

Evaluation of Exposure to Ethinyl Estradiol (EE) With a Low-Dose Combination Transdermal Contraceptive Delivery System (AG200-15) Compared to Low-Dose Combination Oral Contraceptive

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Abstract

Objective: To evaluate the EE pharmacokinetic (PK) profile of a transdermal contraceptive delivery system (TCDS) compared to an OC (oral contraceptive) in healthy female volunteers.

Design: Open-label, comparative, crossover study: Cycle 1 is a run-in cycle with the TCDS administered to all subjects. Cycles 2 and 3 are a crossover design with subjects randomly assigned to sequences of a TCDS and an OC with each treatment given for one cycle. The TCDS was applied to the buttock weekly for three weeks followed by a patch-free week. The OC was administered for 21 days followed by a pill-free week.

Materials and Methods: PK evaluations were performed at the 1st and 3rd weeks for the TCDS cycles and Days 7 and 21 for the OC cycles. Plasma concentrations of EE were determined via LC/MS method. Maximum Plasma concentration levels (C_{max}), steady-state concentration calculated as average concentration at steady-state from the 24-hour trapezoidal area under the curve (C_{avg}), and steady state concentration levels (C_{ss}) were evaluated. Relative bioavailability was determined from an ANOVA model. Calculated test/reference ratios with 90% confidence intervals were calculated. The projected EE daily delivery for the TCDS was estimated with the OC 35 µg EE daily dose as a reference.

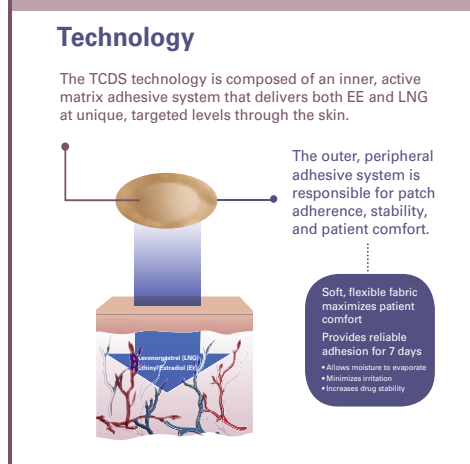
Results: Thirty-two evaluable subjects with mean age of 37 years and mean BMI of 26 kg/m² were included in the analyses. C_{max} was approximately 60% lower for the TCDS. C_{ss} was 15%-20% lower for the TCDS compared to the OC.

Conclusions: The calculated daily dose of the TCDS was equivalent to approximately 30 µg EE and exposure in the TCDS was substantially less than the 35 µg combination OC. Daily EE exposure with the low-dose TCDS (AG200-15) is well within the range reported for low dose OCs.

Background

Poor compliance with daily oral contraceptives (OC) has been correlated with increased contraceptive failure.¹ The use of a transdermal contraceptive delivery system (TCDS), ie, a patch, has been shown to increase contraceptive compliance across all age groups.^{2,3} The first TCDS to receive FDA approval, Ortho Evra[®] has been associated with ethinyl estradiol (EE) exposure levels that are approximately 60% higher than with an OC containing 35 µg/d EE.⁴ Increased estrogen exposure may increase the risk for venous thromboembolism.⁵ A novel TCDS, AG200-15, was developed with the goal of delivering a dose of EE and levonorgestrel (LNG) that is effective and maintains serum EE levels that are similar to concentrations attained with low-dose OCs (Figure 1).

Figure 1. Technology Used in AG200-15, a Novel Transdermal Contraceptive Delivery System



Objective

- Evaluate the EE pharmacokinetic (PK) profile, safety, and tolerability of AG200-15, a TCDS containing EE and LNG, compared with an approved OC (Ortho-Cyclen[®], a combination OC containing 35 µg EE).

Methods

Study Design

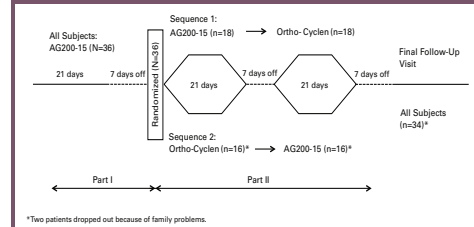
- Open-label, comparative, randomized, crossover study comprised of 2 parts (Figure 2):

– **Part I:** Single-arm, run-in cycle with AG200-15 administered to all subjects.

– **Part II:** Crossover design with subjects randomly assigned to:

- Sequence 1:** AG200-15 followed by Ortho-Cyclen
- Sequence 2:** Ortho-Cyclen followed by AG200-15

Figure 2. Trial Design



*Two patients dropped out because of family problems.

- Both AG200-15 and Ortho-Cyclen were administered as 21/7 day regimens, with 3 weeks of active drug therapy followed by 1 drug-free week.
- Patients were treated with either AG200-15 or Ortho-Cyclen, a combination OC containing 35 µg EE.

Blood Sampling for PK Evaluations

- For the AG200-15 treatment cycles, blood sampling was performed at 0, 6, 12, 24, 48, 72, 120, 144, and 168 hours after the application of each patch and 6, 12, 24, 48, and 72 hours after removal of the third patch.
- For the Ortho-Cyclen treatment cycle, blood sampling was performed on cycle days 7 and 21 at the following time points: 0, 0.5, 1, 1.5, 3, 6, 9, 12, 16, and 24 hours postdosing, and 36, 48, and 72 hours following the Day 21 dose.

PK Assessment of EE

- Plasma concentrations of EE were determined via a validated liquid chromatography-mass spectrometry method.
- The following PK parameters were calculated for each subject and for each cycle week of patch wear:
 - C_{max} : Maximum concentration level
 - AUC_{0-168h} , AUC_{0-240h} , AUC_{0-inf} , AUC_{0-t} : Area under the concentration versus time curve from time 0 to 168 hours, 240 hours, infinity, or the last measurable observation (t), respectively
 - C_{ss} : Steady-state concentration calculated as:
 - Average concentration (C_{avg}) within the 48-168 hours time interval
 - C_{avg} at steady-state calculated from trapezoidal $AUC_{48-168h}$
 - C_{avg} at steady-state calculated from trapezoidal AUC_{0-168h}

Safety

- Safety was assessed by tracking adverse events (AEs), discontinuation information, and vital signs, as well as changes in physical and gynecologic examinations and laboratory tests from screening to the end of the study.

Results

Demographics and Disposition

- Subject demographics were similar across both randomization groups (Table 1).

Table 1. Demographics and Baseline Characteristics

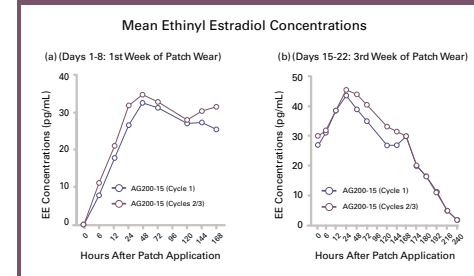
Parameter	Randomization Group		All Subjects N=36
	AG200-15/Ortho-Cyclen n=18	Ortho-Cyclen/AG200-15 n=18	
Age (y)			
Mean (SD)	37.8 (5.85)	36.2 (7.66)	37.0 (6.77)
Range	22-44	20-44	20-44
Race, n (%)			
Caucasian	16 (88.9)	16 (88.9)	32 (88.9)
African American	2 (11.1)	2 (11.1)	4 (11.1)
Ethnicity, n (%)			
Hispanic/Latino	16 (88.9)	17 (94.4)	33 (91.7)
Non-Hispanic/Non-Latino	2 (11.1)	1 (5.6)	3 (8.3)
Body mass index (kg/m ²)			
Mean (SD)	26.31 (3.060)	26.21 (3.548)	26.26 (3.264)
Range	21.0-31.8	20.8-31.6	20.8-31.8

- A total of 34 subjects completed the study; 2 (5.6%) subjects discontinued because of family problems after completing Part I of the study.
- 32 evaluable subjects supplied adequate PK data and were included in the comparisons of EE PK parameters between AG200-15 and Ortho-Cyclen.

PK Results

- Mean serum EE concentrations for the first and third week of AG200-15 patch wear are plotted in Figure 3.

Figure 3. Mean EE Concentrations Versus Time in the First (a) and Third (b) Weeks of Patch Wear for Part I (Cycle 1) and Part II (Cycles 2/3)



- Calculated EE PK parameters for the comparative evaluation between AG200-15 and Ortho-Cyclen for the first and third week of treatment in Part II of the study (Cycles 2/3) are shown in Table 2.

Table 2. Comparative Evaluation of EE PK Parameters: AG200-15 Versus Ortho-Cyclen (Part II)

Parameter/Period	Mean ± SD		P-value*	Treatment Comparisons	
	AG200-15 (N=32)	Ortho-Cyclen (N=32)		Point Estimate† (%)	90% Confidence Interval‡
Week 1					
C_{max} (pg/mL)	45.5 ± 24.0	135 ± 50.7*	<0.0001	32.08	27.58 - 37.30
AUC_{0-168h} (ng·h/mL)	5.06 ± 2.26	7.28 ± 2.66*	0.0001	65.96	56.76 - 76.65
C_{ss} (1) (pg/mL)	31.4 ± 15.1	43.3 ± 15.9*	0.0009	67.41	56.30 - 80.71
C_{ss} (2) (pg/mL)	32.0 ± 16.2	43.3 ± 15.9*	0.0007	66.35	55.34 - 79.55
C_{ss} (3) (pg/mL)	30.1 ± 13.4	43.3 ± 15.9*	0.0001	65.96	56.76 - 76.65
Week 3					
C_{max} (pg/mL)	51.3 ± 17.3	131 ± 45.4	<0.0001	39.01	35.26 - 43.15
AUC_{0-168h} (ng·h/mL)	6.26 ± 2.46	6.97 ± 2.25	0.0532	85.96	75.67 - 97.66
C_{ss} (1) (pg/mL)	35.7 ± 14.5	41.5 ± 13.4*	0.0167	81.78	71.48 - 93.57
C_{ss} (2) (pg/mL)	35.7 ± 14.4	41.5 ± 13.4*	0.0175	80.13	69.00 - 93.06
C_{ss} (3) (pg/mL)	37.3 ± 14.7	41.5 ± 13.4*	0.0532	85.96	75.67 - 97.66

*ANOVA model with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.

†Point estimate and 90% confidence interval of the least-squares geometric means ratio.

‡90% CI

‡ C_{ss} calculated as average concentration at steady state from the 24-hour trapezoidal AUC (AUC_{0-168h}) for Ortho-Cyclen.

- The C_{max} value was approximately 60% lower for AG200-15 compared with the OC Ortho-Cyclen (51.3 pg/mL vs 131 pg/mL) in Week 3 of treatment (Table 2). The difference for C_{max} was statistically significant ($P < 0.0001$).
- C_{ss} values were 15%-20% lower for AG200-15 (35.7-37.3 pg/mL) compared with Ortho-Cyclen (41.5 pg/mL) in Week 3 (Table 2). The differences between the treatment groups were statistically significant or approached nominal significance level.
- Substantially lower C_{max} and C_{avg} were also observed for the first week of patch wear. Between-treatment differences were statistically significant for all EE PK parameters (Table 2).
- Based on the primary PK endpoint, C_{ss} (1), the calculated daily dose of the AG200-15 patch was equivalent to approximately 30 µg EE.

Safety and Tolerability

- No serious AEs were observed and no subjects discontinued study medication as a result of AEs.
- Table 3 summarizes the most frequently reported AEs.

Table 3. Most Frequently Reported Adverse Events (>10% of subjects in any study period)

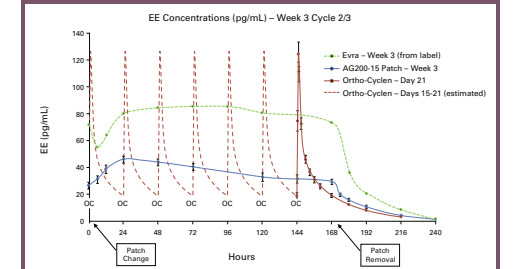
Adverse Event	AG200-15		Ortho-Cyclen
	Part I N=36 n (%)	Part II N=34 n (%)	Part II N=34 n (%)
Headache	10 (27.8)	1 (2.9)	0
Application site irritation	4 (11.1)	1 (2.9)	1 (2.9)
Nausea	4 (11.1)	0	1 (2.9)

†In Part II, 1 subject had application site irritation starting in the AG200-15 cycle, which had recurred during the subsequent Ortho-Cyclen cycle.

Discussion

- The calculated daily exposure to EE for AG200-15 was substantially lower than with the 35 µg combination OC and was roughly equivalent to an OC containing 30 µg EE.
- The daily EE exposure with AG200-15 was substantially lower than the 50-60 µg daily EE exposure reported for Ortho Evra in Weeks 2-3 of the third treatment cycle.⁴
- Figure 4 illustrates the relative PK profiles of AG200-15 compared with a daily 35 µg EE OC and Ortho Evra.

Figure 4. PK Profile of AG200-15 Compared With a Daily 35 µg EE OC and Ortho Evra Week 3 of the Second AG200-15 Cycle



- Rates of hormone-related AEs were low and within the range reported for low-dose combination OCs.
- Phase 3 studies evaluating the efficacy and safety of AG200-15 are ongoing.

Conclusions

- The low-dose transdermal contraceptive delivery system, AG200-15, delivers a low dose of ethinyl estradiol (EE).
- Treatment with AG200-15, compared with the marketed oral contraceptive (OC) Ortho-Cyclen, was associated with significantly lower maximum and steady-state concentrations for plasma EE levels in Weeks 1 and 3 of patch wear.
- AG200-15 has a daily EE exposure of approximately 30 µg, a value that is well within the range reported for low dose OCs.
- Overall, lower EE exposure was evident for AG200-15 when compared with Ortho-Cyclen.
- AG200-15 was generally safe and well-tolerated.

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