questionnaire and validated via physician diagnostic and clinical record and blinded adjudication	Age, BMI, family history of VTE, duration of current COC use	Drospironone (All EE doses) 7.2/10,000	Drospironone (All EE doses) 0.8	0.4, 1.6
									Levonorgestrel (All EE doses) 9.8/10,000		
									NR	Drospironone (30 ug EE) 0.9	
							NR		Drospironone (20 ug EE) 0.7	0.3, 1.8	
							Idiopathic VTE	Drospironone (All EE doses) 4.9/10,000	Drospironone (All EE dose) 0.7	0.3, 1.6	
								Levonorgestrel (All EE doses) 7.2/10,000			

Vinogradov a Y. 2015 ²⁶	CPRD, Q Research UK	Nested Case Control	2001 - 2013	15 -49	History of VTE, oophorectomy, hysterectomy, sterilization, pregnancy, conflicting medication, prior anticoagulation therapy, absence of a matched case/control.	Current use of COCs containing norethisterone, levonorgestrel, norgestimate, desogestrel, drospirenone	Fatal and non-fatal incident VTE	Age practice (matching), BMI, smoking Alcohol consumption, ethnic group, chronic and acute conditions, trauma/event leading to immobilization, PCOS, use of other hormonal contraceptives	NR	Norethisterone 1.08	0.89, 1.3
									NR	Norgestimate 1.06	0.9, 1.26
									NR	Desogestrel 1.80	1.52, 2.13
									NR	Drospirenone 1.75	1.43, 2.12
Dinger J. 2016 ⁵	LASS-OC Austria Belgium Denmark France Germany Netherlands UK	Prospective Cohort	2000 - 2010	11 - 65	No specific inclusion and exclusion criteria	Starters, switchers, restarters of COC containing levonorgestrel, drospirenone with 30 ug EE	Confirmed Fatal and non-fatal VTE (primary)	Age, BMI, duration of OC use, family history of VTE, by self-report as time varying confounders.	Drospirenone: 10.7/10,000	Drospirenone 1.0	0.6, 1.5
					Pregnancy, delivery, trauma, immobilization, long travel, surgery, chemotherapy				Idiopathic VTE (secondary) Self-report validated by clinical diagnoses and diagnostic test	Levonorgestrel 10.9/10,000	
Weill A. 2016. ³⁷	SNIIRAM, PMSI France	Retrospective Cohort	July 2010, September 2012	15 - 49	History of PE, ischemic stroke, myocardial infarction, cancer, neoplastic disease	Current use of levonorgestrel, desogestrel, gestodene, norethisterone, norgestrel	1 st PE, stroke, or myocardial infarction	Age, complimentary universal health insurance, medical risk factors (hypertension, diabetes) gynecological visit during the previous year	Desogestrel 4.69/10,000	Desogestrel: 2.16	1.93, 2.41
									Desogestrel 3.95/10,000	Gestodene: 1.63	
Larivee N. 2017 ⁴	CPRD/HES England	Retrospective Cohort	May 2002, March 2015	16 - 45	<3 years of CPRD history, history of hormonal contraceptive, previous visit to family planning clinic, prescription for >= 2 OC at	Starters: 1 st prescription of drospirenone or levonorgestrel-containing COC Re-starters: New prescription of drospirenone or levonorgestrel-	Incident VTE (DVT/PE) with anticoagulation therapy or death within 90 days of VTE diagnosis	HDPS: age, family history of VTE, smoking, alcohol use, comorbidities hospital events and procedures, major general surgery, orthopedic surgery, parity,	Drospirenone 4.6/10,000	Drospirenone: 3.2	Drospirenone: 1.1, 9.1
									Drospirenone 5.2/10,000	Drospirenone: 2.0	Drospirenone 1.1, 3.4
									Levonorgestrel 3.7/10,000	1	
										Gestodene: 1.63	1.34, 1.97

					1 st OC prescription, history of thrombosis.	containing COC after at least 6 months of non-use.		spinal cord injury, trauma, and prescribed medications			
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Drug Utilization Review

Date: October 4, 2019

Reviewer: Patty Greene, Pharm.D.
Drug Utilization Data Analyst
Division of Epidemiology II

Team Leader: Corinne Woods, MPH, RPh
Division of Epidemiology II

Deputy Director
for Drug Utilization: LCDR Grace Chai, Pharm.D.
Division of Epidemiology II

Subject: Hormonal Contraceptive Utilization 2006-2018

Drug name: levonorgestrel and ethinyl estradiol transdermal delivery system

Application Type/Number: NDA 204017

Applicant/sponsor: Agile Therapeutics

OSE RCM #: 2019-1371 and 2019-1347

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EXECUTIVE SUMMARY

This review assessed drug utilization patterns of hormonal contraceptives in support of the Bone, Reproductive, and Urologic Drugs Advisory Committee meeting (BRUDAC) in October 2019. Advisory Committee members will discuss the safety and benefit/risk of a contraceptive transdermal system containing levonorgestrel and ethinyl estradiol. The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested the Division of Epidemiology II (DEPI II) to provide utilization data on hormonal contraceptives from 2006 through 2018. This information will be used to provide context and background for the Advisory Committee discussion.

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

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

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

In the U.S. retail pharmacy setting, use of combined oral contraceptives appears to remain the most common method of hormonal contraception in women of reproductive age. Current use of the transdermal system is low, with decreases in prescription estimates since 2006.

1 INTRODUCTION

On October 30, 2019, the Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) will meet to discuss a new drug application (NDA 204017) for the levonorgestrel and ethinyl estradiol transdermal delivery system. The safety and benefit/risk profile of the levonorgestrel/ethinyl estradiol transdermal delivery system for the prevention of pregnancy in women of reproductive potential is under review by the Agency. To provide context on the utilization of contraceptive products by progestin type and the frequency of product use containing the progestin levonorgestrel in the U.S. retail setting, the Division of Epidemiology II (DEPI II) examined utilization of hormonal contraceptives annually from 2006 through 2018 to assess change in use.

2 METHODS AND MATERIAL

2.1 DATA SOURCES USED

Proprietary drug utilization databases available to the Agency were used to conduct the analyses in this review (see Appendix B for full database descriptions).

The IQVIA National Sales Perspectives™ (NSP) database was used to determine the primary setting of care for the use of hormonal contraceptives and to provide the estimated number of packages (pill packs, vials/syringes, implants, or boxes) sold from manufacturers to all U.S. channels of distribution from 2006 through 2018, annually.

The IQVIA National Prescription Audit™ (NPA) database was used to provide the estimated number of prescriptions dispensed for hormonal contraceptives from U.S. retail pharmacies from 2006 through 2018, annually.

The IQVIA Total Patient Tracker™ (TPT) database was used to provide the estimated number of patients with a dispensed prescription for hormonal contraceptives stratified by patient age (<16, 17-24, 25-34, 35+ years) from U.S. retail pharmacies from 2006 through 2018, annually. For patient-level analysis (Section 3.4), proportions of use by progestin type were calculated based on the total number of CHC patients in each age group.

For each database, hormonal contraceptives were grouped into two categories: 1) CHCs which include both an estrogen component and a progestin component and 2) progestin only contraceptives (POCs). Data were further stratified by formulation (oral, transdermal, vaginal ring, injectable, and implants) within each respective group. For CHCs, oral contraceptives were grouped by progestin type into six categories:

- 1) norethindrone (NORE),
- 2) norgestimate (NGM),
- 3) levonorgestrel (LNG),
- 4) drospirenone (DRSP),
- 5) desogestrel (DESO), and
- 6) norgestrel, ethynodiol, and dienogest (other COCs).

Note: Due to low sales in the retail setting, national estimates of prescription or patient utilization of medroxyprogesterone injection and contraceptive implants were not included. Additionally, hormonal intrauterine devices for the prevention of pregnancy were not included in this review due to an incomplete capture of sales in the data sources.

2.2 PRODUCTS INCLUDED

Table 1 lists the hormonal contraceptives included in this review. Barrier contraceptive methods (i.e. diaphragm, cervical cap, condoms, vaginal foam/gel, and spermicides) were not included.

Table 1. Hormonal Contraceptives

Combined Hormonal Contraceptives (CHCs)	Progestin Only Contraceptives (POCs)
Norethindrone acetate/ethinyl estradiol	Norethindrone
Norethindrone/ethinyl estradiol/FE fumarate	Norgestrel

Norethindrone/ethinyl estradiol/iron	Levonorgestrel
Norethindrone/mestranol	Ulipristal acetate
Norgestimate/ethinyl estradiol	Medroxyprogesterone acetate (Injection)
Levonorgestrel/ethinyl estradiol	Etonogestrel (Implant)
Levonorgestrel/ethinyl estradiol/iron	
Drospirenone/ethinyl estradiol	
Drospirenone/ethinyl estradiol/levomefolate calcium	
Desogestrel/ethinyl estradiol	
Norelgestromin/ethinyl estradiol (Transdermal system)	
Etonogestrel/ethinyl estradiol (Ring)	
OTHERS COCs	
Dienogest/estradiol valerate	
Norgestrel/ethinyl estradiol	
Ethinodiol/ethinyl estradiol	

3 RESULTS

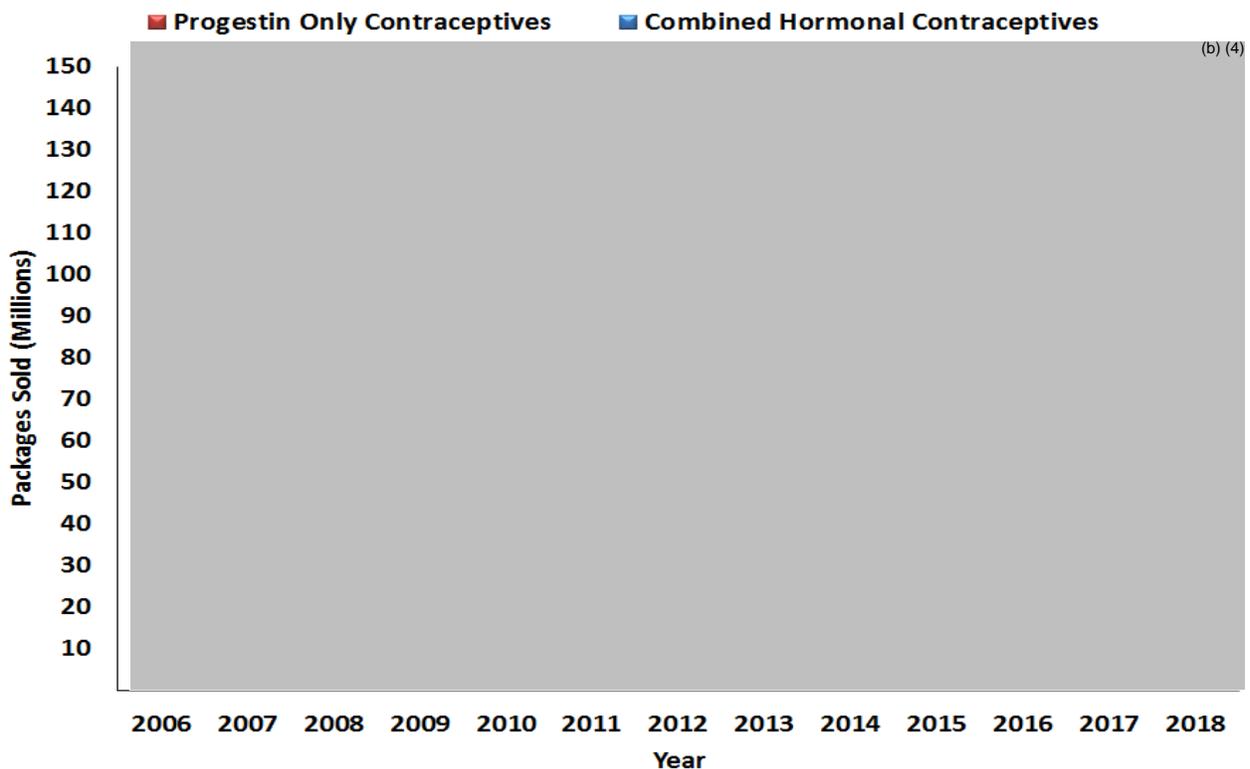
3.1 SETTINGS OF CARE

From 2014 through 2018, approximately 79%, 14%, and 7% of hormonal contraceptives were sold from U.S. manufacturers to retail, non-retail, and mail-order/specialty pharmacies, respectively.¹ Medroxyprogesterone injection and contraceptive implants were mainly sold to non-retail settings. Therefore, the estimated sales of hormonal contraceptives from manufacturers to all U.S. channels of distribution and utilization from retail pharmacies were examined in this review.

3.2 SALES DISTRIBUTION DATA

An estimated 150 million packages of hormonal contraceptives from U.S. manufacturers were sold in 2018, a net increase of (b)(4)% from 2015. CHCs accounted for (b)(4)% of sales ((b)(4) packages) and POCs accounted for (b)(4)% of sales ((b)(4) packages) in 2018. Approximately (b)(4)% of sales for CHCs were oral contraceptives, followed by the vaginal ring ((b)(4)%) and transdermal system ((b)(4)%). Approximately (b)(4)% of sales for POCs were oral contraceptives, followed by the medroxyprogesterone injection ((b)(4)%) and implants ((b)(4)%) (see Table 1 in Appendix A and Figure 1 below).

Figure 1. Estimated number of packages sold for hormonal contraceptives from U.S. manufacturers to all channels of distribution, 2006-2018



Source: IQVIA National Sales Perspectives™, 2006-2018. Data Extracted July 2019.

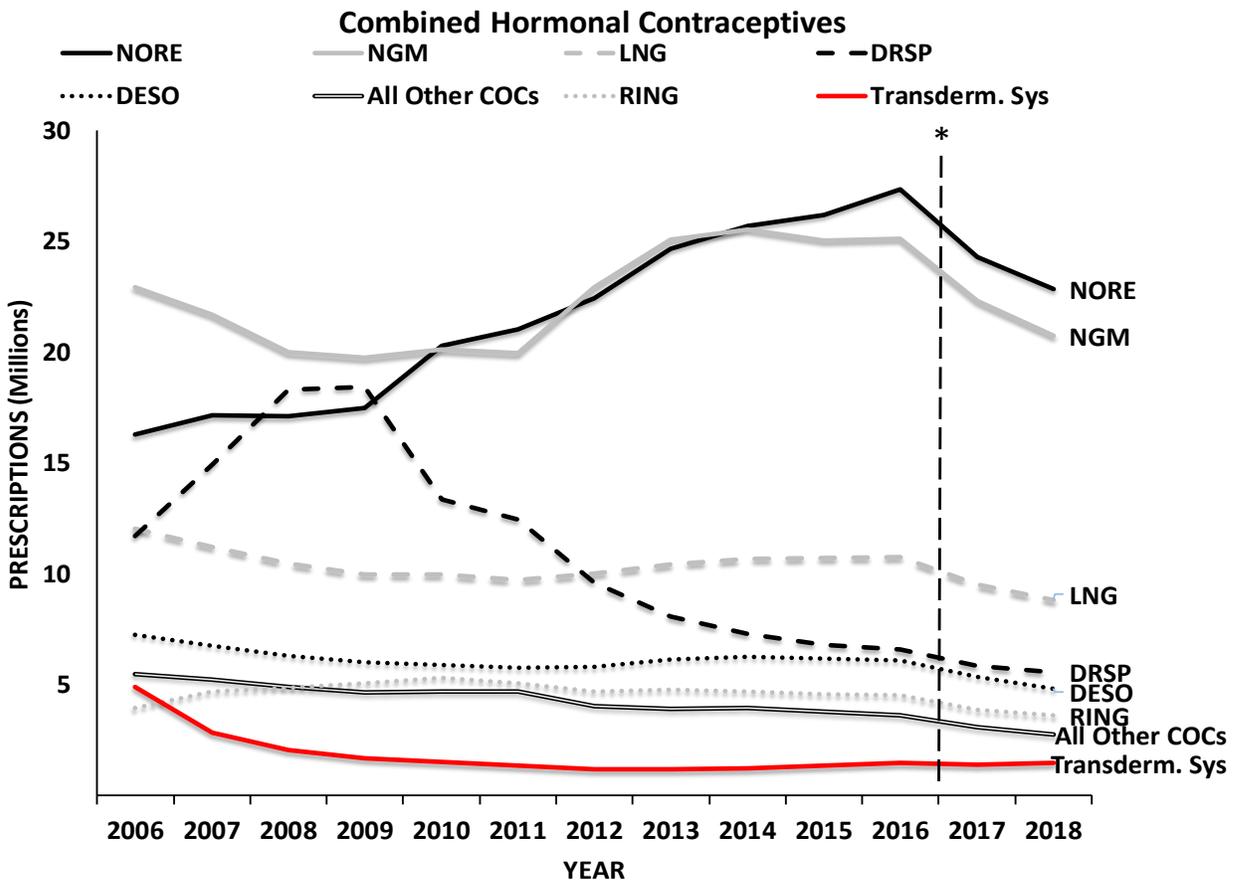
¹ Source: IQVIA National Sales Perspectives™, 2014-2018. Data extracted July 2019. File: NSP 2019-1371 Contraceptives by channel 7-25-19

3.3 DISPENSED PRESCRIPTION DATA

An estimated (b) (4) prescriptions were dispensed for CHCs from U.S. retail pharmacies in 2018. In 2009, most prescriptions were dispensed for COCs containing the progestins norgestimate and drospirenone, followed by norethindrone. Thereafter, prescriptions of COCs containing the progestins norgestimate and norethindrone increased while prescriptions of drospirenone-containing COCs declined. An estimated (b) (4) prescriptions were dispensed for drospirenone-containing COCs in 2018, a (b) (4)% decrease from 2009.

By 2018, most prescriptions were dispensed for COCs containing the progestins norethindrone and norgestimate, followed by levonorgestrel. An estimated (b) (4) prescriptions were dispensed for levonorgestrel from U.S. retail pharmacies in 2018. Transdermal system prescriptions decreased by approximately (b) (4)% from (b) (4) prescriptions in 2006 to approximately (b) (4) prescriptions in 2018 (see Figure 2 below and Table 2 in Appendix A).

Figure 2. Estimated number of prescriptions dispensed for combined hormonal contraceptives from U.S. retail pharmacies stratified by progestin type, 2006-2018



Source: IQVIA National Prescription Audit™, 2006-2018. Data extracted July 2019. COC=Combined Oral Contraceptive. EE=ethinyl estradiol. NORE=norethindrone/EE or mestranol. NGM=norgestimate/EE. LNG=levonorgestrel/EE. DRSP=drospirenone/EE. DESO=desogestrel/EE. Other COCs=norgestrel, ethynodiol, and dienogest/EE products. RING=etonogestrel/EE. TRANSDERM. SYS=transdermal system-norelgestromin/EE.

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

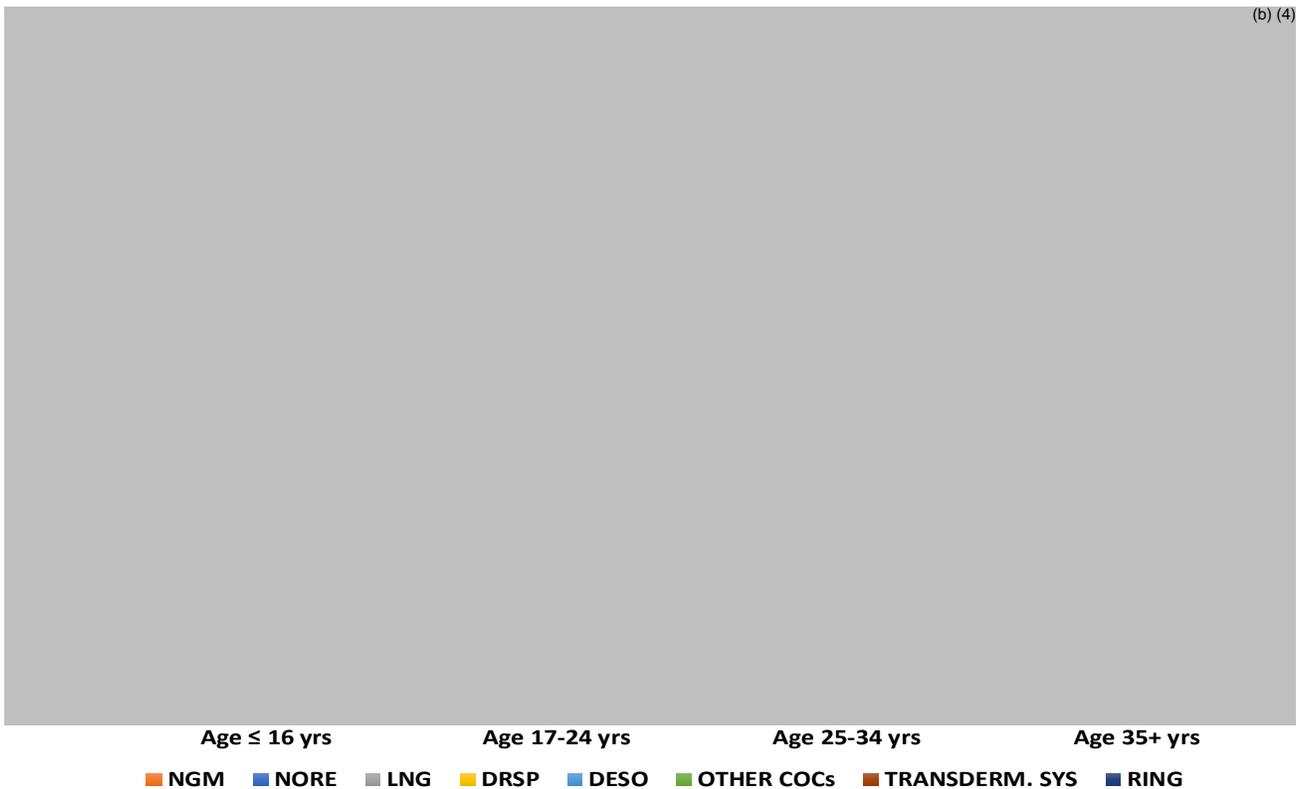
3.4 PATIENT-LEVEL DATA

An estimated (b) (4) patients filled a dispensed prescription for CHCs from U.S. retail pharmacies in 2018. Most patients were aged 25-34 years (36% of patients) or aged 17-24 years (35% of patients). Patients aged 35+ years and ≤16 years accounted for 25% and 5% of patients, respectively, in 2018. For all ages combined, an estimated (b) (4) patients filled a dispensed prescription for the transdermal system in 2018(see Table 3 in Appendix A).

The transdermal system accounted for 3.5% of use among patients aged 16 years or younger; 3% among patients 17-24 years; 2.6% among patients 25-34 years; and 1.6% of use among patients aged 35 years or older. COCs containing norgestimate or norethindrone accounted for the largest proportion of patients with a dispensed prescription for CHC products in 2018, regardless of age. Approximately 40% of patients aged 16 years or younger filled norgestimate-containing COCs, compared to 25% of patients aged 35+ years. Approximately 37% of patients aged 35 years or older filled norethindrone-containing COCs, higher than all other age groups.

The proportion of patients filling COCs containing levonorgestrel ((b) (4) %), drospirenone ((b) (4) %), desogestrel ((b) (4) %), and other COCs ((b) (4) %) were similar within each age group examined. Use of the vaginal ring ranged from ((b) (4) %) among patients aged 16 years or younger to ((b) (4) %) among patients aged 25-34 years.

Figure 3. Age distribution of combined hormonal contraceptives from U.S. retail pharmacies, stratified by progestin type in 2018



Source: IQVIA Total Patient Tracker™, 2018. Data extracted July 2019. COC=Combined Oral Contraceptive. EE=ethinyl estradiol. NORE=norethindrone/EE or mestranol NGM=norgestimate/EE LNG=levonorgestrel/EE DRSP=drospirenone/EE DESO=desogestrel/EE Other COCs= norgestrel ethynodiol, and dienogest/EE products RING=etonogestrel/EE TRANSDERM. SYS=transdermal system-norelgestromin/EE.

4 DISCUSSION

This review assessed drug utilization patterns of hormonal contraceptives in support of the BRUDAC meeting. Our findings show that sales of hormonal contraceptives remained relatively stable from 2006 through 2018. CHC products — including the vaginal ring, transdermal system, and oral formulations — comprised the largest proportion of sales or dispensed prescriptions while POC products comprised a smaller proportion of sales. Combined oral contraceptives comprised 90% or more of all CHC prescriptions, with norethindrone and norgestimate being the most commonly dispensed products from retail pharmacies nationwide since 2010, accounting for (b) (4) % and (b) (4) % of COC prescriptions dispensed in 2018, respectively. Levonorgestrel-containing COCs followed next and accounted for (b) (4) % of COC prescriptions in 2018. Of note, drospirenone and the transdermal system showed the largest decrease in utilization for the review period. The transdermal system accounted for approximately (b) (4) % of sales or dispensed prescriptions for CHC products in 2018, a decrease from approximately (b) (4) % of sales or dispensed prescriptions for CHC products in 2006.

We also examined the proportion of patients with a dispensed prescription for CHC products by age and progestin type from the retail setting in 2018. The transdermal system accounted for a very small proportion of use among patients across all ages in 2018. Norgestimate-containing COCs had the highest proportion of use among patients aged 16 years or younger, while norethindrone-containing COCs had the highest proportion of use among patients 35 years and older. The proportion of patients with a dispensed prescription of COC products containing levonorgestrel, drospirenone, desogestrel, and other COCs (norgestrel, ethynodiol, and dienogest) was comparable across age groups.

In December 2014, the Centers for Disease Control, National Center for Health Statistics published a report from the National Survey of Family Growth (NSFG) on contraceptive use among a sample of women aged 15-44 years in the United States from 2011-2013. The report showed approximately 62% or an estimated 37.6 million U.S. women of reproductive age were currently using some form of contraception.² Among contraceptive users, birth control pills represented the most common method (16%) reported by survey respondents, followed closely by female sterilization (15.5%). Only 4.4% of women reported use of the transdermal system, contraceptive ring, or medroxyprogesterone.

Another study examined the prevalence of COC utilization by progestin type among a sample of women in the United States from 2006-2010 using data from NSFG. In this study, contraceptives were stratified by generation (1st generation = norethindrone and ethynodiol; 2nd generation = levonorgestrel and norgestrel; 3rd generation = desogestrel, etonogestrel, and norgestimate; and 4th generation = drospirenone and dienogest). The survey found that approximately 17% or an estimated 10.6 million women aged 15-44 years were current COC users based on data from the 2010 U.S. Census Bureau estimates.³ Most women used third-generation products (41%), followed by first-generation (22%), second-generation (19%), and fourth-generation (17%) products. Norgestimate and norethindrone were the most common used progestins reported during the study

² Daniels, K., Daugherty, J., & Jones, J. (2014). *Current contraceptive status among women aged 15-44: United States, 2011-2013*. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.

³ Hall, K. S., & Trussell, J. (2012). Types of combined oral contraceptives used by US women. *Contraception*, 86(6), 659-665. doi:10.1016/j.contraception.2012.05.017

period. These results were consistent with our retail utilization findings in 2018, which suggest that the use of COCs remains the most common method of hormonal contraception in U.S. women of reproductive age.

Findings should be interpreted in the context of the known limitations of the databases used. Hormonal intrauterine systems for the prevention of pregnancy were not included in this review due to an incomplete capture of sales in the data sources. Therefore, this analysis can only be generalized to the retail pharmacy setting and may not apply to other settings of care such as physician offices or family planning clinics where contraceptives are administered or dispensed.

The IQVIA National Prescription Audit™ (NPA) database was used to provide estimates of the number of dispensed prescriptions for hormonal contraceptives from the U.S. retail setting. In January 2017, IQVIA implemented changes to its prescription database to manage prescription voids, reversals, and abandonments. Prescription estimates have been adjusted and restated in the database back to January 2017; data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 prescription volumes dispensed from the retail pharmacies. Statistical tests of trends over time or between products were not conducted for any of the data presented in this review; any changes over time must be interpreted in the context of the changes in the underlying data and methodology. Our analyses identified that an estimated 8% of total prescription claims for combined hormonal contraceptives dispensed from U.S. retail pharmacies were voided or reversed in 2018. Specifically, approximately 6% of prescription claims for the contraceptive system or the contraceptive ring appeared to have been voided or reversed in 2018.

Regarding the unique patient estimates, it is important to mention that patients may be counted more than once under certain conditions. A patient switching between products who was dispensed both a COC and the transdermal system in the same calendar year would be counted once under each product category. A patient may also age into a different age group in the same calendar year and be counted more than once in that year. The estimated patient counts provided are based on projections of sample data and therefore have some degree of inherent sampling error. Due to these limitations, these estimates are not intended to be representations of exact enumerations but provide general estimates of potential exposure.

Progestin only emergency contraceptive products that are available over-the-counter (OTC) were approved in 2009. Sales of these products were captured under levonorgestrel sales in this review. However, it should be noted that IQVIA estimates their projections of OTC products to be approximately 50% of the OTC market. Due to these missing data, manufacturer sales of OTC contraceptives may be underestimated in this review.

5 CONCLUSION

In the U.S. retail pharmacy setting, use of combined oral contraceptives appears to remain the most common method of hormonal contraception in women of reproductive age. The transdermal system accounted for approximately $\frac{(b)}{(4)}\%$ of the hormonal contraceptive market in 2018, a net decrease of $\frac{(b)}{(4)}\%$ since 2006. Of all combined oral contraceptives, norethindrone- and norgestimate-containing COCs were the most commonly dispensed products in 2018, followed by levonorgestrel-containing COCs.

APPENDIX A – TABLES

Table 1. Estimated number of packages sold for hormonal contraceptives from manufacturers to all U.S. channels of distribution, 2006-2018

	2006		2007		2008		2009		2010		2011		2012		2013		2014		2015		2016		2017		2018	
	Packages Sold	%																								
Grand Total	(b) (4)																									
combined hormonal contraceptives																										
Oral																										
norethindrone/EE and norethindrone/mestranol [NORE]																										
norgestimate/EE [NGM]																										
levonorgestrel/EE [LNG]																										
drospirenone/EE [DRSP]																										
desogestrel/EE [DESO]																										
All Others (norgestrel/EE; ethynodiol/EE; dienogest/estradiol)																										
Vaginal ring (etonogestrel/EE)																										
Transdermal patch (norelgestromin/EE)																										
progestin only contraceptives																										
Oral																										
norethindrone																										
levonorgestrel																										
ulipristal acetate																										
norgestrel																										
Injectable (medroxyprogesterone)																										
Implant (etonogestrel)																										

Source: IQVIA National Sales Perspectives™, 2006-2018. Data extracted July 2019. File: NSP 2019-1371 Contraceptives by year 7-18-19.xlsx
 Packages=pill packs, vial/syringes, implants, boxes, or devices. EE = ethinyl estradiol

Table 2. Estimated number of prescriptions for oral, transdermal, or vaginal ring hormonal contraceptives dispensed from U.S. retail pharmacies, stratified by molecule, 2006-2018

	2006		2007		2008		2009		2010		2011		2012		2013		2014		2015		2016		2017		2018	
	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%
Grand Total	(b) (4)																									
combined hormonal contraceptives																										
Oral																										
norethindrone/EE and norethindrone/mestranol [NORE]																										
norgestimate/EE [NGM]																										
levonorgestrel/EE [LNG]																										
drospirenone/EE [DRSP]																										
desogestrel/EE [DESO]																										
All Others (norgestrel/EE; ethynodiol/EE; dienogest/estradiol)																										
Vaginal ring (etonogestrel/EE)																										
Transdermal patch (norelgestromin/EE)																										
progestin only contraceptives (oral)																										
norethindrone																										
levonorgestrel																										
ulipristal acetate																										
norgestrel																										

Source: IQVIA National Prescription Audit™, 2006-2018. Data extracted July 2019. File: NPA 2019-1371 Contraceptives by year 7-18-19.xlsx

TRx = number of dispensed prescriptions, EE = ethinyl estradiol.

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

Table 3. Estimated number of patients with a dispensed prescription for oral, transdermal, or vaginal ring hormonal contraceptives dispensed from U.S. retail pharmacies, stratified by molecule and patient age, 2006-2018

	2006		2007		2008		2009		2010		2011		2012		2013		2014		2015		2016		2017		2018	
	Patients	%																								
Grand Total	(b) (4)																									
combined hormonal contraceptives																										
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										
norethindrone/EE and norethindrone/mestranol [NORE]																										
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										
norgestimate/EE [NGM]																										
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										
levonorgestrel/EE [LNG]																										
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										

Source: IQVIA Total Patient Tracker™, 2006-2018. Data extracted July 2019. File: TPT 2019-1371 Contraceptives by age 7-19-19.xlsx. EE = ethinyl estradiol.

Unique patient counts may not be added across time periods or drug categories due to the possibility of double counting those patients who received multiple treatments in a year or received treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories. For this reason, summing across drug categories, time periods, or patient age bands is not advisable and may result in overestimates of patient counts.

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

Table 3 (continued). Estimated number of patients with a dispensed prescription for oral, transdermal, or vaginal ring hormonal contraceptives dispensed from U.S. retail pharmacies, stratified by molecule and patient age, 2006-2018

	2006		2007		2008		2009		2010		2011		2012		2013		2014		2015		2016		2017		2018	
	Patients	%																								
drospirenone/EE [DRSP]	(b) (4)																									
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										
desogestrel/EE [DESO]																										
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										
All Others (norgestrel/EE; ethynodiol/EE; dienogest/estradiol)																										
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										
Vaginal ring (etonogestrel/EE)																										
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										
Transdermal patch (norelgestromin/EE)																										
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										
progestin only contraceptives (oral)																										
Age ≤ 16 years																										
Age 17-24																										
Age 25-34																										
Age 35+																										
Unknown Age																										

Source: IQVIA Total Patient Tracker™, 2006-2018. Data extracted July 2019. File: TPT 2019-1371 Contraceptives by age 7-19-19.xlsx. . EE = ethinyl estradiol.

Unique patient counts may not be added across time periods or drug categories due to the possibility of double counting those patients who received multiple treatments in a year or received treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories. For this reason, summing across drug categories, time periods, or patient age bands is not advisable and may result in overestimates of patient counts.

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

APPENDIX B – DATABASE DESCRIPTIONS AND LIMITATIONS

IQVIA National Sales Perspectives™

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

The manufacturer sales distribution data do not provide an estimate of direct patient use, rather, they provide a national estimate of units sold from the manufacturer to various retail and non-retail settings of care. The amount of product purchased by these settings of care may be a possible surrogate for use if we assume that facilities purchase drugs in quantities reflective of actual patient use.

IQVIA National Prescription Audit™

The IQVIA National Prescription Audit™ (NPA) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, and long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is sold to the patient. Data for the NPA audit is a national level-estimate of the drug activity from these three channels. NPA receives over (b) (4) retail prescription claims per year, captured from a sample of the universe of approximately 58,900 retail pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent ~92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part D prescriptions. Data are also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available in IQVIA’s business intelligence tool SMART for 72-rolling months. Each month, NPA is updated to include the most recent data and made available between 12-18 days after the end of the month.

IQVIA Total Patient Tracker™ (TPT)

IQVIA Total Patient Tracker™ (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick, reliable, and unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about (b) (4) transactions annually. TPT is projected to the known universe of retail pharmacies.

Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database to manage prescription voids, reversals, and abandonments that span multiple

weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Projected estimates have been adjusted and restated in the database back to January 2017; data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 prescription volumes dispensed from the retail pharmacies. Any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

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/

PATTY A GREENE
10/04/2019 04:33:08 PM
drug use data cleared by database vendor 10/4/19

CORINNE M WOODS
10/07/2019 09:48:08 AM

GRACE CHAI
10/07/2019 11:29:11 AM

Clinical Inspection Summary

Date	August 8, 2019
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Gerald Willett, M.D., Team Leader Nneka McNeal-Jackson, M.D., Medical Officer Jeannie Roule, Regulatory Project Manager Division of Bone, Reproductive, and Urologic Products (DBRUP)
NDA#	204017
Applicant	Agile Therapeutics
Drug	Levonorgestrel/ethinyl estradiol 120/30 mcg/day transdermal contraceptive delivery system
NME	No
Review Priority	Priority
Proposed Indication	Prevention of pregnancy
Consultation Request Date	June 24, 2019
Summary Goal Date	August 23, 2019
Action Goal Date	November 15, 2019
PDUFA Date	November 16, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical site of Dr. Dosik was inspected in support of this NDA. The primary efficacy endpoint for this application was wearability; i.e., patch adhesion, rather than contraceptive efficacy as would be typical for most contraceptive products. This contraceptive patch has been the subject of two prior review cycles, and, in the current cycle, the application is intended to demonstrate that the patch's adhesiveness is not inferior to Xulane, the only approved transdermal contraceptive delivery system (TCDS) which is itself a generic version of the Ortho-Evra TCDS. This issue is addressed in further detail in the "Rationale for Site Selection" section. Based on the results of this inspection which focused on the validation of the data regarding the adhesiveness of the test product, the studies (Protocols ATI-CL25 and ATI-CL26) appear to have been conducted adequately at Dr. Dosik's clinical site. The data generated at this site and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

The Applicant submitted these protocols to the NDA to evaluate the 7-day wear potential of AG200-15 in support of the drug's indication of use for the prevention of pregnancy.

Clinical inspections were requested for the following protocols in support of this application:

Protocol ATI-CL25

Title: A Randomized, Open-Label, Single-Dose, Two-Treatment Comparative Crossover Adhesion Study of AG200-15 and Xulane Transdermal Contraceptive Delivery Systems in Healthy Female Volunteers

This was a single center, randomized, open-label, single dose, two-treatment, two-period crossover adhesion study comparing the 7-day adhesion of the AG200-15 and Xulane contraceptive patches in healthy female volunteers.

The primary objective of this study was to evaluate the adhesion of AG200-15 patch via a head-to-head comparison with the Xulane (Norelgestromin/Ethinyl Estradiol) transdermal contraceptive delivery systems (TCDS), the generic version of the Ortho Evra patch.

The primary endpoint of the study was wearability assessment. The patches were applied to the lower part of the abdomen below the umbilicus. Patch adhesion was evaluated by trained study site personnel on a 5-point scale (below), and the estimated percentage of patch adherence determined:

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

Adhesion of the first patch was assessed daily at 0, 24, 48, 72, 96, 120, 144, and 168 hours (± 2 hrs.) by trained study site personnel. Similarly, the second patch was assessed at daily intervals during the second week. Subjects with self-reported prolonged water exposure greater than 10 consecutive minutes on any day were excluded from the per-protocol (PP) population. Adhesion measurements were made independently by a single assessor, with the assessor blinded to the patch adhesion score from the previous day.

The main inclusion criteria of the study included generally healthy females aged 18 to 35 years. Subjects must have been willing to sign the informed consent form and temporarily discontinue hormonal contraceptives, including oral contraceptives, patch or vaginal ring, if applicable. The main exclusion criteria included BMI ≥ 35 kg/m² or weight ≥ 90 kg (198 lbs); presence on either side of the lower abdomen of skin changes that, at the discretion of the Investigator, would potentially interfere with patch adhesion or patch application site assessment. This includes tattoos, scarring or other skin damage, diffuse skin disease (e.g., psoriasis, eczema, rash of any etiology), excessive stretch marks, or excess hair at the patch application site; and contraindication to combined estrogen-progestin contraceptive use (as defined by a category 3 or 4 CDC U.S. Medical Eligibility Criteria for Contraceptive Use).

Female subjects were screened for eligibility. Once determined by history, physical examination, and screening laboratories to be eligible for admission, subjects were randomized to one of two treatment arms (i.e., wearing the AG200-15 or Xulane patch for the first 7 days). Trained study site personnel applied a patch to the subject's abdomen. Patches were worn for one (1) week (7 days/168 hours). Following removal of the first patch and per the crossover design of the study, the second patch was placed as soon as possible on the contralateral side of the subject's lower abdomen. The second patch was worn for one (1) week (7 days/168 hours) and was removed by study site personnel at the end of the treatment period.

The study randomized 83 subjects in a single U.S. site. The first subject enrolled on January 4, 2019 and the last subjects completed the last visit in this study on February 7, 2019.

Protocol ATI-CL26

Title: A Single-Dose Adhesion Study of the AG200-15 Transdermal Contraceptive Delivery System in Healthy Female Volunteers

This was a single center, single-dose, open-label adhesion study of the AG200-15 transdermal contraceptive delivery system in healthy female volunteers. The primary objective of this study was to assess the 7-day *in vivo* adhesion performance of AG200-15.

The primary endpoint was the mean patch adhesion score in the Per Protocol population. The adhesion of the AG200-15 patch over seven days was compared with that of the Xulane TDS patch. The primary efficacy endpoint of adhesion was determined using a clear plastic overlay held above but not touching the patch, upon which areas of nonadherence were marked in red pen. An estimate was then made of the percentage of the patch's area that did not adhere; i.e., the area marked in red on the clear plastic overlay. The scores reported were an average of the seven days of assessments.

The primary endpoint of the study was wearability assessment. Patch adhesion was evaluated by trained study site personnel on a 5-point scale (below), and the estimated percentage of patch adherence determined:

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

Adhesion of each patch was assessed daily at 0, 24, 48, 72, 96, 120, 144, and 168 hours (\pm 2 hrs.) by trained study site personnel. Subjects with self-reported water exposure greater than 10 consecutive minutes on any day were not to be included in the PP population. Adhesion measurements were made independently by a single assessor, with the assessor blinded to the patch adhesion score from the previous day.

The main inclusion criteria of the study included generally healthy females aged 18 to 35 years. Subjects must have been willing to sign the informed consent form and temporarily discontinue hormonal contraceptives, including oral contraceptives, patch or vaginal ring, if applicable. The main exclusion criteria included BMI ≥ 35 kg/m² or weight ≥ 90 kg (198 lbs) and contraindication to combined estrogen-progestin contraceptive use (as defined by a category 3 or 4 CDC U.S. Medical Eligibility Criteria for Contraceptive Use).

Female subjects were screened for eligibility. Once determined by history, physical examination, and screening laboratories to be eligible for admission, subjects were treated with a single 7-day patch.

The study screened 54 subjects and randomized 30 subjects in a single U.S. site. The first subject enrolled on November 12, 2018 and the last subjects completed the last visit in this study on November 19, 2018.

Rationale for Site Selection

The applicant has undergone two review cycles of the new drug application for Twirla under NDA 204017 to which FDA has issued a complete response letter. For the second complete response, the FDA based its decision on the benefit/risk and *in vivo* adhesion of the product. The Applicant filed a formal dispute resolution against the Division to address the *in vivo* adhesion quality of the product which the Division denied. The decision was upheld by the Office of Drug Evaluation and the Office of New Drugs. As a path forward, the Applicant proposed to conduct a formal design wear study to demonstrate non-inferiority of adhesion quality only of Twirla to the only other approved transdermal contraceptive delivery system (TCDS), Xulane, a generic version of the Ortho-Evra transdermal contraceptive system (TCDS). The Applicant has submitted the new drug application for a third review cycle with the results of that adhesion trial for FDA review in support of its approvability. Given the Applicant has not changed the formulation of the TCDS since the NDA's first review cycle and the Applicant's heavy reliance on the results of their wear study, the Division has requested a clinical site inspection to ensure that the two adhesion studies (pilot study and comparative study) were performed appropriately.

III. RESULTS

Jonathan Dosik M.D.
TKL Research, Inc.
One Promenade Blvd
Suites 1101 & 1201
Fair Lawn, NJ 07410
Inspection dates: 7/15/2019-7/23/2019

Protocol ATI-CL25

At this study site, 135 subjects were screened, 83 subjects were enrolled, and 79 subjects completed the study. The records of 36 enrolled subjects and ten subjects who failed screening were reviewed.

There was a 30-day exclusion period for subjects entering this study from the endpoint of any other study. However, Study ATI-CL-25's exclusion criterion #25 allowed enrollment of subjects from Study ATI-CL-26, the pilot study, even if the period of time from the end of the first study to the date of randomization of the second study was less than 30 days. Of the 83 subjects in Study ATI-CL-25, 18 subjects were in both studies and all 18 subjects met the 30-day time restriction. The firm stated its belief that as an adhesion study, no bias was introduced by the inclusion of these 18 subjects.

The informed consent forms for 35 of the enrolled subjects and nine of the screen failure subjects were reviewed with consent being obtained appropriately prior to any study-related activities.

The training for assessment of patch adhesion was reviewed and appeared adequate. The primary efficacy endpoint; i.e., patch adherence, was reviewed by comparing the actual marked plastic overlays used with the adhesion scores reported in the Clinical Study Report.

Discontinuations/disqualifications were evaluated. Subjects (b) (6) in Protocol ATI-CL25 were disqualified from the per protocol population for showering more than ten minutes but were retained in the safety population.

Subjects were instructed not to re-adhere partially detached patches or sleep on their stomachs; however, as noted by the field investigator, since subjects were not prevented from sleeping on their stomachs, the patches could have been pressed back on to the skin. This may account for multiple subjects whose adhesion scores improved from one day to the next. There did not appear to be any instances where patches were deliberately re-applied.

The enrollment log identified which subjects were disqualified due to excessive stretch marks. The subjects' study charts were reviewed to confirm that these subjects were disqualified due to stretch marks.

The sponsor conducted on-site monitoring of Study ATI-CL-25. The field investigator stated that he did not have access to the monitoring plan to evaluate whether the sponsor's frequency of monitoring was in compliance with the monitoring plan.

The Director of Corporate Quality Assurance noted during the inspection that TKL employees, i.e., the study coordinators and the clinical investigators, received initial and ongoing training in Good Clinical Practices (GCP). One employee, specifically trained by TKL and Agile, was responsible for scoring adhesion patch contact. The training was monitored by the chief statistician who provided a statistical analysis of the scoring training. Copies of the Adhesion Evaluation Procedure and the training analysis results were obtained.

Additional information regarding the scoring of the patches was provided in a Note to File describing the division of the smaller (Round) Agile patch into 16 sections and 32 sections for the larger rectangular comparator patch. Two individuals were involved in the assessment of adherence of the patch: first, the "Tracer" who would generate a picture of the patch on the clear plastic overlay marking areas of adherence vs. non-adherence, and, second, the "Rater", another trained individual, who would estimate the percentage of non-adhesion from the overlay and enter

that value for each section into the Excel worksheet which calculated the overall percentage of adhesion for each patch for each day.

The calculations on each worksheet were developed by the Director of Corporate Quality Assurance and verified by the chief statistician. The worksheet calculation involved multiplying the percentage of non-adhesion (From 0 to 0.99) by the surface area of each section of each patch. The Agile Patch had 32 sections and the value for each section was 3.125. The Xulane Patch had 16 Sections and each section had a value of 6.25. Finally, the sum of the 16 or 32 sections was taken and used as the score. The rationale behind the numbers for each patch section (3.125 or 6.25) was explained in a Note to File.

The primary efficacy measures for Studies ATI-CL-26 (9 Subjects) and ATI-CL-25 (10 Subjects) were evaluated by reviewing the scores of the actual plastic overlays for each patch section for each day and for the entire two-week period; one-week for the use of the Agile patch and one week for the Xulane patch and comparing the scores to the adhesion scores reported in the Clinical Study Report (CSR). Adhesion scores for both arms were often between 90 and 100% and represented an average over the seven days of the study. No deficiencies were observed in the calculations of the primary efficacy endpoints.

As part of the inspection, all source data were reviewed and were accurately reflected in the data line listings. The primary efficacy endpoint was verifiable and there was no evidence of under-reporting of adverse events for the study.

Protocol ATI-CL26

At this study site, 54 subjects were screened, 30 subjects were enrolled, and all 30 subjects completed the study. The records of the 30 enrolled subjects and the 24 subjects who failed screening were reviewed.

Review of this study had similar findings to that of Protocol ATI-CL25. As part of the inspection, all source data were reviewed and were accurately reflected in the data line listings. The primary efficacy endpoint was verifiable and there was no evidence of under-reporting of adverse events.

The sponsor did not conduct on-site monitoring of this 7-day pilot study.

There were no water exposure evaluations in this pilot study.

In general, the clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Min Lu, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Susan D. Thompson, M.D., for
Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.\NDA 204017
DBRUP\Division Director\Hylton Joffe
DBRUP\Team Leader\Gerald Willett
DBRUP\Reviewer\Nneka McNeal-Jackson
DBRUP\Project Manager\Jeannie Roule
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Susan Thompson
OSI\DCCE\GCPAB\Team Leader\Min Lu
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analyst\Yolanda Patague

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/s/

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MIN LU
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SUSAN D THOMPSON
08/08/2019 06:54:12 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 6, 2017

To: Charlene Williamson, Regulatory Project Manager
Division of Bone, Reproductive, and Urology Products (DBRUP)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew J Falter, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for TWIRLA (levonorgestrel and ethynyl estradiol) transdermal contraceptive system

NDA: NDA 204017

This memo is in response to DBRUP's labeling consult requests dated July 31, 2017 and August 1, 2017. As indicated in DBRUP's November 27, 2017 letter to the applicant, deficiencies have been identified that preclude discussion of labeling at this time. Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DBRUP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
12/06/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: December 5, 2017

To: Hylton V. Joffe, MD
Director
Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): TWIRLA (levonorgestrel and ethynyl estradiol)

Dosage Form and Route: transdermal contraceptive delivery system

Application Type/Number: NDA 204017

Applicant: Agile Therapeutics

1 INTRODUCTION

On June 27, 2017, Agile Therapeutics resubmitted for the Agency's review a New Drug Application (NDA) for TWIRLA (levonorgestrel/ethinyl) transdermal contraceptive delivery system. TWIRLA (levonorgestrel/ethinyl) transdermal contraceptive delivery system was originally submitted on April 12, 2012. A Complete Response (CR) letter was issued for the NDA on February 13, 2013, by the Agency. TWIRLA (levonorgestrel/ethinyl) transdermal contraceptive delivery system is indicated for the prevention of pregnancy.

On July 31, 2017, the Division of Bone, Reproductive and Urologic Products (DBRUP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed PPI and IFU for TWIRLA (levonorgestrel/ethinyl) transdermal contraceptive delivery system.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for TWIRLA (levonorgestrel/ethinyl) transdermal contraceptive delivery system.

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHARON W WILLIAMS
12/05/2017

LASHAWN M GRIFFITHS
12/05/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: November 22, 2017

Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products (DBRUP)

Application Type and Number: NDA 204017

Product Name and Strength: Twirla^{***a} (levonorgestrel and ethinyl estradiol) transdermal system
120 mcg/30 mcg/day

Product Type: Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Agile Therapeutics

Submission Date: June 26, 2017

OSE RCM #: 2017-1316

DMEPA Safety Evaluator: Chad Morris, PharmD, MPH

DMEPA Team Leader: Lolita White, PharmD

^a *** Proposed proprietary name currently under review. Panorama # 2017-16401702

1 REASON FOR REVIEW

This review evaluates the proposed patch label, pouch labeling, carton labeling, prescribing information, and guide of use for Twirla*** (ethinyl estradiol and levonorgestrel) transdermal system NDA 204017 for areas of vulnerability which may increase the risk for medication errors. This review is written in response to a request from the Division of Bone, Reproductive, and Urologic Products (DBRUP).

2 REGULATORY HISTORY

Agile Therapeutics submitted a 505(b)(2) NDA 204017 on April 13, 2012; however, the Agency determined the application was not approvable and sent a Complete Response (CR) Letter^b on February 13, 2013 citing Clinical and Product Quality concerns and several non-CR issues relating to Clinical, Chemistry, Manufacturing, and Controls, and Clinical Pharmacology disciplines.

This review evaluated the labels and labeling Agile submitted within the Class 2 Resubmission package on June 26, 2017.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed 6-patch carton labeling, 3-pack carton labeling, pouch labeling, patch label, Prescribing Information (PI), and Guide for Use identified the following areas that can be improved to decrease risk of medication error:

^b Link to CR Letter: <http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af802b94a4>

1. (b) (4) 3-pack Carton labeling, Pouch label and Professional Sample Carton labeling
 - The storage statement for unused patches uses a negative statement, which may lead to confusion.
 - Disposal instructions for used patches are not present on the (b) (4) 3-pack carton labeling and can be improved on the foil pouch.
 - The format for the expiration date is not acceptable.
 - The labels and labeling uses a placeholder for the NDC number.
2. 3-pack Carton labeling, Professional Sample
 - The NDC placeholder is presented vertically while all other labeling information is presented horizontally.
3. Pouch Labeling
 - The net quantity statement is not in compliance with 21 CFR 201.51.
 - The front of the patch pouch label contains information (that is active and inactive ingredients) which decreases the readability of important product information (that is, Rx only, route of administration, storage and handling).
4. Guide for Use
 - How should I use Twirla***
 - The terminology “patch-free week” can be improved to decrease risk of confusion.
 - Detailed instructions
 - There are no instructions to prompt the user to make note of their patch-change day.
5. Section 16 How Supplied section of the Prescribing Information
 - The NDC number is denoted by a placeholder and should be updated to be in alignment with the carton labeling and pouch label.

We provide recommendations regarding these areas below in Section 4.1 to help minimize the potential for medication errors to occur with the use of the product.

5 CONCLUSION & RECOMMENDATIONS

We identified areas of the (b) (4) 3-pack carton labeling, pouch labeling, PI, and Guide for Use that can be improved to increase the prominence, clarity, and readability of important product information to mitigate the potential for medication errors and promote safe use of Twirla***. We provide recommendations in Sections 5.1 and 5.2 to address our concerns. We advise these recommendations are implemented prior to the approval of this product.

5.1 RECOMMENDATIONS FOR DBRUP

Prescribing Information (PI)

1. Section 16.1 How Supplied
 - a) The NDC number is denoted by a placeholder and we are unable to evaluate this important product identifier for risk of medication error. The PI should be updated

once the NDC number is defined in recommended below in 1.d. recommendations for Agile Therapeutics.

2. Guide for Use - How should I use Twirla***

- a) To improve clarify and to decrease the risk for confusion, we recommend defining the terminology “patch-free week” prior to its use in sentence 5. For example, revise the sentence (b) (4)

“This is your patch-free week.”

3. Detailed instruction

- a) To assist the user to remember their “patch-change day”, we recommend adding the following sentence, “You may note your patch-change day on the back panel of the box” after the sentence “Your patch change day will be on this day every week.”

5.2 RECOMMENDATIONS FOR AGILE THERAPEUTICS

We recommend Agile implement the following prior to approval of NDA 204017:

1. (b) (4) 3-pack Carton labeling, Pouch labeling and Professional Sample Carton labeling
 - a) As currently presented, the storage instructions for unused patches is described using a negative statement which may lead to confusion. We recommend you remove the statement (b) (4) from the back panel and revise the storage instructions to include to affirmative language, such as “Store patch in pouch until ready to use. Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).”
 - b) As currently presented, disposal instructions are not present on the professional sample, (b) (4) 3-pack carton labeling and can be improved on the pouch labeling. To reduce the risk for disposal medication errors. We recommend you add a disposal statement to the carton, such as “dispose used patches in the trash only. See prescribing information for detailed instructions.” We recommend you list this statement after “each transdermal system is intended to be worn for 7 days (b) (4) .”
 - c) As currently presented, the format for the expiration date is not acceptable. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).
 - d) As currently presented, the NDC number is denoted by a placeholder. In addition, the NDC number placeholder lacks prominence and readability. We recommend you define the NDC number ensuring the last 2 digits (-XX) are adequately differentiated between package sizes in alignment with 21 CFR 201.57(c)(17). We also recommend you, increase the font size of the NDC number so that it is prominently displayed.

2. 3-pack Carton labeling, Professional Sample

- a) The NDC placeholder is presented vertically while all other labeling information is presented horizontally. We recommend you increase the readability of the NDC number on the 3-pack trade carton and the professional sample by orienting the NDC number in a horizontal position.

3. Pouch Labeling

- a) As currently presented, the net quantity (for example; “1 Week Therapy”) is not clearly stated and is not in alignment with 21 CFR 201.51. We recommend you revise the statement “(b) (4)” to indicate the net quantity of the package. Specifically, state: “Contains 1 transdermal system”
- b) As currently presented the front of the pouch is cluttered with product information (that is, inactive and active ingredients), which decreases the prominence and readability of important product information (that is, Rx only, route of administration, storage and handling). We recommend you move the following to the back of the pouch: the active and inactive ingredients of the patch and the manufacturing information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Twirla*** that Agile submitted on June 26, 2017.

Table 2. Relevant Product Information for Twirla***	
Initial Approval Date	N/A
Active Ingredient	Levonorgestrel/ethinyl estradiol
Indication	Prevention of pregnancy
Route of Administration	Transdermal
Dosage Form	Transdermal system
Strength	120 mcg/30 mcg/day
Dose and Frequency	Cycle: 1 patch once weekly x3 weeks, then 1 week off
How Supplied	3 patches per carton
Storage	Store at 25° C (77° F), excursions permitted to 15° to 30° C (59° to 86° F)
Container Closure	 (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 24, 2017, we searched the L: drive and AIMS using the terms, Twirla*** and levonorgestrel / ethinyl estradiol to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous finalized reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Twirla*** labels and labeling submitted by Agile on June 26, 2017.

(b) (4)

- 3-patch Carton labeling
 - Trade
 - Professional Sample
- Pouch Label
- Patch label
- Guide for Using (excerpt)
- Prescribing Information (no image)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JOHN C MORRIS
11/22/2017

LOLITA G WHITE
11/22/2017

Clinical Inspection Summary

Date	November 14, 2017
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Charlene Williamson, Regulatory Project Manager Nneka McNeal-Jackson, Clinical Reviewer Catherine Sewell, Clinical Team Leader Division of Bone, Reproductive, and Urologic Products (DBRUP)
NDA #	204017
Applicant	Agile Therapeutics, Inc.
Drug	Twirla Transdermal Contraceptive Delivery System (levonorgestrel/ethinyl estradiol 120/30 mcg/day)
NME	No
Review Priority	Standard Review
Proposed Indication	Prevention of pregnancy
Consultation Request Date	July 26, 2017
Summary Goal Date	November 22, 2017
Action Goal Date	December 22, 2017
PDUFA Date	December 26, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Strout and Kimble were inspected in support of this NDA.

Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final classification of the inspection of Dr. Strout's site was No Action Indicated (NAI) and of Dr. Kimble's site was Voluntary Action Indicated (VAI).

2. BACKGROUND

The Applicant submitted this NDA to support the use of Twirla for the prevention of pregnancy.

Inspections were requested for the following protocol in support of this application:

Protocol ATI-CL23, A single-arm, open-label, multicenter Phase 3 study of the contraceptive efficacy, safety and tolerability of the AG200-15 transdermal contraceptive delivery system.

This study was conducted domestically at 102 sites with a total enrollment of 2032 subjects.

The primary objective of this study was to evaluate the contraceptive efficacy of AG200-15. Other objectives included assessments of overall safety and tolerability, patch adhesion, and subject compliance.

The primary efficacy endpoint was the Pearl Index (defined as the number of on treatment pregnancies times 1300 divided by the number of on-therapy cycles) for subjects in the ITT dataset of the contraceptive efficacy population who were ≤ 35 years of age.

Rationale for Site Selection

The clinical sites of Drs. Strout and Kimble were chosen for inspection because Dr. Strout's site had a large number of subjects, a high discontinuation rate, numerous major protocol violations, and higher than average efficacy. Dr. Kimble's site was chosen for inspection because the site had a high discontinuation rate and lower than average efficacy.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects	Inspection Dates	Classification
Site #1082 Cynthia Strout, M.D. 1156 Bowman Road Suite 102 Mt. Pleasant, SC 29464	ATI-CL23 Subjects: 161	2-5 Oct 2017	NAI
Site #1079 Thomas Kimble, M.D. 601 Colley Avenue Norfolk, VA 23507	ATI-CL23 Subjects: 45	5-7 Sep 2017	VAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

1. Cynthia Strout, M.D.

At this site for Protocol ATI-CL23, 161 subjects were screened, 69 subjects were randomized, and 32 subjects completed the study. IRB approval of the protocol and informed consent forms was obtained prior to subjects undergoing any study-specific procedures.

The study records for 25 of the subjects completing the study and for five additional subjects who withdrew from the study were reviewed. Informed consent was obtained properly for each of these subjects.

Source documents were compared with the data listings. Records reviewed included, but were not limited to, organizational charts, financial disclosure forms, training documentation, delegation of authority logs, IRB and monitoring correspondence, screening and enrollment logs, inclusion/exclusion criteria, adverse events, concomitant medications, diary compliance, protocol deviations, and test article accountability,

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Thomas Kimble, M.D.

At this site for Protocol ATI-CL23, 45 subjects were screened, 24 subjects were enrolled, and 14 subjects completed the study. IRB approval of the protocol and informed consent forms was obtained prior to subjects undergoing any study-specific procedures.

The study records of 28 subjects were reviewed. The records reviewed for these subjects included, but were not limited to, IRB and monitor correspondence, financial disclosure, laboratory certifications, delegation of responsibilities, inclusion/exclusion criteria, patient diaries, adverse event reporting, and test article storage conditions.

A Form FDA 483 was issued at the conclusion of the inspection noting that a sub-investigator continued his participation in the study after his formal removal from the protocol by the sponsor because of a potential financial conflict of interest. The sub-investigator, after his removal from the study, conducted physical examinations on three subjects (#s (b) (6), and (b) (6)) and evaluated an adverse event of headache for Subject (b) (6).

The Form FDA 483 also noted that the site failed to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, Subject (b) (6) experienced a non-serious adverse event of severe pelvic cramping attributed as definitely related to study treatment. This adverse event was not contained in the data listings.

In addition, two subjects, (b) (6), used concomitant medications that were not reported in the data listings. Subject (b) (6) used Vyvanse 40 mg, while Subject (b) (6) used Levaquin 500 mg and Biaxin 500 mg. Antibiotics, when used with hormonal contraceptives, can decrease contraceptive efficacy.

Dr. Kimble responded to the Form FDA 483 in writing in a letter dated September 26, 2017. His response was adequate.

The sub-investigator's conduct of physical examinations on three subjects and his evaluation of an adverse event experienced by another subject following his removal from the study by the sponsor would appear to have negligible impact on the outcome of the study. However, the review division may wish to assess the significance, if any, of the adverse event experienced by Subject (b) (6) that was not reported or of the concomitant medications used by Subjects (b) (6) and (b) (6) that were not included in the data listings. Otherwise, neither safety nor efficacy considerations appear to have been affected. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

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CC:

Central Doc. Rm.\NDA 204017

DBRUP\Division Director\ Hylton Joffe

DTBRUP\Team Leader\Catherine Sewell

DBRUP\Medical Officer\ Nneka McNeal-Jackson

DTOP\Project Manager\Charlene Williamson

OSI\DCCE\Division Director\Ni Khin

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OSI\ DCCE\GCPAB\Team Leader\Phillip Kronstein

OSI\ DCCE\GCPAB\Reviewer\Roy Blay

OSI\ DCCE\Program Analysts\Joseph Peacock\Yolanda Patague

OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
11/14/2017

PHILLIP D KRONSTEIN
11/14/2017

KASSA AYALEW
11/16/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: February 12, 2013

To: Hylton Joffe, MD,
Director
Division of Reproductive and Urology Products (DRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, RN, BSN, MSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI)

Drug Name (established name): TWIRLA (levonorgestrel/ethinyl estradiol)

Dosage Form and Route: transdermal patch

Application Type/Number: NDA 204017

Applicant: Agile Therapeutics

1 INTRODUCTION

On April 12, 2012, Agile Therapeutics submitted an original NDA for TWIRLA (levonorgestrel/ethinyl estradiol) a low dose estrogen/progestin combination weekly transdermal patch indicated for use by women to prevent pregnancy.

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) for TWIRLA (levonorgestrel/ethinyl estradiol) transdermal patch.

2 CONCLUSIONS

Due to outstanding Clinical and CMC deficiencies, DRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHARON W WILLIAMS
02/12/2013

MELISSA I HULETT
02/12/2013

LASHAWN M GRIFFITHS
02/13/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 14, 2013

TO: Charlene Williamson Regulatory Project Manager
Dan Davis, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204017

APPLICANT: Agile Therapeutics

DRUG: AG200-15 transdermal contraceptive patch (Twirla™)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Contraception

CONSULTATION REQUEST DATE: June 28, 2012
CLINICAL INSPECTION SUMMARY DATE: January 15, 2013
DIVISION ACTION GOAL DATE: February 13, 2013
PDUFA DATE: February 13, 2013

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Twirla (AG200-15 transdermal contraceptive patch) for contraception.

The pivotal study protocol ATI-CL12 entitled “An Open-label, Randomized, Parallel Group, Phase 3 Study of the Contraceptive Efficacy and Safety of Agile Transdermal Contraceptive Delivery System (TCDS) in Comparison to a Low-dose Oral Contraceptive Containing 0.02 mg Ethinyl Estradiol and 0.1 mg Levonorgestrel in a 21-day Regimen”, was submitted and inspected in support of the indication of requested contraception where the primary efficacy parameter was the pregnancy rate as calculated using the Pearl Index (the index generally being defined as the number of contraceptive failures per 100 woman years of exposure).

Site 31 was selected for inspection because of its large enrollment and notable discontinuation rate. Sites 23 and 33 were selected because of their high Pearl Indices. Sites 23 and 31 also had notable adverse event rates.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
Charles Eubank, Jr., M.D. 5920 Saratoga Blvd., Suite 100 Corpus Christi, TX 78414	ATI-CL12/ Site #23/ 47 subjects	5-14 Sept 2012	VAI
Richard Groom, M.D. 1001 South Rancho Drive Las Vegas, NV 89106	ATI-CL12/ Site #31/ 73 subjects	18 Nov - 4 Dec 2012	VAI-RR
Lydia Hazen, M.D. 5800 Wilshire Blvd. Los Angeles, CA 90036	ATI-CL12/ Site #33/ 121 subjects	11-19 Sep 2012	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

VAI-RR = Deviation(s) from regulations-Response Requested (the investigator’s written response to noted deficiencies is requested)

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Charles Eubank, Jr., M.D.

5920 Saratoga Blvd., Suite 100
Corpus Christi, TX 78414

- a. **What was inspected:** At this site, for Protocol ATI-CL12, 56 subjects were screened, 47 subjects were enrolled, and 22 subjects completed the study. The records of 42 study subjects were reviewed, including, but not necessarily limited to, informed consent forms, inclusion/exclusion criteria, the primary efficacy endpoint, test article

storage and accountability, sponsor, monitor, and IRB correspondence, laboratory reports, concomitant medications, and adverse event reports.

- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Review of the records noted above revealed the following deficiencies in the conduct of Protocol ATI-CL12: a lack of PK samples for Subjects (b) (6) at Visit 5, numerous minor discrepancies between source documents and eCRFs with regard to test article accountability, and additional discrepancies with regards to concomitant medications and adverse events, including their start/stop dates and relatedness to drug treatment. Additional discrepancies were noted with regards to subjects who became pregnant with respect to pregnancy testing dates and treatment cycles (Subject (b) (6)), date of conception (Subject (b) (6)), and adverse events and pregnancy testing dates (Subject (b) (6)).
- c. Assessment of data integrity:** Dr. Eubank responded to the inspection findings in a letter dated October 3, 2012, in which he addressed each discrepancy noted on the Form FDA 483. Dr. Eubank acknowledged some transcription errors while noting that other discrepancies resulted from data being entered into eCRFs in response to interim queries without corrections being made to source data. In other cases, Dr. Eubank stated that eCRF data was consistent with source documents (i.e. laboratory reports) but did not provide copies of these laboratory reports for review. Dr. Eubank addressed and appeared to have resolved the data discrepancies for those subjects who became pregnant (Subjects (b) (6)). Other than minor discrepancies, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Richard Groom, M.D.
1001 South Rancho Drive
Las Vegas, NV 89106

- a. What was inspected:** At this site, for Protocol ATI-CL12, 113 subjects were screened, 73 subjects were randomized, and 22 subjects completed the study. An audit of nine enrolled subjects' records was conducted. Signed informed consent forms were present for all enrolled subjects; however, there was no documentation of consent for Subjects (b) (6) who participated in a PK sub-study for which each subject provided a single blood sample. Records reviewed included, but were not necessarily limited to, inclusion/exclusion criteria, subject stratification, medical histories, progress notes, worksheets, Case Report Forms (CRFs), subject diaries, blood sampling, concomitant medications, and drug accountability.
- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Observations included, but were not necessarily limited to, a lack of consent forms for participation by three subjects in a PK sub-study as noted above; one or more missing blood draws for determination of sex hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) in 27 of 57 subjects; one or more missing blood draws for determination of levonorgestrel and/or ethinyl estradiol for 30 of 57 subjects; the incorrect stratification of at least three subjects; at least three subjects incorrectly classified as new users of hormonal contraception; the lack of

assessment of focal neurological symptoms in three subjects complaining of a history of headache; multiple missing Subject Satisfaction Questionnaires; the placement of patches on different anatomical sites during a given cycle for at least two subjects; examples of source data lacking

attribution or dates; errors in documentation of subjects' use of hormonal contraceptives; discrepancies in concomitant medication documentation for at least two subjects; and examples of discrepancies regarding location of patch application and dates that patches were worn, removed, or replaced for at least five subjects.

- c. **Assessment of data integrity:** Though numerous deficiencies were identified in the conduct of this study, the deficiencies, would not appear to seriously affect data integrity of the primary efficacy endpoint (pregnancy/non-pregnancy) or the safety of study subjects. On this basis, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

- 3. Lydia Hazen, M.D.
5800 Wilshire Blvd.
Los Angeles, CA 90036

- a. **What was inspected:** At this site, for Protocol ATI-CL12, 180 subjects were screened, 121 subjects were enrolled, 5 subjects withdrew from the study, and 36 subjects completed the study. An audit of 20 subjects' records was conducted. Signed informed consent forms were present for all subjects. Other records reviewed included, but were not limited to, source documents, drug accountability, laboratory reports, progress notes, test records, and concomitant medications. Efficacy endpoint and adverse event reporting was reviewed for all subjects completing the study.
- b. **General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection with a single two-part observation: the failure to collect blood samples for nine subjects for SHBG/CBG at Visit 7 and PK samples for another two subjects at Visit 3. Dr. Hazen responded in writing noting that the central laboratory (PRL) failed to send SHBG/CBG sampling kits to the site. PRL, according to Dr. Hazen, acknowledged that it shipped the kits to the wrong address. In the case of the missed PK samples, Dr. Hazen acknowledged that it was the site's oversight in failing to collect the two samples. According to Dr. Hazen, there were a total of 360 samples to be collected with only two failing to be collected for an error rate of 0.005%. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Eubank's, Groom's and Hazen's clinical investigator sites were inspected in support of this NDA. Dr. Hazen was not issued a Form FDA 483 and the final classification of the inspection was NAI (No Action Indicated). Both Drs. Eubank and Groom were issued Form FDA 483s. The final classification for Dr. Eubank's site was VAI and the classification for Dr. Groom's site was VAI-RR (Voluntary Action Indicated - Response Requested).

Though numerous deficiencies were identified at Drs. Eubank's and Groom's sites as noted above, the deficiencies, overall, would not appear to seriously affect data integrity or the safety of study subjects; therefore, the data generated by these three clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

{See appended electronic signature page}

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/s/

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01/15/2013

JANICE K POHLMAN
01/15/2013

SUSAN D THOMPSON
01/15/2013

Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion/Division of Consumer Drug
Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: January 14, 2013

To: Charlene Williamson
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer
Division of Prescription Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

CC: Andrew Haffer, PharmD, Acting Division Director (DPDP)
Jessica Cleck-Derenick, PhD, Regulatory Review Officer (DPDP)

Subject: **NDA 204017**
Twirla™ (levonorgestrel/ethinyl estradiol transdermal system)

Background

We acknowledge the receipt of your July 31, 2012, consult request for the Package Insert (PI) for Twirla™ (levonorgestrel/ethinyl estradiol transdermal system). OPDP notes an email correspondence from DRUP on January 11, 2012, which indicated that final labeling negotiations will not be initiated during the current review cycle because a Complete Response letter will be issued to the sponsor. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle.

OPDP requests that DRUP submits a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on the proposed product labeling. If you have any questions, please contact Melinda McLawhorn at 6-7559 or at Melinda.McLawhorn@fda.hhs.gov.

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/s/

MELINDA W MCLAWHORN
01/14/2013