

Pharmacokinetics, tolerability and cycle control of three transdermal contraceptive delivery systems containing different doses of ethinylestradiol and levonorgestrel

Frank Z. Stanczyk^{1,*}, Arkady Rubin², Lisa Flood² and Marie Foegh²

¹Departments of Obstetrics and Gynecology and Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

²Agile Therapeutics, Inc., Princeton, NJ, USA

Abstract

Background: The only available contraceptive patch, Ortho Evra[®], delivers a relatively high dose of estrogen.

Materials and methods: Three transdermal contraceptive delivery systems (TCDS) containing low doses of ethinylestradiol (EE) and levonorgestrel (LNG) were evaluated in two open-label randomized trials. In a phase 1, two-period, cross-over trial, AG200-12.5 and AG200LE were compared with a 150 µg LNG/30 µg EE oral contraceptive (OC) (Levlen[®]) in 39 women. In a phase 2, parallel-group, multicenter, three-cycle study, AG200LE, AG200-12.5 and a higher-dose formulation, AG200-15, were evaluated in 123 women.

Results: In Study 1, mean steady-state plasma concentrations (C_{ss} , pg/mL) for the TCDS were 17 pg/mL to 26 pg/mL for EE and 1117 pg/mL to 1505 pg/mL for LNG (for AG200LE and AG200-12.5 respectively). Maximum concentration (C_{max}) and C_{ss} for both analytes were significantly lower than for Levlen. In both studies, the C_{ss} levels for EE and LNG in all groups were within the ranges reported for low-dose OCs. Cycle control for AG200-15, assessed by breakthrough bleeding and spotting episodes as well as number of days of unscheduled bleeding and/or spotting, was similar to that reported for low-dose OCs. Most adverse events were considered mild to moderate in intensity. The incidence of patches falling off was <2%.

Conclusions: All three patches exhibited excellent safety and wearability profiles while maintaining plasma drug levels required for ovulation suppression and adequate cycle control. A slight increase in the EE dose in AG200-15 still places this TCDS within the range of low-dose OCs, with EE exposure much lower than reported for Ortho Evra. AG200-15 was selected for further testing in phase 3 studies.

Keywords: ethinylestradiol; levonorgestrel; oral contraceptive; pharmacokinetics; transdermal contraceptive patch.

*Corresponding author: Frank Z. Stanczyk, PhD, Reproductive Endocrine Research Laboratory, Livingston Research Building, Room 201, 1321 N. Mission Road, Los Angeles, CA 90033, USA Phone: +1 323 226 3220, E-mail: fstanczyk@socal.rr.com Received November 19, 2010; accepted January 12, 2011; previously published online March 8, 2011

Introduction

Although oral contraceptives (OCs) are one of the most effective reversible contraceptive methods used, they have a 9% probability of failure in the USA during the first 12 months of use [1]. Compliance problems with OCs are common and are an underlying cause of OC failure. Patient surveys estimate that approximately one-half of women miss at least one pill per cycle and up to one-quarter miss at least two pills per cycle [2–4]. Pregnancy rates range from 3% to 8% with poor compliance compared with 0.1%–2% for consistent users of OCs [5–7].

Transdermal contraceptive delivery via a skin patch applied once per week is an attractive option for patients who cannot comply with daily OCs. Several studies demonstrate increased adherence with the use of a skin patch compared with a daily OC pill [7–9]. Studies also report higher patient satisfaction levels with the use of a skin patch compared with a daily OC pill [9–11]. However, the only currently available contraceptive patch, Ortho Evra[®] (Ortho-McNeil-Janssen Pharmaceuticals, Inc., Raritan, NJ, USA), is associated with estrogen exposure that is approximately 60% higher than combination OCs containing ethinylestradiol (EE) 35 µg [12]. This observation has resulted in a warning from the US Food and Drug Administration pertaining to a possible increased risk of estrogen-related adverse events (AEs), including venous thromboembolism [13–15]. Consequently, there is a need for an efficacious and well-tolerated contraceptive patch with estrogen delivery similar to low-dose combination OCs. A weekly contraceptive patch that utilizes transdermal technology to deliver a low dose of EE in combination with levonorgestrel (LNG) is under development. This article presents data from two studies performed to evaluate the pharmacokinetic profile, cycle control, safety and tolerability of three transdermal contraceptive delivery systems (TCDS) containing three different amounts of EE and two different amounts of LNG.

Materials and methods

Study population

Two studies enrolled healthy, non-smoking women aged 18–45 years who had a 24- to 35-day menstrual cycle. Subjects were enrolled if they were normotensive with systolic blood pressure below 140 mm Hg and diastolic blood pressure under 90 mm Hg and had a body mass index between 18 kg/m² and 32 kg/m² inclusive. Subjects were required to use a non-hormonal method of con-

Table 1 Contraceptive patch formulations.

Patch	Quantity in patch (intended daily dose)		Patch size (cm ²)	
	LNG	EE	Active matrix core	Overall area
AG200LE (Study 1 and 2)	2.17 mg (75 µg/day)	1.28 mg (15 µg/day)	12.5	25.0
AG200-12.5 (Study 1 and 2)	2.17 mg (100 µg/day)	1.92 mg (20 µg/day)	12.5	25.0
AG200-15 (Study 2)	2.60 mg (120 µg/day)	2.30 mg (25 µg/day)	15.0	26.0

LNG, levonorgestrel; EE, ethinylestradiol.

trapection for the entire duration of the study or to have undergone previous tubal ligation. Use of over-the-counter medications, alcohol and grapefruit juice was prohibited in the first (pharmacokinetic) study. All subjects read and signed an informed consent document prior to participation.

Subjects were excluded from the study if they were pregnant or breast-feeding or if they had a history of significant illness or any disorder that contraindicated the use of contraceptive steroids, dermal hypersensitivity in response to topical applications, a recent abnormal cervical Pap smear, or positive hepatitis B, hepatitis C or HIV antibody test. Subjects who had used OCs or other sex steroid hormones, a contraceptive implant or hormone-medicated intrauterine device or an injectable hormonal contraceptive within the past 1, 2 and 6 months, respectively, or medications that might interfere with the metabolism of hormone contraceptives within 3 months of screening were also excluded from the study.

Studies design

Study 1 (ATI-CL10) Two contraceptive patches, AG200-12.5 and AG200LE, designed to deliver either 100 µg/day LNG with 20 µg/day EE or 75 µg/day LNG with 15 µg/day EE, respectively (Table 1), and an approved 150 µg LNG/30 µg EE OC (Levlen®; Bayer HealthCare Pharmaceuticals, Montville, NJ, USA) were evaluated in this single-center, open-label, randomized, two-period, cross-over study. The study was conducted at Heart of America Research Institute, Inc. (Shawnee Mission, KS, USA) from May to November 2007. Study protocol and informed consent were approved by an independent Investigational Review Board.

Study 1 consisted of a screening period of at least 7 days, a 7-day placebo patch run-in period, two 21-day treatment periods separated by a washout period of 21–28 days and a post-treatment follow-up (final) visit (Figure 1). After obtaining written informed consent and screening for eligibility, a placebo patch was placed on the subject's lower abdomen and subjects were given a diary card to record patch adherence. One week later, the patch and application site were visually inspected by site personnel and subjects demonstrating good patch adherence and minimal to no irritation were randomly assigned to one of four treatment sequences: (i) AG200-12.5 followed by AG200LE; (ii) AG200-12.5 followed by Levlen; (iii) AG200LE followed by AG200-12.5; and (iv) AG200LE followed by Levlen (Figure 1). During each treatment period, subjects wore patches for three consecutive 7-day periods, totalling 21 days, or took Levlen daily for 21 days. The total study duration for each subject was approximately 3 months.

Study 2 (ATI-CL11) Three contraceptive patches, AG200LE, AG200-12.5 and AG200-15, designed to deliver 75 µg/day LNG with 15 µg/day EE, 100 µg/day LNG with 20 µg/day EE or 120 µg/day LNG with 25 µg/day EE, respectively (Table 1), were

evaluated in this multicenter, open-label, randomized, parallel-group study (Part I), which was followed by a multicenter, open-label, single-arm extension (Part II). Part I of the study evaluated AG200-12.5 and AG200LE, whilst Part II evaluated AG200-15, a third contraceptive patch with the same formulation as AG200-12.5 but with a 20% larger drug delivery area (Table 1). The study was conducted at 13 clinical research centers located throughout the USA between September 2007 and February 2008.

After providing informed consent, eligible subjects in Part I were randomly assigned to receive either AG200-12.5 or AG200LE for three cycles (Figure 2). In Part II of the study, another group of subjects received AG200-15 for three cycles (Figure 2). Enrolled subjects applied the contraceptive patch to the lower abdomen on the morning of Cycle Day 1 (Day 1 of their menstrual cycle). The patch was replaced on Cycle Days 8 and 15 and was removed without being replaced on the morning of Cycle Day 22. Subjects were to record in their diary cards information about patch wear, including dates of patch applications, reasons for unscheduled patch replacements and information about daily occurrence of bleeding and spotting. During office visits, the diary cards were reviewed for accuracy and patient compliance.

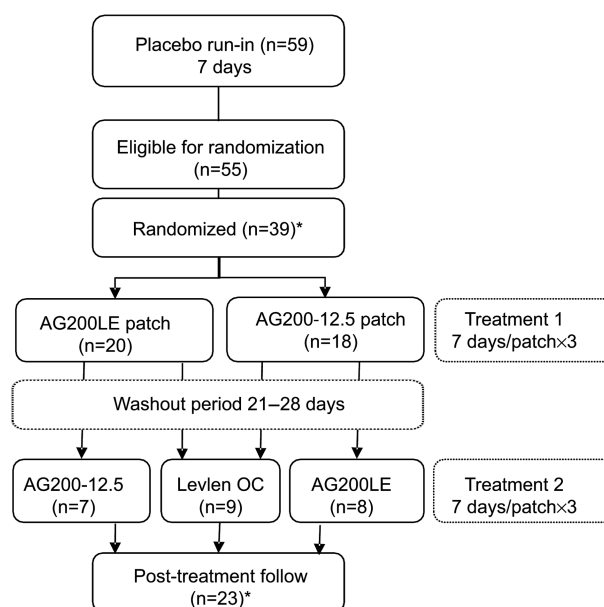


Figure 1 Patient disposition and study design for Study 1. *Twenty subjects (33.9%) discontinued after placebo run-in and 16 randomized subjects (27.1%) prematurely discontinued because of consent withdrawal, loss to follow-up, adverse events or non-compliance. One of the 16 subjects withdrew consent prior to patch application.

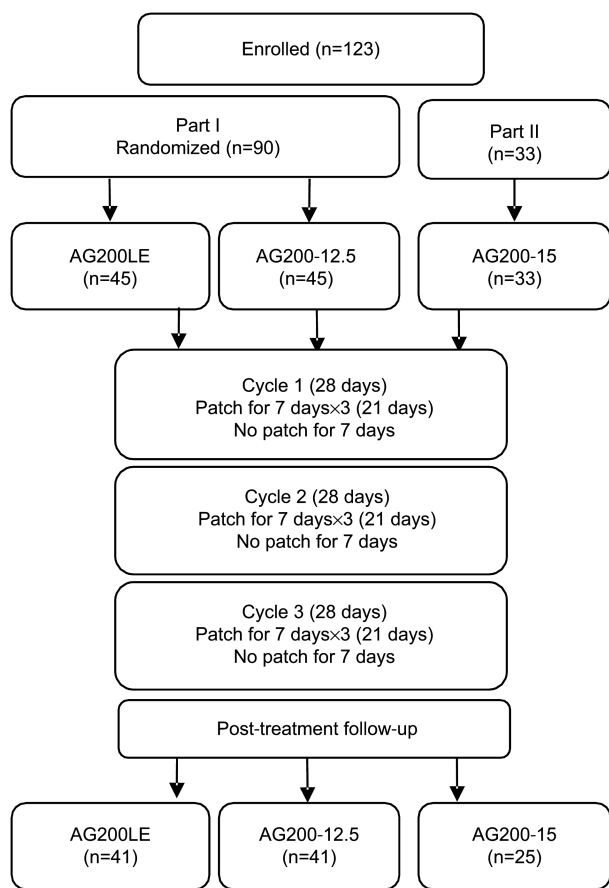


Figure 2 Patient disposition and study design for Study 2.

Study drugs

Three contraceptive patch formulations containing different quantities of EE and LNG were evaluated (Table 1). All patches were supplied by Corium International (Grand Rapids, MI, USA) and contained, in addition to EE and LNG, vinylpyrrolidone/vinyl acetate copolymer, dimethyl sulphoxide, lauryl lactate, ethyl lactate, capric acid and DURO-TAK® 87-4098 acrylic adhesive. Placebo patches contained these same components without LNG and EE. In Study 1, each Levlen tablet contained 30 µg EE and 150 µg LNG.

Pharmacokinetics

All plasma samples were frozen and shipped to the bioanalytical laboratory PPD (Richmond, VA, USA) for analysis. Plasma concentrations of LNG and EE were determined via a validated liquid chromatography/mass spectrometry method.

In Study 1, serial blood samples were collected immediately prior to dosing (time point 0) and at 6, 12, 24, 48, 72, 96, 120, 144 and 168 h after application of the first and third patch, as well as at 6, 12, 24, 48 and 72 h after removal of the third patch. For OC (Levlen) treatment cycles, blood sampling was performed on Treatment Days 1 and 21 immediately prior to dosing (time point 0), at 0.5, 1, 1.5, 3, 6, 9, 12, 16 and 24 h following dosing and at 36, 48 and 72 h following administration of the last dose on Day 21. Parameters describing the pharmacokinetics of EE and LNG after contraceptive patch or OC administration were calculated, including maximum plasma concentration (C_{max}), areas under the plasma concentration-time curve from time 0 to various time points (e.g., $AUC_{0-24\text{ h}}$, $AUC_{0-168\text{ h}}$) deter-

mined using linear trapezoidal summation, average 24-h concentration (C_{avg}) for OC treatment cycles, steady-state concentration (C_{ss}) for TCDS cycles, and time to reach C_{max} .

In Study 2, drug plasma concentration levels were obtained at Cycle Days 8, 15 and 22 of all treatment cycles.

Cycle control

In Study 2, cycle control assessments were based on bleeding/spotting information recorded by subjects on daily diary cards. The primary endpoint was subject incidence of breakthrough bleeding and/or spotting episodes in Cycle 3. Another important endpoint was the number of bleeding and/or spotting days across the three treatment cycles that are not a part of withdrawal bleeding (“unscheduled” bleeding and/or spotting days). Spotting was defined as bloody vaginal discharge that did not require sanitary protection, and bleeding was defined as bloody vaginal discharge that required sanitary protection.

Safety

Safety was assessed by tracking AEs, discontinuation information and vital signs as well as changes in physical and gynecological examinations and laboratory tests from screening to the end of the study. All subjects who received any amount of study drug were included in the safety analyses.

Patch wearability

In Study 1, patch wearability was evaluated based on subject self-assessment of patch adhesion and site personnel assessment of irritation. Patch adhesion metrics included presence or detachment of patch, and skin irritation assessments were scored as none, mild, moderate or significant.

In Study 2, evaluations of patch wearability and adhesion were based on information recorded by subjects on the diary cards (patch presence and/or reasons for unscheduled patch change). Skin irritation information was collected by monitoring of related AEs.

Statistical methods

In Study 1, pharmacokinetic parameters for individual subjects were evaluated using a non-compartmental pharmacokinetic analysis model with WinNonlin 5.0.1 (Pharsight Corporation, St. Louis, MO, USA) software. Scheduled sampling time points were used for the calculations. Pharmacokinetic parameters of the two contraceptive patches and Levlen were compared. Between-treatment statistical comparisons were based on the parametric analysis of variance model.

In Study 2, for the primary cycle control endpoint, two-sided 95% confidence intervals (CI) for the differences across the treatment groups (AG200-12.5 vs. AG200LE, AG200-12.5 vs. AG200-15, and AG200LE vs. AG200-15) were provided. CIs not including zero were interpreted as the presence of a statistically significant treatment difference at the 0.05 significance level.

Results

Demographic characteristics and disposition

In Study 1, 59 healthy women were enrolled in the placebo run-in period and 39 subjects were randomized to receive study medication (Figure 1). Twenty-three randomized subjects (60.5%) completed the study. Most premature discon-

Table 2 Subject demographics and baseline characteristics for Study 1.

Characteristic	Population	
	All screened subjects (n=59)	All treated subjects (n=38)
Age (years)		
Mean (SD)	28.9 (7.83)	27.4 (7.55)
Range	18–45	18–42
Race [n (%)]		
Caucasian	30 (50.8)	21 (55.3)
Black	26 (44.1)	15 (39.5)
Other	3 (5.1)	2 (5.3)
Weight (kg)		
Mean (SD)	66.9 (12.10)	66.8 (10.58)
Range	48.1–104.3	49.9–93.9
Height (cm)		
Mean (SD)	164.4 (6.08)	164.6 (5.22)
Range	149.9–177.8	152.4–172.7
BMI (kg/m ²)		
Mean (SD)	24.7 (3.93)	24.6 (3.49)
Range	17.6–36.0	18.9–31.5

SD, standard deviation; BMI, body mass index.

tinuations resulted from withdrawal of informed consent (n=6). Only two subjects discontinued the study because of AEs. A summary of demographics and baseline characteristics for the screened and randomized populations is presented in Table 2.

In Study 2, a total of 123 women were enrolled and 107 subjects completed the study (Figure 2). The most common reasons for discontinuation were subject decision (n=3), AEs (n=3) and sponsor decision (n=3). Five enrolled subjects did not take the study drug and were excluded from all safety and efficacy analyses. Therefore, data from 118 subjects are summarized. Demographics for Study 2 were similar across all three treatment groups (Table 3).

Pharmacokinetics

Major pharmacokinetic parameters in Study 1 are summarized by treatment group in Tables 4 and 5 for EE and LNG,

respectively. Mean plasma concentrations of EE and LNG over the first and third weeks of patch wear during the first treatment period are plotted in Figure 3A and B. There was a general trend of increased EE exposure in Week 3 compared with Week 1 for each treatment (Table 4). However, this increase in EE exposure was less notable both in terms of increase and percentage increase than observed among subjects in the Levlen treatment group (Table 4). From Week 1 to Week 3 of patch wear, mean C_{max} increased 6% and 10%, mean AUC increased 31% and 33%, and mean C_{ss} increased 24% and 21% for AG200-12.5 and AG200LE, respectively, whereas with Levlen mean C_{max} increased 35%, mean AUC increased 53%, and mean C_{ss} increased 54% (Table 4). There was also a general trend of increased LNG exposure over the 21-day treatment period with both TCDSS and Levlen (Table 5). For AG200-12.5 and AG200LE, respectively, increases of 35% and 40% in mean C_{max} , 172% and 160% in mean AUC, and 149% and 139% in mean C_{ss}

Table 3 Demographics and baseline characteristics for Study 2 (subjects receiving study drug).

Characteristic	AG200LE (n=43)	AG200-12.5 (n=44)	AG200-15 (n=31)
Age (years)			
Mean (SD)	31.7 (7.4)	31.0 (6.9)	32.1 (7.8)
Range	19–45	18–45	18–43
Race [n (%)]			
Black	9 (21)	10 (23)	12 (39)
Caucasian	29 (68)	32 (73)	17 (55)
Other	5 (12)	2 (5)	2 (6)
BMI (kg/m ²)			
Mean (SD)	28.7 (6.0)	27.7 (6.6)	27.5 (7.0)
Range	19–46	18–45	17–52
Weight (lb)			
Mean (SD)	170.4 (36.8)	167.9 (42.6)	164.5 (44.8)
Range	101–285	99–262	109–315

SD, standard deviation; BMI, body mass index.

Table 4 Pharmacokinetic data for serum ethinylestradiol concentrations over all treatment cycles in Study 1.

Pharmacokinetic parameter	Treatment		
	AG200-12.5 (n=25)	AG200LE (n=28)	Levlen® (n=9)
C_{max} , pg/mL			
Days 1–8			
Mean (SE)	33 (2.4)	21 (1.3)	80 (21)
Median	31	20	58
CV%	37	34	76
Days 15–22			
Mean (SE)	35 (2.7)	23 (1.8)	108 (11)
Median	32	22	105
CV%	36	41	29
C_{ss} , pg/mL ^a			
Days 2–8			
Mean (SE)	21 (1.4)	14 (0.7)	33 (7.4)
Median	19	14	25
Days 15–22			
Mean (SE)	26 (2.2)	17 (1.2)	51 (4.0)
Median	24	17	51
AUC, pg day/mL ^b			
Days 1–8			
Mean (SE)	141 (9.7)	92 (4.7)	158 (32)
Median	128	93	130
CV%	33	27	60
Days 15–22			
Mean (SE)	185 (15.2)	122 (8.2)	242 (22)
Median	167	116	244
CV%	38	34	26
T_{max} (h) ^c			
Days 1–10			
Median	192	192	1.5
Days 15–24			
Median	48	48	1.0
Comparison of AG200LE, AG200-12.5 and Levlen: mean daily AUC, pg day/mL			
Days 1–8			
Mean (SD)	20.1 (6.6)	13.2 (3.5)	22.5 (13.5)
	p<0.05 vs. AG200LE	p<0.05 vs. Levlen	
Days 15–22			
Mean (SD)	26.4 (10.0)	17.5 (6.0)	34.5 (9.0)
	p<0.05 vs. Levlen	p<0.05 vs. Levlen	
	p<0.05 vs. AG200LE		

C_{max} , maximum plasma concentration; C_{ss} , mean steady-state plasma concentration; AUC, area under the concentration-time curve; T_{max} , time to reach C_{max} ; CV, coefficient of variation; SD, standard deviation; SE, standard error. ^aFor Levlen, average concentration levels over 24-h period are reported. ^bFor Levlen, calculated AUCs over 7-day period are reported. ^cFor Levlen, T_{max} for Days 1–4 and Days 21–24 are reported.

were observed. With Levlen, the LNG mean C_{max} increased 38%, mean AUC increased 72%, and mean C_{avg} increased 66% from Week 1 to Week 3 (Table 5).

Overall, exposure to EE as measured by C_{max} , C_{ss} and AUC was substantially lower during treatment with AG200LE compared with AG200-12.5 (Table 4). Although AG200LE and AG200-12.5 were designed to deliver equivalent doses of LNG, there was a trend toward lower LNG exposure with AG200LE compared with AG200-12.5 (Figure 3C and D). This may be explained by the pharmacodynamic interactions between EE, LNG and sex hormone-binding globulin (SHBG): the latter is directly correlated with EE concentration levels and increased SHBG levels trigger higher LNG plasma concentrations. Importantly,

mean daily exposure to LNG and EE during treatment with either AG200-12.5 or AG200LE was significantly lower ($p<0.05$) than EE and LNG exposure during Levlen treatment, with the exception of EE exposure for AG200-12.5 compared with Levlen during the first week of treatment (Tables 4 and 5).

The mean and median EE and LNG levels across all three cycles for Study 2 are plotted in Figure 4 for subjects treated with AG200LE, AG200-12.5 and AG200-15. As expected, the EE and LNG levels were lowest for AG200LE and highest for AG200-15. Mean EE concentrations ranged from 11 pg/mL to 17 pg/mL with AG200LE, from 18 pg/mL to 27 pg/mL with AG200-12.5 and from 24 pg/mL to 33 pg/mL with AG200-15 (Figure 4). For LNG, mean levels ranged

Table 5 Pharmacokinetic data for serum levonorgestrel concentrations over all treatment cycles in Study 1.

Pharmacokinetic parameter	Treatment		
	AG200-12.5 (n=25)	AG200LE (n=28)	Levlen® (n=9)
C_{max} , pg/mL			
Days 1–8			
Mean (SE)	1405 (162)	1059 (96)	3462 (312)
Median	1150	929	2990
CV%	58	48	27
Days 15–22			
Mean (SE)	1896 (184)	1420 (144)	4790 (624)
Median	1650	1155	4305
CV%	45	52	37
C_{ss} , pg/mL ^a			
Days 2–8			
Mean (SE)	604 (71)	467 (37)	1657 (308)
Median	503	409	1470
Days 15–22			
Mean (SE)	1505 (163)	1117 (106)	2751 (385)
Median	1269	881	2674
AUC, pg d/mL ^b			
Days 1–8			
Mean (SE)	3874 (452)	2999 (239)	9107 (2219)
Median	3195	2665	7203
CV%	55	41	73
Days 15–22			
Mean (SE)	10,540 (1141)	7819 (742)	15,659 (2380)
Median	8879	6167	16,107
CV%	50	34	43
T_{max} (h) ^c			
Days 1–10			
Median	216	216	1.5
Days 15–24			
Median	48	48	1.3
Comparison of AG200LE, AG200-12.5 and Levlen: mean daily AUC, pg d/mL			
Days 1–8			
Mean (SD)	553 (303)	428 (177)	1301 (952)
	p<0.0001 vs. Levlen	p<0.0001 vs. Levlen	
Days 15–22			
Mean (SD)	1506 (746)	1117 (541)	2237 (962)
	p<0.05 vs. Levlen	p<0.05 vs. Levlen	

C_{max} , maximum plasma concentration; C_{ss} , mean steady-state plasma concentration; AUC, area under the concentration-time curve; T_{max} , time to reach C_{max} ; SE, standard error; SD, standard deviation; CV, coefficient of variation. ^aFor Levlen, average concentration levels over 24-h period are reported. ^bFor Levlen, calculated AUCs over 7-day period are reported. ^cFor Levlen, T_{max} for Days 1–4 and Days 21–24 are reported.

from 443 pg/mL to 774 pg/mL with AG200LE, from 653 pg/mL to 1165 pg/mL with AG200-12.5 and from 771 pg/mL to 1392 pg/mL with AG200-15. No notable increase in LNG and EE plasma concentration levels was observed over the duration of the study (Figure 4).

Cycle control

In Study 2, the primary endpoint for the cycle control evaluation was the subject incidence of breakthrough bleeding or spotting episodes in Cycle 3 (Table 6). In the AG200-15 group, 85% of women reported no breakthrough bleeding or spotting in Cycle 3 compared with 71% in the AG200LE and AG200-12.5 groups. Treatment differences in the incidence of breakthrough bleeding/spotting episodes were not

statistically significant (AG200LE vs. AG200-12.5, 95% CI –19.3 to 19.3; AG200LE vs. AG200-15, 95% CI –5.4 to 32.9; and AG200-12.5 vs. AG200-15, 95% CI –5.4 to 32.9), possibly because of the relatively small sample size. The number of unscheduled bleeding and/or spotting days across the three cycles of therapy also exhibited a dose-response correlation and was within ranges expected for the low-dose combined hormonal contraceptives (Table 6) [16, 17].

Safety

In Study 1, a total of 19 (76.0%) and 17 (60.7%) subjects reported AEs following application of AG200-12.5 or AG200LE, respectively, over two cycles of therapy. Safety data for the two patches were collected approximately twice

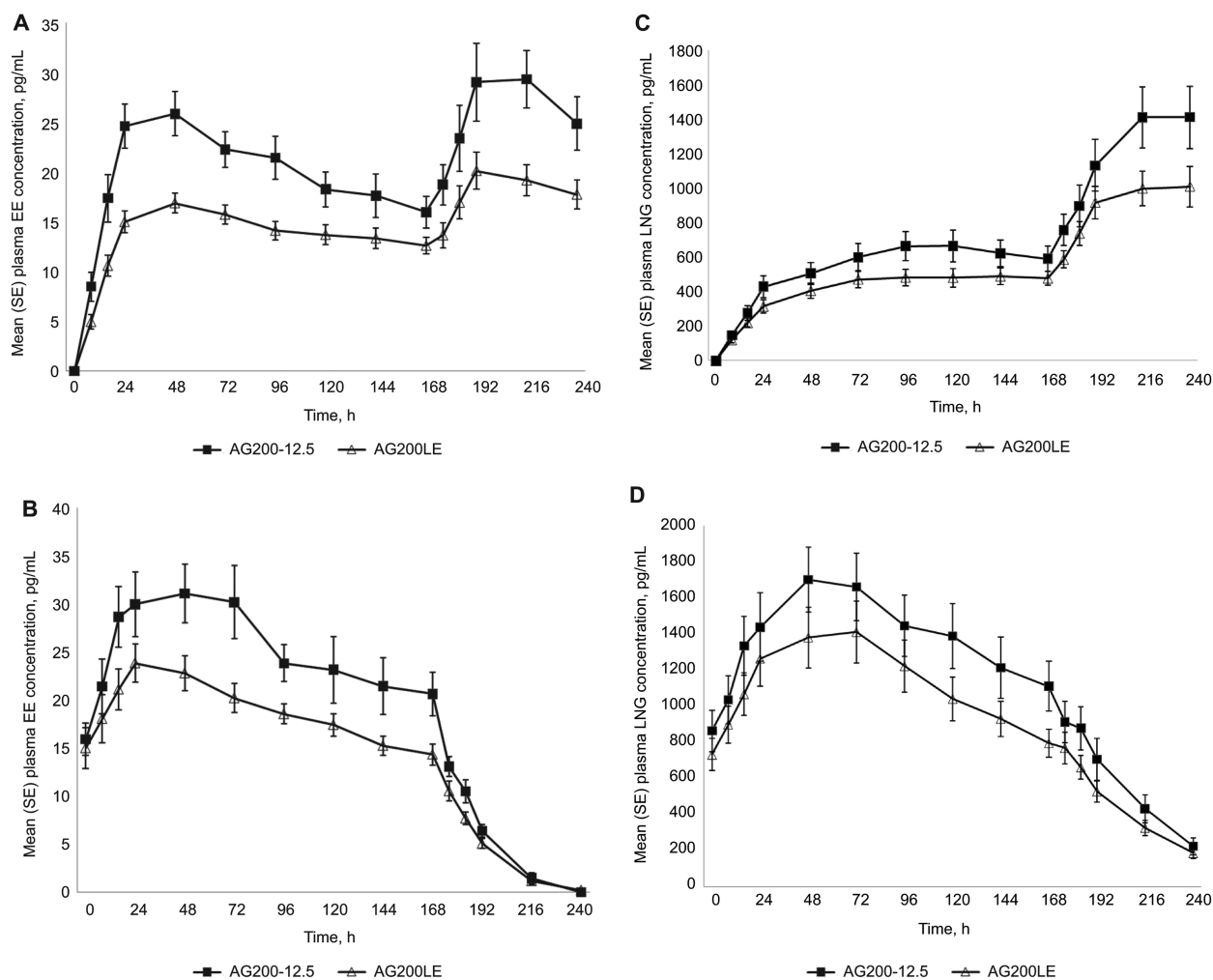


Figure 3 Mean (\pm standard error) (A, B) plasma ethinylestradiol (EE) and (C, D) levonorgestrel (LNG) concentrations vs. time plots for AG200LE and AG200-12.5 for Days 1–10 (0–240 h) and Days 15–25 (0–240 h; Day 15=0 h) of the first patch treatment cycle in Study 1. (A) Plasma EE concentrations over the first 10 days of the first treatment cycle (0–240 h) and following application of the second patch on Day 7 (168 h). (B) Plasma EE concentrations over Day 15 (0 h) through Day 25 (240 h) of the first treatment cycle and following removal of the final patch on Day 22 (168 h). (C) Plasma LNG levels over the first 10 days (0–240 h) of the first treatment cycle and following application of a new patch on Day 7 (168 h). (D) Plasma LNG levels during Day 15 (0 h) through Day 25 (240 h) of the first treatment cycle and following patch removal on Day 22 (168 h).

weekly. Four subjects (44.4%) reported AEs following administration of Leven over one treatment cycle. AE data for the OC were collected once at the end of the cycle. The most common AEs, occurring in $\geq 10\%$ of subjects in one treatment group, were nausea, application-site pruritus, headache, dysmenorrhea and metrorrhagia (see Table 7 for incidence rates by treatment group). Most AEs were considered mild or moderate in intensity. One AE, a headache reported by one subject receiving AG200-12.5, was considered severe in intensity. Two subjects discontinued study participation because of AEs. The first subject discontinued because of mild nausea during treatment with the AG200-12.5 patch; the second was because of mild dysmenorrhea, nausea and vomiting during treatment with AG200LE. No serious AEs were reported in Study 1.

In Study 2, treatment-emergent AEs occurred in 19 subjects (44%) in the AG200LE group and in 29 subjects (66%)

and 19 subjects (61%), respectively, in the AG200-12.5 and AG200-15 treatment groups over the three treatment cycles. Table 7 lists AEs with incidence rates $\geq 10\%$. One subject in the AG200LE treatment group experienced a migraine considered severe in intensity. All other AEs were rated as mild or moderate in intensity. Treatment-emergent AEs associated with study discontinuation included dyspnea in one subject treated with AG200-15, and hypertension in one subject treated with AG200-15 and one subject treated with AG200LE; all were considered unrelated to study drug. No serious AEs occurred during Study 2.

Patch wearability/acceptability

By the end of the 7-day placebo run-in period for Study 1, no patches had fallen off and only 1 patch out of 59 (1.7%) was partially detached. Investigator assessment of skin irri-

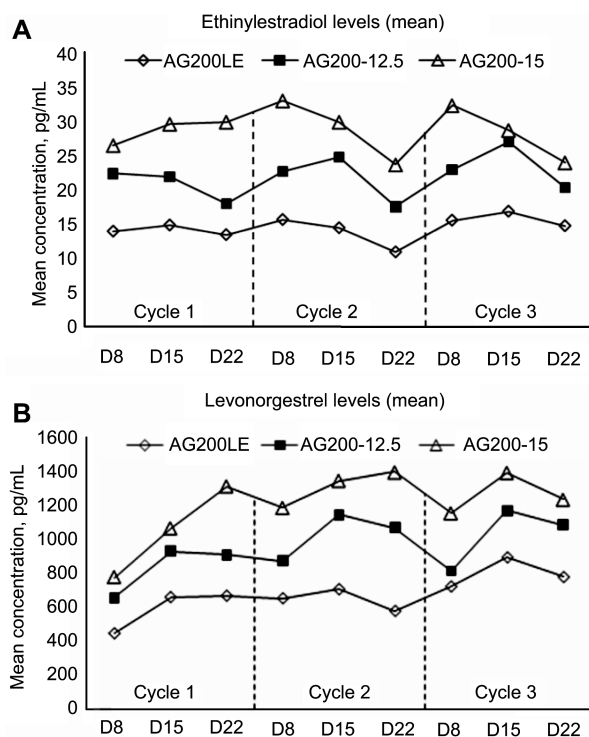


Figure 4 Mean (A) ethinylestradiol and (B) levonorgestrel levels for AG200LE, AG200-12.5 and AG200-15 on Days 8, 15 and 22 during the three treatment cycles in Study 2.

tation indicated that 49 (90.7%) of 54 evaluable subjects had no skin irritation, 4 (7.4%) had mild irritation and 1 (1.9%) experienced moderate irritation at the patch site. During the drug treatment periods, moderate irritation was noted after the application of three AG200-12.5 patches (4.7% of 64 total) and three AG200LE patches (3.8% of 79 total). No cases of significant irritation were reported.

In Study 2, for all treatment groups combined 1.5% (16/1062) of the total number of patches detached completely. The proportion of subjects with at least one patch that was completely detached decreased over the course of the study

[9.3% (11/118) in Cycle 1, 2.7% (3/113) in Cycle 2 and 1.8% (2/111) in Cycle 3], indicating better patch adhesion with more experience using the patch. Similar results were observed for the proportion of patches that were partially detached (data not shown).

Of the 118 subjects in the study, 17 (14%) experienced at least one application-site reaction: 13 (11%) had skin irritation, 4 (3%) had pruritus and 1 (1%) had erythema. The incidence of application-site reactions was not dose-related and the majority of events were mild in severity. Furthermore, the majority of these events occurred during Cycle 1, and no application-site reaction was associated with AEs related to delayed sensitisation (i.e., no systemic rashes were observed following any event). The proportions of patches that were changed as a result of skin irritation [0.8% (3/380) in Cycle 1, 0.3% (1/351) in Cycle 2 and 0% (0/331) in Cycle 3] also suggest an improvement in wearability metrics with more exposure to the patch.

Discussion

Study 1 characterized the pharmacokinetic profiles of two TCDSs, AG200LE and AG200-12.5, containing two different low EE doses in combination with the same dose of LNG. Comparisons of mean daily AUCs indicated that AG200LE had significantly lower EE exposure levels than AG200-12.5 in the third week of patch wear. Both AG200-12.5 and AG200LE resulted in significantly lower EE exposure in the first and third weeks of treatment compared with Levlen, an OC containing 30 µg EE. EE exposure levels with both patches were less than one-half of those previously reported for Ortho Evra [12, 18, 19]. Steady-state EE concentrations during treatment with AG200-12.5 corresponded roughly to levels achieved with combination OCs containing 20 µg EE, and were even lower in subjects treated with AG200LE [19, 20].

For AG200LE and AG200-12.5, steady-state LNG plasma concentrations ranged from 1117 pg/mL to 1505 pg/mL in the third week of patch wear and were within the range of

Table 6 Major cycle control parameters: Study 2.

Cycle control parameter	AG200LE (n=42)	AG200-12.5 (n=42)	AG200-15 (n=27)
Incidence of bleeding/spotting episodes (Cycle 3) [n (%)]	12 (28.6)	12 (28.6)	4 (14.8)
No. of unscheduled bleeding/spotting days (Cycles 1–3)			
Mean ± SD	5.5 ± 5.0	4.4 ± 4.7	3.4 ± 4.4
Median	5.5	3.0	1.0
No. of unscheduled spotting days (Cycles 1–3)			
Mean ± SD	0.5 ± 1.9	0.7 ± 1.5	1.2 ± 2.6
Median	0.0	0.0	0.0
No. of unscheduled bleeding days (Cycles 1–3)			
Mean ± SD	3.4 ± 3.9	2.7 ± 3.8	1.7 ± 2.9
Median	2.5	0.0	0.0

SD, standard deviation. A breakthrough bleeding/spotting episode is defined as any number of days with breakthrough bleeding/spotting preceded and followed by at least 2 bleeding-free days. Unscheduled bleeding/spotting days are determined by subtracting the number of bleeding/spotting days during the withdrawal period from the total number of bleeding/spotting days.

Table 7 Treatment-emergent adverse events occurring in $\geq 10\%$ of subjects in any treatment group in Studies 1 and 2.

Adverse event	Treatment group		
	AG200LE (n=28)	AG200-12.5 (n=25)	Levlen® (n=9)
Study 1 [n (%)] ^a			
Nausea	4 (14.3)	5 (20.0)	0 (0)
Application-site pruritus	1 (3.6)	3 (12.0)	0 (0)
Headache	4 (14.3)	3 (12.0)	0 (0)
Dysmenorrhea	5 (17.9)	2 (8.0)	2 (22.2)
Menorrhagia	0 (0)	1 (4.0)	1 (11.1)
Metrorrhagia	12 (42.9)	12 (48.0)	2 (22.2)
Study 2 [n (%)] ^b			
	AG200LE (n=43)	AG200-12.5 (n=44)	AG200-15 (n=31)
Nausea	2 (5)	6 (14)	4 (13)
Application-site irritation	3 (7)	6 (14)	4 (13)
Headache	1 (2)	5 (11)	2 (6)
Breast tenderness	2 (5)	4 (9)	3 (10)

^aIn Study 1, treatment duration was two cycles with AG200LE and AG200-12.5 but only one cycle with Levlen. ^bIn Study 2, treatment duration was three cycles with AG200LE, AG200-12.5 and AG200-15.

plasma levels required for ovulation suppression [21]. Both AG200-12.5 and AG200LE were associated with significantly lower LNG exposures compared with Levlen (150 μg LNG/day). Despite equivalent amounts of LNG within the two patches, there was a trend of lower LNG exposure during treatment with AG200LE compared with AG200-12.5. Increased plasma LNG with increasing doses of EE may be attributed to serum elevations in SHBG at higher estrogen concentrations [22].

Both AG200LE and AG200-12.5 were associated with good safety and tolerability profiles, and the incidence of AEs was similar to that of other low-dose OCs [20, 23]. Further evaluation of patch pharmacodynamics was therefore merited. The EE levels observed with AG200LE and AG200-12.5 permitted the addition of a higher dose of EE and, consequently, a higher-dose LNG patch into Study 2 (ATI-CL11), a dose-finding study.

Mean and median plasma concentrations from Study 2 indicated that EE and LNG levels were consistent over treatment Cycles 2 and 3. EE concentrations for AG200-15 (24–34 pg/mL) appear to be within the range of those reported for low-dose OCs [19, 20, 24] and are approximately 50% lower than blood concentrations reported for Ortho Evra [12].

The bleeding profile for the AG200-15 patch exhibited improved cycle control compared with the other two patches studied and was also similar to that reported for low-dose marketed OCs [16, 17]. The incidences of hormone-related AEs, such as headache, nausea and breast tenderness, were lower with AG200-15 compared with the Ortho Evra patch and were within range of low-dose combination OCs [12, 16, 19].

Conclusions

All three patch formulations evaluated in these studies exhibited excellent safety and wearability profiles while maintaining plasma LNG levels required for ovulation suppression. However, treatment with AG200LE and AG200-12.5 result-

ed in EE concentrations that may be associated with suboptimal cycle control. A slight increase in the EE dose in AG200-15 still places this TCDS within the range of low-dose OCs, with EE exposure much lower than that reported for Ortho Evra. Based on these results as well as ovulation suppression data reported previously [25], AG200-15 was selected for further testing in phase 3 contraceptive efficacy and safety studies.

Acknowledgements

Editorial support was provided by Phase Five Communications Inc. (New York, NY), which was funded by Agile Therapeutics, Inc.

References

- Kost K, Singh S, Vaughan B, Trussell J, Bankole A. Estimates of contraceptive failure from the 2002 National Survey of Family Growth. *Contraception* 2008;77:10–21.
- Hooper DJ. Attitudes, awareness, compliance and preferences among hormonal contraception users: a global, cross-sectional, self-administered, online survey. *Clin Drug Investig* 2010;30:749–63.
- Abma JC, Chandra A, Mosher WD, Peterson LS, Piccinino LJ. Fertility, family planning, and women's health: new data from the 1995 National Survey of Family Growth. *Vital Health Stat* 1997;23:1–114.
- Potter L, Oakley D, de Leon-Wong E, Caneonar R. Measuring compliance among oral contraceptive users. *Fam Plann Perspect* 1996;28:154–8.
- Rosenberg MJ, Waugh MS, Long S. Unintended pregnancies and use, misuse and discontinuation of oral contraceptives. *J Reprod Med* 1995;40:355–60.
- Rosenberg M, Waugh MS. Causes and consequences of oral contraceptive noncompliance. *Am J Obstet Gynecol* 1999;180:276–9.
- Archer DF, Cullins V, Creasy GW, Fisher AC. The impact of improved compliance with a weekly contraceptive transdermal

- system (Ortho Evra) on contraceptive efficacy. *Contraception* 2004;69:189–95.
8. Archer DF, Bigrigg A, Smallwood GH, Shangold GA, Creasy GW, Fisher AC. Assessment of compliance with a weekly contraceptive patch (Ortho Evra/Evra) among North American women. *Fertil Steril* 2002;77(Suppl 2):S27–31.
 9. Urdl W, Apter D, Alperstein A, Koll P, Schönian S, Bringer J, Fisher AC, Preik M, ORTHO EVRA/EVRA 003 Study Group. Contraceptive efficacy, compliance and beyond: factors related to satisfaction with once-weekly transdermal compared with oral contraception. *Eur J Obstet Gynecol Reprod Biol* 2005;121:202–10.
 10. Crosignani PG, Nappi C, Ronsini S, Bruni V, Marelli S, Sonnino D, Italian EVRA Contrast Study Group. Satisfaction and compliance in hormonal contraception: the result of a multicentre clinical study on women's experience with the ethinylestradiol/norelgestromin contraceptive patch in Italy. *BMC Womens Health* 2009;9:18.
 11. Bodner K, Bodner-Adler B, Grünberger W. Evaluation of the contraceptive efficacy, compliance, and satisfaction with the transdermal contraceptive patch system Evra: a comparison between adolescent and adult users. *Arch Gynecol Obstet* 2010 Jan 29 [Epub ahead of print].
 12. Devineni D, Skee D, Vaccaro N, Massarella J, Janssens L, LaGuardia KD, Leung AT. Pharmacokinetics and pharmacodynamics of a transdermal contraceptive patch and an oral contraceptive. *J Clin Pharmacol* 2007;47:497–509.
 13. Burkman RT. Transdermal hormonal contraception: benefits and risks. *Am J Obstet Gynecol* 2007;197:134.e1–6.
 14. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol* 2007;109:339–46. Erratum in: *Obstet Gynecol* 2008;111:1449.
 15. Ortho Evra® [package insert]. Raritan, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 2008.
 16. LaGuardia KD, Shangold G, Fisher A, Friedman A, Kafrisen M. Efficacy, safety and cycle control of five oral contraceptive regimens containing norgestimate and ethinyl estradiol. *Contraception* 2003;67:431–7.
 17. Hampton RM, Fisher AC, Pagano S, LaGuardia KD. Scheduled and unscheduled bleeding patterns with two combined hormonal contraceptives: application of new recommendations for standardization. *Fertil Steril* 2009;92:434–40.
 18. Abrams LS, Skee DM, Wong FA, Anderson NJ, Leese PT. Pharmacokinetics of norelgestromin and ethinyl estradiol from two consecutive contraceptive patches. *J Clin Pharmacol* 2001;41:1232–7.
 19. van den Heuvel MW, van Bragt AJ, Alnabawy AK, Kaptein MC. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception* 2005;72:168–74.
 20. Lybrel® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; 2010.
 21. Spona J, Feichtinger W, Kindermann C, Wunsch C, Brill K. Inhibition of ovulation by an oral contraceptive containing 100 micrograms levonorgestrel in combination with 20 micrograms ethinylestradiol. *Contraception* 1996;54:299–304.
 22. Fotherby K. Pharmacokinetics of gestagens: some problems. *Am J Obstet Gynecol* 1990;163:323–8.
 23. Levlen® [package insert]. Montville, NJ: Bayer Healthcare Pharmaceuticals; 1996.
 24. Westhoff CL, Torgal AH, Mayeda ER, Stanczyk FZ, Lerner JP, Benn EK, Paik M. Ovarian suppression in normal-weight and obese women during oral contraceptive use: a randomized controlled trial. *Obstet Gynecol* 2010;116:275–83.
 25. Mishell DR Jr, Archer DF, Rubin A, Foegh M. Ovulation suppression and cycle control of ethinyl estradiol and levonorgestrel combination patches. Presented at: American College of Obstetricians and Gynecologists Annual Meeting, 15 May 2010; San Francisco, CA.