1. TITLE PAGE

AGILE THERAPEUTICS, INC.

CLINICAL STUDY REPORT

Indication:	Prevention of Pregnancy
Name of Study Drug/ Investigational Product:	Twirla® (levonorgestrel and ethinyl estradiol) transdermal system
Protocol Number:	ATI-CL28
Clinical Phase:	Phase 4 / Post-Marketing Commitment
Study Title:	A Postmarketing Open-Label Study to Assess Residual Levonorgestrel (LNG) and Ethinyl Estradiol (EE) Content of TWIRLA® (levonorgestrel and ethinyl estradiol) Transdermal System
Study Design:	Open-label study
Study Initiation Date:	25 October 2021
Study Completion Date:	16 November 2021
Report Date:	26 May 2022
Responsible Medical Officer:	Paul Korner, MD, MBA Chief Medical Officer Agile Therapeutics, Inc.
Company/Sponsor Contact Person(s):	Michelle L. Previtera, PhD Associate Director, Clinical Development Agile Therapeutics, Inc.

This study was designed and performed according to the guidelines for Good Clinical Practice.

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2. SYNOPSIS

Sponsor/Company Name: Agile Therapeutics, Inc.
Name of Finished Product: Twirla® (levonorgestrel and ethinyl estradiol) transdermal system
Name of Active Ingredient: Levonorgestrel/ethinyl estradiol (LNG/EE)
Title: A Postmarketing Open-Label Study to Assess Residual Levonorgestrel (LNG) and Ethinyl Estradiol (EE) Content of TWIRLA® (levonorgestrel and ethinyl estradiol) Transdermal System
Investigators: Jonathan S. Dosik, MD – Primary Investigator Igor Genkin, MD – Sub Investigator Michael Casser, MD – Sub Investigator Jesson Yeh, MD – Sub Investigator Steven Schreiber, MD – Sub Investigator Kameno Bell, MD – Sub Investigator
Study Center(s): TKL Research, Inc. One Promenade Blvd., Suites 1101 & 1201 Fair Lawn, NJ 07410
Study Period: First Participant In: 25 October 2021 Last Participant Out: 16 November 2021
Clinical Phase of Development: 4/Post-Marketing Commitment
Study Objectives and Endpoints: Objectives: The primary objective of this study was to assess residual EE and LNG content on used Twirla® (levonorgestrel and ethinyl estradiol) transdermal system (TDS), packaging, and the skin surface at the application site after 7 full days of wear and to estimate EE and LNG loaded on control TDSs using valid analytical methods. Endpoints: • The sum of means for EE and LNG content on used TDSs, storage pouches, release liners, and skin swabs. • The sum of means for EE and LNG content on control TDSs, storage pouches, and release liner.
Methodology: This was an open-label study in healthy female participants. This included a screening period of up to 28 days, 7 full days of treatment for each participant, where one TDS was applied and removed after 7 full days of wear, and a safety follow-up period that occurred 7 days following removal of the TDS.
Number of Participants (planned and analyzed): 30 Participants Planned, 28 Participants Enrolled. 27 Participants Completed
Main Criteria for Inclusion and Exclusion: Inclusion: - Willing and able to give signed informed consent - No evidence of Coronavirus Disease 2019 (COVID-19) infection based on Centers for Disease Control and Prevention (CDC) testing and/or screening procedures - Healthy woman, 18 to 40 years of age - Body mass index (BMI) $\geq$ 18 kg/m^2 and < 30 kg/m^2

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- Willing to refrain from use of alcohol and grapefruit juice from 48 hours prior until completion of the follow-up period
- In good general health, confirmed by medical history, physical examination, and laboratory testing
- Willing to not use other hormonal contraception including oral contraceptive, TDS, or vaginal ring, for the treatment and follow-up period.

Exclusion:

- Known or suspected pregnancy
- Breast-feeding or within 1 month after stopping breast-feeding
- User of injectable contraceptives (e.g., depot-medroxyprogesterone acetate) and less than 3 months since last injection
- User of progestin intrauterine device (IUD) and less than 3 months since last IUD insertion
- Recent pregnancy (within 2 months), including vaginal or cesarean delivery, surgical or medically induced abortion, spontaneous abortion, or ectopic pregnancy
- Unexplained vaginal bleeding
- Undiagnosed abnormal genital bleeding
- Diagnosis of sickle cell
- Known hypersensitivity to, or intolerance of, progestins or estrogens (leading to discontinuation), including hormonal contraception; or history of serious or severe adverse event (SAE) related to progestins or estrogens, including hormonal contraception (e.g., worsening of a disease or condition while on hormonal contraception)
- History of dermal hypersensitivity in response to medicated TDSs (e.g., nicotine TDS) or topical applications (bandages, surgical tape, etc.); known hypersensitivity to any components of the Twirla®, or prior difficulties with transdermal methods for any indication
- Presence on the lower abdomen of skin changes that, at the discretion of the Investigator, would have potentially interfered with TDS adhesion or TDS application site assessment, including for example tattoos, striae, scarring or other skin damage, skin lesions, skin irritation, diffuse skin disease (e.g., psoriasis, eczema, rash, or any etiology), excessive stretch marks, or excess hair at the TDS application site
- Preclusion of TDS placement, at the discretion of the Investigator, on the lower abdomen
- Has a contraindication to combined estrogen-progestin contraceptive use (as defined by a category 3 or 4 condition of the 2016 U.S. Medical Eligibility Criteria for Contraceptive Use)[8], including:
    - Personal history of or DVT or venous thromboembolism
    - History of stroke, vascular or cerebral vascular disease including TIAs or coronary artery disease
    - Known inherited or acquired hypercoagulopathy, including thrombogenic mutations (e.g., factor V Leiden; prothrombin mutation; protein S, protein C, or antithrombin deficiency)
    - Systemic Lupus Erythematosus with positive or unknown antiphospholipid antibodies
    - Known or suspected carcinoma of the breast, including past personal history of breast cancer
    - Jaundice with prior CHC use
    - Hepatocellular adenoma or carcinoma
    - Severe cirrhosis
    - Symptomatic current gallbladder disease

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- Current smokers 35 years of age or over, or smoker who would have turned 35 years old during the course of the trial (Smoking includes cigarettes, cigars, smokeless tobacco, e-cigarettes, hookah, etc.)
- Headaches with focal neurological symptoms (i.e., migraines with auras)
- Migraines of any type in women over 35 years of age
- Diabetes mellitus with nephropathy, neuropathy, retinopathy, or other vascular disease; diabetes mellitus of >20 year's duration
- Elevated blood pressure, defined as screening sitting blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic; or hypertension with known vascular disease
- History of peripartum cardiomyopathy

- Known thrombophilia, including antiphospholipid antibody syndrome
- History of any other condition that in the Investigator's opinion suggests an elevated risk of arterial or venous thromboembolic disease
- Carcinoma of the endometrium, ovary, fallopian tubes, or other known or suspected estrogen-dependent malignant or pre-malignant neoplasia
- Other active malignancy, excluding non-melanoma skin cancer
- Known history of acute or chronic hepatocellular disease with a history of significantly abnormal liver function, or liver function tests (LFTs) ≥ 2x normal
- Known history of Triglycerides ≥ 350 mg/dL
- Thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease or atrial fibrillation).
- Uncontrolled diabetes mellitus; participants with a history of gestational diabetes are eligible for the study if they are currently euglycemic
- Uncontrolled thyroid disorder
- Known HIV and/or hepatitis B or C infection
- History of suicidal ideation or attempt, or history of severe depression requiring hospitalization within the past year
- Recent history (within prior 12 months) of drug or alcohol abuse or at Investigator discretion, history greater than 12 months prior and at risk for noncompliance
- Positive urine drug screen for Cocaine, Methamphetamine, Opiates, Phencyclidine unless there is a documented prescription with supporting medical history and diagnosis
- Administration of any investigational drug and/or experimental device within 30 days prior to enrollment; planned administration of an experimental drug or device during the duration of the study; current participation in any investigational studies
- In the Investigator's judgement, woman was unsuitable for participation in the study or who could not comply with study procedures
- Participant was a dependent of (e.g., relative or family member) and/or was a member of the Investigator's staff.

Test Product, Dose and Mode of Administration, and Batch Number: Twirla® (levonorgestrel and ethinyl estradiol) transdermal system contains 2.30 mg of EE and 2.60 mg of LNG. The batch/lot number was 41211.

Duration of Treatment:

Female participants were screened for eligibility. Once determined by history, physical examination, and screening laboratories to be eligible for admission, participants were enrolled in the study.

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Each participant wore one TDS for 7 full consecutive days (168 ± 2 hrs.) and underwent daily adhesion assessments. The TDS was removed by trained personnel after 7 full days of wear. Seven days following TDS removal, a safety follow-up phone call occurred.

Criteria for Adhesion Evaluation:

Wearability:

TDS adhesion was evaluated by trained study site personnel daily on a 5-point scale (below), and the estimated percentage of TDS adherence determined:

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

If the daily adhesion score was <2, the participant was permitted to re-adhere the TDS to the skin. No overlays, tape or other coverings were used to reinforce TDS adhesion. Participants with an adhesion score ≥ 2 during any adhesion assessments would have been discontinued from the study since an adhesion score ≥ 2 involves lifting of the TDS area containing the active drug.

Statistical Methods:

Data from skin swabs, used TDSs, release liners, and storage pouches collected from participants who completed 7 full days of wear was included in the analysis. Data from skin swabs, used TDSs, release liners, and storage pouches from those participants who had > 10 continuous minutes of water exposure were excluded from analysis.

Descriptive statistics for EE/LNG content (i.e., arithmetic mean, median, standard deviation, minimum amount, maximum amount, coefficient of variation) were calculated for used TDSs with release liners, the skin swabs, and storage pouch swabs. The mean EE and LNG content on used TDSs with release liners, skin swabs, and storage pouches swabs was added for each drug to calculate residual EE/LNG content.

Descriptive statistics for EE/LNG content (i.e., arithmetic mean, median, standard deviation, minimum amount, maximum amount, coefficient of variation) were calculated for Controls. The mean EE and LNG content on TDSs with release liners and storage pouch swabs was added for each drug to estimate the amount loaded.

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Summary of Results for Safety and Adhesion:

Twelve (12) treatment emergent adverse events (TEAEs) were reported across 9 participants during this study. Overall, most TEAEs were mild, and one was moderate. No SAEs were reported.

No participants had an adhesion score of ≥2 during the study. The worst score for 5 participants was 1 (17.9%).

Conclusions:

- For the per protocol population:
  - Residual EE on the used TDS and release liners had a mean of 2026.5 µg with a SD of 43.72 µg. Residual LNG on the used TDS and release liners had a mean of 2187.3 µg with a SD of 63.34 µg.
  - Residual EE on the storage pouches had a mean of 0.2 µg with a SD of 0.77 µg. Residual LNG on the storage pouches had a mean of 0.2 µg with a SD of 0.87 µg.
  - Residual EE on the skin swabs had a mean of 2.0 µg with a SD of 1.29 µg. Residual LNG on the skin swabs had a mean of 2.2 µg with a SD of 1.93 µg.
  - The mean total residual drug for EE was 2028.7 µg with SD of 43.01 µg and the sum of means was 2028.6685. The mean total residual drug for LNG was 2189.6 µg with a SD of 62.35 µg and the sum of means was 2189.6323 µg.
- For the controls:
  - The mean total drug for EE (unused TDS and release liners) was 2102.0 µg with a SD of 85.26 µg and the sum of means was 2102 µg. The mean total drug for LNG (unused TDS and release liners) was 2454.0 µg with a SD of 93.70 µg and the sum of means was 2454 µg.

Final Report Date: 26 May 2022