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RESEARCH**

APPLICATION NUMBER:

204017Orig1s000

NON-CLINICAL REVIEW(S)

**PHARMACOLOGY/TOXICOLOGY
SUPERVISOR REVIEW**

Date:	February 13, 2020
NDA #	204017
Sponsor:	Agile Therapeutics Inc.
Submission Date:	May 26, 2019
Drug:	Twirla: Levonorgestrel/Ethinyl estradiol 120/30 mcg/day) Transdermal Contraceptive Delivery System
Indication:	Prevention of Pregnancy
Reviewer:	Mukesh Summan, PhD, DABT

Background: There are a large number of combination hormonal contraceptives that contain levonorgestrel (LNG) and ethinyl estradiol (EE). LNG and EE are well characterized progestin and estrogen products that are the active components in a number of U.S. marketed contraceptive drug products. The current maximum LNG dose in conventional oral contraceptives is 0.15 mg/day. The dose of EE in combined oral contraceptives (COC) has decreased over the years and currently prescribed COC contain EE at 35 mcg or less.

Agile Therapeutics, Inc. (Agile) has developed a 7-day transdermal contraceptive delivery system (TDDS) containing 2.60 mg LNG and 2.30 mg EE for the prevention of pregnancy. The TDDS releases (by AUC) LNG and EE at 120 mcg and 30 mcg per day, respectively, over a 7-day period. The patch is replaced every 7 days for 3 weeks and this is followed by a 7-day patch free period.

NDA 204017 was submitted as a 505(b)2 NDA on April 13, 2012 and received a complete response February 13, 2013 due to clinical and product quality issues. The sponsor subsequently resubmitted the NDA June 26, 2017. This second cycle submission also received a complete response December 21, 2017 due to clinical, facility inspections and product quality issues. The sponsor re-submitted NDA 204017 for a third cycle review May 16, 2019. As part of the NDA re-submission no new nonclinical pharmacology and toxicology studies were submitted by the applicant.

Refer to the January 29, 2020 DARRTS (Dr. Mukesh Summan) submission for the pharmacology and toxicology discipline assessment of the NDA 204017.

Label:

The following table notes the current sponsor proposed changes, and the pharmacology/toxicology review team accepted changes. The strikethrough denotes deletions and the red text denotes additions.

the red text denotes additions.

Agile Therapeutics Inc. proposed (2018)	Pharm/Tox proposed (2020)
<p>8.1 Pregnancy <u>Risk Summary</u> TWIRLA is contraindicated in pregnancy because there is no reason to use CHCs in pregnancy. Discontinue TWIRLA if pregnancy occurs. (b) (4)</p>	<p>8.1 Pregnancy <u>Risk Summary</u> TWIRLA is contraindicated in pregnancy because there is no reason to use CHCs in pregnancy. Discontinue TWIRLA if pregnancy occurs. (b) (4)</p>
<p>Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low-dose CHCs before conception or during early pregnancy.</p>	<p>(b) (4) Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low-dose CHCs before conception or during early pregnancy.</p>
<p>(b) (4)</p>	<p>(b) (4)</p>
	<p>In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.</p>

<p>8.2 Lactation <u>Risk Summary</u> Contraceptive hormones and/or metabolites are present in human milk. (b) (4) (b) (4)</p> <p>(b) (4) CHCs can reduce milk production in breast-feeding (b) (4) (b) (4)</p> <p>(b) (4) advise the nursing (b) (4) to use (b) (4) methods of contraception until she discontinues breast-feeding. [See also Dosage and Administration 2.2]. (b) (4) (b) (4)</p>	<p>8.2 Lactation <u>Risk Summary</u> Contraceptive hormones and/or metabolites are present in human milk. (b) (4) (b) (4)</p> <p>(b) (4) CHCs can reduce milk production in women (b) (4) (b) (4)</p> <p>(b) (4) Advise the nursing (b) (4) to use (b) (4) methods of contraception until she discontinues breast-feeding. [See also Dosage and Administration 2.12]. (b) (4) (b) (4)</p> <p><u>Human Data</u> No studies have been conducted on the use of TWIRLA in breastfeeding women.</p>
<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility [see Warnings and Precautions (5.10), and Pregnancy (8.1)] (b) (4) (b) (4)</p>	<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility [see Warnings and Precautions (5.10), and Pregnancy (8.1)] (b) (4) (b) (4)</p>

Outstanding Nonclinical Issue:

None.

Conclusion(s):

The changes in the table were proposed and accepted by the sponsor.

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/s/

MUKESH SUMMAN
02/13/2020 09:48:07 PM

**PHARMACOLOGY/TOXICOLOGY
SUPERVISOR REVIEW**

Date:	January 29, 2020
NDA #	204017
Sponsor:	Agile Therapeutics Inc.
Submission Date:	May 26, 2019
Drug:	Twirla: Levonorgestrel/Ethinyl estradiol 120/30 mcg/day) Transdermal Contraceptive Delivery System
Indication:	Prevention of Pregnancy
Reviewer:	Mukesh Summan, PhD, DABT

Background: There are a large number of combination hormonal contraceptives that contain levonorgestrel (LNG) and ethinyl estradiol (EE). LNG and EE are well characterized progestin and estrogen products that are the active components in a number of U.S. marketed contraceptive drug products. The current maximum LNG dose in conventional oral contraceptives is 0.15 mg/day. The dose of EE in combined oral contraceptives (COC) has decreased over the years and currently prescribed COC contain EE at 35 mcg or less.

Agile Therapeutics, Inc. (Agile) has developed a 7-day transdermal contraceptive delivery system (TDDS) containing 2.60 mg LNG and 2.30 mg EE for the prevention of pregnancy. The TDDS releases (by AUC) LNG and EE at 120 mcg and 30 mcg per day, respectively, over a 7-day period. The patch is replaced every 7 days for 3 weeks and this is followed by a 7-day patch free period.

NDA 204017 was submitted as a 505(b)2 NDA on April 13, 2012 and received a complete response February 13, 2013 due to clinical and product quality issues. The sponsor subsequently resubmitted the NDA June 26, 2017. This second cycle submission also received a complete response December 21, 2017 due to clinical, facility inspections and product quality issues. The sponsor re-submitted NDA 204017 for a third cycle review May 16, 2019. As part of the NDA re-submission no new nonclinical pharmacology and toxicology studies were submitted by the applicant.

Refer to the November 21, 2017 DARRTS (Dr. Mukesh Summan) submission for the pharmacology and toxicology discipline assessment of the NDA 204017.

Outstanding Nonclinical Issue: None.

Conclusion(s): Based on the extensive clinical experience with LNG/EE products and the nonclinical studies conducted by the sponsor, Pharmacology and Toxicology recommends approval of Agile Therapeutics' LNG/EE TDDS.

Recommendations on Labeling: Labeling will be completed in a separate review.

Recommendation: There are no nonclinical safety issues which would preclude approval of this NDA.

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/s/

MUKESH SUMMAN
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P/T supports AP



Memorandum

PHARMACOLOGY/TOXICOLOGY
SUPERVISOR MEMO

Date:	21 st November 2017
NDA #	204017
Sponsor:	Agile Therapeutics Inc.
Submission Date:	27 th June 2017
Drug:	Twirla: Levonorgestrel/Ethinyl estradiol 120/30 mcg/day) Transdermal Contraceptive Delivery System
Indication:	Prevention of Pregnancy
Reviewer:	Mukesh Summan, PhD, DABT

Background: There are a large number of combination hormonal contraceptives that contain levonorgestrel (LNG) and ethinyl estradiol (EE). LNG and EE are well characterized progestin and estrogen products that are the active components in a number of U.S. marketed contraceptive drug products. The current maximum LNG dose in conventional oral contraceptives is 0.15 mg/day. The dose of EE in combined oral contraceptives (COC) has decreased over the years and currently prescribed COC contain EE at 35 mcg or less.

Agile Therapeutics, Inc. (Agile) has developed a 7-day transdermal contraceptive delivery system (TDDS) containing 2.60 mg LNG and 2.30 mg EE for the prevention of pregnancy. The TDDS releases (by AUC) LNG and EE at 120 mcg and 30 mcg per day, respectively, over a 7-day period. The patch is replaced every 7 days for 3 weeks and this is followed by a 7-day patch free period.

NDA 204017 was submitted as a 505(b)2 NDA on April 13th 2012 and received a complete response February 13th 2013 due to clinical and product quality issues. The sponsor subsequently resubmitted the NDA June 27th 2017.

As a 505(b)2, NDA 20417 relies on the public literature that supports findings of safety and efficacy of approved combined oral contraceptives and clinical and clinical pharmacology studies conducted by the sponsor. The applicant also relied upon published literature and dermal toxicity studies conducted under IND 57,731 to support nonclinical pharmacology and toxicology.

As part of the NDA re-submission the drug product quality reviewer, Dr. Caroline Strasinger notified the nonclinical pharmacology and toxicology discipline of a change in

the drug product impurity specifications. In the original NDA submission the drug product specification for LNG related substances were:

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

Source: 3.2.P.5.1 Specification(s) (AG200-15, Transdermal Patch) [06.24.2013]

In the NDA resubmission the sponsor revised the drug product specification for LNG related substances to the following:

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

Source: 3.2.P.5.1 Specification(s) (AG200-15, Transdermal Patch) [10.18.2017]

It appears that the sponsor has revised the acceptance criteria of (b) (4) and the total LNG impurities, due an increase in these impurities under long term stability studies, as shown in the sponsor's table below:

Analytical Attribute	29588	30793	30941	31357	35249	35274	35620	29588 24 Month Stability Results	35249 27 Month Stability Results
Batch Use	Phase 3 Clinical Trials, Pharmacokinetic Studies	Phase 3 Clinical Trials	Phase 3 Clinical Trials						
(b) (4)									
Total LNG Impurities	(b) (4)								

Abbreviations: ND = not detected; EE = ethinyl estradiol; LNG = levonorgestrel.

Per the sponsor, 24- and 27-month old TDDS patches were used in clinical trial ATI-CL23 using drug product lot numbers 35249, 35274 and 35260. Clinical study ATI-CL23 was a single-arm, open label study evaluating the TDDS in 13 twenty-eight day cycles, in over 2000 treated subjects.

Nonclinical defers to the clinical team with regard to the adequacy of clinical trial ATI-23. Exposure of clinical trial participants to the drug product also likely resulted in exposure to these LNG impurities. Thus, these impurities are deemed qualified by their presence in the drug product and use in this clinical trial. In addition, on the basis of a PubMed.gov search for toxicity associated with [REDACTED] (b) (4) [REDACTED] evaluated either singly or in combination and without a date range restriction, revealed no toxicological concerns

The primary pharmacology and toxicology reviewer Dr. Krishan Raheja, reviewed both NDA 204017 and the dermal toxicity studies under IND 57,731 and recommended approval of the LNG/EE TDDS for the prevention of pregnancy during the first review cycle.

Outstanding Nonclinical Issue: None.

Conclusion(s): Dr. Krishan Raheja, the primary nonclinical reviewer in the first NDA cycle, concludes that the pharmacology and toxicology data support approval of the LNG/EE TDDS. I concur with Dr. Raheja's assessment.

Based on the extensive clinical experience with LNG/EE products and the nonclinical studies conducted by the sponsor, Pharmacology and Toxicology recommends approval of Agile's LNG/EE TDDS.

Recommendations on Labeling: Labeling will be completed in a separate review.

Recommendation: There are no nonclinical safety issues which would precluded approval of this NDA.

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/s/

MUKESH SUMMAN
11/21/2017
Nonclinical supports AP

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 204017 eCTD Sequence No. 0000; SD No. 0
Supporting document/s: e-Submission
Applicant's letter date: 4/12/2012
CDER stamp date: 4/13/2012
Product: Ethinyl estradiol/Levonorgestrel (EE/LNG)
Contraceptive Transdermal Patch. Code name
AG200-15
Indication: Contraception
Applicant: Agile Therapeutics, Inc. 101 Poor Farm Road,
Princeton, NJ
Review Division: Reproductive & Urologic Products
Reviewer: Krishan L. Raheja, D.V.M., Ph.D.
P/T Expert Reviewer: Alex Jordan, Ph.D.
Division Director: Audrey Gassman, M.D.
Project Manager: Charlene Williamson
Entered in DARRTS: 5/9/2012

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204017 are owned by Agile Therapeutics Inc. or are data for which Agile Therapeutics Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 204017 that Agile Therapeutics Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204017.

1 Executive Summary

1.1 Introduction: This 505 (b)(2) application is filled based on efficacy and safety data generated from clinical studies conducted by the sponsor as well data from published scientific literature. AG200-15 is a transdermal patch with a combination of the hormones, ethinyl estradiol and levonorgestrel, intended for the prevention of pregnancy in women who choose to use transdermal patch for contraception.

1.2 Brief Discussion of Nonclinical Findings: No new preclinical toxicology studies have been conducted. Instead, sponsor has referred to the dermal toxicity studies that were conducted under IND 57,731. These studies constituted evaluation of the irritation and sensitization potential of (b) (4) in rabbit and guinea pig, respectively. (b) (4) prototype patch of the AG200-15 formulation (b) (4) which is subject of this NDA.

1.3 Recommendations

1.3.1 Approvability: Pharmacology/Toxicology recommends approval of NDA 204017 for EE/LNG transdermal patch for prevention of pregnancy.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: Sponsor has submitted draft labeling text.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional) EE: 57-63-6 LNG: 797-63-7

Generic Name: Ethinyl estradiol (EE) and levonorgestrel (LNG) combination product

Code Name: AG200-15

Chemical Name: EE: 19-nor-17 alpha pregna-1,3,5(10)-trien-20-yne-3,17 beta-diol
LNG: 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,(17 α)-

Molecular Formula/Molecular Weight: EE C₂₀H₂₄O₂/296.41
LNG: C₂₁H₂₈O₂/312.45

Structure or Biochemical Description: The AG₂₀₀₋₁₅ transdermal patch is a combination product composed of EE and LNG for prevention of pregnancy

Pharmacologic Class: EE (estrogen) and LNG (progestin)

2.2 Relevant INDs, NDAs, BLAs and DMFs: IND 57,731

2.3 Drug Formulation: Transdermal patch

2.4 Comments on Novel Excipients: Drug product formulation and composition is given in table below:

Component	Function
Levonorgestrel	Active Substance
Ethinyl estradiol	Active Substance
(b) (4)	(b) (4)
Dimethylsulfaoxide	
Lauryl lactate	
Ethyl lactate	
Capric acid	
(b) (4)	

2.5 Comments on Impurities/Degradants of Concern: None given

2.6 Proposed Clinical Population and Dosing Regimen: Women who elect to use EE/LNG patch as a method of contraception. AH200-15 transdermal contraceptive patch contains 2,6 mg levonorgestrel and 2.3 mg ethinyl estradiol and delivers 120 ug LNG and 30 ug EE/day over a 7-day period. The patch is to be replaced ever 7 days for 3 weeks, followed by a 1-week "patch-free" period.

2.7 Regulatory Background: In a Type B meeting on 9/22/2008, presented the following 2 questions for P/T:

Sponsor question 1. Does the Division concur that the existing nonclinical safety studies for LNG and EE are sufficient to support a future NDA submission for EE and LNG for the prevention of pregnancy?

Division response: YES

Sponsor question 2: Does the Division agree that no additional nonclinical studies need to be conducted on lauryl lactate, ethyl lactate, and capric acid in order to support a future NDA for the prevention of pregnancy?

Division response: No. There is safety concern about capric acid, which is one of the three excipients in the proposed patch formulation. The P/T review of the sponsor's submission of March 29, 1999 (SS# 003) and April 21, 1999 (SS# 004) determined that lauryl lactate and ethyl lactate are safe for use as found in the proposed patch formulation, but the information on capric acid was not adequate. More information should be submitted regarding its chronic dermal safety and mutagenic potential. If this information is not available in the literature, the sponsor will need to conduct these studies.

Note: Sponsor subsequently provided adequate literature and drug product references where capric acid has been used to reviewer's satisfaction.

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/s/

KRISHAN L RAHEJA
05/09/2012

ALEXANDER W JORDAN
05/09/2012