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Original Research Article

Efficacy, safety, and tolerability of a levonorgestrel/ethinyl estradiol transdermal delivery system: Phase 3 clinical trial results

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ABSTRACT

Objective: To assess the contraceptive efficacy, safety, and tolerability of a contraceptive transdermal delivery system, (TDS; TWIRLA®) containing levonorgestrel (LNG) and ethinyl estradiol (EE).

Study design: This single-arm, open-label, multicenter, 1-year (13 cycle), phase 3 study enrolled sexually active women ≥18 years old at risk for pregnancy irrespective of body mass index (BMI). Women used patches in 28-day cycles (3 consecutive administrations of 7-day patches followed by 7 days off-treatment/patch-free week). We assessed contraceptive efficacy by the Pearl Index (PI) in women 18 to 35 years, excluding cycles without intercourse or when other contraceptive methods were used.

Results: The study enrolled 2032 demographically diverse women in the US, of which 35.3% had a BMI ≥30 kg/m^2. In the primary efficacy analysis, the PI (95% confidence interval) was 5.8 (4.5–7.2) pregnancies per 100 woman-years. PIs trended higher as BMI increased; the PI was 4.3 (2.9–5.8) in women with BMI <30 kg/m^2 and 8.6 (5.8–11.5) in women with BMI ≥30 kg/m^2. Hormone-related treatment-emergent adverse events included nausea (4.1%) and headache (3.6%); 11% of women discontinued due to adverse events. Four women (all with BMIs ≥30 kg/m^2) reported thromboembolic events considered related to treatment.

Conclusions: The low-dose LNG/EE TDS was effective in preventing pregnancy in a population of women representative of US demographics. Efficacy was reduced in women with BMI ≥30 kg/m^2. The TDS safety and tolerability profile was consistent with other similar dose combined hormonal contraceptives. Results of this phase 3 study supported the US Food and Drug Administration approval of TWIRLA® for prevention of pregnancy in women with BMI <30 kg/m^2.

Implications: TDS (120 μg/day levonorgestrel and 30 μg/day ethinyl estradiol) is an effective, low-dose transdermal contraceptive patch with favorable tolerability profile approved for prevention of pregnancy in women with BMI <30 kg/m^2. TDS has reduced effectiveness in women with BMI ≥30 kg/m^2.

1. Introduction

The contraceptive transdermal delivery system (TDS; TWIRLA®, Agile Therapeutics, Inc., Princeton, NJ) was designed to address the need for a low-dose, noninvasive transdermal contraceptive

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patch that avoids daily dosing. TDS was designed as a once-weekly patch delivering exposure similar to daily oral doses of 120 μg levonorgestrel (LNG)/30 μg ethinyl estradiol (EE). The first marketed contraceptive patch was associated with high levels of EE exposure (comparable to a 50 μg pill) and norelgestromin, which has been thought to have higher prothrombotic impacts than LNG. Use of this patch declined following concerns of higher rates of thromboembolism [1,2]. In collaboration with the US Food and Drug Administration (FDA), the phase 3 Study to Evaluate Contraceptive Use, Reliability, and Effectiveness (SECURE) evaluated the contraceptive efficacy, safety, and tolerability of TDS in a representative population of potential users in the United States.

2. Methods

SECURE (ClinicalTrials.gov NCT02158572) was an open-label, single-arm, multicenter, 13 cycle, phase 3 study of TDS in women ≥18 years old, and included rigorous design features consistent with the latest FDA recommendations for hormonal contraceptive trials, including no BMI restrictions [3,4].

2.1. Study treatment

Each TDS contains 2.6 mg levonorgestrel (LNG) and 2.3 mg ethinyl estradiol (EE) and delivers daily hormone exposure similar to oral doses of 120 μg LNG/30 μg EE pills [5]. Each <1 mm thick TDS is round, with a soft, flexible fabric outer surface covering an active drug core of 15 cm^2 in area; this core is surrounded by an outer perimeter adhesive system designed to ensure drug delivery in the event of partial patch lifting, for a total area of 28 cm^2 [6]. A cycle of TDS consists of 3 consecutive weekly patches (21 days of active treatment) followed by a patch-free week (7 days).

2.2. Participants, inclusion and exclusion criteria

The study was conducted at 102 US-based sites (see **Supplemental Materials**). The protocol was approved by the Advarra Institutional Review Board and local IRBs. All women provided written informed consent.

The target enrollment for the study included approximately 2100 women, ≥18 years old (200 women were aged >35 years) with regular 21 to 38 day cycles, at risk for pregnancy, desiring hormonal contraception for ≥1 year, and meeting the 2016 US Medical Eligibility Criteria for Contraceptive Use for combined hormonal methods [7]. Women confirmed anticipated sexual intercourse ≥1 per cycle for the duration of their participation and agreed to rely exclusively on the TDS for contraception. Exclusion criteria included known or suspected pregnancy, desire for pregnancy within the study period, anticipated need for other contraception, and dermal hypersensitivity to patches, adhesives, or any other components of the patch. Complete inclusion and exclusion criteria are described in **Appendices A.1** and **A.2,** respectively.

2.3. Contraceptive history

Women who had never used any hormonal contraceptives were categorized as “naïve users”; “former users” had used hormonal contraceptives previously but not within 6 months of enrollment; “recent users” were not currently using hormonal contraception but had used one within 6 months before enrollment; and “current users” were using hormonal contraception at the time of enrollment.

2.4. Study visits

Following the initial screening visit, women were assessed on their ability to enter study-related data into electronic diaries (eDiaries; LogPad 5.9.1 or LogPad LW 5.9.1 devices) over a 2-week period. eDiary data were transmitted as an XML document for analysis. Women were eligible for TDS initiation if they had 90% compliance with daily data entry and responded to 2 phone calls from the study site during that 2-week period.

At the patch initiation visit on the first day of the next menses, enrolled women were given instructions on patch application and subsequently applied the first patch onto the abdomen, buttock, or upper torso (excluding the breast) under direct supervision of an investigator. Women applied subsequent patches at home; sites reviewed instructions for at-home patch applications at each study visit. Women returned at cycles 2, 3, 5, 7, 9, and 13, when lab urine pregnancy tests were performed, concomitant medications, compliance, patch application site (skin), patch adhesion, and treatment-emergent adverse events (TEAEs) were recorded. Six telephone contacts were conducted between study visits to assess study medication and eDiary compliance and to record TEAEs. A Data Safety Monitoring Board regularly monitored the progress of the trial and made recommendations on whether the trial should be stopped, undergo modifications, or continue, based on periodic review of safety.

2.5. Populations and analysis datasets

The study defined 5 populations for analysis: Safety, Contraceptive Efficacy, intention-to-treat (ITT), Cycle Control, and Completer Population. The Safety Population included all women who wore ≥1 patch for any period; safety outcomes included incidence of TEAEs and study discontinuation information. The Contraceptive Efficacy population included women who wore ≥1 patch for any period and had a negative enrollment serum beta human chorionic gonadotropin (β-hCG). The ITT population was a subset of the Contraceptive Efficacy population that included all complete or incomplete cycles in which intercourse occurred and no backup contraception was used. The Cycle Control population included women in the Contraceptive Efficacy population who provided information on bleeding and patch application to assess scheduled and unscheduled bleeding/spotting days. Women who completed the study were included in the Completer Population.

Women received home pregnancy tests and were advised to test for pregnancy in the event of delayed patch application and/or symptoms concerning for pregnancy. Positive urine pregnancy test was confirmed using serum β-hCG testing, pelvic examination, and transvaginal ultrasound. An independent adjudication committee classified each pregnancy as pretreatment, on-treatment, or post-treatment; the sponsor and the FDA determined final pregnancy classification. The primary efficacy analysis (ITT) evaluated the Pearl Index (PI) in all women 18 to 35 years old. The PI was defined as the number of pregnancies times 1300, divided by the number of eligible 28-day on-therapy cycles; this yielded the number of pregnancies per 100 woman-years of product use. We counted all pregnancies where conception occurred after placement of the first patch or within 7 days of removal of the last patch. We included all complete or incomplete on-study cycles (excluding cycles where no intercourse occurred or when other contraceptives were used) in the denominator. We analyzed the primary endpoint by BMI subgroups using protocol-specified analyses and performed secondary efficacy analysis according to BMI above and below 30 kg/m^2. To estimate cumulative probabilities of pregnancy, we computed supportive life table analyses by Kaplan-Meier method within SAS PROC LIFETEST (SAS Institute, Cary, NC).

2.6. Cycle control evaluation

Women reported daily bleeding (use of ≥1 tampon or sanitary pad) and/or spotting (use of pantyliners or less) occurrence and in-

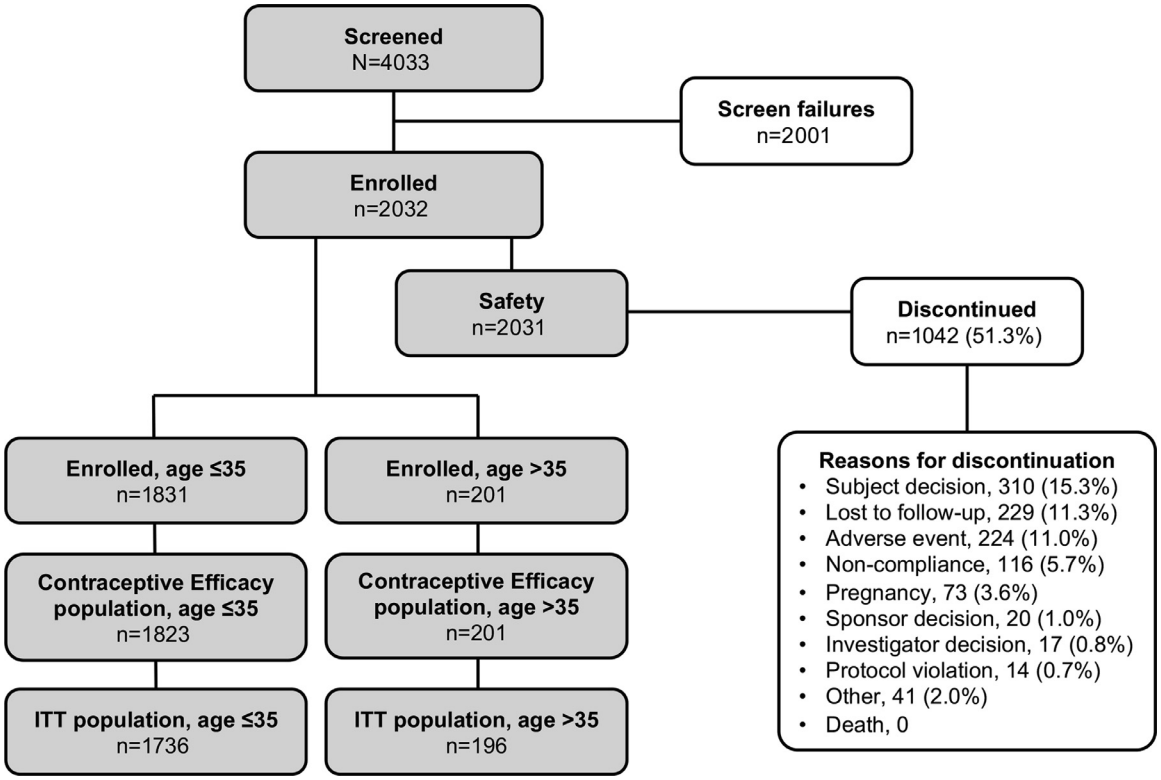

Fig. 1. Study population disposition of the SECURE study.
The Safety population included women who wore at least one patch for any period of time. The Contraceptive Efficacy population included women who wore at least one patch and had a negative enrollment serum β-hCG. The ITT population was a subset of the Contraceptive Efficacy population and included all complete or incomplete cycles in which intercourse occurred and no backup contraception was used.
[a]Reasons for screen failure included: medical reason, eDiary compliance, unwillingness to participate, abnormal pap test, limited ability to comply with protocol as deemed by the investigator, irregular menses, unwilling to use TDS.
ITT = intention-to-treat; TDS = transdermal delivery system.

tensity in their eDiaries. We defined a bleeding/spotting episode as ≥1 consecutive days of bleeding/spotting bounded on either side by ≥2 days of no bleeding/spotting. "Scheduled" bleeding/spotting occurred when the patch was not worn; "unscheduled" bleeding/spotting occurred while women wore a patch, except for when bleeding/spotting had begun in the previous hormone-free period and continued through no more than day 4 of the new treatment cycle.

2.7. Patch wearability

Women recorded patch application timing, anatomic placement, patch adhesion, patch site skin irritation/itching information, and reasons for unscheduled patch changes in daily eDiaries. Women graded patch adhesion as 0 = no lifting/small amount of lifting at patch edges, 1 = some edges showing lifting, 2 = at least half of system lifting, 3 = more than half of patch is lifted, but remains attached, or 4 = patch completely off. Skin irritation/itching were graded daily as 0 = none, 1 = mild, 2 = moderate, or 3 = severe. At each scheduled visit, investigators rated patch adhesion and irritation using the same scales.

3. Results

3.1. Enrollment, disposition, and participant characteristics

SECURE enrolled 2032 women, of whom 2031 were included in the Safety population and 1736 women in the ITT population, which included women ≤35 years who contributed 15,165 cycles in the primary efficacy PI analysis (Fig. 1). Overall, 48.7% women (989/2031) completed the study; of the 1042 women who discontinued the study prematurely, the most common reasons cited were woman's decision (15%, n = 310), lost to follow-up (LTFU; 11%, n = 229), and TEAE (11%, n = 224).

The mean ± SD age of participants was 27.5 ± 6.2 years (Table 1). Mean ± SD BMI was 28.3 ± 7.1 kg/m^2 (median: 26.8, range 15.1–63.0). One woman's weight was not recorded. Of 2030 women, 35.3% had BMI of ≥30 kg/m^2 including 7.5% who had BMI of ≥40 kg/m^2. The majority of the women in the Safety population were white (66.9%) and were of non-Hispanic/Latina origin (80.3%). Race and ethnicity were separately assessed. Most women (82.7%) had never used transdermal contraception, and 9.4% (n = 190) had never used systemic hormonal contraception.

3.2. Efficacy

The primary efficacy analysis for women ≤35 years old (ITT; n = 1736) yielded a PI (95% CI) of 5.8 (4.5–7.2) pregnancies per 100 woman-years (Table 2). Women with BMI <30 kg/m^2 had a lower PI (95% CI) (4.3, 2.9–5.8) than women with BMI ≥30 kg/m^2 (8.6, 5.8–11.5). BMI subgroup analysis showed a trend toward higher PIs as BMI increased (Fig. 2). PIs were lower for current (3.2, 1.5–4.8) and naïve (4.6, 0.6–8.6) contraceptive users than for former (7.5, 5.0–9.9) and recent (9.6, 4.6–14.7) users. The estimated life table cumulative pregnancy rate through Cycle 13 in all women ≤35 years in the Contraceptive Efficacy population (n = 1823) was 5.3% (Fig 3). Consistent with the differences in PI analysis by BMI, life table analysis followed similar outcomes with respect to BMI.

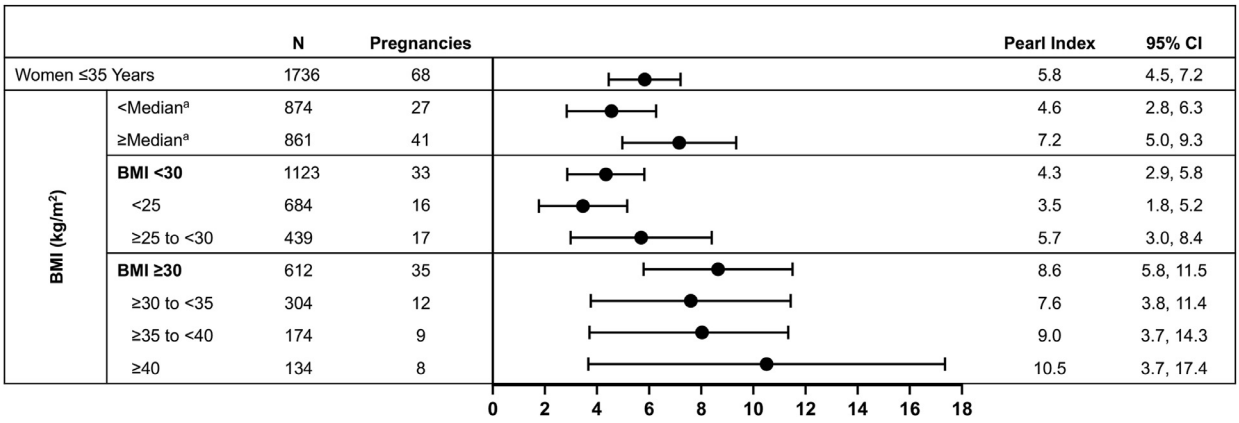

Fig. 2. Forest plot of the efficacy analyses in women ≤35 years by median BMI and BMI subgroups in the ITT dataset. [a]Median BMI was 26.8.
BMI = body mass index; ITT = intention-to-treat.

Table 1
Demographics, baseline characteristics, and previous contraceptive use in the phase 3 trial for TDS.

Characteristic	Overall (N = 2031)
Age in years, mean ± SD	27.5 ± 6.2
≤35	1830 (90.1)
>35	201 (9.9)
Race, n (%)	
White	1358 (66.9)
Black or African American	493 (24.3)
Asian	65 (3.2)
American Indian or Alaska Native	11 (0.5)
Native Hawaiian or Other Pacific Islander	8 (0.4)
Other	96 (4.7)
Ethnicity, n (%)	
Hispanic or Latina	400 (19.7)
Not Hispanic or Latina	1631 (80.3)
BMI (kg/m²), n (%)[a]	
Normal (<25)	800 (39.4)
Overweight (≥25 to <30)	513 (25.3)
Obese (≥30)	717 (35.3)
Previous contraceptive use[b]	
Naive	190 (9.4)
Former	875 (43.1)
Recent	262 (12.9)
Current	704 (34.7)
Naïve to transdermal contraceptive, n (%)	
Yes	1680 (82.7)
No	351 (17.3)

BMI, body mass index; SD, standard deviation; TDS, transdermal delivery system.
Safety population = women who wore at least one patch for any length of time.
[a] One woman's weight/BMI was not recorded (n = 2030).
[b] Naïve = women who have never used any hormonal contraceptive; Former = women with use of hormonal contraceptives >6 months before enrollment; Recent = women not currently using a hormonal contraceptive but who have used a hormonal contraceptive within 6 months of enrollment; Current = women who are currently using a hormonal contraceptive.

Table 2
Efficacy analysis of TDS in women ≤35 years old (ITT population), >35 years old, and overall.

Statistic	Age group ≤35 years (primary analysis)	>35 years	Overall
Number of women	1736	196	1932
Number of pregnancies	68	6	74
Number of cycles	15,165	1961	17,126
Pearl Index, 95% CI	5.8 (4.5–7.2)	4.0 (0.8–7.2)	5.6 (4.3–6.9)

ITT, intention-to-treat; TDS, transdermal delivery system.
ITT population = a subset of the Contraceptive Efficacy population that includes all complete or incomplete on-therapy cycles in which intercourse occurred and no back-up contraception was used (unless a woman became pregnant during the cycle).

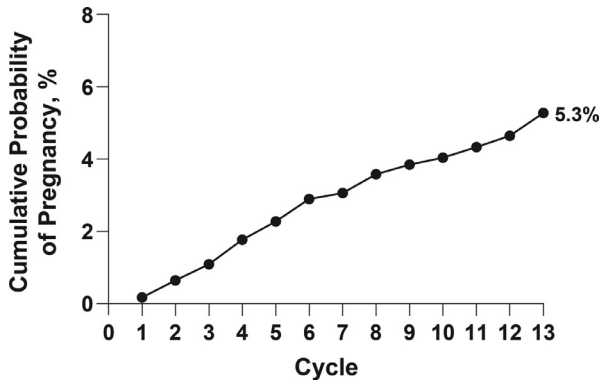

Fig. 3. Cumulative probability of pregnancy in women ≤35 years over 13 cycles of use with the TDS (Contraceptive Efficacy population).
Contraceptive Efficacy population = women who wore ≥1 patch and had a negative enrollment serum β-hCG.
TDS = transdermal delivery system.

3.3. Cycle control

In the Cycle Control population (n = 2017), the mean ± SD number of total bleeding/spotting days in a cycle decreased from 6.2 ± 4.5 in Cycle 1 to 4.9 ± 3.5 in Cycle 13 (Fig. 4). The percentage of women with no bleeding/spotting days (amenorrhea) in 13 cycles ranged from 6.3% to 11.9% (excluding days 1–7 in cycle 1). The mean ± SD number of scheduled bleeding/spotting days was 3.7 ± 2.5 in Cycle 2 and 3.3 ± 2.5 in Cycle 13. The proportion of women reporting ≥1 day of unscheduled bleeding/spotting decreased from 60.4% (Cycle 1) to 42.3% (Cycle 13). The mean ± SD number of unscheduled bleeding/spotting days ranged from 3.1 ± 3.4 in Cycle 1 to 1.6 ± 2.5 in Cycle 13. A total of 45 women (2.2%) discontinued the study due to bleeding/spotting-related TEAEs.

3.4. Safety

In the Safety population (n = 2031), 53.4% of women (n = 1085) reported experiencing a TEAE and 27.2% of women (n = 552) reported experiencing a study-drug related TEAE (Table 3). The incidence of TEAEs was similar between the 2 BMIs (<30 kg/m^2 and

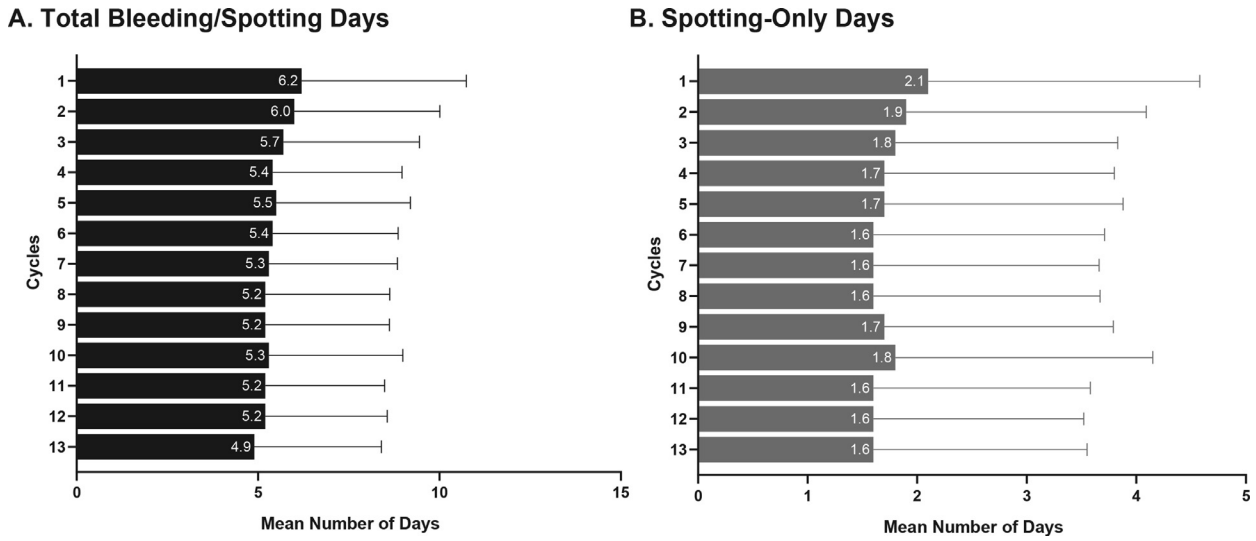

Fig. 4. Mean number (SD) of (**A**) total bleeding and/or spotting days and (**B**) spotting-only days by cycle in the Cycle Control population. Number within bars is the mean number of days.
Cycle Control population = women who contributed cycle data and reported bleeding and/or spotting data via eDiaries (n = 2017). Bleeding = evidence of blood loss on any cycle day that required the use of sanitary protection with at least one tampon or sanitary pad. Spotting = evidence of minimal blood loss on any cycle day that required the use of pantyliners only or no sanitary protection.
SD = standard deviation.

Table 3
Summary of women experiencing treatment-emergent adverse events with the TDS over 13 cycles of use by BMI category (Safety population).

	BMI category		
	<30 kg/m^2 (n = 1313)	≥30 kg/m^2 (n = 717)	Overall (N = 2031)
Women with any TEAE[a]·n (%)	700 (53.3)	381 (53.1)	1085 (53.4)
Women with study-drug related TEAE	361 (27.5)	188 (26.2)	552 (27.2)
TEAEs leading to early discontinuation, n (%)	153 (11.7)	69 (10.0)	224 (11.0)
Relationship of TEAEs, n (%)[b]			
Unrelated			533 (26.2)
Possibly related			286 (14.1)
Probably related			136 (6.7)
Definitely related			130 (6.4)
Intensity of TEAEs			
Mild			467 (23.0)
Moderate			526 (25.9)
Severe			92 (4.5)

BMI, body mass index; TDS, transdermal delivery system; TEAE, treatment-emergent adverse event.
Safety population = women who wore at least one patch for any length of time.
[a] Adverse events are coded using MedDRA version 18.1. TEAEs were defined as adverse events with an onset date on or after the first patch application through Day 28 of the woman's final treatment cycle.
[b] Assessed by the investigator.

≥30 kg/m^2) groups. The most frequently reported hormone-related TEAEs were nausea (4.1%, n = 84) and headache (3.6%, n = 72). Most women rated their highest severity TEAEs as mild (23.0%, n = 467) or moderate (25.9%, n = 526) in severity; 130 (6.4%) women reported experiencing at least one TEAE that was "definitely" related to treatment.

Of 2031 women, 40 women (2.0%) reported having experienced ≥1 serious TEAE (SAE) during the study (**Table 4**); 3.1% (22/717) were in the BMI ≥30 kg/m^2 group and 1.4% (18/1313) were in the BMI <30 kg/m^2 group. Between Cycles 5 and 13, 5 women, all with BMIs >30 kg/m^2, experienced 6 venous thromboembolism events (VTE; deep vein thrombosis [DVT], n = 3; pulmonary embolism [PE], n = 3). Of the 6 embolic events, investigators considered 5 events from 4 women related to treatment (DVT, n = 2; PE, n = 3). Three women with treatment-related VTE had at least one other potential risk factor, including family history of clots and recent air travel, and the fourth woman was diagnosed with new onset hyperthyroidism during her admission for PE. The fifth woman, who used the patch for 2 days, experienced a DVT postoperatively more than 2 months later; the FDA deemed it unrelated to treatment. No application site or bleeding SAEs were reported; no deaths were reported.

The most common hormone-related TEAE resulting in discontinuation was nausea (0.9%, n = 18), application site irritation (1.1%, n = 23), pruritus (0.8%, n = 16), rash (0.7%, n = 14), dermatitis (0.5%, n = 10), and erythema (0.4%, n = 9).

3.5. Compliance/Wearability

The most common site for patch placement was the buttock area (44.8%). Throughout the study, 78% of women applied all 3 patches per cycle; 7.1% of patches were changed at an unscheduled time with complete detachment cited as the most common reason (2.4%). During Cycles 1 to 13, <1% of women did not wear

Table 4
Summary of women experiencing serious treatment-emergent adverse events with use of the TDS over 13 cycles of use (Safety population).

	BMI category		
	<30 kg/m^2 (n = 1313)	≥30 kg/m^2 (n = 717)	Overall (N = 2031)
Women with SAEs, n (%)[a]	18 (1.4)	22 (3.1)	40 (2.0)
Cholelithiasis	0	4 (0.6%)	4 (0.2%)
Deep vein thrombosis	0	3 (0.4%)	3 (0.2%)
Pulmonary embolism	0	3 (0.4%)	3 (0.2%)
Major depression	1 (0.1%)	2 (0.3%)	3 (0.2%)
Cholecystitis	0	2 (0.3%)	2 (0.1%)
Ectopic pregnancy	0	2 (0.3%)	2 (0.1%)
Gastroenteritis	2 (0.2%)	0	2 (0.1%)
Relationship of SAEs, n (%)[b]			
Unrelated			25 (1.2)
Possibly related			12 (<1)
Probably related			3 (<1)
Definitely related			0
Intensity of SAEs			
Mild			1 (<1)
Moderate			13 (<1)
Severe			26 (1.2)

BMI, body mass index; SAE, serious treatment-emergent adverse event; TDS, transdermal delivery system.
Safety population = women who wore at least one patch for any length of time.
[a] Adverse events are coded using MedDRA version 18.1. A SAE is treatment-emergent if it has an onset date on or after the first patch application.
[b] Assessed by the investigator.

the patch on ≥2 consecutive days during cycle days 1–21 per cycle. During Cycles 2 to 13, the percentage of women with >7 days between last patch removal and first patch application in the subsequent cycle ranged from 3.9% to 7.1%.

Most investigators (99.4%) and women (88.7%) reported adhesion scores of 0 = no detachment or 1 = some edge lifting. Women reported improvement in adhesion scores over time (0/1 score: Cycle 2, 84.1%; Cycle 13, 92.5%). In total, 5.0% of the cumulative number of patches applied completely detached (Score = 4); complete detachment rates decreased over time (Cycle 1, 9.9%; Cycle 13, 2.4%). Low rates of moderate/severe irritation were reported by investigators (2/3 score: Cycle 2, 0.2%; Cycle 13, 0.3%; overall, 0.5%) and by women (Cycle 2, 6.9%; Cycle 13, 4.7%; overall, 6.3%); itching was reported by 13.1% and 9.6% of women in Cycle 2 and Cycle 13, respectively.

4. Discussion

The phase 3 SECURE trial demonstrated the safety and efficacy of the LNG/EE TDS in a demographically representative US population of women, using stringent design and analysis methods reflected in the 2019 FDA Draft Guidance "Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy" [3,4]. The SECURE trial did not restrict eligibility based on weight or BMI. The rigorous study design, distinguishing study features, and regular and frequent pregnancy testing ensured accurate determination of pregnancy.

The primary efficacy analysis yielded a PI of 5.8 (ITT). Women with BMI <30 kg/m^2 had a PI of 4.3 but effectiveness was reduced in women with BMI ≥30 kg/m^2. These results are consistent with results from the FDA meta-analysis demonstrating a tendency of higher pregnancy rate with combined hormonal contraceptive (CHC) by obese women (BMI ≥30 kg/m^2) than nonobese women [8]. The higher proportion of women with elevated BMIs enabled evaluation of these groups independently and distinguishes the study from other phase 3 CHC trials. The use of eDiaries with associated prompts and reminders might result in greater compliance than in the general population outside of a clinical trial. A woman was considered "noncompliant" if she entered a "no" response to patch wear in her eDiary for ≥2 consecutive days during days 1 to 21 of each cycle. Self-reported noncompliance rates were low (0%–0.8% in Cycles 1–13), so it is difficult to evaluate between pregnancy rates due to noncompliance. Additional analyses could evaluate whether compliance was impacted by other parameters, such as BMI [9,10]. The overall discontinuation rate in SECURE was 51.3%, similar to rates seen in other phase 3 CHC trials. The segesterone acetate vaginal ring study [11] and various oral LNG/EE studies [12,13] report discontinuation rates between 42% and 57%. Additionally, the LTFU rate in SECURE (11%) fell within the range of the LTFU rates reported in these studies (10%–16%). Overall, the efficacy results suggest that the aggregate effect of all these design elements, in particular the enrollment of women without BMI exclusions, had substantial impacts on contraceptive effectiveness.

The TDS was well tolerated, with low rates of patch detachment and site irritation. Most TEAEs were mild or moderate; SAE rates were low. Five women all with BMI ≥30 kg/m^2 experienced 6 embolic events, of which 4 women were considered to have study-drug related events consistent with the increased baseline risk of embolic events in obese women [14]. Due to increased risk of VTE and reduced efficacy in women with BMI ≥30 kg/m^2 from SECURE, TDS is contraindicated in these women. As patient populations in contraceptive trials such as SECURE become more representative of the real-world population, rates of embolic events may be higher than seen in past studies, with absolute risk remaining relatively low in women with BMI <30 kg/m^2.

The results of the primary efficacy analysis, in conjunction with key secondary and subgroup efficacy analyses, demonstrate that TDS was effective in preventing pregnancy in a diverse population of sexually active, reproductive-aged US women. The SECURE trial results led to the FDA approval of TWIRLA® in February 2020 as a contraceptive method for women with BMI <30 kg/m^2. TDS addresses a gap in the contraceptive landscape by offering nonobese women a nondaily transdermal contraceptive option that reduces estrogen exposure with favorable efficacy, safety, and tolerability [1,15].

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Clinical trial registration: This clinical trial was registered at www.ClinicalTrials.gov as: NCT02158572; Efficacy, Safety and Tolerability Study of Agile AG200-15 Transdermal Contraceptive Delivery System. The URL can be found at: https://clinicaltrials.gov/ct2/show/NCT02158572.

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Declaration of competing interest:

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

ALN: Consultant/Advisor: Agile Therapeutics, Inc., AMAG, American Regent, Bayer HealthCare, Merck, Sebela Pharmaceuticals, TherapeuticsMD; Honoraria/Speaker: American Regent, Bayer HealthCare, Merck, TherapeuticsMD; Grants/Research Support: Agile Therapeutics, Inc., Mayne Pharma, Merck, Myovant Sciences, Sebela Pharmaceuticals.

AMK: Consultant/Advisor: Merck, Mithra, Pfizer; Research Support (institution): AbbVie, Agile Therapeutics, Inc., Mithra.

RK: Research Support: Astellas, Myovant Sciences, Sebela, TherapeuticsMD.

JAS: Consultant/Advisor: AbbVie, Allergan, AMAG, Amgen, Ascend, Azure, Millendo, Nuelle, Radius, Regeneron, Roivant, Sanofi, Sebela Pharmaceuticals, Sermonix, Shionogi, Symbiotec, TherapeuticsMD, Valeant; Speaker: Novo Nordisk, Shionogi, Valeant; Research Support: AbbVie, Agile, Allergan, Bayer HealthCare, New England Research Institute, Palatin, Symbio, TherapeuticsMD; Stock Ownership: Sermonix.

ANP: Consultant/Advisor: Agile Therapeutics, Inc., Allergan, Bayer HealthCare, Pfizer; Research Support: Agile Therapeutics, Inc.

PMC: Consultant/Advisor: Bayer HealthCare, Merck; Research Support: Agile Therapeutics, Inc., Bayer HealthCare.

RTA: Research Support: Abbott, AbbVie, Agile Therapeutics, Inc., Allergan, Acoustic Wave, Sebela Pharmaceuticals, Starpharma, VivEve.

JAC: Employee: Agile Therapeutics, Inc., Princeton, NJ.

LF: Employee/Consultant: Agile Therapeutics, Inc., Princeton, NJ.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.contraception.2020.11.011.

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