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APPLICATION NUMBER:

204017Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA or BLA Number	204017
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Submission Date	May 16, 2019 (SDN060); December 13, 2019 (SDN071); December 18, 2019 (SDN072); January 27, 2020 (SDN075)
Submission Type	Resubmission/Class 2
Brand Name	Twirla®
Generic Name	Levonorgestrel and ethinyl estradiol transdermal system
Dosage Form and Strength	Transdermal contraceptive system contains 2.3 mg ethinyl estradiol and 2.6 mg levonorgestrel.
Route of Administration	Transdermal
Proposed Indication	Prevention of pregnancy
Applicant	Agile Therapeutics, Inc.
Associated IND	IND 057731
OCP Review Team	Peng Zou, PhD; Fang Li, Ph.D; Yanhui Lu, PhD; Jingyu Yu, PhD
OCP Final Signatory	Yanhui Lu, PhD

Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 Recommendations	3
1.2 Post-Marketing Requirements and Commitments	4
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT	4
2.1 Pharmacology and Clinical Pharmacokinetics	4
2.2 Dosing and Therapeutic Individualization	5
2.2.1 General dosing	5
2.2.2 Therapeutic individualization	5
2.3 Outstanding Issues	5
2.4 Summary of Labeling Recommendations	5
3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW	6
3.1 Overview of the Product and Regulatory Background	6
3.2 General Pharmacology and Pharmacokinetic Characteristics	6
3.3 Clinical Pharmacology Review Questions	7
3.3.1 Is the steady-state systemic exposure to EE from AG200-15 equivalent to that of orally administered 30 mcg EE?	7
3.3.2 Does premature re-application(s) of a new AG200-15 system increase EE and LNG exposures	8
3.3.3 What are the daily doses of EE and LNG delivered by AG200-15?	12

1. EXECUTIVE SUMMARY

Agile Therapeutics, Inc. (Agile) originally submitted a 505(b)(2) New Drug Application (NDA) on 4/12/2012 for a levonorgestrel (LNG) and ethinyl estradiol (EE) Transdermal Contraceptive Delivery System (TCDS) for the prevention of pregnancy in women who use a TCDS (hereafter referred to as AG200-15) as a method of contraception. The system is a patch, containing 2.3 mg EE and 2.6 mg LNG. The proposed dosing regimen is to apply one patch to abdomen, buttock, or upper torso once every week for three weeks followed by one patch-free week.

On 2/13/2013, the Division of Bone, Reproductive and Urologic Products (DBRUP) issued a Complete Response Letter (CRL) to the Applicant citing Clinical and Chemistry, Manufacturing and Controls (CMC) deficiencies. The clinical pharmacology information submitted in original NDA 204017 was found acceptable (*refer to Clinical Pharmacology Review by Dr. Hyunjin Kim dated 1/11/2013 in DARRTS*). However, potential carry-over effects of both EE and LNG between adjacent treatment cycles (in Study ATI-CL14) and adjacent periods (in Studies ATI-CL14, ATI-CL15 and ATI-CL16) were identified. The Agency recommended that the Applicant address this concern..

In a response to the CRL dated 6/21/2013, Agile assessed potential carry-over effects of both EE and LNG using the pharmacokinetics (PK) data collected from Study ATI-CL14. The clinical pharmacology reviewer found that steady-state concentrations of EE and LNG were achieved by Week 3 of the second cycle during two consecutive cycles of patch therapy, and concluded that the exposure of EE and LNG would not significantly increase in subjects receiving three and more consecutive cycles of patch therapy (*refer to Clinical Pharmacology Review by Dr. Peng Zou dated 12/1/2017 in DARRTS*).

In a resubmission dated 06/26/2017, Agile submitted a report for a new Phase 3 Study ATI-CL23. In that submission, the Applicant also addressed the Agency's concern on the observed increases in EE and LNG exposure in Studies ATI-CL15 and ATI-CL16. Agile received a 2nd CRL on 12/21/2017 due to deficiencies in AG200-15 adhesion property, efficacy and safety.

In this resubmission dated 05/16/2019, Agile submitted responses to the deficiencies listed in the CRL dated 12/21/2017 and included a report for a comparative wear trial using AG200-15 and Xulane (150 mcg norelgestromin /35 mcg EE per day), a transdermal system approved under ANDA 200910. During the review cycle of this resubmission, the review team raised three clinical pharmacology-related questions: (1) Is the steady-state systemic exposure to EE from AG200-15 equivalent to that of orally administered 30 mcg EE? (2) Does premature re-application(s) of a new AG200-15 system increase EE and LNG exposures? and (3) What are the daily doses of EE and LNG delivered by AG200-15? This review will focus on the three questions.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 204017 and finds this NDA acceptable from a clinical pharmacology perspective, provided that the EE/LNG strength issue is addressed through a postmarketing requirement (PMR) study.

The key review issues with specific recommendations/comments are summarized in the table below:

Review Issue	Recommendations and Comments
Low-dose EE contraceptive	Based on the findings from Study ATI-CL14, the Applicant claimed that the systemic exposure to EE delivered from AG200-15 was equivalent to that from orally administered 30 mcg EE. The review team does not agree with Applicant's analysis and conclusion. Our analysis showed that the systemic exposure to EE delivered from AG200-15 was equivalent to that from orally administered 35 mcg EE.
Safety risk of frequent reapplication of AG200-15 due to inadequate patch adherence	Due to the higher release rate within the first 48 hours post-application, premature re-application of a new AG200-15 may slightly increase the systemic exposure to EE and LNG by < 25%. Following labeling language is added to Section (b) (4) to mitigate potential safety risk (b) (4)
Daily doses of EE and LNG delivered by AG200-15	A PMR study will be requested by the CMC review team to determine the daily doses of EE and LNG delivered by AG200-15.
Labeling	See Section 2.4 of this review.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

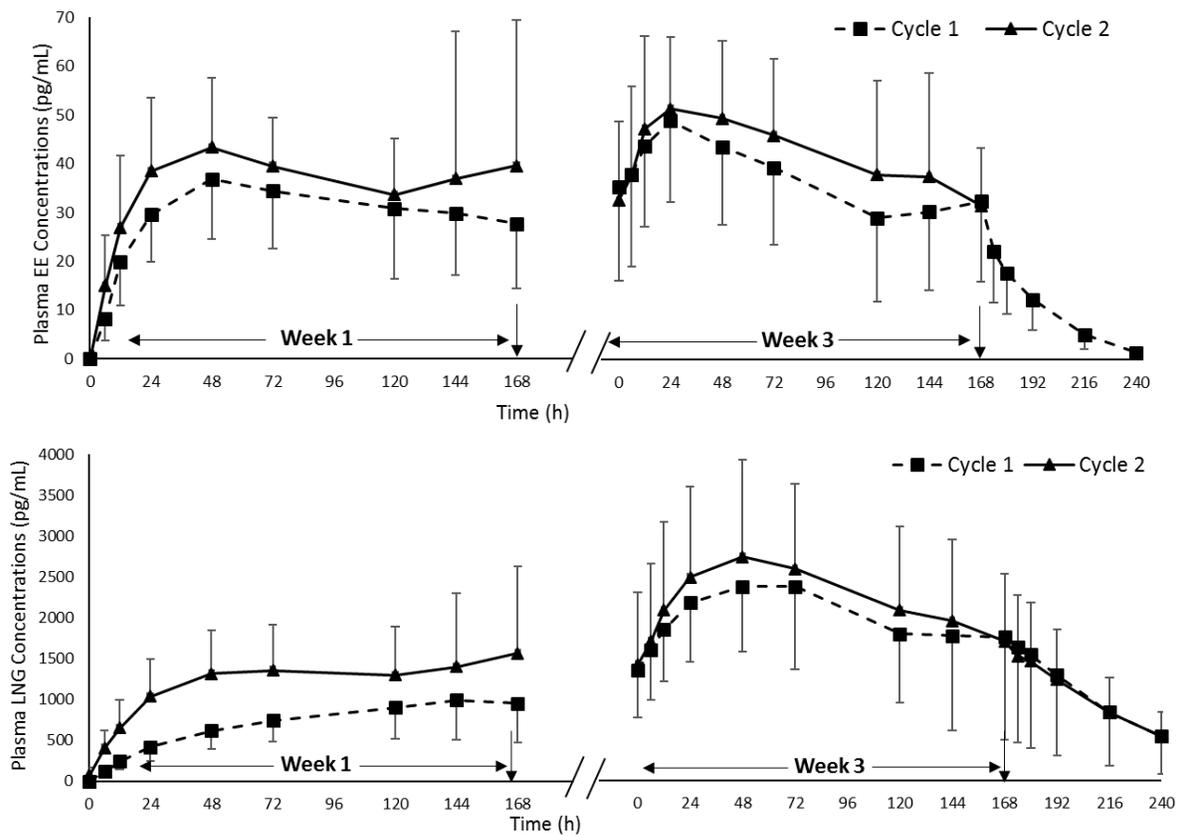
The PK profiles of EE and LNG in healthy female subjects following two consecutive cycles of AG200-15 wear on the buttock are shown in **Figure 1**.

Absorption: In a three-cycle study, the mean concentrations of EE and LNG reached steady-state conditions during the Week 3 of Cycle 2 after two consecutive cycles of wear. The steady-state systemic exposure to EE delivered from AG200-15 was equivalent to that from orally administered 35 mcg EE.

Due to the higher release rates of EE and LNG within the first 48 hours post-application, population PK model-based simulations showed that premature re-application of a new AG200-15 slightly increased the systemic exposure to EE and LNG by < 25%. The simulation also showed that three premature AG200-15 replacements within a 7-day wear period resulted in a steady-state EE exposure slightly lower than that of orally administered 50 mcg EE.

Clinical Pharmacology Data Used to Support AG200-15 Strength: A relative bioavailability study between AG200-15 and an oral contraceptive product was used to support the EE strength of AG200-15, which did not account for the absolute bioavailability of EE from the oral product. The strength of LNG was determined by a cross-study comparison between AG200-15 and an approved oral contraceptive containing LNG. The approach did not account for the absolute bioavailability of LNG from the oral contraceptive and the cross study PK comparison added additional uncertainty. Therefore, the CMC review team will require a PMR study to determine the strength of the proposed product.

Figure 1. Mean Plasma Ethinyl Estradiol (EE) (Upper Panel) and Levonorgestrel (LNG) (Bottom Panel) Concentrations in Healthy Female Subjects Following Two Consecutive Cycles of AG200-15 Wear on the Buttock (Vertical arrow indicates time of patch removal) (Study ATI-CL14, N = 18)



Source: The figure was prepared by the reviewer using the data submitted in Study ATI-CL14 report.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

AG200-15 is used in a 28-day (four-week) cycle. A new AG200-15 is applied and worn for seven days for three consecutive weeks (Weeks 1, 2, and 3). No AG200-15 is worn during Week 4 (the AG200-15-free week). Every new patch should be applied on the same day of the week.

2.2.2 Therapeutic individualization

Not applicable.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The major labeling recommendations are listed below:

- The language (b) (4) is added to Section (b) (4).
- Ovulation inhibition data is added to Section 12.2.
- Pharmacokinetic profiles (Figures 4) and parameters (Table 6) of AG200-15 in Section 12.3 should be updated based on the data from 18 subjects who wore AG200-15 for two consecutive cycles in Study ATI-CL14.
- The elimination half-lives of EE and LNG observed in Study ATI-CL14 are added to Section 12.3 (b) (4).

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

AG200-15 is a 28 cm² matrix type transdermal system (TDS) containing 2.60 mg of LNG and 2.30 mg of EE. The proposed dosing regimen for one cycle of AG200-15 is one TDS to be applied to either the abdomen, buttock, or upper torso every 7 days for three consecutive weeks followed by one TDS-free week. The Applicant received two CRLs on 2/13/2013 and 12/21/2017, respectively. The NDA was resubmitted on 5/16/2019 and an advisory committee (AC) meeting was held on 10/30/2019 to obtain input on whether the contraceptive benefits of AG200-15 outweigh the safety risks to support approval. The advisory committee voted 14 to 1, with 1 abstention, in favor of approval.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Combination hormonal contraceptives lower the risk of becoming pregnant primarily by suppressing ovulation.
Active Moieties	LNG and EE
General Information	
Bioanalysis	LC-MS/MS methods were used to determine LNG and EE in plasma and serum.
Healthy vs. Patients	No dedicated comparative PK study between healthy subjects and patients was conducted.
Drug exposure (Mean ± SD)	Cycle 2, Week 3 LNG: AUC _{0-168h} = 378 ± 166 ng*h/mL, EE: AUC _{0-168h} = 7.12 ± 2.61 ng*h/mL
Maximally tolerated dose or exposure	Maximally tolerated dose was not established.
Variability	Inter-subject variability during Cycle 2, Week 3 (Study ATI-CL14) LNG: C _{max} 41% and AUC _{0-168h} 44%, EE: C _{max} 31% and AUC _{0-168h} 37%
Absorption	
Bioavailability	Not available
T_{max} [Median (range)]	Cycle 2, Week 3 (Study ATI-CL14) LNG: T _{max} = 48 (24 – 120) h, EE: T _{max} = 36 (12 – 144) h
Distribution	
Volume of distribution	The Applicant proposed to rely on the clinical pharmacology information from hormonal contraceptive class labeling and literature.
Elimination	
Terminal elimination half-life (Mean ± SD)	Cycle 2, Week 3 LNG: T _{1/2} = 40.5 ± 6.23 h, EE: T _{1/2} = 20.5 ± 3.73 h

Metabolism and Excretion	
Primary metabolic and excretion pathway(s)	The Applicant proposed to rely on the clinical pharmacology information from hormonal contraceptive class labeling and literature.

3.3 Clinical Pharmacology Review Questions

3.3.1 Is the steady-state systemic exposure to EE from AG200-15 equivalent to that of orally administered 30 mcg EE?

No. Based on the PK data from Study ATI-CL14, the Applicant claimed that the steady-state systemic exposure to EE from AG200-15 was equivalent to that of orally administered 30 mcg EE. The review team does not agree with the Applicant's analysis.

In Study ATI-CL14, 18 subjects in Group 1 received two consecutive cycles of AG200-15 and then one cycle of the marketed oral contraceptive Ortho-Cyclen®. The other 16 subjects in Group 2 received one cycle of AG200-15, and then one cycle of Ortho-Cyclen followed by another cycle of AG200-15. The duration of each treatment cycle was 28 days. In each cycle, both AG200-15 and Ortho-Cyclen were administered as a 21-7 day regimen, i.e., three consecutive weeks of drug-taking followed by a drug-free week. Each AG200-15 patch was to be worn for 7 days by applying to buttock only. In AG200-15 cycles, blood PK sampling was performed during the 1st and 3rd weeks and up to 72 hours following removal of the third patch (4th week). In Ortho-Cyclen cycles, blood PK sampling was performed on Cycle Days 7 and 21 and up to 72 hours following the last dose administered on Day 21.

The Applicant pooled Cycle 2/Week 3 PK data from Group 1 (AG200-15/AG200-15/Ortho-Cyclen) and Cycle 3/Week 3 data from Group 2 (AG200-15/Ortho-Cyclen/AG200-15). The Applicant's analysis showed that average AUC_{0-168h} of EE from AG200-15 patch (6.26 ng*h/mL) was 10% lower than that of EE from Ortho Cyclen (6.97 ng*h/mL). The Applicant concluded that the calculated steady-state systemic exposure to EE from AG200-15 was equivalent to approximately 30 mcg orally administered EE. However, we do not agree with the applicant's analysis because AG200-15 exhibited between-cycle increases in EE exposure while Ortho-Cyclen did not. The inclusion of Ortho-Cyclen cycle between two AG200-15 cycles in Group 2 prevented between-cycle increases in EE exposure and resulted in a Cycle 3/Week 3 AUC_{0-168h} of EE from AG200-15 of 5.25 ng*h/mL, which was 26% lower than Cycle 2/Week 3 AUC_{0-168h} of EE from AG200-15 in Group 1 (7.12 ng*h/mL) following two consecutive cycles of AG200-15 wear. The observed EE exposure at Cycle 3/Week 3 in Group 2 might not represent the steady-state PK of EE for a treatment of AG200-15 with two or more consecutive cycles. Therefore, to represent consecutive cycles of AG200-15 wear in clinical use, PK data from Group 1 only rather than pooled PK data from Groups 1 and 2 as proposed by the Applicant should be used for the comparison between AG200-15 and Ortho-Cyclen (Table 1). This reviewer concluded that the steady-state AUC_{0-168h} of EE from AG200-15 (7.12 ng*h/mL) was comparable to that of 35 mcg EE from Ortho-Cyclen (7.31 ng*h/mL and 6.47 ng*h/mL for Week1 and Week 3, respectively).

Table 1. Mean (SD) of Pharmacokinetic Parameters of Ethinyl Estradiol Following Two Consecutive Cycles of AG200-15 Wear and Then One Cycle of Ortho-Cyclen® (Study ATI-CL14, Treatment sequence: AG200-15 Cycle/AG200-15 Cycle/Ortho-Cyclen Cycle)

Parameter	AG200-15 (2.3 mg EE/ 2.6 mg LNG)				Ortho-Cyclen (0.035 mg EE/0.25 mg Norgestimate)	
	Cycle 1 Week 1 (N=18)	Cycle 1 Week 3 (N=18)	Cycle 2 Week 1 (N=18)	Cycle 2 Week 3 (N=18)	Cycle 3 Week 1 (N=18)	Cycle 3 Week 3 (N=18)

C _{max} (pg/mL)	38.9 (14.8)	57.0 (17.1)	55.1 (27.1)	57.8 (18.2)	138 (56.2)	126 (56.1)
AUC _{0-168h} (ng·h/mL)	5.04 (1.78)	6.21 (2.12)	6.06 (2.17)	7.12 (2.61)	7.31 (2.97)	6.47 (2.73)
T _{max} (h)*	60 (24 – 144)	24 (0 – 120)	72 (24 – 168)	36 (12 - 144)	1 (1 – 1.5)	1 (1 – 3)
T _{1/2} (h)	N.A.	19.7 (3.72)	N.A.	20.5 (3.73)	N.A.	18.2 (4.14)

*Median (range) values are presented.

Source: Modified from Tables 1 and 2 in the Summary of Clinical Pharmacology Studies submitted on 06/26/2017.

In Section 12.3 of the drug labeling, we recommend that the Applicant include steady-state PK data of LNG and EE, which is the data collected from 18 subjects who wore AG200-15 for two consecutive cycles in Study ATI-CL14.

3.3.2 Does a premature re-application(s) of a new AG200-15 system increase EE and LNG exposures?

Yes, due to the burst release of EE and LNG during 0-48 hours post application of AG200-15, a premature re-application(s) of a new AG200-15 system may increase EE and LNG exposures.

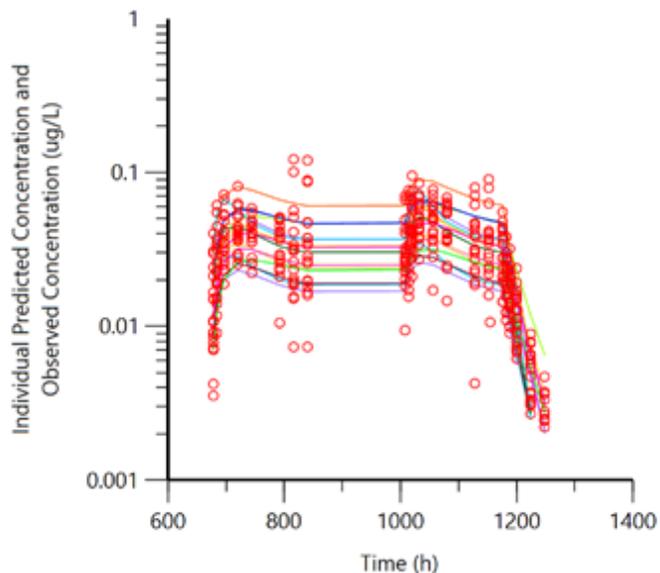
On 11/21/2019, the following information request (IR) was sent to the Applicant: *“In Study ATI-CL14, the pharmacokinetic profile at Week 3 showed the maximum plasma concentration (C_{max}) values for EE and LNG were reached between 24 - 48 hours post application, suggesting a potential burst release within this timeframe. A premature TDS replacement, even to a different application site, could result in higher than expected exposures to EE and LNG. Provide data to justify that a premature replacement with a new TDS would not have a clinically meaningful impact on EE and LNG exposures.”*

In the Applicant’s response letter to the IR, the Applicant stated that no formal PK study was conducted to assess the impact of premature TDS replacement on EE and LNG exposures. The Applicant provided three types of data (simulations using a population PK model, observed data, and superpositioning analysis) to investigate the effect of premature replacements on the PK profile of EE and LNG. Since both EE and LNG showed C_{max} between 24 - 48 hours post application, AG200-15 replacement is expected to have similar effect on the PK of EE and LNG. Furthermore, since the severe adverse effects of AG200-15 such as venous thromboembolism (VTE) are more related to increased exposure of EE compared to that of LNG, the reviewer’s analysis focused more on EE data.

Population PK model-based simulations:

The Applicant developed a population pharmacokinetic (popPK) model for EE using PK data of Cycle 2 from subjects who wore two consecutive cycles of AG200-15 in Study ATI-CL14 (N = 18). A one-compartment model with zero order infusion into the central compartment and first order absorption from a dosing compartment adequately fit the observed data. The duration of the zero-order absorption into the central compartment was assumed to be 168 hours. The popPK model reasonably described the individual subject’s EE PK profiles during Cycle 2 in Study ATI-CL14 (Figure 4).

Figure 4. Predicted and Observed Individual Pharmacokinetic Profiles of EE at Cycle 2/Week 3



Source: Figure 7 in (b) (4) report submitted on 12/18/2019.

The popPK model was used to simulate three scenarios for AG200-15 premature replacement:

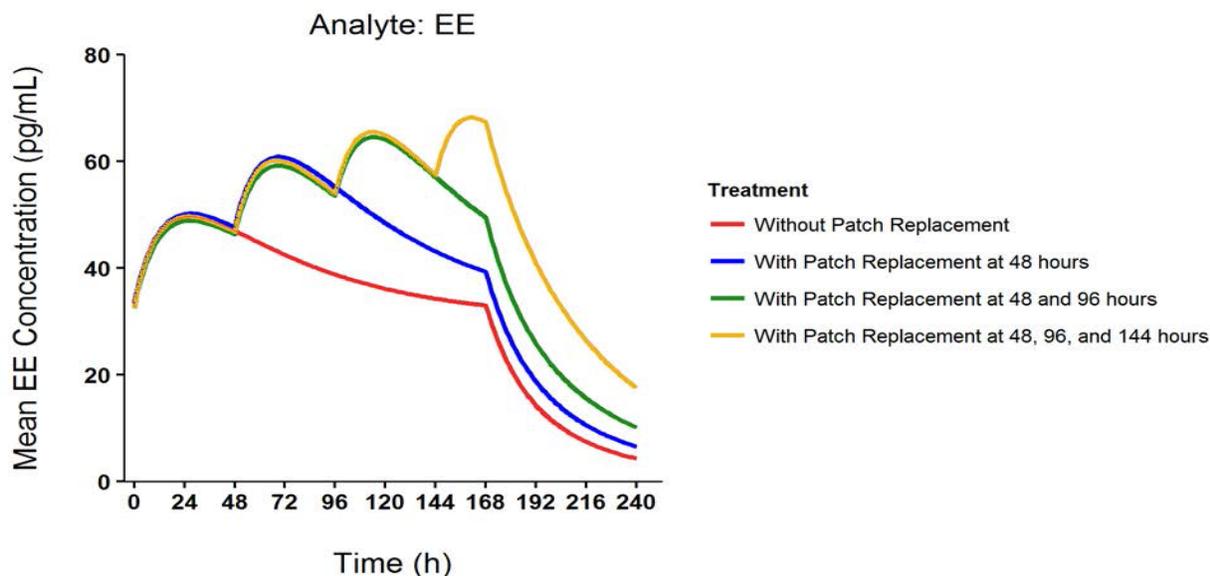
- Scenario 1: One AG200-15 replacement at 48 hours after the application of original AG200-15
- Scenario 2: Two AG200-15 replacements, one at 48 hours and the other one at 96 hours after the application of original AG200-15
- Scenario 3: Three AG200-15 replacements, one replacement at 48 hours, one at 96 hours, and one at 144 hours after the application of original AG200-15

The simulated mean EE concentrations versus time profiles for no patch replacement and under the three replacement scenarios overlaid are presented in Figure 5. The predicted AUC and C_{max} values for these scenarios are presented in Table 2. The simulated C_{max} and AUC values of EE are increased by the patch replacement; however, the simulated C_{max} is lower than that of Ortho Cyclen (68.5 versus 135 pg/mL) even when three premature AG200-15 replacements occur within a 7-day wear period.

The highest currently available dose for EE oral products on the U.S. market is 50 mg and above which there are increased risk of serious adverse reactions, such as VTE [Gerstman *et al.*, 1991, *Am J Epidemiol*, 133(1):32-37]. Assuming orally administered EE exhibits a linear PK from 35 mcg to 50 mcg, the AUC_{0-168h} for 50 mcg oral EE would be approximately 9.96 ng·h/mL. These simulations suggested that the AUC_{0-168h} of EE under the scenario that three premature AG200-15 replacements occur within a 7-day wear period (i.e. 9.55 ng·h/mL) is slightly lower than that of EE oral products at 50 mcg (i.e. approximately 9.96 ng·h/mL).

Similarly, the popPK simulations showed that the AUC of LNG increased 43% when three premature AG200-15 replacements occur within a 7-day wear period, which is not expected to have a clinically relevant impact on the efficacy and safety of AG200-15.

Figure 5. Mean Simulated Cycle 2 Week 3 EE Concentration-Time Profiles for Each Simulated Scenario with or without Replacement Patch Application



Source: Figure 1 in the Applicant's response to the information request submitted on 1/27/2020.

Table 2. Summary of Mean (SD) EE Pharmacokinetic Parameters

	No Replacement Observed	No Replacement Simulated	One Replacement Simulated	Two Replacements Simulated	Three Replacements Simulated	Ortho Cyclen Observed
Ethinyl Estradiol						
C_{max} (pg/mL)	57.8 (18.4)	50.4 (17.6)	62.1 (20.4)	65.0 (20.9)	68.5 (22.3)	135 (52)
AUC_{0-168h} (ng·h/mL)	7.12 (2.66)	6.81 (2.62)	8.48 (2.92)	9.14 (2.99)	9.55 (3.11)	6.97 (2.41)
Levonorgestrel						
C_{max} (ng/mL)	2.84 (1.17)	2.49 (0.95)	3.15 (1.15)	3.58 (1.35)	3.84 (1.50)	N.A.
AUC_{0-168h} (ng·h/mL)	378 (166)	355 (156)	442 (178)	496 (190)	508 (193)	N.A.

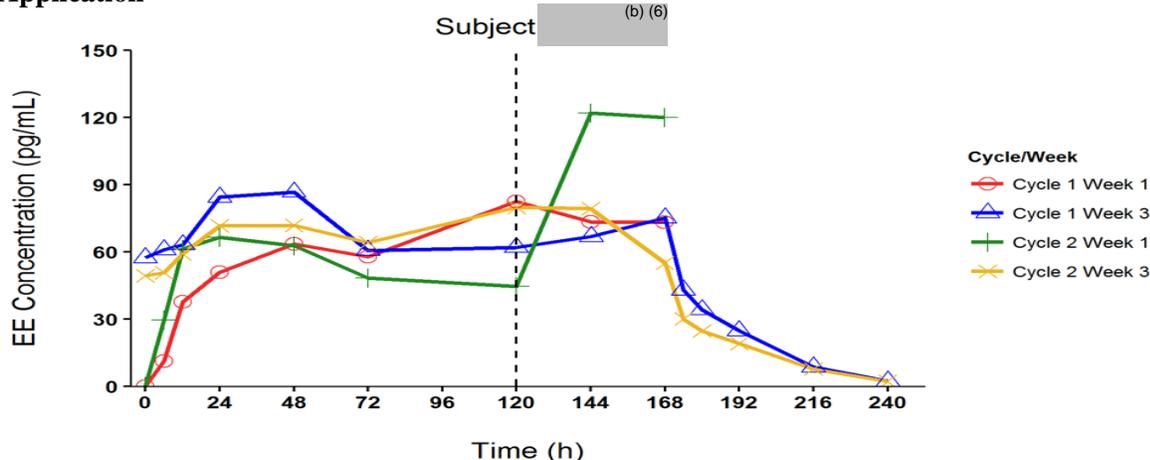
Among the 2023 subjects enrolled in Study ATI-CL23, 185 subjects reported two or more AG200-15 replacements within at least one 7-day wear period. Of these subjects, 175 reported two replacements in a 7-day wear period; 15 subjects reported three replacements in a 7-day wear period; and 1 subject experienced four replacements in a 7-day wear period. Therefore, the occurrence of four or more replacements is expected to be rare.

Overall, premature reapplication of AG200-15 may increase the exposure to EE. To mitigate the potential unknown risk, following language should be added to Section (b) (4)

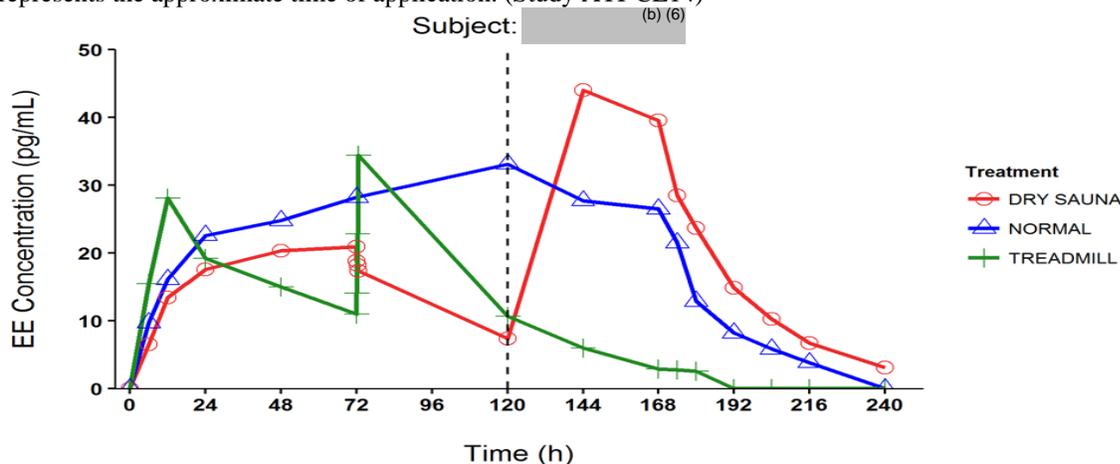
Observed data:

In Studies ATI-CL14 and ATL-CL16, there were 2 subjects who applied replacement patches mid-week. The individual subject concentration versus time profiles are presented in Figure 2. The EE concentration-time profiles in Subject (b) (6) and Subject (b) (6) showed an initial increase in the first 24 hours after application of the replacement patch to approximately 2.7-fold (Subject (b) (6)) and 5-fold (Subject (b) (6)) compared to the pre-replacement concentration (120 hour). The dramatic increase in EE concentrations after AG200-15 replacement was inconsistent with the observed moderate increase in EE concentrations after the application of new AG200-15 in Phase 1 studies. In Study ATI-CL14 (Figure 1, right figure in the upper panel), the application of the Cycle 2/Week 3 patch increased the mean EE concentration by 57% only (pre-application EE concentration 32.5 pg/mL versus C_{max} 51.1 pg/mL). Similar magnitude of increase in EE concentrations was observed in Study ATI-11. Therefore, the dramatic increase in EE concentrations observed in the two subjects are not representative of the increased EE exposure observed when a new patch was put on. Therefore, data from Subject (b) (6) and Subject (b) (6) may be outliers and no conclusions can be drawn on the PK profile of EE when premature AG200-15 replacement occurs.

Figure 2. Individual EE Concentrations versus Time for Subjects with Replacement Patch Application



Note: On Day 6 of Cycle 2 Week 1 (green line), this subject applied a replacement patch. The vertical dashed line represents the approximate time of application. (Study ATI-CL14)



Note: On Day 6 of the Dry Sauna treatment (red line), this subject applied a replacement patch. The vertical dashed line represents the approximate time of application. (Study ATI-CL16)

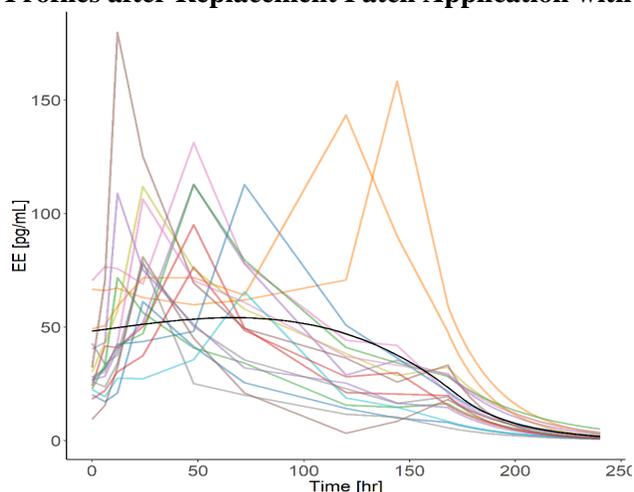
Source: Figure 1 in (b) (4) report submitted on 12/18/2019.

Superpositioning analysis:

The superpositioning analysis assumes that each subject applies a replacement at T_{max} of the original patch and the pre-dose corrected C_{max} immediately appears in plasma (i.e. assumes no absorption delay). Concentration versus time profiles for individual subjects from Cycle 2 Week 3 in Study ATI-CL14 were used to generate predicted concentration time curves. The following three components were added together to generate the predicted concentration versus time curves for each individual subject:

1. Each subject's observed data until T_{max} , at which time a log-linear decline was assumed.
2. At each subject's T_{max} , the subject's corrected C_{max} from Cycle 2 Week 3 was added to the observed C_{max} . The corrected C_{max} was derived by subtracting one-third of the pre-dose concentration from observed C_{max} . The scaling factor of $1/3$ was determined empirically.
3. Each subject's corrected concentration vs time profile continued through 168 total hours of dosing. At 168 hours, a log-linear decline was assumed.

Figure 3. Individual Cycle 2 Week 3 Superpositioning Predicted EE Concentrations versus Time Profiles after Replacement Patch Application with Loess Curve Overlaid



Source: Figure 3 in (b) (4) report submitted on 12/18/2019.

The individual superpositioning predicted concentration versus time profiles are displayed in Figure 3. The superpositioning analysis represents worst-case scenario by assuming patch replacement at each subject's T_{max} . As shown in Figure 3, however, EE concentrations follow a log-linear decline after each subject's T_{max} , which is inconsistent with the observed flat PK profiles of EE in Study ATI-CL14. The rapid decline in EE concentration may under-predict the AUC of EE. Also, the application of a small empirical scaling factor ($1/3$) to the pre-dose concentration may over-predict the C_{max} of EE. The superpositioning analysis is inappropriate for assessing the effect of premature patch replacement on the PK profile of EE.

3.3.3 What are the daily doses of EE and LNG delivered by AG200-15?

In the proposed drug labeling, the Applicant claimed dosage form and strength as “120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol” based on following clinical data:

- EE: Study ATI-CL14 showed that AG200-15 yielded an exposure to EE equivalent to orally administered 30 mcg EE (AUC of EE from AG200-15 was 10-15% lower than that from Ortho Cyclen® containing 35 mcg EE).

- LNG: Based on Cycle 1 LNG C_{ss} from ATI-CL14, the calculated daily LNG dose of the AG200-15 was comparable to a daily oral dose of 120 mcg LNG. This is a cross-study comparison between AG200-15 and an approved combined oral contraceptive (COC) containing LNG. The Applicant did not specify the name of the COC.

In the response letter to the FDA's IR issued on 12/10/2019, the Applicant confirmed that neither an absolute bioavailability study nor measurement of residual EE/LNG in used AG200-15 was conducted. The relative bioavailability study between a TDS and an oral product did not account for the absolute bioavailability of EE and LNG. The AG200-15 daily delivery doses for EE and LNG were likely overestimated because of the higher magnitude of first-pass metabolism of orally administered EE/LNG compared to transdermal delivery. Furthermore, the strength of LNG was determined by a cross-study comparison between AG200-15 and a COC containing LNG, which added additional uncertainty.

The Chemistry review team will request a PMR study to assess the residual drug contents of EE and LNG in AG200-15 after 7-day wear in order to determine the strength of AG200-15. The Applicant will submit a labeling supplement to revise the strength when the PMR study results are available.

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204017 Class II resubmission	Submission Dates: 06/26/2017
Proposed Brand Name:	Twirla®
Generic Name:	Levonorgestrel and ethinyl estradiol transdermal system
Clinical Pharmacology Primary Reviewer:	Peng Zou, PhD
Clinical Pharmacology Secondary Reviewer:	Doanh Tran, PhD
OCP Divisions:	Division of Clinical Pharmacology 3 (DCP3)
OND Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Sponsor:	Agile Therapeutics, Inc.
Submission Type:	Original NDA/Resubmission
Relevant IND	IND 057731
Formulation, Strength, and Dosing Regimen	Transdermal contraceptive system containing 2.3 mg ethinyl estradiol and 2.6 mg levonorgestrel. A patch is applied every 7 days for 3 weeks, followed by a 1 week “patch free” period.
Indication:	Prevention of pregnancy

Table of Contents

1	EXECUTIVE SUMMARY	1
1.1	Recommendation	2
1.2	Post-marketing Requirements or Commitments	2
1.3	Summary of Important Clinical Pharmacology Findings	3
2	QUESTION BASED REVIEW	3
2.1	General Attributes	3
2.2	General Clinical Pharmacology	3
2.3	Intrinsic Factors	14
2.4	Extrinsic Factors	14
2.5	General Biopharmaceutics	14
2.6	Bioanalytical Methods	14
3	DETAILED LABELING RECOMMENDATIONS	14

1 EXECUTIVE SUMMARY

Agile Therapeutics, Inc. (Agile) submitted a 505(b)(2) New Drug Application on April 12, 2012 for a levonorgestrel (LNG) and ethinyl estradiol (EE) Transdermal Contraceptive Delivery System (TCDS) for the prevention of pregnancy in women who elect to use a TCDS (hereafter referred to as “the patch” or AG200-15) as a method of contraception. Each patch contains 2.3 mg EE and 2.6 mg LNG. The proposed dosing regimen is to apply one patch to abdomen, buttock, or upper torso once every week for three weeks followed by one patch free week. On February 13, 2013, the Division of Bone, Reproductive and Urologic Products (DBRUP) issued a Complete Response Letter (CRL) to the Applicant citing Clinical and Chemistry, Manufacturing and

Controls (CMC) deficiencies. In the CRL, DBRUP raised concerns regarding study conduct problems for the two Phase 3 studies (ATI-CL12 and ATI-CL13), which limited the DBRUP's confidence in the study results and the ability to draw valid conclusions concerning the demonstrated efficacy of the study drug. The CRL noted that Agile would need to conduct a new Phase 3 trial before Twirla could be considered for marketing approval. Although the clinical pharmacology information submitted in original NDA 204017 was found acceptable, potential carry-over effects of both EE and LNG between adjacent treatment cycles (in Study ATI-CL14) and adjacent periods (in Study ATI-CL14, ATI-CL15 and ATI-CL16) were identified. The applicant was recommended to correct for/compensate for the potential carry-over effects of both EE and LNG or provide details on how to obtain this information post-marketing along with a suitable labeling to address this lack of information.

In its June 21, 2013 Response to the CRL, Agile acknowledged the potential carry-over effects of both EE and LNG and provided an assessment of potential carry-over effects of both EE and LNG using the pharmacokinetic data collected from Study ATI-CL14. The clinical pharmacology reviewer found that steady-state concentrations of EE and LNG were achieved by Week 3 of the first cycle and the second cycle of a two consecutive cycles of patch therapy, respectively, and concluded that the exposure of EE and LNG would not significantly increase in subjects receiving three and more consecutive cycles of patch therapy. However, the reviewer's concern on the potential carry-over effect in Study ATI-CL15 and ATI-CL16 was not addressed in Agile's response dated June 21, 2013. At the Pre-NDA Meeting on March 14, 2017, the DBRUP requested a detailed discussion regarding the observed increases in EE and LNG exposure in Study ATI-CL15 and ATI-CL16, including an explanation of the root cause and justification and a data analysis method to interpret the effect of application site and external conditions on the pharmacokinetic (PK) of AG200-15. No additional questions regarding Study ATI-CL14 were raised.

The current NDA was resubmitted by Agile on 06/26/2017 to address the Clinical and CMC deficiencies. This submission contains a report for Study ATI-CL23. The objectives of this new phase 3 study are to assess the contraceptive efficacy, safety and tolerability, and patch adhesion of the product. No pharmacokinetic endpoint was included in the study. The meeting minutes dated July 27, 2016 showed that Agile proposed to bridge the clinical and commercial products using comparative in vitro dissolution and in vitro skin permeation studies. The CMC review team informed Agile that the final acceptance of the comparative in vitro dissolution and skin permeation studies to bridge the clinical and commercial products would be a review issue. No in vivo bioequivalence study was submitted in current NDA. To address the Agency's concern on the observed increases in EE and LNG exposure in Study ATI-CL15 and ATI-CL16, Agile provided a clinical pharmacology update in current NDA. This review is focused on this update. In addition, the potential impact of the product quality deficiencies described in the CRL on the findings in clinical pharmacology studies is assessed.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) has reviewed NDA 204017 class II resubmission dated on June 26, 2017. The overall Clinical Pharmacology information submitted to support this NDA resubmission is acceptable.

1.2 Post-marketing Requirements or Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

Agile's reanalysis of pharmacokinetic data showed that the inter-period increases in EE and LNG exposure observed in Study ATI-CL15 and Study ATI-CL16 were not caused by carry-over effect. It is not expected that repeated dosing of Twirla will result in sustained increases in EE or LNG exposure.

Although a bioequivalence conclusion among the three application sites (abdomen, buttock, and upper torso) cannot be drawn from Study ATI-CL15, it is concluded that the three anatomical sites can be switched interchangeably (as was done in the clinical trials) without appreciable clinical consequences. Based on the data of Study ATI-CL16, this reviewer concludes that no clinically significant effect of any of the four external conditions (cold water, whirlpool, dry sauna and treadmill) on the drug delivery profiles is expected.

It is unlikely that the product quality deficiencies issued in the February 13, 2013 Complete Response Letter (CRL) and their resolutions would have an impact on the validity of clinical pharmacology findings of Twirla provided Agile's responses are found acceptable by CMC reviewers.

2 QUESTION BASED REVIEW

2.1 General Attributes

Reviewed by Dr. Hyunjin Kim dated 01/11/2013 and no new data was submitted.

2.2 General Clinical Pharmacology

2.2.1 How does the Applicant explain the observed increases in EE and LNG exposure in Study ATI-CL14, Study ATI-CL15 and Study ATI-CL16? Is this a safety concern?

Agile re-analyzed PK data to assess the potential carry-over effects of both ethinyl estradiol and levonorgestrel between adjacent treatment cycles (in Study ATI-CL14) and adjacent periods (in Study ATI-CL15 and ATI-CL16). The following responses were provided.

Study ATI-CL14:

ATI-CL14 was a two-part open-label study to evaluate the PK profile of AG200-15 and to compare exposure to EE from AG200-15 to that from Ortho Cyclen®, an oral contraceptive (OC) containing 250 mcg of Norelgestromin and 35 mcg EE.

Part I of the study was a single-arm, run-in cycle with AG200-15 administered to all subjects as a 21-7 day regimen (three consecutive weeks of patch wear followed by a patch-free week).

Part II employed a crossover design with subjects randomly assigned to one of the two treatment sequences. Each sequence included AG200-15 and the OC as described below:

- Sequence 1: AG200-15 (Period 1) followed by OC (Period 2)
- Sequence 2: OC (Period 1) followed by AG200-15 (Period 2)

The total duration of treatment for each subject was 84 days, i.e., two cycles of AG200-15 administered as a 21-7 day regimen (three consecutive weeks of patch wear followed by a patch-free week) and one cycle of OC therapy (three consecutive weeks of daily drug intake followed by a drug-free week). Drug-free weeks served as washout periods with no additional between-cycle breaks.

The PK profiles of EE and LNG in Weeks 1 and 3 of both Parts I and II are shown in Figure 1 and Figure 2, respectively.

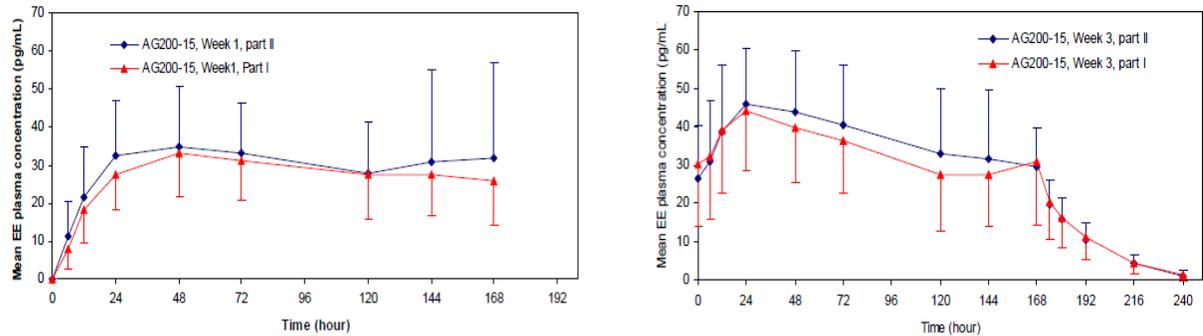


Figure 1. Mean (SD) EE concentrations in Weeks 1 and 3 of both Parts I and II from AG200-15 (PK population); ATI-CL14

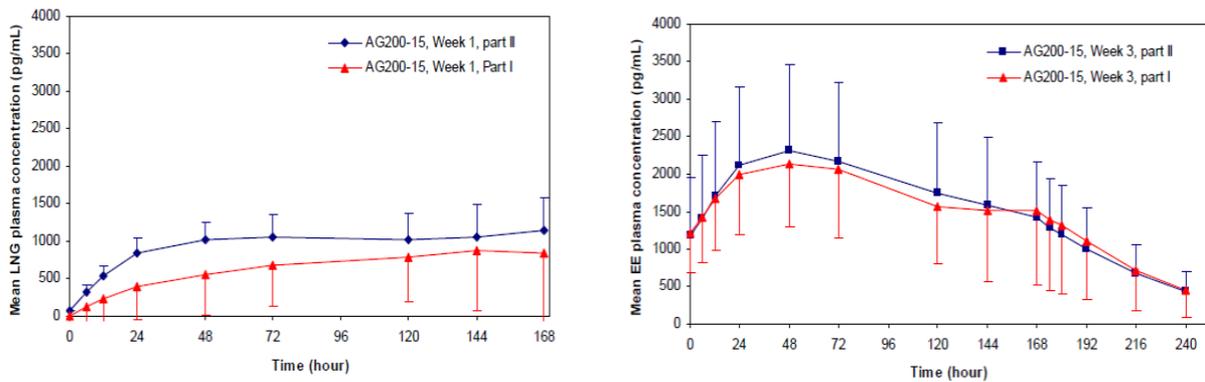


Figure 2. Mean (SD) LNG concentrations in Weeks 1 and 3 of both Parts I and II from AG200-15 (PK population); ATI-CL14

In Agile's submission dated June 21, 2013, Agile did a T test analysis on the pharmacokinetic data of Study ATI-CL14. As shown in Table 1 and Table 2, Agile acknowledged that statistically significant carry-over effects for both EE and LNG were only observed from week 1 cycle 1 to week 1 cycle 2 in the cohort of subjects receiving two consecutive cycles of patch therapy. Agile concluded that no significant carry-over effect was detected for week 3 of patch wear. The exposure to EE was lower with the patch than with Ortho Cyclen.

Table 1. Evaluations of EE PK Parameters (Study ATI-CL14) - Assessment of Carry-Over Effects

PK Parameter	Week	Sequence AG200-15 - AG200-15 - Ortho Cyclen				Sequence AG200-15 - Ortho-Cyclen - AG200-15			
		Cycle 1	Cycle 2	Difference: Cycle 2 – Cycle 1	P- value: Paired t-test	Cycle 1	Cycle 3	Difference: Cycle 3 – Cycle 1	P- value: Paired t-test
		AG200- 15 N=17	AG200- 15 N=17			AG200- 15 N=15	AG200- 15 N=15		
C_{max} (pg/mL)	1	40.1 ± 14.4	56.8 ± 26.9	16.7 ± 20.4	0.0038	30.5 ± 9.8	32.7 ± 10.6	2.2 ± 12.3	0.5090
AUC_{0-168h} (ng.h/mL)		5.19 ± 1.73	6.20 ± 2.14	1.02 ± 1.31	0.0054	4.04 ± 1.03	3.75 ± 1.62	-0.28 ± 1.68	0.5234
C_{max} (pg/mL)	3	59.0 ± 15.5	58.7 ± 18.4	-0.3 ± 16.8	0.9446	44.5 ± 16.0	42.9 ± 11.6	-1.6 ± 18.6	0.7494
AUC_{0-168h} (ng.h/mL)		6.37 ± 2.07	7.22 ± 2.66	0.85 ± 2.29	0.1460	4.98 ± 1.34	5.18 ± 1.72	0.19 ± 1.81	0.6845

Table 2. Evaluations of LNG PK Parameters (Study ATI-CL14) - Assessment of Carry-Over Effects

PK Parameter	Week	Sequence AG200-15 - AG200-15 - Ortho-Cyclen				Sequence AG200-15 - Ortho-Cyclen - AG200-15			
		Cycle 1	Cycle 2	Difference: Cycle 2 – Cycle 1	P- value: Paired t-test	Cycle 1	Cycle 3	Difference: Cycle 3 – Cycle 1	P- value: Paired t-test
		AG200- 15 N=17	AG200- 15 N=17			AG200- 15 N=15	AG200- 15 N=15		
C_{max} (pg/mL)	1	1026 ± 494	1831 ± 1033	805 ± 763	0.0005	733 ± 322	861 ± 355	128 ± 240	0.0583
AUC_{0-168h} (ng.h/mL)		122 ± 48	210 ± 93	88 ± 63	<0.0001	94 ± 43	105 ± 42.8	11 ± 38	0.2764
C_{max} (pg/mL)	3	2724 ± 1001	2833 ± 1206	109 ± 1086	0.6841	2053 ± 828	1871 ± 881	-182 ± 602	0.2615
AUC_{0-168h} (ng.h/mL)		347 ± 140	376 ± 171	29 ± 140	0.4007	249 ± 100	243 ± 116	-6 ± 74	0.7436

Reviewer's comment:

- This reviewer concurs with Agile that for subjects treated in AG200-15/Ortho-Cyclen/AG200-15 sequence, there were no carry-over effects for both EE and LNG due to the presence of a 28 days Ortho-Cyclen treatment between the two AG200-15 treatments.
- This reviewer also concurs with Agile that the exposure to EE in subjects treated with two consecutive cycles of patch therapy was slightly lower than that in subjects treated with Ortho Cyclen (AUC_{0-168h} of 7.22 ng*h/mL vs. 7.52 ng*h/mL).
- This reviewer concludes that the increase in EE exposure observed for Cycle 2 Week 1 vs. Cycle 1 Week 1 in Study ATI-CL14 is unlikely to affect the safety of AG200-15 patch based on following observations. As shown in Figure 1, the Week 3 mean plasma concentrations of EE at 240 hour were close to zero (1.25 pg/mL for Part I and 1.08 pg/mL for Part 2), indicating that one week washout is sufficient to eliminate the carry-over effects of EE between two consecutive cycles of patch therapy. In addition, the Week 1, Part II plasma concentration of EE at 0 hour was zero, indicating no carry-over from previous cycle. Furthermore, for both Part I and Part II, the Week 1 plasma concentrations of EE at 168 hour (25.9 pg/mL for Part I and 31.9 pg/mL for Part II) were

comparable to the Week 3 plasma concentrations of EE at 0 hour (30.4 pg/mL for Part I and 26.5 pg/mL for Part II) and at 168 hour (30.9 pg/mL for Part I and 29.4 pg/mL for Part II), indicating a steady state was achieved after one cycle of patch therapy. Therefore, it is unlikely that the systemic exposure of EE will significantly further increased in subjects receiving three or more consecutive cycles of patch therapy and the exposure to EE at steady state should be comparable to that in subjects treated with Ortho Cyclen.

- This reviewer concludes that the increase in LNG exposure observed for Cycle 2 Week 1 vs. Cycle 1 Week 1 in Study ATI-CL14 is unlikely to affect the safety of AG200-15 patch based on following observations. Compared with EE, LNG exhibited an intra-cycle and inter-cycle drug accumulation (more than 3-fold increase in LNG exposure post two consecutive cycles of patch therapy). As shown in Figure 2, for Part I study, the plasma concentrations of LNG increased from 845 pg/mL at Week 1, 168 hour to 1210 pg/mL at Week 3, 0 hour, and to 1510 pg/mL at Week 3, 168 hour, indicating a steady state was not achieved in Cycle 1. However, for Part II study, the plasma concentrations of LNG at Week 1, 168 hour (1150 pg/mL), and Week 3, 0 hour (1170 pg/mL) were comparable. The plasma concentration of LNG at Week 3, 168 hour (1430 pg/mL) was slightly higher than that at Week 3, 0 hour but slightly lower than Cycle 1 Week 3 at 168 hours. The data suggest that a steady-state concentration of LNG was almost achieved in Week 3 of the second cycle of a two consecutive cycles of patch therapy. It is not expected that the exposure of LNG will significantly increase in subjects receiving three or more consecutive cycles of patch therapy.

Overall, it is unknown whether the observed increase in EE and LNG exposure was caused by carry-over effect or not. However, the increase in EE and LNG exposure is unlikely to affect the efficacy or safety of AG200-15 patch.

Study ATI-CL15:

ATI-CL15 was an open-label, randomized, three-period crossover study to evaluate the safety and PK profile of AG200-15 following application at three different anatomical sites (abdomen, buttock, and upper torso). Twenty-four healthy females were randomly assigned to one of six treatment sequences. Each sequence included three patch application sites:

- Sequence 1: lower abdomen (Period I) then buttock (Period II) then upper torso (Period III);
- Sequence 2: buttock (Period I) then upper torso (Period II) then lower abdomen (Period III);
- Sequence 3: upper torso (Period I) then lower abdomen (Period II) then buttock (Period III);
- Sequence 4: lower abdomen (Period I) then upper torso (Period II) then buttock (Period III);
- Sequence 5: buttock (Period I) then lower abdomen (Period II) then upper torso (Period III);
- Sequence 6: upper torso (Period I) then buttock (Period II) then lower abdomen (Period III);

In each case, the patch was worn for 1 week (7 days) and the treatment periods were separated by 1-week (7-day) washout.

In Agile's submission dated June 26, 2017, Agile evaluated the impact of potential carry-over by subtracting subject pre-dose baseline values from subsequent EE or LNG concentrations. The plasma concentration data showed that no pre-dose EE concentration was observed for both Period II and Period III, indicating no evidence of carry-over for EE. Pre-dose baseline subtraction was not done for EE. During Period II and Period III, 13.6% and 27.3% of subjects had measurable pre-dose LNG levels. Agile did a baseline subtraction of plasma LNG levels in Period II and Period III. The results (Table 3) showed that pre-dose baseline subtraction had no effect on the medians and a minimal impact on means (approximately 1% and 2% differences

between adjusted and non-adjusted values for Periods II and III, respectively).

Table 3. Evaluation of the Impact of Measurable Pre-Dose LNG Levels on the Steady State Concentration ($C_{av48-168}$), Study: ATI-CL15, Period II and Period III

Study Period	Statistics	LNG Levels (pg/mL) in Subjects with Measurable Pre-Dose Concentrations	$C_{av48-168}$ with and without adjustment for baseline LNG Levels	
			Without Adjustment**	With Adjustment**
Period 2 (All Application Sites Combined)	N	3 (13.6%)*	22	22
	Mean (SD)	71.6 (19.0)	1341 (691)	1331 (687)
	Median	77.5	1128	1128
Period 3 (All Application Sites Combined)	N	6 (27.3%)*	22	22
	Mean (SD)	90.4 (37.5)	1567 (975)	1542 (939)
	Median	72.0	1420	1420

*Percentage of subjects with pre-dose LNG concentrations (out of total number of subjects)

** Adjustment is performed by subtracting baseline (pre-dose) values from the LNG concentrations recorded after patch application

Reviewer's comment:

The non-detectable pre-dose level of EE and negligible pre-dose levels of LNG suggested that the inter-period increases in EE and LNG exposure observed in Study ATI-CL15 were not caused by carry-over effect.

Agile conducted additional analyses to compare percent changes in exposure (mean AUC_{0-168}) of EE and LNG across all study periods (from Period I to Period II and from Period II to Period III) for Study ATI-CL15. A summary of percent change for EE exposure (mean AUC_{0-168}) across various application sites is presented in Table 4 below. The percent change for the buttock from Period 1 to Period 2 was 203.2%, while the percent change for the buttock from Period 2 to Period 3 was 78.3%. Similar evaluations were performed for LNG (Table 5). The percent change for the buttock from Period 1 to Period 2 was 274.0%, while the percent change for the buttock from Period 2 to Period 3 was 87.1%. The data showed that the exposure of EE and LNG did not consistently increase across all three study periods.

Table 4. Effect of Application Sequence on Mean EE exposure when AG200-15 is Applied to Three Different Anatomical Sites, Study ATI-CL15

PK parameter and Statistics	Abdomen (A)			Buttock (B)			Upper Torso (C)		
	First, n=8 (ABC or ACB)	Second, n=7 (BAC or CAB)	Last, n=7 (BCA or CBA)	First, n=8 (BAC or BCA)	Second, n=7 (ABC or CBA)	Last, n=8 (ACB or CAB)	First, n=8 (CAB or CBA)	Second, n=8 (ACB or BCA)	Last, n=7 (ABC or BAC)
Mean AUC_{0-168} (ng*hr/mL) (SD)	5.42 (1.45)	5.26 (1.52)	6.78 (4.59)	4.71 (1.55)	9.57 (2.54)	7.49 (1.94)	7.14 (1.48)	5.92 (2.11)	7.61 (3.57)
% increase of mean AUC (last/first)	125.1%			159.0%			106.6%		
% change of mean AUC (second/first)	97.0%			203.2%			82.9%		
% change of mean AUC (last/second)	128.9%			78.3%			128.5%		

Table 5. Effect of Application Sequence on Mean LNG exposure when AG200-15 is Applied to Three Different Anatomical Sites, Study ATI-CL15

PK parameter and Statistics	Abdomen (A)			Buttock (B)			Upper Torso (C)		
	First, n=8 (ABC or ACB)	Second, n=7 (BAC or CAB)	Last, n=7 (BCA or CBA)	First, n=8 (BAC or BCA)	Second, n=7 (ABC or CBA)	Last, n=8 (ACB or CAB)	First, n=8 (CAB or CBA)	Second, n=8 (ACB or BCA)	Last, n=7 (ABC or BAC)
Mean AUC ₀₋₁₆₈ (ng*hr/mL) (SD)	161 (56)	141 (52)	248 (222)	96 (37)	263 (145)	229 (69)	142 (76)	222 (82)	251 (133)
% change of mean AUC (last/first)	154.0%			238.5%			176.8%		
% change of mean AUC (second/first)	87.6%			274.0%			156.3%		
% change of mean AUC (last/second)	175.9%			87.1%			113.1%		

Reviewer's comment:

This reviewer agrees with Agile that the exposure of EE and LNG did not consistently increase across all three study periods. It is not expected that repeated dosing of AG200-15 will result in sustained increases in EE or LNG exposure.

Agile's analysis showed high inter-period ratios of mean AUC of EE (i.e. 203.2% for buttock from Period I to Period II) and LNG (i.e. 274.0% for buttock from Period I to Period II), which was likely caused by the large inter-subject variability in the AUC of EE (CV 37-48%) and LNG (CV 51-74%) and the relatively small study sample size (N = 24 per site). Due to the high variability, it is difficult to do a reliable comparison of EE and LNG exposures from three application sites. However, this reviewer concludes that the three anatomical sites can be switched interchangeably (as in the clinical trials) without appreciable clinical consequences based on following considerations.

- *Although bioequivalence analysis showed that for buttock vs. abdomen and upper torso vs. abdomen, both AUC₀₋₁₆₈ and C_{max} of EE failed to meet BE criteria, the exposure of EE from three application sites was still comparable (90% CIs were within or close to 66.7-150%).*

BE assessment for EE PK parameters; ATI-CL15

Comparison	% geometric mean ratio (90% CI)	
	C _{max}	AUC ₀₋₁₆₈
Buttock (B) vs. Lower abdomen (A)	130 (113 – 151)	123 (108 – 140)
Upper torso (C) vs. Lower abdomen (A)	115 (99.2 – 133)	121 (106 – 138)

- *For buttock vs. abdomen and upper torso vs. abdomen, AUC₀₋₁₆₈ and C_{max} of LNG either meet BE criteria or close to the upper BE limit.*

BE assessment for LNG PK parameters; ATI-CL15

Comparison	% geometric mean ratio (90% CI)	
	C _{max}	AUC ₀₋₁₆₈
Buttock (B) vs. Lower abdomen (A)	107 (89.9-127)	107 (92.0-124)
Upper torso (C) vs. Lower abdomen (A)	117 (98.0-139)	117 (101-136)

- *The mean C_{ss} levels of EE and LNG from three application sites were within the target plasma concentration range observed in the dose-ranging study (Study ATI-CL11).*
- *In both the original Phase 3 study (Study ATI-CL12) and the new Phase 3 study (Study ATI-CL23), the patch was applied to abdomen, buttock or upper torso. Study ATI-CL15 showed that patch application to abdomen resulted in a lower exposure of EE and LNG than application to buttock or upper torso. In the Phase 3 Study ATI-CL12, 38.8% of*

patches were applied to abdomen. Therefore, although a BE conclusion among the three application sites cannot be drawn from Study ATI-CL15, the Phase 3 efficacy/safety data support to the proposed patch application to three sites: abdomen, buttock, or upper torso.

Study ATI-CL16:

ATI-CL16 was an open-label, randomized, three-period, five-treatment, incomplete block design, crossover study to evaluate the PK profile, wearability and safety of AG200-15 under normal conditions and various external conditions (dry sauna, whirlpool, treadmill exercise, and cold water immersion). Twenty-four healthy females were randomly assigned to one of six external condition sequences. In each of the three treatment periods, subjects wore AG200-15 on the lower abdomen under normal wear conditions as well as after two of the following four activities: treadmill, dry sauna, whirlpool, or cool water immersion. The subjects were assigned randomly to 1 of the 6 sequences:

- Sequence 1: Normal (Period I), Dry Sauna (Period II), Cold Water (Period III);
- Sequence 2: Cold Water (Period I), Normal (Period II), Whirlpool (Period III);
- Sequence 3: Whirlpool (Period I), Treadmill (Period II), Normal (Period III);
- Sequence 4: Normal (Period I), Cold Water (Period II), Dry Sauna (Period III);
- Sequence 5: Dry Sauna (Period I), Normal (Period II), Treadmill (Period III);
- Sequence 6: Treadmill (Period I), Whirlpool (Period II), Normal (Period III)

The patch was worn for 1 week (7 days) and was removed following the 168-hour blood draw. Treatment periods were separated by a 1-week (7-day) washout.

In Agile’s submission dated June 26, 2017, Agile evaluated the impact of potential carry-over by subtracting subject pre-dose baseline values from subsequent EE or LNG concentrations. Only one subject had a measurable pre-dose EE level reported in this study. Pre-dose baseline subtraction was not done for EE. During Period II and Period III, 25.0% and 37.5% of subjects had measurable pre-dose LNG levels. Agile did a baseline subtraction of plasma LNG levels in Period II and Period III. The results (Table 6) showed that pre-dose baseline subtraction had a minimal effect on the means (approximately 2% and 2.5% differences between adjusted and non-adjusted values for Periods II and III, respectively) and a minimal impact on the medians (approximately 3.5% and 4.5% differences between adjusted and non-adjusted values for Periods II and III, respectively).

Table 6. Evaluation of the Impact of Measurable Pre-Dose LNG Levels on the Steady State Concentration ($C_{av48-168}$), Study: ATI-CL16, Second and Third Treatment Periods

Study Period	Statistics	LNG Levels (pg/mL) in Subjects with Measurable Pre-Dose Concentrations	$C_{av48-168}$ with and without adjustment for baseline LNG Levels	
			Without Adjustment**	With Adjustment**
Period 2 (All External Conditions Combined)	N	6 (25%)*	24	24
	Mean (SD)	74.0 (30.2)	925 (403)	907 (396)
	Median	63.2	928	895
Period 3 (All External Conditions Combined)	N	9 (37.5%)*	24	24
	Mean (SD)	79.1 (28.1)	1171 (527)	1141 (517)
	Median	70.7	1122	1073

*Percentage of subjects with pre-dose LNG concentrations (out of total number of subjects)

** Adjustment is performed by subtracting baseline (pre-dose) values from the LNG concentrations recorded after patch application

Reviewer's comment:

The negligible pre-dose levels of EE and LNG suggested that the inter-period increases in EE and LNG exposure observed in Study ATI-CL16 were not caused by carry-over effect.

Agile conducted additional analyses to compare percent changes in exposure (mean AUC₀₋₁₆₈) of EE and LNG across all study periods (from Period I to Period II and from Period II to Period III) for Study ATI-CL16. A summary of percent change for EE and LNG exposure (mean AUC₀₋₁₆₈) under different external conditions is presented in Table 7 and Table 8, respectively. The data showed that the exposure of EE and LNG did not consistently increase across all three study periods.

Table 7. Effect of Application Sequence on Mean EE Exposure When AG200-15 is applied under different external conditions, ATI-CL16

PK parameter and Statistics	Normal (N)			Cold Water (C)			Whirlpool (W)			Dry Sauna (D)			Treadmill (T)		
	First, n=8 (NDC or NCD)	Second, n=8 (CNW or DNT)	Last, n=8 (BAC or CAB)	First, n=4 (CNW)	Second, n=4 (NCD)	Last, n=4 (NDC)	First, n=4 (WTN)	Second, n=4 (TWN)	Last, n=4 (CNW)	First, n=4 (DNT)	Second, n=4 (NDC)	Last, n=4 (NCD)	First, n=4 (TWN)	Second, n=4 (WTN)	Last, n=4 (DNT)
Mean AUC ₀₋₁₆₈ (ng*hr/mL) (SD)	4.53 (1.92)	3.89 (1.52)	5.74 (0.73)	3.59 (1.70)	4.97 (3.28)	5.96 (1.34)	4.11 (0.71)	4.76 (0.90)	3.99 (2.33)	2.77 (0.70)	5.25 (1.98)	4.98 (2.45)	4.35 (0.72)	4.13 (1.08)	3.14 (1.34)
% change of mean AUC (last/first)	126.7%			166.0%			97.1%			179.8%			72.2%		
% change of mean AUC (second/first)	85.9%			138.4%			115.8%			189.7%			94.9%		
% change of mean AUC (last/second)	147.6%			119.9%			83.8%			94.9%			76.0%		

Table 8. Effect of Application Sequence on Mean LNG Exposure When AG200-15 is applied under different external conditions, ATI-CL16

PK parameter and Statistics	Normal (N)			Cold Water (C)			Whirlpool (W)			Dry Sauna (D)			Treadmill (T)		
	First, n=8 (NDC or NCD)	Second, n=8 (CNW or DNT)	Last, n=8 (BAC or CAB)	First, n=4 (CNW)	Second, n=4 (NCD)	Last, n=4 (NDC)	First, n=4 (WTN)	Second, n=4 (TWN)	Last, n=4 (CNW)	First, n=4 (DNT)	Second, n=4 (NDC)	Last, n=4 (NCD)	First, n=4 (TWN)	Second, n=4 (WTN)	Last, n=4 (DNT)
Mean AUC ₀₋₁₆₈ (ng*hr/mL) (SD)	124 (57)	137 (73)	210 (67)	104 (64)	138 (54)	216 (75)	90 (21)	169 (68)	153 (119)	78 (44)	135 (53)	141 (39)	119 (29)	107 (42)	130 (68)
% change of mean AUC (last/first)	169.4%			207.7%			170.0%			180.8%			109.2%		
% change of mean AUC (second/first)	110.5%			132.7%			187.8%			173.1%			89.9%		
% change of mean AUC (last/second)	153.3%			156.5%			90.5%			104.4%			121.5%		

Reviewer's comment:

This reviewer agrees with Agile that the exposure of EE and LNG did not consistently increase across all three study periods in Study ATI-CL16. It is not expected that repeated dosing of AG200-15 will result in sustained increases in EE or LNG exposure.

Agile's analysis showed high inter-period ratios of mean AUC of EE (i.e. 189.7% for dry sauna from Period I to Period II) and LNG (i.e. 207.7% for cold water from Period I to Period III), which was likely caused by the large inter-subject variability in the AUC of EE (CV 28-47%) and LNG (CV 39-59%) and the relative small study sample size (N = 12 per external conditions). Due to the high variability, it is difficult to do a reliable comparison of EE and LNG exposures under the five conditions. However, this reviewer concludes that no clinically significant effect of any of the four environmental conditions (cold water, whirlpool, dry sauna and treadmill) on the drug

delivery profiles is expected based on following considerations.

- Bioequivalence analysis showed that AUC_{0-168} of EE for dry sauna and cold water met BE criteria. The AUC_{0-168} of EE for whirlpool and treadmill was comparable to that for normal conditions (90% CIs were within 66.7-150%).

BE assessment for EE PK parameters; ATI-CL16

Comparison	% geometric mean ratio (90% CI)	
	C_{max}	AUC_{0-168}
Dry sauna vs. Normal	90.5 (78.5-104.4)	93.0 (82.7-104.5)
Cold water vs. Normal	94.3 (81.8-108.8)	99.5 (88.6-111.9)
Whirlpool vs. Normal	80.7 (70.0-93.0)	86.7 (77.1-97.4)
Treadmill vs. Normal	79.8 (69.3-92.0)	82.2 (73.2-92.4)

- Bioequivalence analysis showed that AUC_{0-168} of LNG for cold water met BE criteria. The AUC_{0-168} of LNG for dry sauna, whirlpool and treadmill was comparable to that for normal conditions (90% CIs were within 66.7-150%).

BE assessment for LNG PK parameters; ATI-CL16

Comparison	% geometric mean ratio (90% CI)	
	C_{max}	AUC_{0-168}
Dry sauna vs. Normal	79.1 (66.7-93.8)	78.6 (68.0-90.8)
Cold water vs. Normal	90.1 (76.0-106.8)	97.8 (84.7-113.0)
Whirlpool vs. Normal	78.4 (66.1-92.9)	79.1 (68.5-91.3)
Treadmill vs. Normal	75.3 (63.5-89.3)	78.1 (68.4-91.2)

- The mean C_{ss} levels of EE and LNG under four external conditions were within the target plasma concentration range observed in the dose-ranging study (Study ATI-CL11).

2.2.2 Do the product quality deficiencies described in the CRL have an impact on the clinical pharmacology findings of Twirla®?

It is unlikely that the product quality deficiencies 5 ((b) (4)), 6 (updated post-approval stability protocols), and 7 (DMF) and their resolutions would affect the clinical pharmacology data of Twirla. Agile assessed potential effect of product quality deficiencies 1 and 4 (laser etching of the TDS), 2 (cold flow and shear specifications), 3 (excipient specifications), and 8 (equipment) on clinical pharmacology findings.

Product quality deficiencies 1 and 4 (laser etching of the TDS): The TDS used in the clinical pharmacology studies were not laser etched, while the commercial TDS will be laser etched. The (b) (4) visual test procedure ((b) (4) – AG200-15 Active Matrix Backing Appearance) was implemented by Agile to determine whether the (b) (4) compromised the TDS. (b) (4)

The (b) (4) testing showed that the current laser etching process did not compromise the

active backing of the TDS. In addition, a review of the comparability batches has shown that laser etching had no effect on quality of the Twirla product.

Reviewer's comment:

Laser etching is not expected to change the clinical pharmacology data if it does not compromise the active backing of TDS. The drug product review dated Nov 16, 2017 by Dr. Caroline Strasinger (available from Panorama, <http://panorama.fda.gov/document/view?ID=5a0c59f4002bcd26d99a20f0e10469be>) showed that the new ^{(b) (4)} test is sufficient to identify compromised TDSs and Agile's response is adequate to address the laser etching issue. Therefore, the absence of laser etching on TDS used in the clinical pharmacology studies has no impact on the validity of the results.

Product quality deficiency 2 (cold flow and shear specifications): The CRL requested that Agile establish acceptance criteria for cold flow and shear. Agile has established these criteria based on three standard deviations from the average using data from both the original stability batches and the Study ATI-CL23 stability batches. As shown in Table 9, the major difference between the resubmission clinical batches (Study ATI-CL23 batches) and product development/original NDA clinical batches (used in clinical pharmacology studies) is the laser etching. Laser etching is not expected to alter cold flow or shear. Therefore, the lack of acceptance criteria at the time of production of batches used in the clinical pharmacology studies is unlikely to have an impact on the findings of these studies or their applicability to commercial product.

Table 9. Twirla Drug Product Batches Referenced in Resubmission

Batch Number	Manufacturing Line	Used to Set Specifications	Etching	Clinical Study No.
Product Development Batches				
31974	Clinical	Yes	EE/LNG TDS	N/A
31978A1	Clinical	Yes	EE/LNG TDS	N/A
Clinical/Registration Batches for Original NDA				
29588	Clinical	Yes	None	ATI-CL12/13
30793	Clinical	Yes	None	ATI-CL12/13
30941	Clinical	Yes	None	ATI-CL12/13
31357	Clinical	Yes	None	ATI-CL12/13
Clinical Batches for Resubmission				
35249*	Clinical	Yes	Twirla 120/30	ATI-CL23
35274*	Clinical	Yes	Twirla 120/30	ATI-CL23
35620*	Clinical	Yes	Twirla 120/30	ATI-CL23
Comparability Batches for Resubmission				
36099 (pilot scale)**	Commercial	No	Twirla 120/30	N/A
36172 (pilot scale)**	Commercial	No	Twirla 120/30	N/A
37620 (full scale)**	Commercial	No	Twirla 120/30	N/A
* Identical to Product Development and Original NDA batches with the exception of etching on the TDS.				
** Identical to commercial batches (to be manufactured) with the exception of the wording of the etching on the TDS.				

Product quality deficiency 3 (excipient specifications): The CRL requested that Agile justify the upper and lower bounds of the permeation enhancer excipients. Agile provided justification for those bounds and the patches used in the clinical pharmacology studies were manufactured with excipients within the same upper and lower bounds. Therefore, the lack of justification for

the excipient specifications at the time of production of batches used in the clinical pharmacology studies is unlikely to have an impact on the findings of these studies or their applicability to commercial product.

Product quality deficiency 8 (equipment): The CRL requested that Agile address whether use of new or different manufacturing equipment for the commercial product will impact product performance. As shown in Table 10, Agile provided a side-by-side comparison of the equipment used to make clinical trial supplies for Studies ATI-CL12, ATI-CL13, and ATI-CL23 along with the product development batches and the equipment proposed to be used for commercial product, which was also used in the manufacture of the comparability batches. The bolded items are those that were not included in the original NDA. The clinical equipment and commercial equipment share the same design and operating principle (b) (4) factors are below (b) (4)x. In the meeting comments sent to Agile on Aug 31, 2016, the Agency did not recommend in vivo BE study to bridge the clinical batches and proposed commercial batches. In the resubmission, Agile conducted a full comparability assessment on product produced on the new manufacturing line and the clinical trial batches.

Table 10. Comparison of Clinical Equipment to Proposed Commercial Equipment

(b) (4)



Reviewer's comment:

CMC comparability data and in vitro release and permeation data can be used to support the proposed commercial batch (b) (4). Per the Biopharmaceutics Review by Dr. Peng Duan dated 11/14/2017, the in vitro release and permeation data of NDA 204017 resubmission are adequate to bridge clinical formulation and commercial formulation manufactured at the (b) (4) sites. The NDA resubmission is adequate from a biopharmaceutical perspective. The new manufacturing equipment for the commercial product is unlikely to have an impact on the validity of clinical pharmacology findings.

2.3 Intrinsic Factors

Reviewed by Dr. Hyunjin Kim dated 01/11/2013 and no new data was submitted.

2.4 Extrinsic Factors

Reviewed by Dr. Hyunjin Kim dated 01/11/2013 and no new data was submitted.

2.5 General Biopharmaceutics

2.5.1 Is the clinical formulation same as the to-be-marketed formulation? What are the proposed major changes in Chemistry, Manufacturing, and Controls (CMC) of the to-be-marketed formulation in current NDA?

Yes, the clinical formulation and to-be-marketed formulation have the same formulation composition. The original NDA clinical batches used in Study ATI-CL12 and ATI-CL13 have no laser etching but the resubmission clinical batches used in Study ATI-CL23 were laser-etched product. A new manufacturing line with greater capacity will be used in the manufacturing of commercial batches of Twirla. As shown in Table 10, the clinical equipment and commercial equipment share the same design and operating principle (b) (4) factors are below (b) (4). The wording of etching for the commercial batches will be different from that for the resubmission clinical batches. Per the Biopharmaceutics Review by Dr. Peng Duan dated 11/14/2017, the clinical batches and commercial batches were adequately bridged with CMC data and in vitro dissolution data and no in vivo bioequivalence study is needed.

2.6 Bioanalytical Methods

Reviewed by Dr. Hyunjin Kim dated 01/11/2013 and no new data was submitted.

3 Detailed Labeling Recommendations

No labeling recommendation will be provided in the current review cycle.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PENG ZOU
11/30/2017

DOANH C TRAN
12/01/2017

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA 204017	Submission Dates: 4/12/2012, 6/1/2012, 10/19/2012, 11/29/2012, and 12/12/2012
Brand Name	Twirla
Generic Name	Levonorgestrel/ethinyl estradiol
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Agile Therapeutics, Inc.
Relevant IND	IND 057731
Submission Type	Original, 505(B)2
Formulation and Strength	Transdermal contraceptive system containing 2.3 mg ethinyl estradiol and 2.6 mg levonorgestrel
Indication	Prevention of pregnancy

An Optional Inter-Division Level Clinical Pharmacology Briefing was held on December 20, 2012 in conference room 3300 of White Oak Bldg 51. Attendees included Drs'. Myong-Jin Kim, Li Li, Lisa Soule, Daniel Davis, Peng Duan, Michiyo Yamazaki, Sayed Al Habet, Hae Young Ahn, LaiMing Lee, Yuzhuo Pan and Hyunjin Kim.

Table of Contents

1	Executive Summary.....	2
1.1	Recommendation.....	2
1.2	Phase IV Commitments/Requirements.....	2
1.3	Summary of Important Clinical Pharmacology and Biopharmaceutics Findings.....	2
2	Question Based Review.....	3
2.1	General Attributes.....	3
2.2	General Clinical Pharmacology.....	5
2.3	Intrinsic Factors.....	18
2.4	Extrinsic Factors.....	19
2.5	General Biopharmaceutics.....	20
2.6	Analytical Section.....	20
3	Detailed Labeling Recommendation.....	21
4	Appendices.....	21
4.1	Individual Clinical Study Review.....	21
4.2	OCP Filing memo.....	52

1 Executive Summary

The sponsor submitted a New Drug Application (NDA) under 505(b)(2) for a transdermal contraceptive system (called “patch” hereafter) containing 2.3 mg ethinyl estradiol (EE) and 2.6 mg levonorgestrel (LNG) seeking approval for the indication of prevention of pregnancy. The proposed dosing regimen is to apply one patch to abdomen, buttock, or upper torso once every week for three weeks followed by one patch free week.

In support of the NDA, the sponsor conducted 19 clinical studies, 13 studies with the earlier formulations evaluating safety and/or pharmacokinetics (PK) and 6 studies with the to-be-marketed (TBM) formulation (AG200-15) including 4 PK studies and 2 phase 3 safety and efficacy studies.

The 4 Clinical Pharmacology studies include an ovulation suppression and menstrual cycle control study, a comparative bioavailability study to compare the EE exposure with a marketed oral contraceptive tablet, a PK study to evaluate the systemic exposure of EE and LNG following a single patch application to three different application sites, and a PK study to evaluate the effects of different external conditions such as dry sauna, whirlpool, treadmill exercise, and cold water.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 204017 acceptable provided that the issues identified by the Office of New Drug Quality Assessments for the recommendation for Complete Response are resolved.

1.1.1 Comments to the sponsor

The potential carry-over effects of both ethinyl estradiol (EE) and levonorgestrel (LNG) between adjacent treatment Cycles (in ATI-CL14) and adjacent Periods (in ATI-CL15 and ATI-CL16) were noted in the respective studies. As the FDA considers this to be important information for proper labeling, as part of your response to this Complete Response, you will need to provide a revised analysis which corrects for/compensates for the noted potential carry-over effect or provide details on how you will obtain this information post-marketing along with a suitable labeling to address this lack of information.

1.2 Phase IV Commitments/Requirements

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

To-be-marketed (TBM) formulation of AG200-15

Each AG200-15 patch contains 2.3 mg of EE and 2.6 mg of LNG. The patch has an active hormone containing contact surface area of 15 cm² with a flexible overlay peripheral adhesive.

Dose finding; ATI-CL11

Three different formulations (AG200LE, AG200, and AG200-15) containing different amounts of EE and LNG were tested for ovulation suppression and menstrual cycle control. The tested formulations/doses are as follows:

- AG200LE: a 12.5 cm² patch containing 1.28 mg EE/2.17 mg LNG
- AG200: a 12.5 cm² patch containing 1.92 mg EE/2.17 mg LNG
- AG200-15: a 15 cm² patch containing 2.3 mg EE/2.6 mg LNG; TBM formulation

Study subjects received each formulation for 3 cycles (one cycle consisting 21 days of treatment and 7 days of no treatment). A cycle with ovulation was defined as a cycle with greatest

progesterone concentration ≥ 4.7 ng/mL. The evaluation of menstrual cycle control was based on number of cycles with the incidence of breakthrough bleeding and/or spotting (BTB/S) in Cycle 3. AG200-15 demonstrated the highest ovulation suppression with lowest BTB/S compared to two other formulations, AG200LE and AG200. Therefore, AG200-15 was studied in 2 phase 3 studies.

Comparison of EE exposure with oral contraceptive, Ortho-Cyclen; ATI-CL14

EE exposures from AG200-15 and Ortho-Cyclen containing 0.035 mg EE and 0.25 mg norgestimate were compared in Weeks 1 and 3 during one cycle. There was approximately 13% increase of EE mean C_{max} from Week 1 to Week 3 in AG200-15, whereas there was no increase of EE mean C_{max} in Ortho-Cyclen. Overall, the EE mean C_{max} from AG200-15 was about 39% of EE mean C_{max} from Ortho-Cyclen based on PK data observed in Week 3.

Overall, the AUC and C_{max} of EE from AG200-15 were about 10% and 61% lower than AUC and C_{max} of EE from Ortho-Cyclen based on the PK data observed in Week 3. However, due to the potential between cycle accumulation of EE, the study result may not be reliable.

Comparison of EE and LNG exposure in different application sites; ATI-CL15

Both EE and LNG exposures were compared following a patch application for one week in three different application sites including abdomen, buttock, and upper torso with wash out period of one week. The study result showed that buttock and upper torso were associated with higher C_{max} and higher AUC_{0-168} compared to abdomen. However, exposure change due to the treatment period was observed for both EE and LNG suggesting that one week of patch free period may not be long enough to eliminate both EE and LNG from the systemic circulation. Therefore, the study result may not be reliable.

Comparison of EE and LNG exposure under different external conditions; ATI-CL16

Both EE and LNG exposures were compared under different external conditions (normal, dry sauna, whirlpool, treadmill, and cold water) following a patch application for one week. The study result showed that both EE and LNG exposures were comparable under cold water condition compared to normal condition. Also, the study showed that both EE and LNG exposure were lower under other conditions including dry sauna, whirlpool and treadmill compare to normal condition. However, exposure change due to the treatment period was observed for both EE and LNG suggesting that 1 week patch free period was may not be long enough to eliminate both EE and LNG from the systemic circulation. Therefore, the study result may not be reliable.

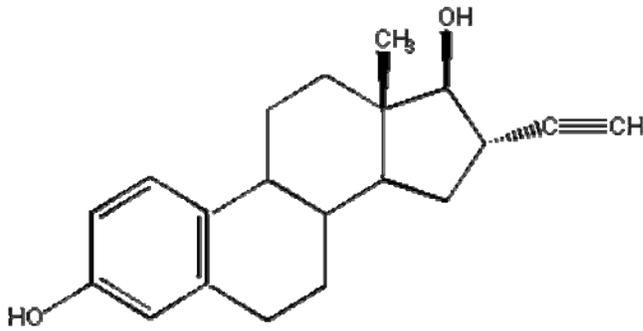
2 Question Based Review

2.1 General Attributes

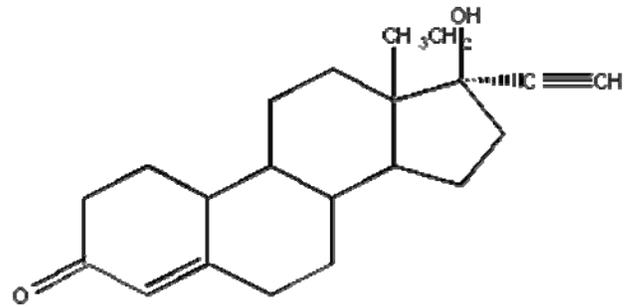
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substances and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Active substances:

The active pharmacological ingredients in AG200-15 are EE and LNG.



EE



LNG

Formulation:

Each AG200-15 patch contains 2.3 mg of EE and 2.6 mg of LNG. The patch has an active hormone containing contact surface area of 15 cm² with a flexible overlay peripheral adhesive. The inactive components are polyisobutylene adhesive, woven polyester fabric, acrylic adhesives, crospovidone, copovidone, lauryl lactate, ethyl lactate, dimethyl sulfoxide, capric acid, polyester backing and polyester release liner. The composition of the AG200-15 and the function of each component are provided in the Table below.

Table 1 Composition of AG200-15 transdermal patch

Component	Function	Dry Weight (mg/Patch)	Target % (w/w)
Active Matrix Adhesive Layer and Backing			
LNG	Drug substance	2.60	0.868
EE	Drug substance	2.30	0.768
Dimethyl Sulfoxide (DMSO)			(b) (4)
Ethyl Lactate, (b) (4)			
Capric Acid (b) (4)			
Copovidone			
Lauryl Lactate (b) (4)			
(b) (4)			

2.1.2 What are the proposed mechanism of action and therapeutic indication?

Mechanism of action:

Combination hormonal contraceptives lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that may reduce the likelihood of sperm transport as well as implantation.

Indication:

Prevention of pregnancy

2.1.3 What is the proposed dosage regimen?

The application schedule for AG200-15 uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (a total 21 days) to abdomen, buttock, or upper torso. Week 4 is patch-free. Every new patch should be applied on the same day of the week. Only one patch should be worn at a time.

2.1.4 What are the clinical pharmacology and clinical studies submitted to support the approval of AG200-15?

Clinical Pharmacology studies:

The sponsor conducted 12 clinical pharmacology studies. Of these 8 studies were conducted with earlier formulations evaluating safety and/or pharmacokinetics (PK). The earlier formulations had different amount of both EE (ranging (b) (4)) and LNG (ranging (b) (4)). The 4 studies were conducted with the TBM, AG200-15 containing 2.3 mg EE and 2.6 mg LNG, and they are as follows:

- Ovulation suppression and cycle control; ATI-CL11
- Comparison of EE exposure with oral contraceptive, Ortho-Cyclen; ATI-CL14
- Comparison of EE and LNG exposures in different application sites; ATI-CL15
- Comparison of EE and LNG exposures under different external conditions; ATI-CL16

Clinical studies:

The sponsor conducted 7 clinical, non-PK studies. Of these 5 studies were conducted with earlier formulations evaluating tolerability and safety. The 2 studies were conducted with the TBM formulation, AG200-15, and they are as follows:

- Comparative evaluation of contraceptive efficacy of AG200-15 with OC, Lessina (ANDA 075803 approved in March, 2002) containing 0.02 mg EE and 0.1 mg LNG; ATI-CL12
- Comparative evaluation of contraceptive efficacy of AG200-15 with OC, Levora (ANDA 073592 approved in December, 1993) containing 0.03 mg EE and 0.15 mg LNG; ATI-CL13

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical studies used to support dosing or claims?

Comparative evaluation of contraceptive efficacy of AG200-15 with OC, Lessina (ANDA 075803 approved in March, 2002) containing 0.02 mg EE and 0.1 mg LNG; ATI-CL12

This was an open-label, randomized, comparative, parallel group, multi-center study. Up to 1,500 sexually active women were enrolled in this study. The subjects were randomized in 3:1 ratio, with 1,125 subjects assigned to AG200-15 for 13 cycles and 375 subjects assigned to OC, Lessina for 6 cycles. After completion of 6 treatment cycles, subjects from the OC group were switched to AG200-15 for 7 additional cycles of treatment. Contraceptive efficacy was evaluated using pregnancy rates. The evaluation of cycle control parameter was based on the bleeding information recorded by the subjects on daily diary cards. The subject incidence of BTB/S episodes during all cycles was considered as primary endpoint for the cycle control analysis. Safety was assessed by tracking adverse events, discontinuation information, vital signs, and physical and gynecological examinations and laboratory test results.

Comparative evaluation of contraceptive efficacy of AG200-15 with OC, Levora (ANDA 073592 approved in December, 1993) containing 0.03 mg EE and 0.15 mg LNG; ATI-CL13

This was an open-label, randomized, comparative, parallel group, multi-center, contraceptive efficacy and safety study. The 407 sexually active women were enrolled in this study. The subjects were randomized in 1:1 ratio, with 201 subjects assigned to AG200-15 and 206 subjects assigned to an OC, Levora. The subjects were treated for 6 cycles. Contraceptive efficacy was evaluated using pregnancy rates. The evaluation of cycle control parameters was based on the bleeding information recorded by the subjects on daily diary cards. The subject incidence of BTB/S episodes during all cycles was considered as primary endpoint for the cycle control analysis. Safety was assessed by tracking adverse events (with a focus on the hormone-related events such as headache, nausea, vomiting, etc.), discontinuation information, vital signs, and from physical and gynecological examinations and laboratory test results (including lipid panel).

2.2.2 What is the basis for selecting the dose/formulation of the patch and how is that measured in clinical pharmacology study?

ATI-CL11 was to evaluate the adequacy of ovulation suppression and cycle control of transdermal patches containing 2 different doses of LNG and 3 different doses of EE during 3 consecutive cycles of administration of each treatment. The AG200-15 contraceptive patch was the appropriate formulation for further study in Phase 3 trials as it demonstrated the most consistent inhibition of ovulation in the populations being analyzed and the definition of ovulation employed. Results of the analyses of cycle control endpoints indicated that the AG200-15 contraceptive patch was the appropriate formulation for further study in Phase 3 trials as it exhibited the lowest bleeding rate out of the 3 patches studied.

Phase 3 studies were all conducted with AG200-15.

Study design; ATI-CL11:

This was a multicenter, open-label, randomized, parallel group study (Part I) followed by a multicenter, open-label, single-arm extension (Part II). Part I of the study evaluated 2 different contraceptive patches, AG200 and AG200LE, while Part II of the study evaluated a third contraceptive patch, AG200-15.

In Part I of the study, subjects were randomly assigned to 1 of 2 treatment groups:

- Group 1: AG200 for 3 cycles (1 cycle consists of 21 days of treatment and 7 days of no treatment)
- Group 2: AG200LE for 3 cycles (1 cycle consists of 21 days of treatment and 7 days of no treatment)

In the Part II of the study, all subjects were assigned to the third treatment group:

- Group 3: AG200-15 for 3 cycles (1 cycle consists of 21 days of treatment and 7 days of no treatment)

Enrolled subjects applied the assigned contraceptive patch to the lower abdomen in the morning of Cycle Day 1 (Day 1 of their menstrual cycle). The patch was to be left in place for 7 days at which time it was to be removed and replaced twice (in the morning of Cycle Days 8 and 15), and removed without being replaced in the morning of Cycle Day 22. Blood samples were drawn to assess ovulation suppression (progesterone) on Cycle Days 8, 11, 15, 19, 22, 25 and 29 (Day 1 of

next cycle) in all 3 cycles. EE and LNG concentration was measured just prior to the patch removal at approximately the same time each visit. Cycle control endpoint was assessed by daily bleeding/spotting reporting by subjects, via diary cards during all 3 cycles, along with data on patch wearability

Study result; ATI-CL11:

Table 2 Summary of ovulation rates; ATI-CL11

Serum progesterone concentration	Number (%) of Cycles		
	AG200LE	AG200	AG200-15
greatest concentration \geq 4.7 ng/mL (possible ovulation)			
All BMI	46/125 (36.8%)	26/129 (20.2%)	16/83 (19.3%)
BMI \leq 32 kg/m ²	39/105 (37.1%)	19/94 (20.2%)	8/63 (12.7%)
greatest concentration \geq 9.0 ng/mL			
All BMI	22/125 (17.6%)	10/129 (7.8%)	4/83 (4.8%)
BMI \leq 32 kg/m ²	18/105 (17.1%)	8/94 (8.5%)	3/63 (4.8%)
2 successive \geq 4.7 ng/mL (probable ovulation)			
All BMI	34/125 (27.2%)	15/129 (11.6%)	8/83 (9.6%)
BMI \leq 32 kg/m ²	28/105 (26.7%)	12/94 (12.8%)	6/63 (9.5%)
4.7 > greatest concentration \geq 3.0 ng/mL (luteal activity)			
All BMI	6/125 (4.8%)	6/129 (4.7%)	1/83 (1.2%)
BMI \leq 32 kg/m ²	6/124 (4.8%)	6/126 (4.8%)	1/78 (1.3%)
greatest concentration \geq 3.0 ng/mL (possible ovulation and/or luteal activity)			
All BMI	52/125 (41.6%)	32/129 (24.8%)	17/83 (20.5%)
BMI \leq 32 kg/m ²	51/124 (41.1%)	32/126 (25.4%)	15/78 (19.2%)

With respect to the 5 efficacy measurements for ovulation suppression, AG200-15 exhibited the greatest ovulation inhibition with a possible ovulation rate of 19.3% for all BMI. For treatment groups AG200LE and AG200, possible ovulation rates were 36.8% and 20.2%, respectively. For AG200-15 treatment group, possible ovulation rates were lower when controlling for BMI (12.7%) compared to no exclusion for larger BMI (19.3%), indicating that the higher BMI may associate with lower rate of ovulation suppression.

Table 3 Summary of breakthrough bleeding/spotting episodes in Cycle 3; ATI-CL11

	AG200LE (N=42)	AG200 (N=42)	AG200-15 (N=27)
Bleeding/Spotting Episode? n (%)			
Yes	12 (28.6%)	12 (28.6%)	4 (14.8%)
No	30 (71.4%)	30 (71.4%)	23 (85.2%)
Number of Episodes			
Mean \pm SD	0.29 \pm 0.46	0.29 \pm 0.46	0.15 \pm 0.36
Median	0.0	0.0	0.0
Range	0.0–1.0	0.0–1.0	0.0–1.0

In the analysis for cycle control, 28.6% (12/42) of subjects in both the AG200LE and the AG200 treatment groups reported episodes of breakthrough bleeding/spotting in Cycle 3, compared to 14.8% (4/27) in the AG200-15 treatment group. The mean number of episodes in both the AG200LE and the AG200 treatment groups was 0.29 compared to 0.15 in the AG200-15 group.

2.2.3 The PK characteristics of active pharmacological components of AG200-15

2.2.3.1 What are the single and multiple dose PK parameters of EE of AG200-15 and Ortho-Cyclen?

ATI-CL14 was to evaluate the EE PK profile of AG200-15 in comparison to the marketed OC Ortho-Cyclen (both administered in a crossover fashion for 1 cycle as 21-7 day treatment regimens).

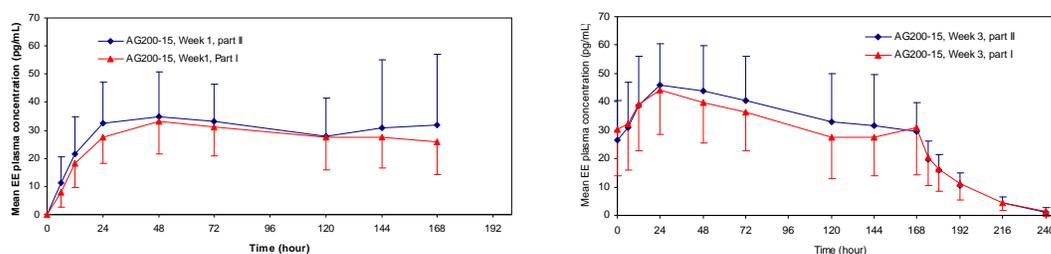


Figure 1 Mean (SD) EE concentrations in Weeks 1 and 3 of both Parts I and II from AG200-15 (PK population); ATI-CL14

Table 4 Summary of EE PK parameters (primary PK analysis population); ATI-CL14

Week	PK parameter	Part I			Part II					
		AG200-15			AG200-15			Ortho-Cyclen		
		All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen in Part II, N=17	Sequence: Ortho-Cyclen/AG200-15 in Part II, N=15	All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen, N=17	Sequence: Ortho-Cyclen/AG200-15, N=15	All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen, N=17	Sequence: Ortho-Cyclen/AG200-15, N=15
1	C_{max} (pg/mL)	35.6 (13.2)	40.1 (14.4)	30.5 (9.78)	45.5 (24.0)	56.8 (26.9)	32.7 (10.6)	135 (50.7)	140 (58.3)	128 (38.9)
	T_{max} (hr)*	48.0 (24 - 144)	60 (24 - 144)	48 (24 - 144)	48 (24 - 168)	72 (24 - 168)	48 (24 - 168)	1 (0.5 - 1.5)	1 (1 - 1.5)	0.75 (0.5 - 1.5)
	AUC_{0-168h} (ng·h/mL)	4.64 (1.53)	5.18 (1.73)	4.04 (1.03)	5.05 (2.26)	6.20 (2.14)	3.75 (1.62)	7.28 (2.66)	7.52 (3.15)	6.92 (1.82)
3	C_{max} (pg/mL)	51.4 (17.3)	57.0 (17.1)	45.0 (15.6)	51.3 (17.3)	58.7 (18.4)	42.9 (11.6)	131 (45.4)	135 (52.1)	126 (37.7)
	T_{max} (hr)*	36 (0 - 168)	24 (0 - 120)	48 (0 - 168)	48 (12 - 144)	36 (12 - 144)	48 (24 - 72)	1 (1 - 3)	1 (1 - 3)	1 (1 - 1.5)
	AUC_{0-168h} (ng·h/mL)	5.71 (1.89)	6.21 (2.12)	5.15 (1.46)	6.26 (2.46)	7.22 (2.66)	5.18 (1.72)	6.97 (2.25)	6.97 (2.41)	6.97 (2.13)
	$t_{1/2}$ (hr)	19.7 (3.25)	19.7 (3.72)	19.7 (2.75)	19.2 (4.12)	20.3 (3.79)	17.9 (4.22)	18.9 (3.78)	18.7 (3.96)	19.1 (3.7)

*Presented as median (range)

The exposure (both AUC and C_{max}) of EE was higher in subjects in AG200-15/Ortho-Cyclen sequence in part II compared to subjects in Ortho-Cyclen/AG200-15 in both AG200-15 and Ortho-Cyclen, although demographics of two groups were comparable. It ~~is was~~ not clear what contributed to the differences in exposure of EE in these subjects.

AG200-15 (All subjects, subjects in AG200-15/Ortho-Cyclen sequence in part II, and subjects in Ortho-Cyclen/AG200-15 sequence) exhibited the within-cycle accumulation shown by the higher AUC in Week 3 compared to Week 1 (observed in both Parts I and II). In addition, there was a trend of between-cycle accumulation in AG200-15 (All subjects, subjects in AG200-15/Ortho-Cyclen sequence in Part II) shown by the followings:

- Higher AUC and C_{max} in Week 1 of Part II compared to Week 1 of Part I
- Higher AUC and C_{max} in Week 3 of Part II compared to Week 3 of Part I

However, the between-cycle accumulation in AG200-15 was not observed in subjects in Ortho-Cyclen/AG200-15 sequence in Part II.

Ortho-Cyclen did not exhibit the accumulation.

The $t_{1/2}$ of EE observed from both AG200-15 and Ortho-Cyclen was similar.

Study design, ATI-CL14:

This was an open-label study comprised of two parts.

Part I of the study was a single-arm, run-in cycle with AG200-15 administered to all subjects as a 21-7 day regimen, i.e., three consecutive weeks of patch wear followed by a patch-free week.

Subjects completing the run-in cycle proceeded to Part II of the study.

Part II employed a crossover design with subjects randomly assigned to one of the two treatment sequences. Each sequence included AG200-15 and a marketed OC (Ortho-Cyclen) as follows:

- Sequence 1: AG200-15 (Period 1) followed by the OC Ortho-Cyclen (Period 2)
- Sequence 2: the OC Ortho-Cyclen (Period 1) followed by AG200-15 (Period 2)

Both AG200-15 and Ortho-Cyclen were administered as 21-7 day regimen, i.e., three consecutive weeks of drug-taking followed by a drug-free week. The duration of each treatment period was 28 days, i.e., one cycle of therapy. Data from Part II supported the study objective, i.e., the evaluation of the exposure to EE of AG200-15 in comparison to the marketed OC Ortho-Cyclen.

The blood sampling for PK evaluations was performed at the following time points.

- Part I:

During the first and third week at the following time points: 0 h (immediately prior to patch application on Cycle Days 1 and 15) and at 6 h, 12 h, 24 h (1 day), 48 h (2 days), 72 h (3 days), 120 h (5 days), 144 h (6 days), and 168 h (7 days) following application of the patch. Following removal of the third patch, blood samples were also collected at 6, 12, 24, 48, and 72 h after removal.

- Part II:

<AG200-15 cycle>

The blood sampling was performed during the first and third week at the following time points: 0 h (immediately prior to patch application on Cycle Days 1 and 15) and at 6 h, 12 h, 24 h (1 day), 48 h (2 days), 72 h (3 days), 120 h (5 days), 144 h (6 days), and 168 h (7 days) following application of the patch. Following removal of the third patch, blood samples were also collected at 6, 12, 24, 48, and 72 h after removal.

<OC (Ortho-Cyclen) cycle>

At the end of the first and third week (Cycle Days 7 and 21) at the following time points: 0 h (immediately prior to dosing) and at 0.5, 1, 1.5, 3, 6, 9, 12, 16 and 24 h following dosing. In addition, blood samples were collected at 36 h, 48 h (2 days) and 72 h (3 days) following the Day 21-dose.

2.2.3.2. How comparable is EE exposure from AG200-15 and Ortho-Cyclen?

ATI-CL14 compared the EE exposure from AG200-15 and Ortho-Cyclen during one cycle (3 weeks of treatment phase) of drug use.

Table 5 Comparative evaluation of EE PK parameters: AG200-15 vs. Ortho-Cyclen (Part II, primary PK population^a); ATI-CL14

Parameter/Period	Arithmetic mean \pm SD		Treatments comparison		
	AG200-15 (N=32)	Ortho-Cyclen (N=32)	p-value	Ratio of Point Estimates	90% CI
Week 1					
C _{max} (pg/mL)	45.5 \pm 24.0	135 \pm 50.7	<0.0001	32.08	27.58 37.30
AUC _{0-168h} (ng·h/mL)	5.06 \pm 2.26	7.28 \pm 2.66	0.0001	65.96	56.76 76.65
C _{avg} (pg/mL)	30.1 \pm 13.4	43.3 \pm 15.8	0.0001	65.96	56.76 76.65
Week 3					
C _{max} (pg/mL)	51.3 \pm 17.3	131 \pm 45.4	<0.0001	39.01	35.26 43.15
AUC _{0-168h} ^b (ng·h/mL)	6.26 \pm 2.46	6.97 \pm 2.25	0.0532	85.96	75.67 97.66
C _{avg} (pg/mL)	37.3 \pm 14.7	41.5 \pm 13.4	0.0532	85.96	75.67 97.66

^aPrimary PK population excludes 2 subjects from PK population because of the abnormally low drug concentrations.

^bAUC_{0-168h} for Ortho-Cyclen was calculated as AUC₀₋₂₄ x 7.

To evaluate the EE PK of AG200-15 in comparison to the marketed OC, Ortho-Cyclen, the PK parameters of EE for both treatments were compared in the 32 subjects in Part II of study. At Week 1, the mean maximum concentrations were 45.5 versus 135 pg/mL, reached at 48 h versus 1 h postdose for AG200-15 and Ortho-Cyclen, respectively. There was approximately 13% increase of EE C_{max} from Week 1 to Week 3 in AG200-15, whereas there was no increase of EE C_{max} in Ortho-Cyclen. Overall, the EE C_{max} from AG200-15 was about 61% lower than EE C_{max} from Ortho-Cyclen based on PK data observed in Week 3.

The systemic exposure over the 168 h time interval was 5.06 ng·h/mL for AG200-15 and 7.28 ng·h/mL for Ortho-Cyclen. A statistically significant (p -value<0.0009) difference was found for all PK parameters at Week 1. There was approximately 24% accumulation of EE from Week 1 to Week 3 in AG200-15, whereas there was no accumulation of EE in Ortho-Cyclen. Overall, the exposure of EE from AG200-15 was about 10% lower than the exposure of EE from Ortho-Cyclen based on PK data observed in Week 3.

However, due to the between cycle accumulation of EE and inter-subject variability (explained in section 2.2.3.1 of this review) between two groups in different sequences (sequence AG200-15/Ortho Cyclen and sequence Ortho Cyclen/AG200-15), the study result may not be reliable.

2.2.3.3. What are the single and multiple dose PK parameters of LNG of AG200-15?

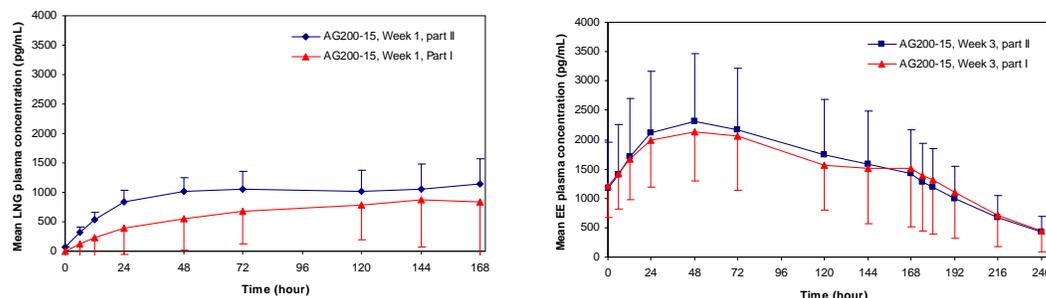


Figure 2 Mean (SD) LNG concentrations in Weeks 1 and 3 of both Parts I and II from AG200-15 (PK population); ATI-CL14

Table 6 Summary of LNG PK parameters (primary PK analysis population); ATI-CL14

Week	PK parameter	Part I			Part II		
		AG200-15			AG200-15		
		All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen in Part II, N=17	Sequence: Ortho-Cyclen/AG200-15 in Part II, N=15	All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen, N=17	Sequence: Ortho-Cyclen/AG200-15, N=15
1	C_{max} (pg/mL)	888 (441)	1026 (494)	733 (322)	1376 (921)	1831 (1033)	861 (354)
	T_{max} (hr)*	144 (72 – 168)	144 (72 – 168)	144 (72 – 168)	72 (24 – 168)	72 (48 – 168)	72 (24 – 168)
	AUC_{0-168h} (ng·h/mL)	108 (47.1)	122 (47.6)	93.5 (43.1)	161 (90.3)	210 (93.1)	105 (42.8)
3	C_{max} (pg/mL)	2374 (958)	2649 (1021)	2065 (801)	2382 (1157)	2833 (1206)	1871 (881)
	T_{max} (hr)*	48 (6 – 168)	48 (6 – 168)	48 (12 – 168)	48 (24 – 120)	48 (24 – 120)	48 (24 – 72)
	AUC_{0-168h} (ng·h/mL)	300 (128)	339 (139)	255 (99)	314 (160)	376 (171)	243 (116)
	$t_{1/2}$ (hr)	37.3 (8.93)	38.2 (8.67)	36.3 (9.40)	39.3 (7.20)	40.2 (6.34)	38.2 (8.15)

*Presented as median (range)

The exposure (both AUC and C_{max}) of LNG was higher in subjects in AG200-15/Ortho-Cyclen sequence in part II compared to subjects in Ortho-Cyclen/AG200-15, although demographics of two groups were comparable. It was not clear what contributed to the differences in exposure of LNG in these subjects.

AG200-15 (All subjects, subjects in AG200-15/Ortho-Cyclen sequence in part II, and subjects in Ortho-Cyclen/AG200-15 sequence) exhibited the within-cycle accumulation shown by the higher AUC in Week 3 compared to Week 1 (observed in both Parts I and II). In addition, there was a trend of between-cycle accumulation in AG200-15 (All subjects, subjects in AG200-15/Ortho-Cyclen sequence in Part II) shown by the followings:

- Higher AUC and C_{max} in Week 1 of Part II compared to Week 1 of Part I
- Higher AUC and C_{max} in Week 3 of Part II compared to Week 3 of Part I

However, the between-cycle accumulation in AG200-15 was not observed in subjects in Ortho-Cyclen/AG200-15 sequence in Part II.

2.2.3.4. What are the characteristics of drug absorption in different application sites?

Study ATI-CL15 was conducted to evaluate the PK profile of AG200-15 following application at 3 different anatomical sites (abdomen, buttock, and upper torso). The exposure for both EE and LNG was compared when AG200-15 was applied to either buttock or upper torso as compared to lower abdomen. Both sites, buttock and upper torso, was associated with higher exposure of both EE and LNG compared to lower abdomen. However, these results are not reliable because there was the effect of sequence (higher the exposure of both EE and LNG, when applied later in the sequence) indicating 1 patch free week was not long enough to eliminate both EE and LNG from the systemic circulation completely.

Study design: ATI-CL15:

This was an open-label, randomized, 3-period crossover study. Twenty four healthy female subjects were enrolled in the study. Female subjects were screened for eligibility. Once determined by medical history and physical examination to be eligible for admission, and once having provided informed consent, these subjects were randomly assigned to 1 of 6 treatment sequences (Table 29). Each sequence included 3 patch application sites. During each treatment period, the patch was applied by the study site personnel. Only 1 patch was worn at a time. On each treatment day, the patch presence was confirmed by subject by using the diary card. After 1 week (7 days) of wear, the patch was removed by the study site personnel. Treatment periods were separated by a 1-week (7 days) washout. The blood sampling for the PK evaluations were performed at the following time points: 0 hour (immediately prior to dosing) and at 3 hours, 6 hours, 12 hours, 24 hours (1 day), 48 hours (2 days), 72 hours (3 days), 120 hours (5 days), 144 hours (6 days), and 168 hours (7 days) following application of the patch. Additional blood samples were collected at 174, 180, 192, 216, and 240 hours following the patch application (i.e. 6, 12, 24, 48, and 72 hours after removal of the patch).

- EE

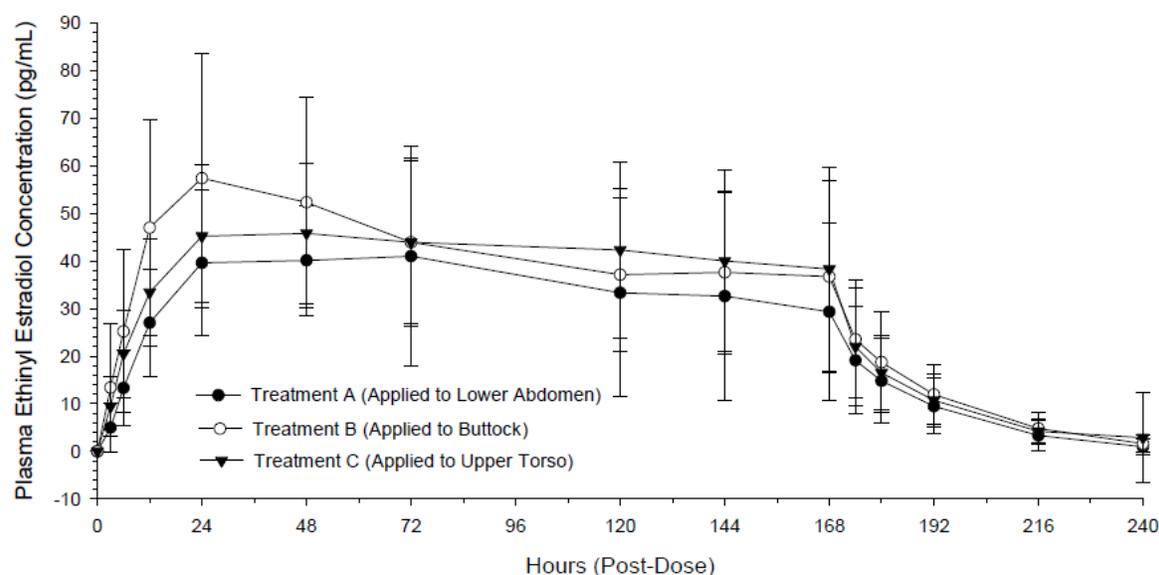


Figure 3 Mean (SD) plasma concentrations of EE; ATI-CL15

The mean concentrations increased for 24 hours from patch application. The concentrations appeared to reach a plateau between 24 to 168 hours after the patch application and dropped sharply after patch removal.

Table 7 Summary of EE PK parameters; ATI-CL15

Application site	Arithmetic mean (SD)			Median (min-max)
	C _{max} (pg/mL)	AUC ₀₋₁₆₈ (ng·hr/mL)	t _{1/2}	t _{max}
Lower abdomen (A)	47.9 (22.8)	5.80 (2.80)	17.6 (3.79)	48 (24-144)
Buttock (B)	61.5 (22.8)	7.12 (2.85)	18.2 (3.42)	24 (12-168)
Upper torso (C)	53.5 (19.9)	6.86 (2.53)	17.6 (4.33)	48 (12-240)

Table 8 Summary of BE assessment for EE PK parameters; ATI-CL15

Comparison	% geometric mean ratio (90% CI)	
	C _{max}	AUC ₀₋₁₆₈
Buttock (B) vs. Lower abdomen (A)	130 (113 – 151)	123 (108 – 140)
Upper torso (C) vs. Lower abdomen (A)	115 (99.2 – 133)	121 (106 – 138)

Buttock (Treatment B) vs. Lower abdomen (Treatment A)

The C_{max} and AUC₀₋₁₆₈ of EE was approximately 30% and 23% higher respectively when AG200-15 was applied to the buttock as compared to the lower abdomen. The upper limit of 90% CIs were higher than 125 for both C_{max} and AUC₀₋₁₆₈. In addition, the both CIs did not contain 100.

Upper torso (Treatment C) vs. Lower abdomen (Treatment A)

The C_{max} and AUC₀₋₁₆₈ of EE was approximately 23% and 21% higher respectively when AG200-15 was applied to the upper torso as compared to the lower abdomen. The upper limit of 90% CIs were higher than 125 for both C_{max} and AUC₀₋₁₆₈. The CI for C_{max} contained 100, whereas CI for AUC₀₋₁₆₈ did not contain 100.

The result of ATI-CL15 suggested that 1 week patch free period may not be long enough to eliminate any residual EE from the AG200-15. To test the statement above, the AUC₀₋₁₆₈ of EE from AG200-15 when it was applied first vs. last in 3 different application sites were compared.

Table 9 Effect of application sequence on mean EE exposure when AG200-15 is applied to 3 different sites; ATI-CL15

Application sequence	Abdomen (A)		Buttock (B)		Upper torso (C)	
	First, n=8 (ABC or ACB)	Last, n=7 (BCA or CBA)	First, n=8 (BAC or BCA)	Last, n=7 (ACB or CAB)	First, n=8 (CAB or CBA)	Last, n=7 (ABC or BAC)
mean AUC ₀₋₁₆₈ (ng·hr/mL)	5.41 (1.45)	6.77 (4.59)	4.71 (1.54)	7.48 (1.93)	7.13 (1.48)	8.53 (3.94)
% increase of AUC (Last/First)	125%		158%		120%	

As shown in Table 32, there were increases of EE exposure when AG200-15 was applied last compared to when AG200-15 was applied first to each application site. This supported that the 1 week patch free period between each treatment was not long enough to eliminate any residual EE completely from systemic circulation. Therefore, the design (1 week patch free period between each treatment) of the study ATI-CL15 did not appear appropriate to meet the objective of the study ATI-CL15, evaluating the PK profiles in 3 different application sites.

- LNG

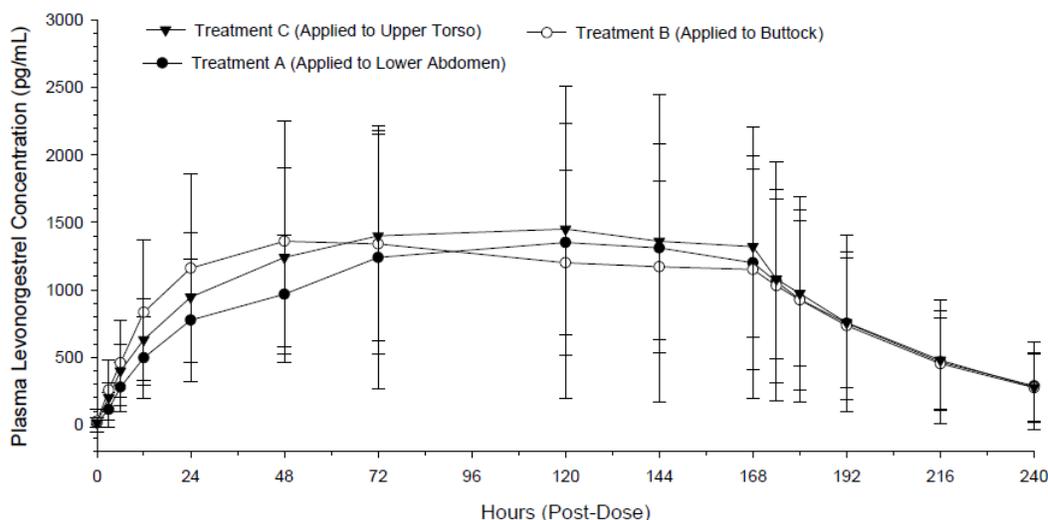


Figure 4 Mean (SD) plasma concentrations of LNG; ATI-CL15

The mean concentrations increased for 72 hours from patch application. The concentrations appeared to reach a plateau between 72 to 168 hours after the patch application and dropped sharply after patch removal.

Table 10 Summary of LNG PK parameters; ATI-CL15

Application site	Arithmetic mean (SD)			Median (min-max)
	C_{max} (pg/mL)	AUC_{0-168} (ng-hr/mL)	$t_{1/2}$	t_{max}
Lower abdomen (A)	1436 (1148)	182 (135)	32.5 (9.49)	120 (48-174)
Buttock (B)	1494 (825)	197 (116)	32.6 (10.6)	72 (24-168)
Upper torso (C)	1589 (825)	206 (106)	33.4 (10.3)	120 (48-168)

Table 11 Summary of BE assessment for LNG PK parameters; ATI-CL15

Comparison	% geometric mean ratio (90% CI)	
	C_{max}	AUC_{0-168}
Buttock (B) vs. Lower abdomen (A)	107 (89.9-127)	107 (92.0-124)
Upper torso (C) vs. Lower abdomen (A)	117 (98.0-139)	117 (101-136)

Buttock (Treatment B) vs. Lower abdomen (Treatment A)

The C_{max} and AUC_{0-168} of LNG was approximately 7% higher when AG200-15 was applied to the buttock as compared to the lower abdomen. The 90% CI for AUC_{0-168} was within the BE limit. However, 90% CI for C_{max} did not meet the BE limit. However, the both CIs contained 100.

Upper torso (Treatment C) vs. Lower abdomen (Treatment A)

The C_{max} and AUC_{0-168} of EE was approximately 17% higher when AG200-15 was applied to the upper torso as compared to the lower abdomen. The upper limit of 90% CIs were higher than 125 for both C_{max} and AUC_{0-168} . The CI for C_{max} contained 100, whereas CI for AUC_{0-168} did not contain 100.

The result of ATI-CL15 suggested that 1 week patch free period may not be long enough to eliminate any residual LNG from the AG200-15. To test the statement above, the AUC_{0-168} of LNG from AG200-15 when it was applied first vs. last in 3 different application sites were compared.

Table 12 Effect of application sequence on mean LNG exposure when AG200-15 is applied to 3 different sites; ATI-CL15

	Abdomen (A)	Buttock (B)	Upper torso (C)

Application sequence	First, n=8 (ABC or ACB)	Last, n=7 (BCA or CBA)	First, n=8 (BAC or BCA)	Last, n=8 (ACB or CAB)	First, n=8 (CAB or CBA)	Last, n=7 (ABC or BAC)
mean AUC ₀₋₁₆₈ (ng·hr/mL)	160 (56.1)	247 (222)	94.8 (37.3)	229 (69.2)	141 (75.5)	250 (133)
% increase of AUC (Last/First)	154%		242%		177%	

As shown in Table 32, there were increases of LNG exposure when AG200-15 was applied last compared to when AG200-15 was applied first to each application site. This supported that the 1 week patch free period between each treatment may not be long enough to eliminate any residual LNG completely from systemic circulation. Therefore, the design (1 week patch free period between each treatment) of the study ATI-CL15 did not appear appropriate to meet the objective of the study ATI-CL15, evaluating the PK profiles in 3 different application sites.

2.2.3.5 What are the characteristics of drug absorption under different conditions?

Study ATI-CL16 was conducted to evaluate the PK profile and wearability of AG200-15 following application under various external conditions (dry sauna, whirlpool, treadmill exercise, and cold water immersion) when compared to the normal conditions. Overall, the EE and LNG exposure was comparable under cold conditions compared to normal condition. The EE and LNG exposures under different external conditions (whirlpool, dry sauna, and treadmill) were lower compared to normal condition. However, these results are not reliable because there was the effect of sequence (higher the exposure of both EE and LNG, when applied later in the sequence) indicating 1 patch free week was not long enough to eliminate both EE and LNG from the systemic circulation completely.

Study design: ATI-CL16

Twenty four healthy females were enrolled in the study and all subjects completed all treatment periods. Female subjects were screened for eligibility. Once determined by history and physical examination to be eligible for admission these subjects were randomly assigned to one of six external conditions sequences. Each sequence included a normal wear period and two external conditions periods. During each treatment period, the patch was applied to the lower abdomen by the study site personnel. The subject participated in a normal wear period or an external condition period (dry sauna, whirlpool, treadmill exercise, or cold water immersion). Only 1 patch was worn at a time during each seven day period. Treatment periods were separated by 1 week (7-day) washout. The blood sampling for the PK evaluations was performed at the following time points: 0 hour (immediately prior to dosing) and at 6 hours, 12 hours, 24 hours (1 day), 48 hours (2 days), 72 hours (3 days), 120 hours (5 days), 144 hours (6 days), and 168 hours (7 days) following application of the patch. Immediately after the 168-hour blood draw, the patch was removed by study site personnel. Additionally, blood samples were collected at 174, 180, 192, 216, 204, and 240 hours following the patch application (i.e., 6, 12, 24, 36, 48, and 72 hours after removal of the patch).

Study results: ATI-CL16

- EE

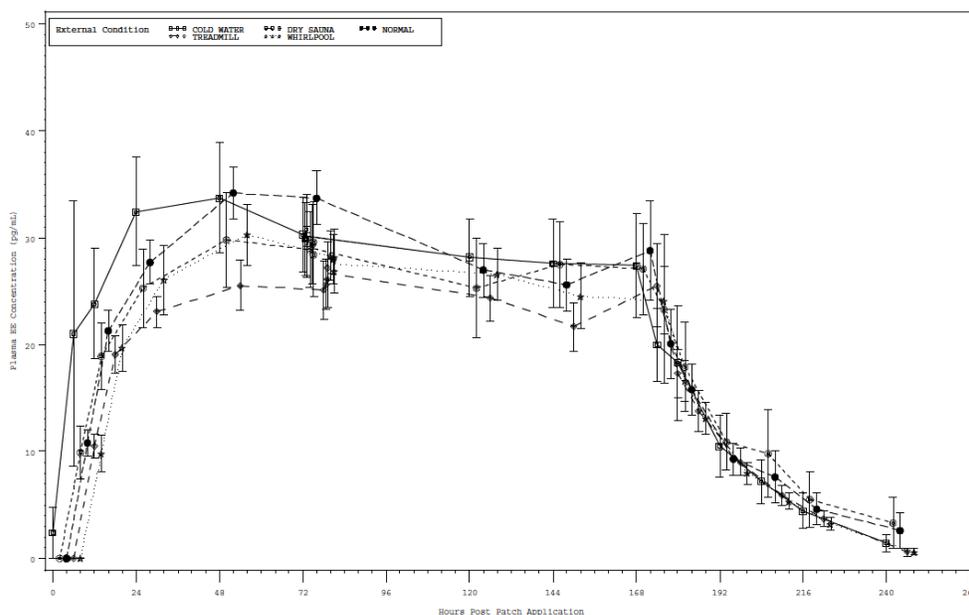


Figure 5 Mean plasma EE concentrations; ATI-CL16

The figure above indicates that, during the course of the study, EE concentrations were generally higher during normal patch wear when compared to external conditions, although the EE concentrations in the cold water external condition were similar. The pattern of the EE delivery appears to be comparable for all conditions studied.

Table 13 Summary of EE PK parameters; ATI-CL16

External conditions	Arithmetic mean (SD)			Median (min-max)
	C _{max} (pg/mL)	AUC ₀₋₁₆₈ (ng·hr/mL)	t _{1/2}	t _{max}
Normal, n=24	42 (20)	4.7 (1.6)	21 (13)	60 (12-168)
Dry sauna, n=12	39 (23)	4.3 (2.0)	21 (8.8)	48 (24-174)
Cold water, n=12	45 (38)	4.9 (2.3)	18 (4.6)	24 (6-144)
Whirlpool, n=12	33 (9)	4.3 (1.4)	22 (8.0)	72 (12-168)
Treadmill, n=12	32 (10)	3.9 (1.1)	23 (14)	60 (12-168)

Table 14 Summary of BE assessment for EE PK parameters; ATI-CL16

Comparison	% geometric mean ratio (90% CI)	
	C _{max}	AUC ₀₋₁₆₈
Dry sauna vs. Normal	90.5 (78.5-104.4)	93.0 (82.7-104.5)
Cold water vs. Normal	94.3 (81.8-108.8)	99.5 (88.6-111.9)
Whirlpool vs. Normal	80.7 (70.0-93.0)	86.7 (77.1-97.4)
Treadmill vs. Normal	79.8 (69.3-92.0)	82.2 (73.2-92.4)

Mean C_{max} concentrations for EE were greater during the normal patch wear group when compared to all of the external conditions with the exception of the cold water immersion condition. The mean EE AUCs for the external conditions was in the order of cold water, normal, dry sauna/whirlpool, and treadmill. The sponsor explained this observation (higher AUC with cold conditions compared to warm/hot conditions) based on the drug's degree of saturation as follows: "The solubility of both EE and LNG in the patch can increase with higher temperatures thus decreasing the drug's degree of saturation and consequently the drug's permeation through skin resulting lower AUC." Half life was comparable across conditions (ranging from 18 hour for normal cold water external conditions to 23 hour for treadmill external condition).

The results of the statistical analyses of bioequivalence for external conditions relative to the normal wear condition for plasma EE are summarized in Table 39. None of the PK parameters met bioequivalence criteria for whirlpool and treadmill. For dry sauna, AUC met the BE criteria whereas C_{max} did not meet the BE criteria. All PK parameters met bioequivalence criteria for cold water.

The result of ATI-CL15 suggested that 1 week patch free period may not be long enough to eliminate any residual EE from the AG200-15. To test the statement above, the AUC_{0-168} of EE from AG200-15 when it was applied first vs. last under different external conditions was compared.

Table 15 Effect of application sequence on mean EE exposure when AG200-15 is applied under different external conditions; ATI-CL16

Application sequence	Normal (N)		Cold water (C)		Whirlpool (W)		Dry sauna (D)		Treadmill (T)	
	First, n=8 (NDC or NCD)	last, n=8 (WTN or TWN)	First, n=4 (CNW)	Last, n=4 (NDC)	First, n=4 (WTN)	Last, n=4 (CNW)	First, n=4 (DNT)	Last, n=4 (NCD)	First, n=4 (TWN)	Last, n=4 (DNT)
mean AUC_{0-168} (ng-hr/mL)	4.52 (1.92)	5.7 (0.73)	3.58 (1.70)	5.95 (1.34)	4.11 (0.71)	3.99 (2.33)	2.77 (0.70)	4.98 (2.45)	4.35 (0.72)	3.64 (1.81)
% increase of AUC (Last/First)	118%		166%		97%		178%		84%	

Under normal, whirlpool, and treadmill conditions, the EE exposures were comparable when AG20015 was applied first vs. last. However, under cold water and dry sauna conditions, there were increases of EE exposure when AG200-15 was applied last compared to when AG200-15 was applied first. This supported that the 1 week patch free period between each treatment may not be long enough to eliminate any residual EE completely from systemic circulation. Therefore, the design (1 week patch free period between each treatment) of the study ATI-CL15 did not appear appropriate to meet the objective of the study ATI-CL16, evaluating the PK profiles under different external conditions.

- LNG

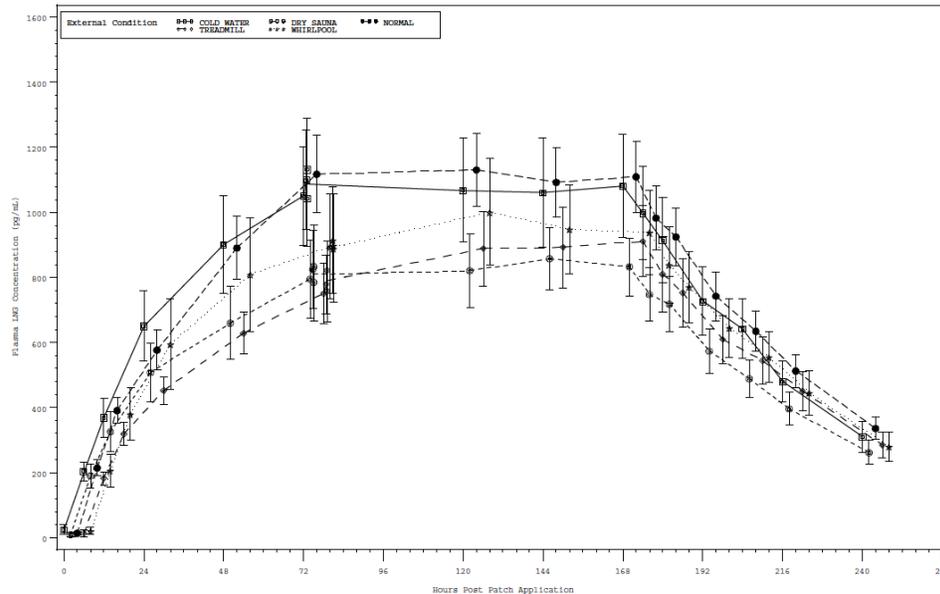


Figure 6 Mean plasma LNG concentrations; ATI-CL16

The figure above indicates that, throughout the course of the study, LNG concentrations were generally higher at sampling time points during normal patch wear when compared to external conditions. The pattern of LNG concentrations appears to be similar for all conditions studied.

Table 16 Summary of LNG PK parameters; ATI-CL16

External conditions	Arithmetic mean (SD)			Median (min-max)
	C _{max} (pg/mL)	AUC ₀₋₁₆₈ (ng·hr/mL)	t _{1/2}	t _{max}
Normal, n=24	1316 (581)	157 (74)	42 (11)	120 (12-168)
Dry sauna, n=12	1013 (396)	118 (51)	38 (6)	144 (72-168)
Cold water, n=12	1223 (622)	153 (76)	40 (13)	132 (48-174)
Whirlpool, n=12	1117 (610)	137 (81)	43 (18)	120 (12-174)
Treadmill, n=12	976 (377)	119 (46)	40 (10)	144 (72-168)

Table 17 Summary of BE assessment for LNG PK parameters; ATI-CL16

Comparison	% geometric mean ratio (90% CI)	
	C _{max}	AUC ₀₋₁₆₈
Dry sauna vs. Normal	79.1 (66.7-93.8)	78.6 (68.0-90.8)
Cold water vs. Normal	90.1 (76.0-106.8)	97.8 (84.7-113.0)
Whirlpool vs. Normal	78.4 (66.1-92.9)	79.1 (68.5-91.3)
Treadmill vs. Normal	75.3 (63.5-89.3)	78.1 (68.4-91.2)

Mean C_{max} concentrations for LNG were greater during the normal patch wear group when compared to any external conditions. Among external conditions, mean C_{max} concentrations for LNG were higher after immersion in the cold water followed by whirlpool, dry sauna, and treadmill. The mean LNG AUC for the normal patch wear group were higher compared to any external conditions, and the mean LNG AUCs for external conditions decreased from cold water to whirlpool to dry sauna, with treadmill providing the lowest AUC. Median T_{max} was generally comparable across the conditions studied and ranged from 120 h to 144 h, while t_{1/2} was also comparable across conditions (ranging from 38 h for dry sauna external condition to 43 h for whirlpool external condition).

Results of the statistical analysis of the BE for external conditions relative to the normal wear condition for plasma LNG pharmacokinetic parameters are summarized in Table 42. Patch wear under most external conditions resulted in the LNG pharmacokinetics not meeting bioequivalence criteria when compared to a period of normal patch wear. None of the PK parameters met BE criteria for dry sauna, whirlpool and treadmill. With exception of C_{max}, BE to normal conditions was observed for the cold water external condition.

The result of ATI-CL15 suggested that 1 week patch free period may not be long enough to eliminate any residual LNG from the AG200-15. To test the statement above, the AUC₀₋₁₆₈ of EE from AG200-15 when it was applied first vs. last under different external conditions was compared.

Table 18 Effect of application sequence on mean LNG exposure when AG200-15 is applied under different external conditions; ATI-CL16

Application sequence	Normal (N)		Cold water (C)		Whirlpool (W)		Dry sauna (D)		Treadmill (T)	
	First, n=8 (NDC or NCD)	last, n=8 (WTN or TWN)	First, n=4 (CNW)	Last, n=4 (NDC)	First, n=4 (WTN)	Last, n=4 (CNW)	First, n=4 (DNT)	Last, n=4 (NCD)	First, n=4 (TWN)	Last, n=4 (DNT)
mean AUC ₀₋₁₆₈ (ng·hr/mL)	123 (56)	209 (66)	103 (64)	215 (75)	89 (20)	152 (118)	77 (43)	140 (38)	118 (29)	129 (68)
% increase of AUC (Last/First)	170%		208%		170%		182%		109%	

Under all the conditions tested, there were increases of LNG exposure when AG200-15 was applied last compared to when AG200-15 was applied first. This supported that the 1 week patch free period between each treatment may not be long enough to eliminate any residual LNG completely from systemic circulation. Therefore, the design (1 week patch free period between each treatment)

of the study ATI-CL15 did not appear appropriate to meet the objective of the study ATI-CL16, evaluating the PK profiles under different external conditions.

2.2.3.6 What are the characteristics of drug distribution?

LNG in serum is primarily bound to sex hormone-binding globulin (SHBG). EE is about 97% bound to serum albumin. Ethinyl estradiol does not bind to SHBG, but increases the synthesis of SHBG.

2.2.3.7 What are the characteristics of drug metabolism?

- EE: CYP3A4 in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation, sulfation, and glucuronidation prior to urinary and fecal excretion. Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation.

- LNG: The most important metabolic pathways are reduction of the Δ^4 -3-oxo group and hydroxylation at positions 2 α , 1 β , and 16 β , followed by conjugation. Most of the circulating metabolites are sulfates of 3 α , 5 β -tetrahydro-LNG, while excretion occurs predominantly in the form of glucuronides. Some of the parent LNG also circulates as 17 β -sulfate. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in LNG concentrations among users.

2.2.3.8 What are the characteristics of drug elimination?

- EE

The terminal elimination half-life of EE in AG200-15 is approximately 20 hours. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic recirculation.

- LNG

The terminal elimination half-life for LNG in AG200-15 is approximately 40 hours. LNG and its metabolites are excreted in the urine (40% to 68%) and in feces (16% to 48%).

2.3 Intrinsic factors

2.3.1 What intrinsic factors (age, race, weight, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Body Mass Index (BMI)

The study ATI-CL12 was an open-label, randomized, comparative, parallel group, multi-center study. The 1,504 sexually active women (age 17-40) were enrolled in this study. The subjects were randomized into 3:1 ratio, with 1,378 subjects randomized to AG200-15 for a one year (13 cycles) and 375 subjects randomized to OC (Lessina containing 0.02 mg EE and 0.1 mg LNG, ANDA 075803 approved in March 2002) for 6 cycles. The subjects who were randomized to OC for 6 cycles were later switched to AG200-15 for additional 7 cycles. A treatment cycle was defined as a 28-day period: 21 days on treatment (consecutive administration of the three 7-day patches or 21 days of active pill-taking) followed by 7 days off treatment (i.e., no patch was applied or no active pills were taken). The patch was applied to the abdomen, the buttock or the upper torso excluding the breasts. During the visits scheduled before application of the last patch at the second, sixth, and thirteenth cycles, blood was drawn to evaluate plasma concentrations of LNG and EE.

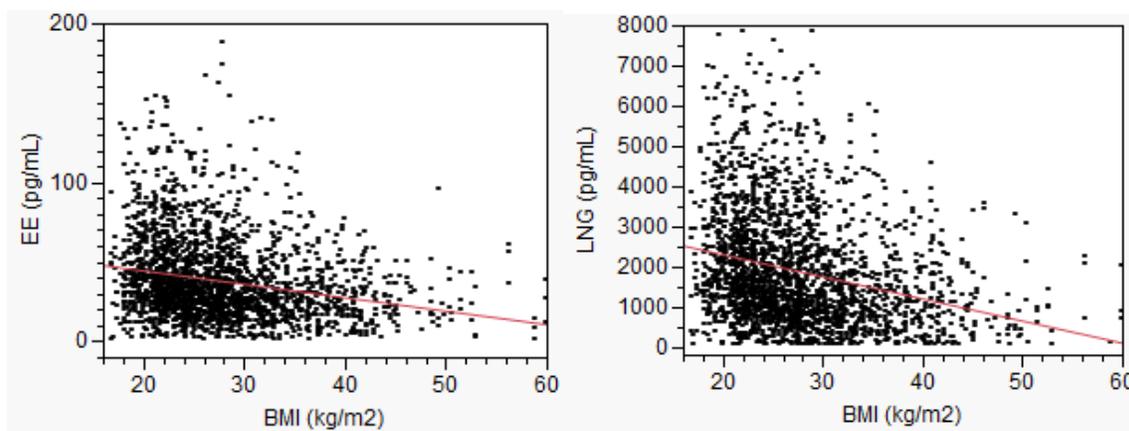


Figure 7 The concentrations of EE and LNG obtained before the 3rd application of the AG200-15 at the 2nd, 6th, and 13th cycles (PK population); ATI-CL12

Based on the both EE and LNG concentrations obtained before the 3rd application of AG200-14 at the 2nd, 6th, and 13th cycles, there has been statistically significant trend (P value <0.001 for both EE and LNG) of decreasing concentrations of both EE and LNG with increasing BMI (BMI at screening) ranging from 16 to 60.

Table 19 Comparison of EE, LNG, and BMI in subjects who became pregnant vs. not pregnant in AG200-15 group (PK population); ATI-CL12

	Pregnant, n=45	Not pregnant, n=1032
EE (pg/mL)	35.0 (27.1)	38.3 (25.9)
LNG (pg/mL)	1806 (1481)	1916 (1455)
BMI (kg/m ²)	27.9 (7.1)	27.7 (7.1)

In study ATI-CL12, there were 45 subjects who became pregnant during the study while on AG200-15. The differences in mean EE, LNG, BMI in subjects who became pregnant vs. not pregnant were smaller than 10% and within the error range (differences are less than SD).

Renal or Hepatic Impairment

No studies have been conducted to evaluate the effect of renal or hepatic impairment on the disposition of AG200-15. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of combination hormonal contraceptive use until markers of liver function return to normal and combination hormonal contraceptive causation has been excluded.

Pediatric subjects

The sponsor submitted a pediatric waiver request claiming that pediatric studies are not applicable in premenarcheal females because the claimed indication is not relevant to the pediatric subpopulation. In addition, the sponsor claimed that efficacy is expected to be the same in post pubertal adolescents under the age of 17 years as for user of 17 years and older.

2.4 Extrinsic factors

Drug-drug interactions

The sponsor did not conduct any drug-drug interaction studies with AG200-15. To address the potential drug interactions in the label, the sponsor proposed the following in their labeling to describe the potential drug interactions:

(b) (4)



(b) (4)

- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

(b) (4) Significant (b) (4)
of the estrogen and progestin have been noted (b) (4)
co-administration (b) (4) HIV protease inhibitors (b) (4) non-nucleoside reverse transcriptase
inhibitors.



2.5 General Biopharmaceutics

2.5.1 Is the clinical formulation same as the to-be-marketed formulation?

Yes. AG200-15 is the clinical formulation used in phase 3 studies and is same as the to-be-marketed formulation. See Table 1 for detailed formulation information.

2.6 Analytical Section

EE and LNG in plasma samples obtained from clinical studies were determined using HPLC-MS/MS method. The method validation reports satisfied the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, May 2001).

Component to measure		EE	LNG
Type of Biological Fluid		Human plasma	Human plasma
Range of Standard Curve		2.00 - 500 pg/mL	50.0 – 25000 pg/mL
QC Sample Accuracy	Intra-assay	2.88 – 13 %	0.766 – 13.4 %
	Inter-assay	5.17 – 15.3 %	2.28 – 14.8%
QC Sample Precision	Intra-assay	-12.6 – 2.18 %	3.23 – 8.37 %
	Inter-assay	-13.5 – 4.07 %	3.88 – 7.4 %
Stability		28 hrs at room temperature; 79 hours at 10-12 C; 8 days at -80 C; 5 cycles of freezing/thawing	28 hrs at room temperature; 79 hours at 10-12 C; ; 8 days at -80 C; 6 cycles of freezing/thawing
Recovery		89.3- 101 %	105 - 113 %

3 Detailed Labeling Recommendations

No labeling recommendation will be provided in the current review cycle.

4 Appendix

4.1 Individual Clinical Study Review

ATI-CL11

- Title

Evaluation of pharmacodynamic effects on ovulation suppression and cycle control of three Agile contraceptive patches containing different doses of EE during three cycles of administration

- Objective

The objective was to evaluate the adequacy of ovulation suppression and cycle control of transdermal contraceptive patches containing 2 different doses of LNG and 3 different doses of EE during 3 consecutive cycles of administration of each treatment.

- Study design

This was a multicenter, open-label, randomized, parallel group study (Part I) followed by a multicenter, open-label, single-arm extension (Part II). Part I of the study evaluated 2 different contraceptive patches, AG200 and AG200LE, while Part II of the study evaluated a third contraceptive patch, AG200-15.

In Part I of the study, subjects were randomly assigned to 1 of 2 treatment groups:

- Group 1: AG200 for 3 cycles (1 cycle consists of 21 days of treatment and 7 days of no treatment)
- Group 2: AG200LE for 3 cycles (1 cycle consists of 21 days of treatment and 7 days of no treatment)

In the Part II of the study, all subjects were assigned to the third treatment group, but not all subjects from Part I participated in Part II:

- Group 3: AG200-15 for 3 cycles (1 cycle consists of 21 days of treatment and 7 days of no treatment)

Enrolled subjects applied the assigned contraceptive patch to the lower abdomen in the morning of Cycle Day 1 (Day 1 of their menstrual cycle). The patch was to be left in place for 7 days at which time it was to be removed and replaced twice (in the morning of Cycle Days 8 and 15), and removed without being replaced in the morning of Cycle Day 22. The patch was to be replaced immediately if it fell off or detached or if there was too much skin irritation and/or itching. Blood samples were drawn to assess ovulation suppression (progesterone) on Cycle Days 8, 11, 15, 19, 22, 25 and 29 (Day 1 of next cycle) in all 3 cycles. Cycle control endpoint was assessed by daily bleeding/spotting reporting by subjects, via diary cards during all 3 cycles, along with data on patch wearability.

- Inclusion criteria

- Healthy adult women, ages 18-45.
- Cycles with a usual duration between 21 and 35 days and an individual variation of +/- 3 days.
- Normotensive (blood pressure < 140/90 mm Hg at rest) at screening and randomization visits
- Willing to use a non-hormonal method of contraception for the entire duration of the study, or have already undergone previous bilateral tubal ligation or vasectomized partner or not at risk of pregnancy.
- Willing to refrain from use of alcohol during the entire duration of the study.
- Willing to give informed consent to participate in the study.
- Negative pregnancy test on each Cycle Day 1.

- Exclusion criteria

- History of significant medical illness or seizures.
- Positive hepatitis B or C antibody or positive HIV antibody.
- Known or suspected pregnancy.
- A recent abnormal cervical smear which has not been resolved or treated.
- Any disorder that contraindicates the use of contraceptive steroids i.e., history of heart attack and stroke, blood clots in the legs, lungs or eyes, history of blood clots in the deep veins of the legs, known or suspected breast cancer, hepatitis or yellowing of the whites of the eyes or the skin (jaundice) during pregnancy or during previous use of hormonal contraceptives, headaches with neurological symptoms, disease of heart valves with complications.
- Uncontrolled thyroid disorder.
- History of or existing thromboembolic disorder, vascular disease, cerebral vascular or coronary artery disease.
- Undiagnosed abnormal genital bleeding.
- Known or suspected breast carcinoma, endometrial carcinoma, or estrogen-dependent neoplasia.
- History or presence of dermal hypersensitivity in response to topical application.
- Use of an injectable hormonal contraceptive (e.g. Depo-Provera) within 6 months prior to Day 1.
- Use of a contraceptive implant (e.g. Implanon or Jadelle) or hormone-medicated intrauterine device within 2 months (60 days) prior to Day 1.
- Use of OCs or other sex steroid hormones within 60 days prior to Day 1.
- Women who are breast-feeding or are within 2 months of stopping breast-feeding.
- Status post-partum or post-abortion within a period of 2 months prior to Day 1.
- Chronic use of any medication that might interfere with the metabolism of hormone contraceptives (e.g., rifampin, barbiturates, phenytoin, primidone, topiramate, carbamazepine, phenylbutazone, ritonavir, modafinil, St John's Wort etc.) or use within the past 3 months prior to Day 1.
- Administration of investigational drug within 30 days prior to Day 1.
- A history (within prior 12 months) of drug or alcohol abuse.
- Women who smoke more than 4-5 cigarettes daily.
- History of skin sensitivity to adhesives.
- Use of over-the-counter medications or herbals that might interfere with the metabolism of hormone contraceptives within 3 days prior to wearing the first patch.

- Treatments

Subjects received 1 of the following 3 contraceptive patch treatments for 3 cycles (21 days on treatment and 7 days on no treatment for each cycle):

- AG200LE: a 12.5 cm² patch containing 2.17 mg LNG/1.28 mg EE
- AG200: a 12.5 cm² patch containing 2.17 mg LNG/1.92 mg EE
- AG200-15: a 15 cm² patch containing 2.60 mg LNG/2.30 mg EE

Subjects applied their assigned contraceptive patch to their lower abdomen in the morning of Cycle Day 1.

- Subject disposition, data sets analyzed and demographics

- Subject disposition

Table 20 Subject Disposition; ATI-CL11

Subject Disposition	Number (%) of Subjects		
	AG200LE (N=45)	AG200 (N=45)	AG200-15 (N=33)
Enrolled in Study	45 (100%)	45 (100%)	33 (100%)
In Safety Population	43 (96%)	44 (98%)	31 (94%)
Not in Safety Population ^a	2 (4%)	1 (2%)	2 (6%)
Completed Study	41 (91%)	41 (91%)	25 (76%)
Prematurely Discontinued	4 (9%)	4 (9%)	8 (24%)
Reasons Discontinued			
Adverse event	0	1 (2%)	2 (6%)
Lost to follow-up	0	1 (2%)	1 (3%)
Subject decision	1 (2%)	0	2 (6%)
Pregnancy	1 (2%)	1 (2%)	0
Protocol violation/non-compliance	0	1 (2%)	1 (3%)
Sponsor decision	1 (2%)	0	2 (6%)
Other	1 (2%)	0	0

^aSubjects (b) (6) became pregnant prior to taking study drug; Subject (b) (6) was lost to follow-up after Visit 1; and Subjects (b) (6) were discontinued by the sponsor (*The reason for discontinuation was not reported by the sponsor.*).

- Data sets analyzed

ITT population was used for analysis and the definition of ITT population is as follows: Population in the cycle during which at least 1 study patch was applied and at least 1 progesterone measurement was available at one of the nominal data collection points of Cycle Days 8, 11, 15, 19, 22, 25 and 29.

- Demographics, safety population

Table 21 Demographic characteristics; ATI-CL11

Characteristic	AG200LE (N=43)	AG200 (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%)
Hispanic	11 (26%)	6 (14%)	3 (10%)
White	18 (42%)	26 (59%)	14 (45%)
Other ^a	5 (12%)	2 (5%)	2 (6%)
BMI (kg/m²)			
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

^a“Other” includes: Native Hawaiian or Pacific Islander, American Indian or Alaskan Native, Asian, and Other races.

- Efficacy measurements

- Ovulation suppression

The evaluation of the ovulation suppression was based on the serum progesterone concentrations determined at Cycle Days 1, 8, 11, 15, 22, 25, and 29 of the treatment cycle. The following definitions of ovulation were employed:

<Primary>

1. Possible ovulation: cycle with greatest progesterone concentration ≥ 4.7 ng/mL. (Primary efficacy variable for ovulation suppression)

The progesterone concentration equal or less than 4.7 ng/mL was used as an indication of ovulation suppression in NDA 021583 (Depo-SubQ Provera 104, approved on July 15, 2009 for prevention of pregnancy; from medical review by Dr. Lesley-Anne Furlong in DARRTS).

<Secondary>

1. Likely ovulation: cycle with greatest progesterone concentration ≥ 9.0 ng/mL.

2. Probable ovulation: cycle with 2 successive progesterone concentrations ≥ 4.7 ng/mL.

3. Luteal activity: cycle with greatest progesterone concentration ≥ 3 ng/mL and < 4.7 ng/mL.

4. Possible ovulation and/or luteal activity: cycle with greatest progesterone concentration ≥ 3.0 ng/mL.

- Cycle Control

The evaluation of the cycle control (incidence of breakthrough bleeding and/or spotting in Cycle 3) was based on the bleeding information recorded by the subjects on daily diary cards.

• Results

- Ovulation suppression

Table 22 Summary of ovulation rates; ATI-CL11

Serum progesterone concentration	Number (%) of Cycles		
	AG200LE	AG200	AG200-15
greatest concentration ≥ 4.7 ng/mL (possible ovulation)			
All BMI	46/125 (36.8%)	26/129 (20.2%)	16/83 (19.3%)
BMI ≤ 32 kg/m ²	39/105 (37.1%)	19/94 (20.2%)	8/63 (12.7%)
greatest concentration ≥ 9.0 ng/mL			
All BMI	22/125 (17.6%)	10/129 (7.8%)	4/83 (4.8%)
BMI ≤ 32 kg/m ²	18/105 (17.1%)	8/94 (8.5%)	3/63 (4.8%)
2 successive ≥ 4.7 ng/mL (probable ovulation)			
All BMI	34/125 (27.2%)	15/129 (11.6%)	8/83 (9.6%)
BMI ≤ 32 kg/m ²	28/105 (26.7%)	12/94 (12.8%)	6/63 (9.5%)
4.7 > greatest concentration ≥ 3.0 ng/mL (luteal activity)			
All BMI	6/125 (4.8%)	6/129 (4.7%)	1/83 (1.2%)
BMI ≤ 32 kg/m ²	6/124 (4.8%)	6/126 (4.8%)	1/78 (1.3%)
greatest concentration ≥ 3.0 ng/mL (possible ovulation and/or luteal activity)			
All BMI	52/125 (41.6%)	32/129 (24.8%)	17/83 (20.5%)
BMI ≤ 32 kg/m ²	51/124 (41.1%)	32/126 (25.4%)	15/78 (19.2%)

With respect to the 5 efficacy measurements for ovulation suppression, AG200-15 exhibited the greatest ovulation inhibition with a possible ovulation rate of 19.3% for all BMI. For treatment groups AG200LE and AG200, possible ovulation rates were 36.8% and 20.2%, respectively. For AG200-15 treatment group, possible ovulation rates were lower when controlling for BMI (12.7%) compared to no exclusion for larger BMI (19.3%), indicating that the higher BMI may associate with lower rate of ovulation suppression.

- Patch adhesion

Table 23 Summary of patch adhesion – AG200-15; ATI-CL11

Parameter	Cycle 1	Cycle 2	Cycle 3	Cycle 1-3 combined
Number of patches completely detached	4/101 (4.0%)	1/86 (1.2%)	1/78 (1.3%)	6/265 (2.3%)
Number of patches partially detached	5/101 (5.0%)	0/86 (0%)	0/78 (0%)	5/265 (1.9%)

For AG200-15 treatment group, 2.3% (6/265) of the total number of patches in Cycles 1-3 combined were completely detached. The proportion of number of patches completely detached decreased over the course of the study: 4.0% in Cycle 1, 1.2% in Cycle 2, and 1.3% in Cycle 3. Similar results were observed for the proportion of number of patches that were partially detached.

- Cycle control

Table 24 Summary of breakthrough bleeding/spotting episodes in Cycle 3; ATI-CL11

	AG200LE (N=42)	AG200 (N=42)	AG200-15 (N=27)
Bleeding/Spotting Episode? n (%)			
Yes	12 (28.6%)	12 (28.6%)	4 (14.8%)
No	30 (71.4%)	30 (71.4%)	23 (85.2%)
Number of Episodes			
Mean \pm SD	0.29 \pm 0.46	0.29 \pm 0.46	0.15 \pm 0.36
Median	0.0	0.0	0.0
Range	0.0–1.0	0.0–1.0	0.0–1.0

In the analysis for cycle control, 28.6% (12/42) of subjects in both the AG200LE and the AG200 treatment groups reported episodes of breakthrough bleeding/spotting in Cycle 3, compared to 14.8% (4/27) in the AG200-15 treatment group. The mean number of episodes in both the AG200LE and the AG200 treatment groups was 0.29 compared to 0.15 in the AG200-15 group.

- EE concentration

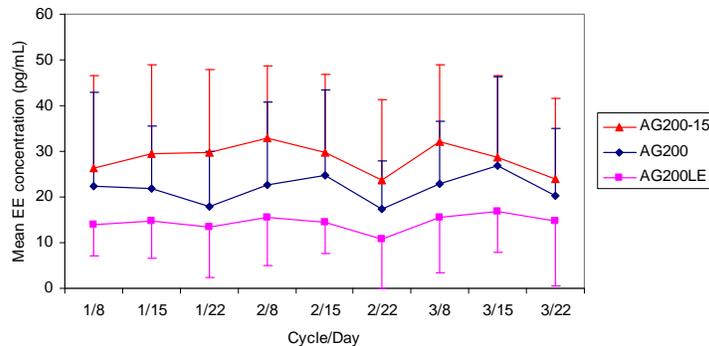


Figure 8 Mean EE concentrations across 3 cycles by treatment group; ATI-CL11

- LNG concentration

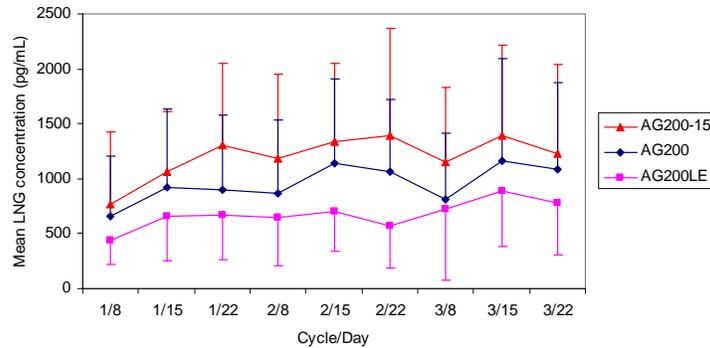


Figure 9 Mean LNG concentrations across 3 cycles by treatment group; ATI-CL11

Drug concentrations were measured at Days 8, 15, and 22 of all 3 cycles. Mean EE and LNG concentrations across the 3 cycles showed separation between 3 treatment groups. Mean concentrations of LNG across 3 cycles were highest in AG200-15 which has the highest amount of LNG. Although LNG amount in AG200 and AG200LE is same, mean concentrations of LNG across 3 cycles were higher in AG200 compared to AG200LE. Mean concentrations of EE across 3 cycles were in the order of the amount of EE in the patch (i.e., AG200-15 > AG200 > AG200LE). In addition, there was no correlation between BMI and the concentration of both EE and LNG.

- **Conclusions**

The AG200-15 contraceptive patch is the appropriate formulation for further study in Phase 3 trials as it demonstrates the most consistent inhibition of ovulation in the populations being analyzed and the definition of ovulation employed. Results of the analyses of cycle control endpoints indicate that the AG200-15 contraceptive patch is the appropriate formulation for further study in Phase 3 trials as it exhibits the lowest bleeding rate out of the 3 patches studied.

Phase 3 studies were all conducted with AG200-15.

ATI-CL14

- **Title**

An open-label study to evaluate PK profile of AG200-15 and to compare exposure of EE to oral contraceptive (Ortho-Cyclen) in healthy female volunteers

- **Objective**

The objective was to evaluate the PK profile of AG200-15 and to compare the exposure of EE to the marketed OC Ortho-Cyclen (both administered in a crossover fashion for 1 cycle as 21-7 day treatment regimens).

- **Study design**

This was an open-label study comprised of two parts.

Part I of the study was a single-arm, run-in cycle with AG200-15 administered to all subjects as a 21-7 day regimen, i.e., three consecutive weeks of patch wear followed by a patch-free week.

Subjects completing the run-in cycle proceeded to Part II of the study.

Part II employed a crossover design with subjects randomly assigned to one of the two treatment sequences. Each sequence included AG200-15 and a marketed OC (Ortho-Cyclen) as follows:

- Sequence 1: AG200-15 (Period 1) followed by the OC Ortho-Cyclen (Period 2)

- Sequence 2: the OC Ortho-Cyclen (Period 1) followed by AG200-15 (Period 2)

Both AG200-15 and Ortho-Cyclen were administered as 21-7 day regimen, i.e., three consecutive weeks of drug-taking followed by a drug-free week. Data from Part II supported the study objective, i.e., the evaluation of the exposure to EE of AG200-15 in comparison to the marketed OC Ortho-Cyclen.

- Blood samplings

The blood sampling for PK evaluations was performed as following:

- Part I:

During the first and third week at the following time points: 0 h (immediately prior to patch application on Cycle Days 1 and 15) and at 6 h, 12 h, 24 h (1 day), 48 h (2 days), 72 h (3 days), 120 h (5 days), 144 h (6 days), and 168 h (7 days) following application of the patch. Blood samples were also collected at 6, 12, 24, 48, and 72 h after removal of the third patch.

- Part II:

<AG200-15 cycle>

The blood sampling was performed during the first and third week at the following time points: 0 h (immediately prior to patch application on Cycle Days 1 and 15) and at 6 h, 12 h, 24 h (1 day), 48 h (2 days), 72 h (3 days), 120 h (5 days), 144 h (6 days), and 168 h (7 days) following application of the patch. Blood samples were also collected at 6, 12, 24, 48, and 72 h after removal of the third patch.

<OC (Ortho-Cyclen) cycle>

At the end of the first and third week (Cycle Days 7 and 21) at the following time points: 0 h (immediately prior to dosing) and at 0.5, 1, 1.5, 3, 6, 9, 12, 16 and 24 h following dosing. In addition, blood samples were collected at 36 h, 48 h (2 days) and 72 h (3 days) following the Day 21-dose.

- Inclusion criteria

- Healthy women, aged 18-45 years old.
- BMI ≥ 18 and ≤ 32 kg/m², and weight ≥ 110 lbs
- Willing to use a non-hormonal method of contraception if at risk of pregnancy, or had already undergone previous bilateral tubal ligation or hysterectomy.
- Willing to refrain from use of alcohol and grapefruit juice from 48 h prior until completion of each treatment period.
- Willing to give informed consent to participate in study.

- Exclusion criteria

- Known or suspected pregnancy.
- Breast-feeding or within 1 month after stopping breast-feeding.
- Status post-partum or post-abortion within a period of 2 months prior to the start of study medication.
- A cervical cytology smear of Papanicolaou (Pap) class III or greater or a Bethesda System report of low-grade squamous intraepithelial lesions (SIL) or greater (Pap smear results within last 6 months were acceptable if properly documented).
- Smoking.
- Uncontrolled hypertension (blood pressure >140 mmHg systolic [SBP] or >90 mmHg diastolic [DBP]).
- Valvular heart disease with complications.
- Diabetes mellitus requiring insulin or non-insulin requiring subjects with vascular disease.
- History of headaches with focal neurological symptoms.
- Uncontrolled thyroid disorder.
- Sickle cell anemia.
- Current or history of clinically significant depression in the last year.
- Known disturbance of lipid metabolism.
- Acute or chronic hepatocellular disease with abnormal liver function.
- Hepatic adenoma or carcinoma.
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use.
- Plans for major surgery.

- History of or existing thromboembolic disorder, vascular disease, cerebral vascular or coronary artery disease.
- Undiagnosed abnormal genital bleeding.
- Known or suspected breast carcinoma, endometrial carcinoma, or estrogen-dependent neoplasia.
- History or presence of dermal hypersensitivity in response to topical applications (bandages, surgical tape, etc.) or known hypersensitivity to any components of this product.
- Use of an injectable hormonal contraceptive within the past 6 months prior to the screening visit.
- Used a contraceptive implant or hormone-medicated IUD within 1 month prior to the screening visit.
- Use of OCs or other sex steroid hormones within 1 month prior to the screening visit.
- Chronic use of any medication that might interfere with the efficacy of hormone contraceptives (including barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's Wort, topiramate, and HIV protease inhibitors), or use of these medications within the past 3 months prior to the screening visit.
- Administration of any investigational drug and/or experimental device within 30 days prior to the screening visit.
- A recent history (within prior 12 months) of drug or alcohol abuse.
- Deemed by the investigator to have had questionable ability to comply with the protocol and provide accurate information.

- Treatments

AG200-15 was an adhesive patch containing 2.30 mg of EE and 2.60 mg of LNG. Each Ortho Cyclen tablet contains 0.250 mg norgestimate and 0.035 mg EE. Both AG200-15 and Ortho-Cyclen were administered as a 21-7 day regimen, i.e., three consecutive weeks of drug-taking followed by a drug-free week. The duration of each treatment period was 28 days, i.e., one cycle of therapy. Each patch was to be worn for 7 days (1 week). Only one patch could be worn at a time. The patches were applied to the buttock. The patch had to be applied to clean, dry, intact healthy skin, in a place where it would not be rubbed by tight clothing. To prevent interference with the adhesive properties of the patch, no make-up, creams, lotions, powder, or other topical products had to be applied on the skin area where the patch was or would have been placed.

- Subject disposition, data sets analyzed and demographics

- Subject disposition

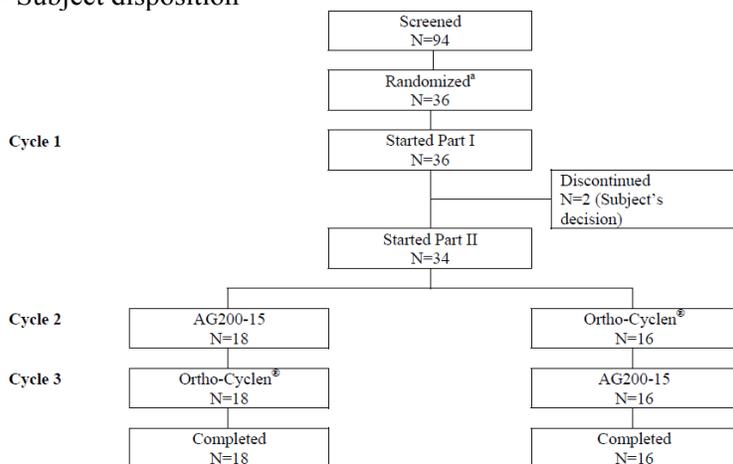


Figure 10 Subject disposition; ATI-CL14

In Part I, 36 (100.0%) subjects completed the first cycle with AG200-15, including the patch-free week. After Part I, two (5.6%, 0001 and 0028) subjects decided to discontinue the study due to family problems. Thirty-four subjects continued in Part II and completed treatment: 18 in the

AG200-15/Ortho-Cyclen sequence and 16 in the Ortho-Cyclen/AG200-15 sequence. In total, 34 (94.4%) subjects completed Part I and Part II.

- Data sets analyzed

The PK population included all randomized subjects who received at least one dose of study medication and provided PK data without major protocol deviations. The PK population consisted of 34 subjects (excluding Subjects (b) (6) as explained above).

The primary PK analysis population included all subjects who completed both treatment cycles during Part II of the study without major protocol deviations. This population consisted of 32 subjects. Subjects (b) (6) were excluded from the PK analysis because they were deemed not compliant with study drug as presented with abnormally low plasma concentrations throughout PK evaluation period.

- Demographics

Table 25 Demographic data; ATI-CL14

Parameter	Randomization Group		All Subjects N=36
	AG200-15/Ortho-Cyclen® N=18	Ortho Cyclen®/AG200-15 N=18	
Age, years			
Mean (SD)	37.8 (5.85)	36.2 (7.66)	37.0 (6.77)
Median (range)	39.0 (22-44)	38.0 (20-44)	38.5 (20-44)
Height, cm			
Mean (SD)	157.96 (3.736)	162.36 (7.046)	160.16 (5.989)
Median (range)	157.85 (151.0-165.1)	163.50 (152.0-178.0)	160.00 (151.0-178.0)
Weight, kg			
Mean (SD)	65.66 (8.073)	69.30 (11.897)	67.48 (10.189)
Median (range)	64.75 (52.3-84.0)	68.20 (50.7-90.0)	65.25 (50.7-90.0)
BMI, kg/m ²			
Mean (SD)	26.31 (3.060)	26.21 (3.546)	26.26 (3.264)
Median (range)	26.35 (21.0-31.8)	27.45 (20.8-31.6)	26.70 (20.8-31.8)
Sex, n (%)			
Female	18 (100.0)	18 (100.0)	36 (100.0)
Race, n (%)			
Caucasian	16 (88.9)	16 (88.9)	32 (88.9)
African American	2 (11.1)	2 (11.1)	4 (11.1)
Ethnicity			
Hispanic/Latino	16 (88.9)	17 (94.4)	33 (91.7)
Non-Hispanic/ Non-Latino	2 (11.1)	1 (5.6)	3 (8.3)

• Results

- EE

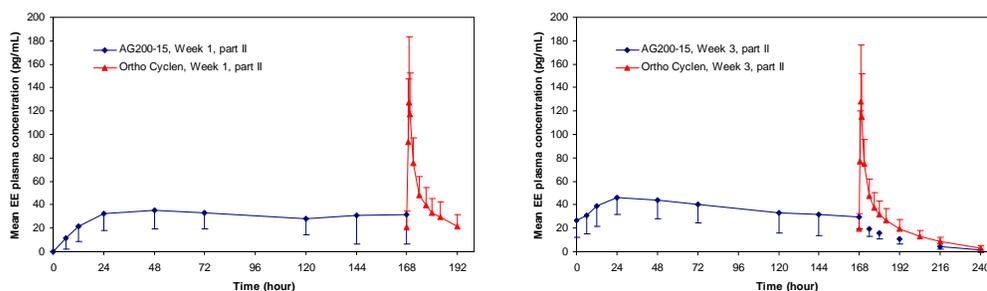


Figure 11 Mean (SD) EE concentrations in Weeks 1 and 3 of Part II from both AG200-15 and Ortho-Cyclen (primary PK analysis population); ATI-CL14

Figure 11 showed the mean EE concentration profiles in Weeks 1 and 3. Overall, the AG200-15 exhibited a flat profile, whereas the Ortho-Cyclen exhibited a typical oral drug profile with high C_{max}.

Table 26 Comparative evaluation of EE PK parameters: AG200-15 vs. Ortho-Cyclen (Part II, primary PK analysis population); ATI-CL14

Parameter/Period	Arithmetic mean ± SD	Treatments comparison
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	AG200-15 (N=32)	Ortho-Cyclen (N=32)	p-value	Ratio of Point Estimates	90% CI	
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 _{avg} (pg/mL)	30.1 ± 13.4	43.3 ± 15.8	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} ^a (ng·h/mL)	6.26 ± 2.46	6.97 ± 2.25	0.0532	85.96	75.67	97.66
C _{avg} (pg/mL)	37.3 ± 14.7	41.5 ± 13.4	0.0532	85.96	75.67	97.66

^aAUC_{0-168h} for Ortho-Cyclen was calculated as AUC₀₋₂₄ × 7.

To evaluate the EE PK of AG200-15 in comparison to the marketed OC, Ortho-Cyclen, the PK parameters of EE for both treatments were compared in the 32 subjects in Part II of study. At Week 1, the mean maximum concentrations were 45.5 versus 135 pg/mL, reached at 48 h versus 1 h postdose for AG200-15 and Ortho-Cyclen, respectively. There was approximately 13% increase of EE C_{max} from Week 1 to Week 3 in AG200-15, whereas there was no increase of EE C_{max} in Ortho-Cyclen. Overall, the EE C_{max} from AG200-15 was about 61% lower than the EE C_{max} from Ortho-Cyclen based on PK data observed in Week 3.

The systemic exposure over the 168 h time interval was 5.06 ng·h/mL for AG200-15 and 7.28 ng·h/mL for Ortho-Cyclen. A statistically significant (p-value<0.0009) difference was found for all PK parameters at Week 1. There was approximately 24% accumulation of EE from Week 1 to Week 3 in AG200-15, whereas there was no accumulation of EE in Ortho-Cyclen. Overall, the exposure of EE from AG200-15 was about 10% lower than the exposure of EE from Ortho-Cyclen based on PK data observed in Week 3.

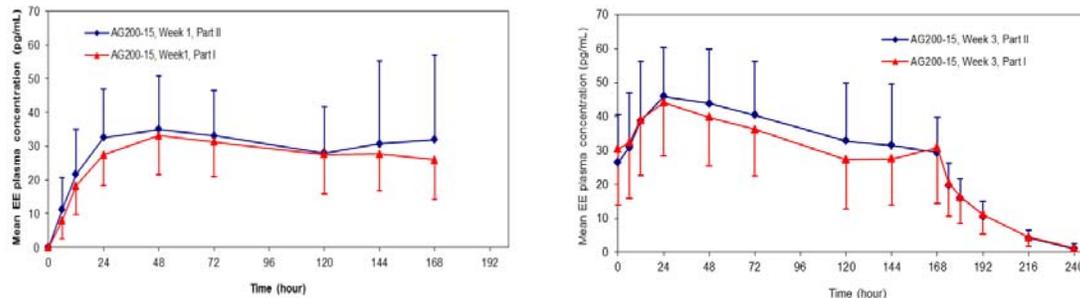


Figure 12 Mean (SD) EE concentrations in Weeks 1 and 3 of both Parts I and II from AG200-15 (primary PK analysis population); ATI-CL14

Table 27 Summary of EE PK parameters (primary PK analysis population); ATI-CL14

Week	PK parameter	Part I			Part II					
		AG200-15			AG200-15			Ortho-Cyclen		
		All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen in Part II, N=17	Sequence: Ortho-Cyclen/AG200-15 in Part II, N=15	All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen, N=17	Sequence: Ortho-Cyclen/AG200-15, N=15	All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen, N=17	Sequence: Ortho-Cyclen/AG200-15, N=15
1	C _{max} (pg/mL)	35.6 (13.2)	40.1 (14.4)	30.5 (9.78)	45.5 (24.0)	56.8 (26.9)	32.7 (10.6)	135 (50.7)	140 (58.3)	128 (38.9)
	T _{max} (hr)*	48.0 (24 - 144)	60 (24 - 144)	48 (24 - 144)	48 (24 - 168)	72 (24 - 168)	48 (24 - 168)	1 (0.5 - 1.5)	1 (1 - 1.5)	0.75 (0.5 - 1.5)
	AUC _{0-168h} (ng·h/mL)	4.64 (1.53)	5.18 (1.73)	4.04 (1.03)	5.05 (2.26)	6.20 (2.14)	3.75 (1.62)	7.28 (2.66)	7.52 (3.15)	6.92 (1.82)
3	C _{max} (pg/mL)	51.4 (17.3)	57.0 (17.1)	45.0 (15.6)	51.3 (17.3)	58.7 (18.4)	42.9 (11.6)	131 (45.4)	135 (52.1)	126 (37.7)
	T _{max} (hr)*	36 (0 - 168)	24 (0 - 120)	48 (0 - 168)	48 (12 - 144)	36 (12 - 144)	48 (24 - 72)	1 (1 - 3)	1 (1 - 3)	1 (1 - 1.5)
	AUC _{0-168h} (ng·h/mL)	5.71 (1.89)	6.21 (2.12)	5.15 (1.46)	6.26 (2.46)	7.22 (2.66)	5.18 (1.72)	6.97 (2.25)	6.97 (2.41)	6.97 (2.13)

	$t_{1/2}$ (hr)	19.7 (3.25)	19.7 (3.72)	19.7 (2.75)	19.2 (4.12)	20.3 (3.79)	17.9 (4.22)	18.9 (3.78)	18.7 (3.96)	19.1 (3.7)
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*Presented as median (range)

The exposure (both AUC and C_{max}) of EE was higher in subjects in AG200-15/Ortho-Cyclen sequence in part II compared to subjects in Ortho-Cyclen/AG200-15 in both AG200-15 and Ortho-Cyclen, although demographics of two groups were comparable. It was not clear what contributed to the differences in exposure of EE in these subjects.

AG200-15 (All subjects, subjects in AG200-15/Ortho-Cyclen sequence in part II, and subjects in Ortho-Cyclen/AG200-15 sequence) exhibited the within-cycle accumulation shown by the higher AUC in Week 3 compared to Week 1 (observed in both Parts I and II). In addition, there was a trend of between-cycle accumulation in AG200-15 (All subjects, subjects in AG200-15/Ortho-Cyclen sequence in Part II) shown by the followings:

- Higher AUC and C_{max} in Week 1 of Part II compared to Week 1 of Part I
- Higher AUC and C_{max} in Week 3 of Part II compared to Week 3 of Part I

However, the between-cycle accumulation in AG200-15 was not observed in subjects in Ortho-Cyclen/AG200-15 sequence in Part II.

Ortho-Cyclen did not exhibit the accumulation.

The $t_{1/2}$ of EE observed from both AG200-15 and Ortho-Cyclen was similar.

- LNG

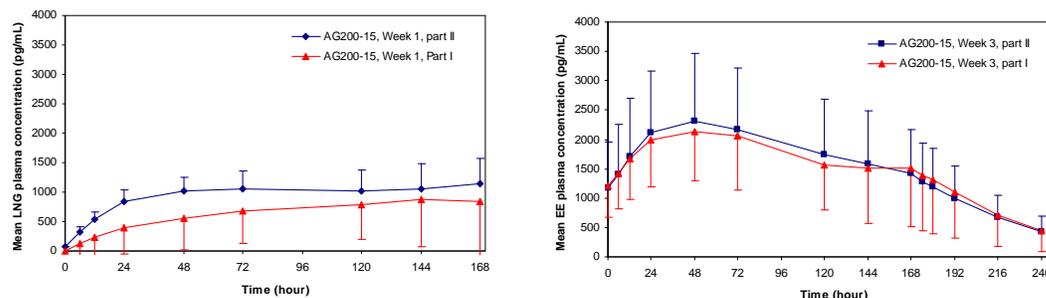


Figure 13 Mean (SD) LNG concentrations in Weeks 1 and 3 of both Parts I and II from AG200-15 (primary PK analysis population); ATI-CL14

Table 28 Summary of LNG PK parameters (primary PK analysis population); ATI-CL14

Week	PK parameter	Part I			Part II		
		AG200-15			AG200-15		
		All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen in Part II, N=17	Sequence: Ortho-Cyclen/AG200-15 in Part II, N=15	All subjects, N=32	Sequence: AG200-15/Ortho-Cyclen, N=17	Sequence: Ortho-Cyclen/AG200-15, N=15
1	C_{max} (pg/mL)	888 (441)	1026 (494)	733 (322)	1376 (921)	1831 (1033)	861 (354)
	T_{max} (hr)*	144 (72 – 168)	144 (72 – 168)	144 (72 – 168)	72 (24 – 168)	72 (48 – 168)	72 (24 – 168)
	AUC _{0-168h} (ng·h/mL)	108 (47.1)	122 (47.6)	93.5 (43.1)	161 (90.3)	210 (93.1)	105 (42.8)
3	C_{max} (pg/mL)	2374 (958)	2649 (1021)	2065 (801)	2382 (1157)	2833 (1206)	1871 (881)
	T_{max} (hr)*	48 (6 – 168)	48 (6 – 168)	48 (12 – 168)	48 (24 – 120)	48 (24 – 120)	48 (24 – 72)
	AUC _{0-168h} (ng·h/mL)	300 (128)	339 (139)	255 (99)	314 (160)	376 (171)	243 (116)
	$t_{1/2}$ (hr)	37.3 (8.93)	38.2 (8.67)	36.3 (9.40)	39.3 (7.20)	40.2 (6.34)	38.2 (8.15)

*Presented as median (range)

The exposure (both AUC and C_{max}) of LNG was higher in subjects in AG200-15/Ortho-Cyclen sequence in part II compared to subjects in Ortho-Cyclen/AG200-15, although demographics of two groups were comparable. It was not clear what contributed to the differences in exposure of LNG in these subjects.

AG200-15 (All subjects, subjects in AG200-15/Ortho-Cyclen sequence in part II, and subjects in Ortho-Cyclen/AG200-15 sequence) exhibited the within-cycle accumulation shown by the higher AUC in Week 3 compared to Week 1 (observed in both Parts I and II). In addition, there was a trend of between-cycle accumulation in AG200-15 (All subjects, subjects in AG200-15/Ortho-Cyclen sequence in Part II) shown by the followings:

- Higher AUC and C_{max} in Week 1 of Part II compared to Week 1 of Part I
- Higher AUC and C_{max} in Week 3 of Part II compared to Week 3 of Part I

However, the between-cycle accumulation in AG200-15 was not observed in subjects in Ortho-Cyclen/AG200-15 sequence in Part II.

- Conclusions

- The PK profiles of EE were different between the AG200-15 patch and Ortho-Cyclen. With AG200-15, EE concentrations increased till 24-48 h postdose and then remained stable till the end of blood sampling, while Ortho-Cyclen EE concentrations increased quickly followed by a quick decrease phase.
- AG200-15 exhibited a trend of both within-cycle accumulation and between-cycle accumulation for EE and LNG, whereas Ortho-Cyclen did not exhibit accumulation of EE.
- Due to the between cycle accumulation of EE and inter-subject variability (explained in section 2.2.3.1 of this review) between two groups in different sequences (sequence AG200-15/Ortho Cyclen and sequence Ortho Cyclen/AG200-15), the quantitative exposure comparison of EE was not reliable.

ATI-CL15

- Title

A PK study of the AG200-15 following weekly application to three anatomical sites (abdomen, buttock and upper torso) in healthy female volunteers

- Objective

The objective of this study was to evaluate the PK profile of AG200-15 following application at 3 different anatomical sites (abdomen, buttock, and upper torso).

- Study design

This was an open-label, randomized, 3-period crossover study. Twenty four healthy female subjects were enrolled in the study. Once determined by medical history and physical examination to be eligible for admission, and once having provided informed consent, these subjects were randomly assigned to 1 of 6 treatment sequences (Table 29). Each sequence included 3 patch application sites. During each treatment period, the patch was applied by the study site personnel. Only 1 patch was worn at a time. On each treatment day, the patch presence was confirmed by subject by using the diary card. After 1 week (7 days) of wear, the patch was removed by the study site personnel. Treatment periods were separated by a 1-week (7 days) washout. The blood sampling for the PK evaluations were performed at the following time points: 0 hour (immediately prior to dosing) and at 3 hours, 6 hours, 12 hours, 24 hours (1 day), 48 hours (2 days), 72 hours (3 days), 120 hours (5 days), 144 hours (6 days), and 168 hours (7 days) following application of the patch. Additional blood samples were collected at 174, 180, 192, 216, and 240 hours following the patch application (i.e. 6, 12, 24, 48, and 72 hours after removal of the patch).

Table 29 Treatment sequence; ATI-CL15

Treatment Sequences	Treatment Assignment		
	Period 1	Period 2	Period 3
Sequence 1 (4 subjects)	A	B	C
Sequence 2 (4 subjects)	B	C	A
Sequence 3 (4 subjects)	C	A	B
Sequence 4 (4 subjects)	A	C	B
Sequence 5 (4 subjects)	B	A	C
Sequence 6 (4 subjects)	C	B	A

A: Lower abdomen
B: Buttock
C: Upper torso (excluding breasts)

- Inclusion criteria
 - Healthy women, aged 18-45 years old.
 - BMI ≥ 18 and ≤ 32 kg/m², and weight ≥ 110 lbs
 - Willing to use a non-hormonal method of contraception if at risk of pregnancy, or had already undergone previous bilateral tubal ligation or hysterectomy.
 - Willing to refrain from use of alcohol and grapefruit juice from 48 h prior until completion of each treatment period.
 - Willing to give informed consent to participate in study.
 - Hemoglobin within normal range.

- Exclusion criteria
 - Known or suspected pregnancy.
 - Breast-feeding or within 1 month after stopping breast-feeding.
 - Status post-partum or post-abortion within a period of 2 months prior to the start of study medication.
 - A cervical cytology smear of Papanicolaou (Pap) class III or greater or a Bethesda System report of low-grade squamous intraepithelial lesions (SIL) or greater (Pap smear results within last 6 months were acceptable if properly documented).
 - Smoking.
 - Uncontrolled hypertension (blood pressure >140 mmHg systolic [SBP] or >90 mmHg diastolic [DBP]).
 - Valvular heart disease with complications.
 - Diabetes mellitus requiring insulin or non-insulin requiring subjects with vascular disease.
 - History of headaches with focal neurological symptoms.
 - Uncontrolled thyroid disorder.
 - Sickle cell anemia.
 - Current or history of clinically significant depression in the last year.
 - Known disturbance of lipid metabolism.
 - Acute or chronic hepatocellular disease with abnormal liver function.
 - Hepatic adenoma or carcinoma.
 - Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use.
 - Plans for major surgery.
 - History of or existing thromboembolic disorder, vascular disease, cerebral vascular, or coronary artery disease.
 - Undiagnosed abnormal genital bleeding.
 - Known or suspected breast carcinoma, endometrial carcinoma, or estrogen-dependent neoplasia.
 - History or presence of dermal hypersensitivity in response to topical applications (bandages, surgical tape, etc.) or known hypersensitivity to any components of this product.
 - Chronic skin conditions including but not limited to: eczema, psoriasis, tattoos, and/or keloids or other scars that may interfere with patch placement or assessment.
 - Use of an injectable hormonal contraceptive within the past 6 months prior to the screening visit.

- Used a contraceptive implant or hormone-medicated IUD within 1 month prior to the screening visit.
- Use of OCs or other sex steroid hormones within 1 month prior to the screening visit.
- Chronic use of any medication that might interfere with the efficacy of hormone contraceptives (including barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's Worth, topiramate, and HIV protease inhibitors), or use of these medications within the past 3 months prior to the screening visit.
- Administration of any investigational drug and/or experimental device within 30 days prior to the screening visit.
- A recent history (within prior 12 months) of drug or alcohol abuse.
- Deemed by the investigator to have had questionable ability to comply with the protocol and provide accurate information.

- Treatments

AG200-15 is an adhesive patch containing 2.30 mg of EE and 2.60 mg of LNG.

Treatments were described as follows:

- Treatment A: AG200-15; Applied to lower abdomen
- Treatment B: AG200-15; Applied to buttock
- Treatment C: AG200-15; Applied to upper torso

On the mornings of Days 1 (Period 1), 15 (Period 2), and 29 (Period 3), subjects were administered a patch placed on the subject's application site (lower abdomen, buttock, or upper torso) by study site personnel, according to the randomization scheme.

- Subject disposition, data sets analyzed and demographics

- Subject disposition

A total of 24 subjects entered the study and were randomized to study treatment. A total of 22 subjects completed the study. There were 2 subjects that discontinued early: Subjects (b) (6) withdrew consent for study participation due to personal reasons.

- Data sets analyzed

Data obtained from 22 subjects excluding subjects (b) (6) were included in the PK analysis.

- Demographics

There were 24 female subjects who participated in the study. Regarding race, 18 subjects were White or Caucasian, 5 were African American, and 1 was Asian. Regarding ethnicity, 17 subjects were not Hispanic or Latino and 7 were Hispanic or Latino. The mean age for all subjects was 32.2 years (range 18 – 45 years), the mean weight was 66.5 kg (range 50 – 91 kg), and the mean height was 164.29 cm (range 152 – 177 cm).

- Results

- EE

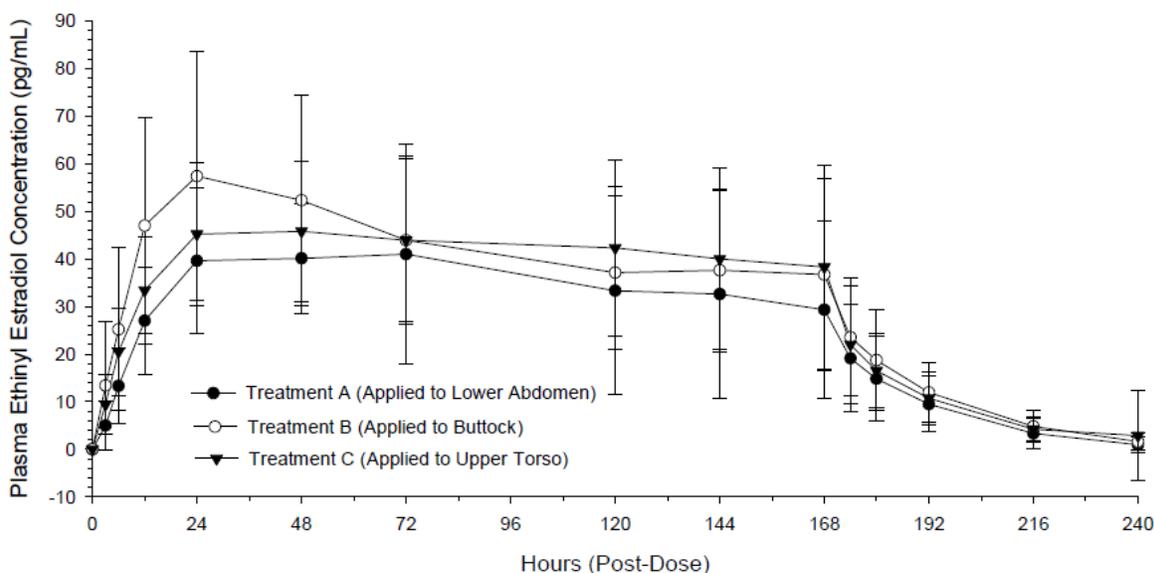


Figure 14 Mean (SD) plasma concentrations of EE; ATI-CL15

The mean concentrations increased for 24 hours from patch application. The concentrations appeared to reach a plateau between 24 to 168 hours after the patch application and dropped sharply after patch removal.

Table 30 Summary of EE PK parameters; ATI-CL15

Application site	Arithmetic mean (SD)			Median (min-max)
	C_{max} (pg/mL)	AUC_{0-168} (ng·hr/mL)	$t_{1/2}$	t_{max}
Lower abdomen (A)	47.9 (22.8)	5.80 (2.80)	17.6 (3.79)	48 (24-144)
Buttock (B)	61.5 (22.8)	7.12 (2.85)	18.2 (3.42)	24 (12-168)
Upper torso (C)	53.5 (19.9)	6.86 (2.53)	17.6 (4.33)	48 (12-240)

Table 31 Summary of BE assessment for EE PK parameters; ATI-CL15

Comparison	% geometric mean ratio (90% CI)	
	C_{max}	AUC_{0-168}
Buttock (B) vs. Lower abdomen (A)	130 (113 – 151)	123 (108 – 140)
Upper torso (C) vs. Lower abdomen (A)	115 (99.2 – 133)	121 (106 – 138)

Buttock (Treatment B) vs. Lower abdomen (Treatment A)

The C_{max} and AUC_{0-168} of EE was approximately 30% and 23% higher respectively when AG200-15 was applied to the buttock as compared to the lower abdomen. The upper limit of 90% CIs were higher than 125 for both C_{max} and AUC_{0-168} . In addition, the both CIs did not contain 100.

Upper torso (Treatment C) vs. Lower abdomen (Treatment A)

The C_{max} and AUC_{0-168} of EE was approximately 15% and 21% higher respectively when AG200-15 was applied to the upper torso as compared to the lower abdomen. The upper limit of 90% CIs were higher than 125 for both C_{max} and AUC_{0-168} . The CI for C_{max} contained 100, whereas CI for AUC_{0-168} did not contain 100.

The result of ATI-CL15 suggested that 1 week patch free period may not be long enough to eliminate any residual EE from the AG200-15. To test the statement above, the AUC_{0-168} of EE from AG200-15 when it was applied first vs. last in 3 different application sites were compared.

Table 32 Effect of application sequence on mean EE exposure when AG200-15 is applied to 3 different sites; ATI-CL15

Application sequence	Abdomen (A)		Buttock (B)		Upper torso (C)	
	First, n=8 (ABC or ACB)	Last, n=7 (BCA or CBA)	First, n=8 (BAC or BCA)	Last, n=7 (ACB or CAB)	First, n=8 (CAB or CBA)	Last, n=7 (ABC or BAC)
mean AUC ₀₋₁₆₈ (ng·hr/mL)	5.41 (1.45)	6.77 (4.59)	4.71 (1.54)	7.48 (1.93)	7.13 (1.48)	8.53 (3.94)
% increase of AUC (Last/First)	125%		158%		120%	

As shown in Table 32, there were increases of EE exposure when AG200-15 was applied last compared to when AG200-15 was applied first to each application site. This supported that the 1 week patch free period between each treatment may not be long enough to eliminate any residual EE completely from systemic circulation. Therefore, the design (1 week patch free period between each treatment) of the study ATI-CL15 did not appear appropriate to meet the objective of the study ATI-CL15, evaluating the PK profiles in 3 different application sites.

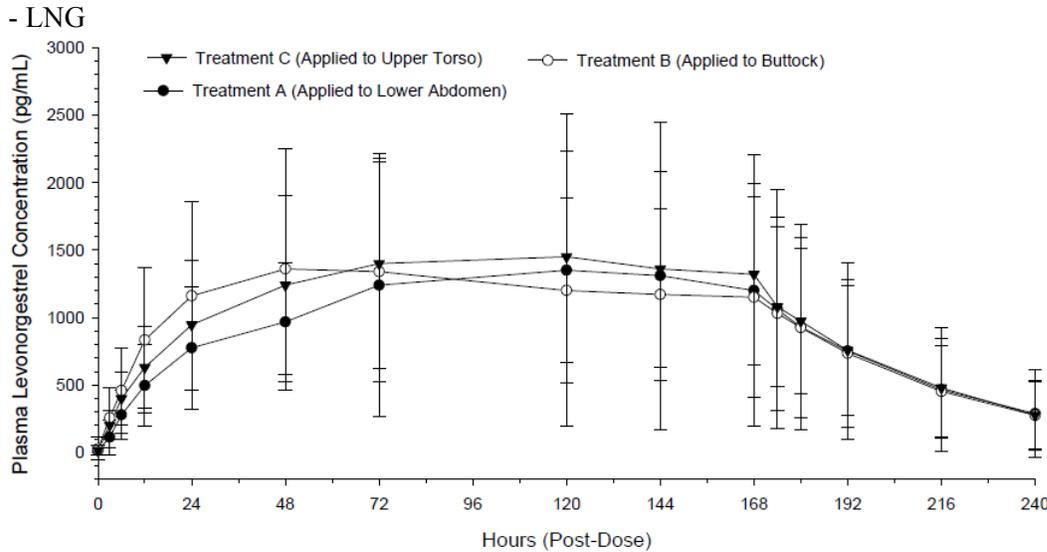


Figure 15 Mean (SD) plasma concentrations of LNG; ATI-CL15

The mean concentrations increased for 72 hours from patch application. The concentrations appeared to reach a plateau between 72 to 168 hours after the patch application and dropped sharply after patch removal.

Table 33 Summary of LNG PK parameters; ATI-CL15

Application site	Arithmetic mean (SD)			Median (min-max)
	C _{max} (pg/mL)	AUC ₀₋₁₆₈ (ng·hr/mL)	t _{1/2}	t _{max}
Lower abdomen (A)	1436 (1148)	182 (135)	32.5 (9.49)	120 (48-174)
Buttock (B)	1494 (825)	197 (116)	32.6 (10.6)	72 (24-168)
Upper torso (C)	1589 (825)	206 (106)	33.4 (10.3)	120 (48-168)

Table 34 Summary of BE assessment for LNG PK parameters; ATI-CL15

Comparison	% geometric mean ratio (90% CI)	
	C _{max}	AUC ₀₋₁₆₈
Buttock (B) vs. Lower abdomen (A)	107 (89.9-127)	107 (92.0-124)
Upper torso (C) vs. Lower abdomen (A)	117 (98.0-139)	117 (101-136)

Buttock (Treatment B) vs. Lower abdomen (Treatment A)

The C_{max} and AUC_{0-168} of LNG were approximately 7% higher when AG200-15 was applied to the buttock as compared to the lower abdomen. The 90% CI for AUC_{0-168} was within the BE limit. However, 90% CI for C_{max} did not meet the BE limit. However, the both CIs contained 100.

Upper torso (Treatment C) vs. Lower abdomen (Treatment A)

The C_{max} and AUC_{0-168} of EE were approximately 17% higher when AG200-15 was applied to the upper torso as compared to the lower abdomen. The upper limit of 90% CIs were higher than 125 for both C_{max} and AUC_{0-168} . The CI for C_{max} contained 100, whereas CI for AUC_{0-168} did not contain 100.

The result of ATI-CL15 suggested that 1 week patch free period may not be long enough to eliminate any residual LNG from the AG200-15. To test the statement above, the AUC_{0-168} of LNG from AG200-15 when it was applied first vs. last in 3 different application sites were compared.

Table 35 Effect of application sequence on mean LNG exposure when AG200-15 is applied to 3 different sites; ATI-CL15

Application sequence	Abdomen (A)		Buttock (B)		Upper torso (C)	
	First, n=8 (ABC or ACB)	Last, n=7 (BCA or CBA)	First, n=8 (BAC or BCA)	Last, n=8 (ACB or CAB)	First, n=8 (CAB or CBA)	Last, n=7 (ABC or BAC)
mean AUC_{0-168} (ng-hr/mL)	160 (56.1)	247 (222)	94.8 (37.3)	229 (69.2)	141 (75.5)	250 (133)
% increase of AUC (Last/First)	154%		242%		177%	

As shown in Table 32, there were increases of LNG exposure when AG200-15 was applied last compared to when AG200-15 was applied first to each application site. This supported that the 1 week patch free period between each treatment may not be long enough to eliminate any residual LNG completely from systemic circulation. Therefore, the design (1 week patch free period between each treatment) of the study ATI-CL15 did not appear appropriate to meet the objective of the study ATI-CL15, evaluating the PK profiles in 3 different application sites.

• Conclusions

The exposures for both EE and LNG were compared when AG200-15 was applied to either buttock or upper torso as compared to lower abdomen. Both sites, buttock and upper torso, was associated with higher exposure of both EE and LNG compared to lower abdomen. However, this result is not reliable because there was the effect of sequence (higher the exposure of both EE and LNG, when applied later in the sequence) indicating 1 patch free week may not be long enough to eliminate both EE and LNG from the systemic circulation completely.

ATI-CL16

• Title

A PK and wearability study of the AG200-15 following weekly application under various external conditions in healthy female volunteers

• Objectives

The objective of this study was to evaluate the PK profile and wearability of AG200-15 following application under various external conditions (dry sauna, whirlpool, treadmill exercise, and cold water immersion) when compared to the normal conditions.

• Study design

Twenty four healthy females were enrolled in the study and all subjects completed all treatment periods. Once determined by history and physical examination to be eligible for admission these subjects were randomly assigned to one of six external condition sequences (Table 36). Each

sequence included a normal wear period and two external condition periods (dry sauna, whirlpool, treadmill exercise, or cold water immersion). During each treatment period, the patch was applied to the lower abdomen by the study site personnel. Only 1 patch was worn at a time during each seven day period. Treatment periods were separated by 1 week (7-day) washout. The blood sampling for the PK evaluations was performed at the following time points: 0 hour (immediately prior to dosing) and at 6 hours, 12 hours, 24 hours (1 day), 48 hours (2 days), 72 hours (3 days), 120 hours (5 days), 144 hours (6 days), and 168 hours (7 days) following application of the patch. Immediately after the 168-hour blood draw, the patch was removed by study site personnel. Additionally, blood samples were collected at 174, 180, 192, 216, 204, and 240 hours following the patch application (i.e., 6, 12, 24, 36, 48, and 72 hours after removal of the patch).

Table 36 External conditions randomization schedule; ATICL16

Sequences	Assignment		
	Period 1	Period 2	Period 3
Sequence 1 (4 subjects)	Normal	Dry Sauna	Cold Water
Sequence 2 (4 subjects)	Cold Water	Normal	Whirlpool
Sequence 3 (4 subjects)	Whirlpool	Treadmill	Normal
Sequence 4 (4 subjects)	Normal	Cold Water	Dry Sauna
Sequence 5 (4 subjects)	Dry Sauna	Normal	Treadmill
Sequence 6 (4 subjects)	Treadmill	Whirlpool	Normal

Description of daily conditions

- Normal period: The subject should have continued activities of daily living but excluded bathing, sunbathing, and strenuous activities that produce a heavy sweat. Showers were acceptable.
- Dry sauna period: The subject was exposed to dry sauna conditions for a period of 10 minutes (temperature between 76°C and 82°C [168.8°F – 179.6°F]).
- Whirlpool period: The subject sat in the whirlpool for a period of 10 minutes (temperature between 39°C and 41°C [102.2°F – 105.8 °F]).
- Treadmill period: The subject walked on the treadmill for 20-30 minutes at 60%-80% maximum heart rate, calculated as 220 minus the age of the subject.
- Cold water immersion period: The subject sat in a cold water bath for 5 to 15 minutes (temperature maximum of 22°C [71.6 °F]).

- Inclusion criteria

- Healthy women, aged 18-45 years old.
- BMI ≥ 18 and ≤ 32 kg/m², and weight ≥ 110 lbs
- Willing to use a non-hormonal method of contraception if at risk of pregnancy, or had already undergone previous bilateral tubal ligation or hysterectomy.
- Willing to refrain from use of alcohol and grapefruit juice from 48 h prior until completion of each treatment period.
- Willing to give informed consent to participate in study.
- Hemoglobin within normal range.

- Exclusion criteria

- Known or suspected pregnancy.
- Breast-feeding or within 1 month after stopping breast-feeding.
- Status post-partum or post-abortion within a period of 2 months prior to the start of study medication.
- A cervical cytology smear of Papanicolaou (Pap) class III or greater or a Bethesda System report of low-grade squamous intraepithelial lesions (SIL) or greater (Pap smear results within last 6 months were acceptable if properly documented).
- Smoking.

- Uncontrolled hypertension (blood pressure >140 mmHg systolic [SBP] or >90 mmHg diastolic [DBP]).
- Valvular heart disease with complications.
- Diabetes mellitus requiring insulin or non-insulin requiring subjects with vascular disease.
- History of headaches with focal neurological symptoms.
- Uncontrolled thyroid disorder.
- Sickle cell anemia.
- Current or history of clinically significant depression in the last year.
- Known disturbance of lipid metabolism.
- Acute or chronic hepatocellular disease with abnormal liver function.
- Hepatic adenoma or carcinoma.
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use.
- Plans for major surgery.
- History of or existing thromboembolic disorder, vascular disease, cerebral vascular, or coronary artery disease.
- Undiagnosed abnormal genital bleeding.
- Known or suspected breast carcinoma, endometrial carcinoma, or estrogen-dependent neoplasia.
- History or presence of dermal hypersensitivity in response to topical applications (bandages, surgical tape, etc.) or known hypersensitivity to any components of this product.
- Chronic skin conditions including but not limited to: eczema, psoriasis, tattoos, and/or keloids or other scars that may interfere with patch placement or assessment.
- Use of an injectable hormonal contraceptive within the past 6 months prior to the screening visit.
- Used a contraceptive implant or hormone-medicated IUD within 1 month prior to the screening visit.
- Use of OCs or other sex steroid hormones within 1 month prior to the screening visit.
- Chronic use of any medication that might interfere with the efficacy of hormone contraceptives (including barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's Worth, topiramate, and HIV protease inhibitors), or use of these medications within the past 3 months prior to the screening visit.
- Administration of any investigational drug and/or experimental device within 30 days prior to the screening visit.
- A recent history (within prior 12 months) of drug or alcohol abuse.
- Deemed by the investigator to have had questionable ability to comply with the protocol and provide accurate information.

- Treatments

A total of three AG200-15 patches were administered during the study. Each patch was worn for 7 days (1 week). Only one patch was worn at a time. The patches were applied to the abdomen and according to the period assigned by the randomization schedule, the subject participated in a daily activity exposing the subject to normal wear conditions as well as various external conditions (treadmill exercise, dry sauna, whirlpool and cold water immersion).

- Subject disposition, data sets analyzed and demographics

- Subject disposition and data sets analyzed

Twenty four (24) subjects were randomized into the study, and all completed the study. Four subjects participated in each of the six sequences (Table 36), and all subjects were included in the PK analysis.

- Demographics

Table 37 Demographic characteristics

Parameter	Category	Statistic	Sequence 1 (NDC) (N=4)	Sequence 2 (CNW) (N=4)	Sequence 3 (WTN) (N=4)	Sequence 4 (NCD) (N=4)	Sequence 5 (DNT) (N=4)	Sequence 6 (TWN) (N=4)	Overall (N=24)
Age (years)		n	4	4	4	4	4	4	24
		Mean	34.2	36.8	35.8	36.2	35.8	32.0	35.1
		SD	5.1	9.3	4.9	9.0	3.4	8.4	6.5
		CV (%)	15.0	25.3	13.8	24.8	9.5	26.4	18.4
		Median	35.5	38.0	35.5	38.0	36.5	33.5	36.0
		Min, Max	(27.0,39.0)	(26.0,45.0)	(30.0,42.0)	(25.0,44.0)	(31.0,39.0)	(22.0,39.0)	(22.0,45.0)
Weight (kg)		n	4	4	4	4	4	4	24
		Mean	69.0	76.8	71.3	70.9	69.9	66.5	70.8
		SD	17.9	14.9	4.4	8.0	6.9	7.0	10.2
		CV (%)	25.9	19.4	6.2	11.3	9.9	10.6	14.5
		Median	65.7	71.7	72.6	72.2	68.6	67.2	70.6
		Min, Max	(51.0,93.6)	(65.2,98.7)	(65.1,75.0)	(60.2,79.2)	(63.1,79.4)	(58.7,73.0)	(51.0,98.7)
Height (cm)		n	4	4	4	4	4	4	24
		Mean	159.0	169.0	160.5	168.0	163.6	161.5	163.6
		SD	12.4	7.4	5.9	7.2	8.6	8.6	8.5
		CV (%)	7.8	4.4	3.7	4.3	5.3	5.3	5.2
		Median	160.0	166.0	159.3	168.5	161.8	161.5	164.0
		Min, Max	(143.5,172.7)	(164.0,180.0)	(155.0,168.5)	(160.0,175.0)	(155.5,175.3)	(152.0,171.0)	(143.5,180.0)
BMI (kg/m ²)		n	4	4	4	4	4	4	24
		Mean	26.9	26.7	27.7	25.0	26.3	25.6	26.4
		SD	3.1	2.9	2.0	1.2	3.5	2.9	2.6
		CV (%)	11.4	11.0	7.2	4.8	13.3	11.4	9.7
		Median	25.7	26.5	28.0	25.3	27.0	25.0	26.0
		Min, Max	(24.8,31.4)	(23.4,30.5)	(25.2,29.7)	(23.5,26.1)	(21.9,29.3)	(22.7,29.6)	(21.9,31.4)
Race	White	n (%)	3 (75.0%)	3 (75.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	3 (75.0%)	21 (87.5%)
	Black	n (%)	1 (25.0%)	1 (25.0%)	0	0	0	0	2 (8.3%)
	Asian	n (%)	0	0	0	0	0	1 (25.0%)	1 (4.2%)
Ethnicity	Hispanic or Latino	n (%)	2 (50.0%)	1 (25.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	0	9 (37.5%)
	Not Hispanic or Latino	n (%)	2 (50.0%)	3 (75.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	4 (100.0%)	15 (62.5%)
Current Alcohol Use	Yes	n (%)	0	0	1 (25.0%)	0	0	0	1 (4.2%)
	No	n (%)	4 (100%)	4 (100%)	3 (75.0%)	4 (100%)	4 (100%)	4 (100%)	23 (95.8%)

N=Normal, D=Dry Sauna, C=Cold Water, W=Whirlpool, T=Treadmill, SD=standard deviation, CV=coefficient of variation, BMI=body mass index

• Results

- EE

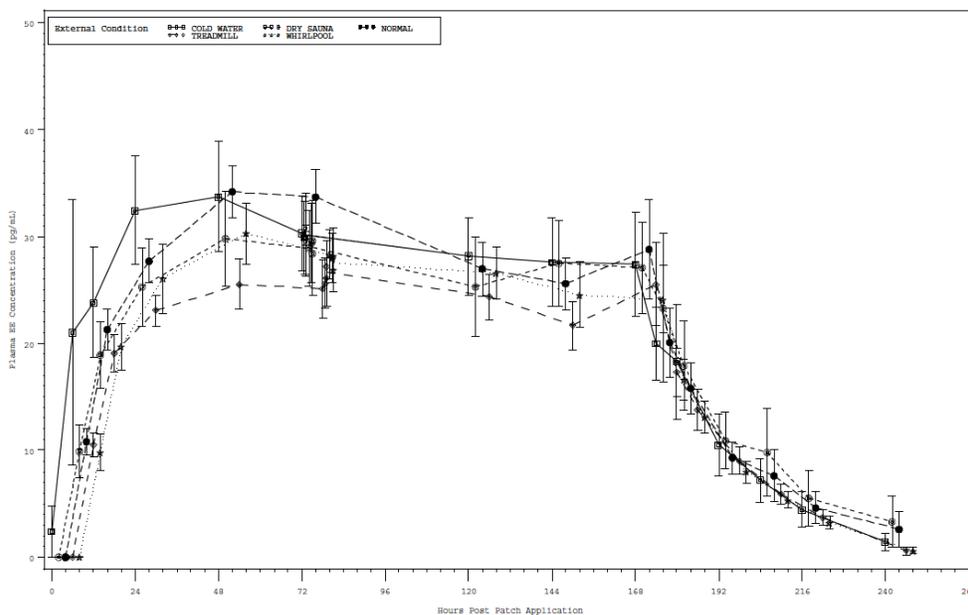


Figure 16 Mean plasma EE concentrations; ATI-CL16

The figure above indicates that, during the course of the study, EE concentrations were generally higher during normal patch wear when compared to external conditions, although the EE concentrations in the cold water external condition were similar. The pattern of the EE delivery appears to be comparable for all conditions studied.

Table 38 Summary of EE PK parameters; ATI-CL16

External conditions	Arithmetic mean (SD)			Median (min-max)
	C _{max} (pg/mL)	AUC ₀₋₁₆₈ (ng·hr/mL)	t _{1/2}	t _{max}
Normal, n=24	42 (20)	4.7 (1.6)	21 (13)	60 (12-168)
Dry sauna, n=12	39 (23)	4.3 (2.0)	21 (8.8)	48 (24-174)
Cold water, n=12	45 (38)	4.9 (2.3)	18 (4.6)	24 (6-144)
Whirlpool, n=12	33 (9)	4.3 (1.4)	22 (8.0)	72 (12-168)
Treadmill, n=12	32 (10)	3.9 (1.1)	23 (14)	60 (12-168)

Table 39 Summary of BE assessment for EE PK parameters; ATI-CL16

Comparison	% geometric mean ratio (90% CI)	
	C _{max}	AUC ₀₋₁₆₈
Dry sauna vs. Normal, n=12	90.5 (78.5-104.4)	93.0 (82.7-104.5)
Cold water vs. Normal, n=12	94.3 (81.8-108.8)	99.5 (88.6-111.9)
Whirlpool vs. Normal, n=12	80.7 (70.0-93.0)	86.7 (77.1-97.4)
Treadmill vs. Normal, n=12	79.8 (69.3-92.0)	82.2 (73.2-92.4)

Mean C_{max} concentrations for EE were greater during the normal patch wear group when compared to all of the external conditions with the exception of the cold water immersion condition. The mean EE AUCs for the external conditions was in the order of cold water, normal, dry sauna/whirlpool, and treadmill. The sponsor explained this observation (higher AUC with cold conditions compared to warm/hot conditions) based on the drug's degree of saturation as follows: "The solubility of both EE and LNG in the patch can increase with higher temperatures thus decreasing the drug's degree of saturation and consequently the drug's permeation through skin resulting lower AUC." Half life was comparable across conditions (ranging from 18 hour for normal cold water external conditions to 23 hour for treadmill external condition).

The results of the statistical analyses of bioequivalence for external conditions relative to the normal wear condition for plasma EE are summarized in Table 39. None of the PK parameters met bioequivalence criteria for whirlpool and treadmill. For dry sauna, AUC met the BE criteria whereas C_{max} did not meet the BE criteria. All PK parameters met bioequivalence criteria for cold water.

The result of ATI-CL15 suggested that 1 week patch free period may not be long enough to eliminate any residual EE from the AG200-15. To test the statement above, the AUC₀₋₁₆₈ of EE from AG200-15 when it was applied first vs. last under different external conditions was compared.

Table 40 Effect of application sequence on mean EE exposure when AG200-15 is applied under different external conditions; ATI-CL16

Application sequence	Normal (N)		Cold water (C)		Whirlpool (W)		Dry sauna (D)		Treadmill (T)	
	First, n=8 (NDC or NCD)	last, n=8 (WTN or TWN)	First, n=4 (CNW)	Last, n=4 (NDC)	First, n=4 (WTN)	Last, n=4 (CNW)	First, n=4 (DNT)	Last, n=4 (NCD)	First, n=4 (TWN)	Last, n=4 (DNT)
mean AUC ₀₋₁₆₈ (ng·hr/mL)	4.52 (1.92)	5.7 (0.73)	3.58 (1.70)	5.95 (1.34)	4.11 (0.71)	3.99 (2.33)	2.77 (0.70)	4.98 (2.45)	4.35 (0.72)	3.64 (1.81)
% increase of AUC (Last/First)	118%		166%		97%		178%		84%	

Under normal, whirlpool, and treadmill conditions, the EE exposures were comparable when AG20015 was applied first vs. last. However, under cold water and dry sauna conditions, there were increases of EE exposure when AG200-15 was applied last compared to when AG200-15 was applied first. This supported that the 1 week patch free period between each treatment may not be long enough to eliminate any residual EE completely from systemic circulation. Therefore, the design (1 week patch free period between each treatment) of the study ATI-CL15 did not appear

appropriate to meet the objective of the study ATI-CL16, evaluating the PK profiles under different external conditions.

- LNG

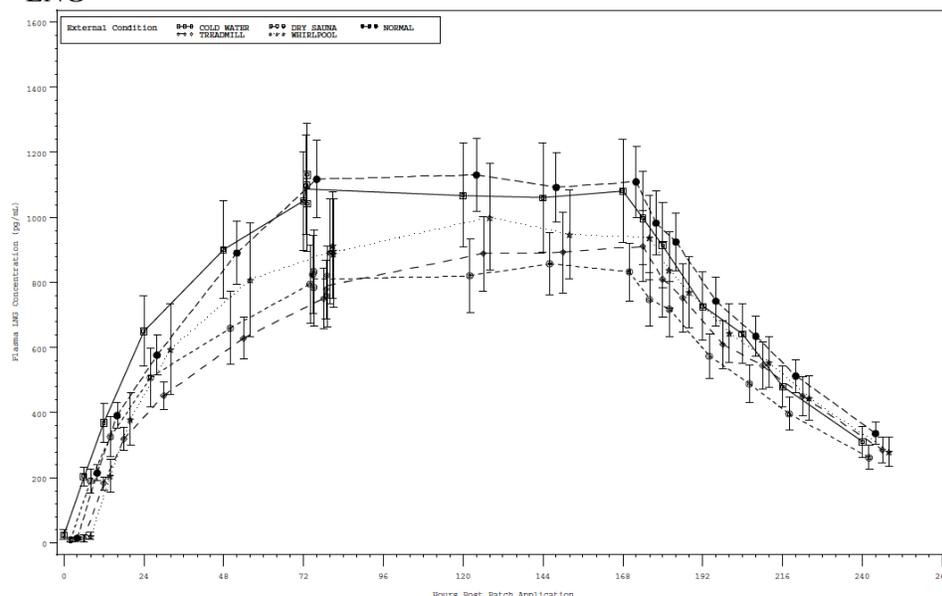


Figure 17 Mean plasma LNG concentrations; ATI-CL16

The figure above indicates that, throughout the course of the study, LNG concentrations were generally higher at sampling time points during normal patch wear when compared to external conditions. The pattern of LNG concentrations appears to be similar for all conditions studied.

Table 41 Summary of LNG PK parameters; ATI-CL16

External conditions	Arithmetic mean (SD)			Median (min-max)
	C_{max} (pg/mL)	AUC_{0-168} (ng-hr/mL)	$t_{1/2}$	t_{max}
Normal, n=24	1316 (581)	157 (74)	42 (11)	120 (12-168)
Dry sauna, n=12	1013 (396)	118 (51)	38 (6)	144 (72-168)
Cold water, n=12	1223 (622)	153 (76)	40 (13)	132 (48-174)
Whirlpool, n=12	1117 (610)	137 (81)	43 (18)	120 (12-174)
Treadmill, n=12	976 (377)	119 (46)	40 (10)	144 (72-168)

Table 42 Summary of BE assessment for LNG PK parameters; ATI-CL16

Comparison	% geometric mean ratio (90% CI)	
	C_{max}	AUC_{0-168}
Dry sauna vs. Normal	79.1 (66.7-93.8)	78.6 (68.0-90.8)
Cold water vs. Normal	90.1 (76.0-106.8)	97.8 (84.7-113.0)
Whirlpool vs. Normal	78.4 (66.1-92.9)	79.1 (68.5-91.3)
Treadmill vs. Normal	75.3 (63.5-89.3)	78.1 (68.4-91.2)

Mean C_{max} concentrations for LNG were greater during the normal patch wear group when compared to any external conditions. Among external conditions, mean C_{max} concentrations for LNG were higher after immersion in the cold water followed by whirlpool, dry sauna, and treadmill. The mean LNG AUC for the normal patch wear group were higher compared to any external conditions, and the mean LNG AUCs for external conditions decreased from cold water to whirlpool to dry sauna, with treadmill providing the lowest AUC. Median T_{max} was generally comparable across the conditions studied and ranged from 120 h to 144 h, while $t_{1/2}$ was also

comparable across conditions (ranging from 38 h for dry sauna external condition to 43 h for whirlpool external condition).

Results of the statistical analysis of the BE for external conditions relative to the normal wear condition for plasma LNG pharmacokinetic parameters are summarized in Table 42. Patch wear under most external conditions resulted in the LNG pharmacokinetics not meeting bioequivalence criteria when compared to a period of normal patch wear. None of the PK parameters met BE criteria for dry sauna, whirlpool and treadmill. With exception of C_{max} , BE to normal conditions was observed for the cold water external condition.

The result of ATI-CL15 suggested that 1 week patch free period may not be long enough to eliminate any residual LNG from the AG200-15. To test the statement above, the AUC_{0-168} of EE from AG200-15 when it was applied first vs. last under different external conditions was compared.

Table 43 Effect of application sequence on mean LNG exposure when AG200-15 is applied under different external conditions; ATI-CL16

Application sequence	Normal (N)		Cold water (C)		Whirlpool (W)		Dry sauna (D)		Treadmill (T)	
	First, n=8 (NDC or NCD)	last, n=8 (WTN or TWN)	First, n=4 (CNW)	Last, n=4 (NDC)	First, n=4 (WTN)	Last, n=4 (CNW)	First, n=4 (DNT)	Last, n=4 (NCD)	First, n=4 (TWN)	Last, n=4 (DNT)
mean AUC_{0-168} (ng·hr/mL)	123 (56)	209 (66)	103 (64)	215 (75)	89 (20)	152 (118)	77 (43)	140 (38)	118 (29)	129 (68)
% increase of AUC (Last/First)	170%		208%		170%		182%		109%	

Under all the conditions tested, there were increases of LNG exposure when AG200-15 was applied last compared to when AG200-15 was applied first. This supported that the 1 week patch free period between each treatment may not be long enough to eliminate any residual LNG completely from systemic circulation. Therefore, the design (1 week patch free period between each treatment) of the study ATI-CL15 did not appear appropriate to meet the objective of the study ATI-CL16, evaluating the PK profiles under different external conditions.

- **Conclusions**

The exposure for both EE and LNG was compared when AG200-15 was applied under different external conditions. Overall, the EE and LNG exposure was comparable under cold conditions compared to normal condition. The EE and LNG exposures under different external conditions (whirlpool, dry sauna, and treadmill) were lower compared to normal condition. However, this result is not reliable because there was the effect of sequence (higher the exposure of both EE and LNG, when applied later in the sequence) indicating 1 patch free week may not be long enough to eliminate both EE and LNG from the systemic circulation completely.

ATI-CL12

- **Title**

An open-label, randomized, parallel group, phase 3 study of the contraceptive efficacy and safety of AG200-15 in comparison to a low-dose oral contraceptive containing 0.02 mg EE and 0.1 mg LNG

- **Objectives**

To provide comparative evaluation of AG200-15 vs. OC with regard to safety, contraceptive efficacy, cycle control (bleeding pattern), subject compliance, and plasma concentrations of EE and LNG

- **Study design**

This was an open-label, randomized, comparative, parallel group, multi-center study. The 1,504 sexually active women (age 17-40) were enrolled in this study. The subjects were randomized into 3:1 ratio, with 1,378 subjects randomized to AG200-15 for a one year (13 cycles) and 375 subjects

randomized to OC (Lessina containing 0.02 mg EE and 0.1 mg LNG, ANDA 075803 approved in March 2002) for 6 cycles. The subjects who were randomized to OC for 6 cycles were later switched to AG200-15 for additional 7 cycles. A treatment cycle was defined as a 28-day period: 21 days on treatment (consecutive administration of the three 7-day patches or 21 days of active pill-taking) followed by 7 days off treatment (i.e., no patch was applied or no active pills were taken). The patch was applied to the abdomen, the buttock or the upper torso excluding the breasts. During the visits scheduled before application of the last patch at the second, sixth, and thirteenth cycles, blood was drawn to evaluate plasma concentrations of LNG and EE.

- Inclusion criteria

- Sexually active women requesting contraception;
- 17 to 40 years old;
- Regular menses every 24 - 35 days; if current continuous use of hormonal birth control historical data will be used to determine qualification;
- In good general health, confirmed by medical history, physical (including gynecologic) examination and screening laboratory values;
- Willing to sign the informed consent form to participate in the study and refrain from using condoms on a regular basis and any other steroid hormonal therapy (other than topical corticosteroids) for the duration of the study.

- Exclusion criteria

- Known or suspected pregnancy;
- Lactating women;
- Breast-feeding within 42 days prior to the start of study medication;
- Women who smoked and were ≥ 35 years old or turned 35 anytime during the study;
- Uncontrolled hypertension (blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) in women with BMI <32 kg/m²;
- History or presence of hypertension (blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) in women with BMI ≥ 32 kg/m²;
- Valvular heart disease with complications;
- Diabetes Mellitus with vascular disease in women with BMI <32 kg/m²;
- Diabetes Mellitus type I and II in women with BMI ≥ 32 kg/m²;
- History of headaches with focal neurological symptoms;
- Uncontrolled thyroid disorder;
- Sickle cell anemia;
- Current or history of clinically significant depression in the last year;
- Known disturbance of lipid metabolism (triglycerides >300);
- Acute or chronic hepatocellular disease with abnormal liver function;
- Hepatic adenoma or carcinoma;
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use;
- Positive HIV and/or hepatitis at screening
- Plans for major surgery with anticipated prolonged immobilization;
- History of or existing thromboembolic disorder, vascular disease, cerebral vascular or coronary artery disease;
- Undiagnosed abnormal genital bleeding;
- Known or suspected breast carcinoma, endometrial carcinoma, or estrogen-dependent neoplasia;
- History or presence of dermal hypersensitivity in response to topical applications (bandages, surgical tape, etc.) or known hypersensitivity to any components of this product;
- Use of an injectable hormonal contraceptive within the past 6 months prior to the screening visit;
- Used a contraceptive implant or hormone-medicated intrauterine device (IUD) within the 2 months prior to the screening visit;

- Other contraceptive methods such as sterilization, tubal ligation or IUD (must be removed prior to randomization);
- Status post-partum or post-abortion within a period of 42 days prior to the start of study medication;
- Chronic use of any medication that might interfere with the efficacy of hormone contraceptives (including barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's Wort, topiramate, and HIV protease inhibitors);
- Administration of any investigational drug and/or experimental device within 30 days prior to the screening visit, or current participation in any observational studies;
- A recent history (within prior 12 months) of drug or alcohol abuse;
- Deemed by the investigator to have questionable ability to comply with the protocol and provide accurate information;
- Positive for chlamydia and gonorrhea;
- Same sex relationship.

- Subject disposition, data sets analyzed and demographics

- Subject disposition and data sets analyzed

Disposition Status	Category	Total	OC	Total AG200-15	OC/AG200-15 Switchers
Screened (total)		2198	---	---	---
Randomized		1504	375	1378	249
Safety Population			344 (91.7%)	1273 (92.4%)	230 (92.4%)
Intent to Treat (ITT) 1 Population			330 (88.0%)	1226 (89.0%)	228 (91.6%)
ITT2 Population			312 (83.2%)	1158 (84.0%)	216 (86.7%)
PK Population			326 (86.9%)	1077 (78.2%)	144 (57.8%)
Completed Study			249 (66.4%)	635 (46.1%)	150 (60.2%)
Did not Complete Study			126 (33.6%)	743 (53.9%)	99 (39.8%)
Reason for Premature Discontinuation	Any Reason		126 (33.6%)	743 (53.9%)	99 (39.8%)
	Adverse Event(s)		15 (4.0%)	139 (10.1%)	16 (6.4%)
	Death		1 (0.3%)	0	0
	Non-Compliance		9 (2.4%)	48 (3.5%)	6 (2.4%)
	Lost to Follow-up		61 (16.3%)	266 (19.3%)	37 (14.9%)
	Subject's Decision		30 (8.0%)	211 (15.3%)	28 (11.2%)
	Pregnancy ^a		4 (1.1%)	42 (3.0%)	8 (3.2%)
	Protocol Violation		4 (1.1%)	11 (0.8%)	0
	Investigator's Decision		1 (0.3%)	15 (1.1%)	2 (0.8%)
	Sponsor's Decision		0	0	0
	Other		1 (0.3%)	11 (0.8%)	2 (0.8%)

- Safety population: all subjects who received the study drug
- PK population: all subjects with available PK data
- Intent to treat (ITT)1 population: all subjects in complete or incomplete on-therapy cycles
- ITT2 population: all subjects in complete or incomplete on-therapy cycles with intercourse and no other birth control methods were used. This was the pre-specified primary efficacy dataset.

It is notable that there are high discontinuation rates (53.9%: AG200-15 vs. 33.6%: OC) of this study.

- Demographics (Safety population)

Parameter	Category	Statistic	OC N=344	Total AG200-15 N=1273	OC/AG200-15 Switchers N=230
Age (years)		n	344	1273	230
		Mean	26.4	26.5	26.9
		Median	25.0	26.0	26.0
		SD, CV (%)	5.7, 21.8	5.7, 21.5	5.7, 21.4
		Min, Max	(17.0, 40.0)	(17.0, 40.0)	(17.0, 40.0)
Weight (kg)		n	344	1273	230
		Mean	73.7	73.9	72.8
		Median	68.4	69.0	67.6
		SD, CV (%)	19.6, 26.6	19.9, 26.9	18.6, 25.6
		Min, Max	(34.8, 149.7)	(41.1, 172.3)	(45.5, 147.2)
Height (cm)		n	344	1273	230
		Mean	163.5	163.8	163.2
		Median	163.2	163.5	163.2
		SD, CV (%)	7.2, 4.4	7.0, 4.3	7.2, 4.4
		Min, Max	(143.0, 185.4)	(134.6, 188.0)	(143.0, 185.4)
BMI (kg/m ²)		n	344	1273	230
		Mean	27.5	27.5	27.3
		Median	26.4	26.0	26.2
		SD, CV (%)	6.8, 24.6	7.1, 25.7	6.6, 24.2
		Min, Max	(15.6, 56.6)	(16.5, 59.8)	(17.6, 52.4)
Race/Ethnicity	White (Not Hispanic)	n (%)	191 (55.5%)	733 (57.6%)	140 (60.9%)
	Hispanic (White)	n (%)	61 (17.7%)	191 (15.0%)	37 (16.1%)
	Black	n (%)	71 (20.6%)	275 (21.6%)	36 (15.7%)
	Asian	n (%)	12 (3.5%)	44 (3.5%)	9 (3.9%)
	Other	n (%)	9 (2.6%)	30 (2.4%)	8 (3.5%)
Age Category (years)	≤ 35 years	n (%)	313 (91.0%)	1163 (91.4%)	208 (90.4%)
	> 35 years	n (%)	31 (9.0%)	110 (8.6%)	22 (9.6%)

Each treatment groups are comparable in terms of the demographic parameters.

- Results

The reviewer presents only PK results.

Table 44 Mean (SD) concentration of EE and LNG by treatment cycle (PK population); ATI-CL12

Analyte	Cycle	AG200-15 N=933	OC N=326
EE (pg/mL)	2	30.5 (23.3), n=921	35.4 (31.4), n=319
	6	36.7 (30.2), n=629	40.1 (51.7), n=222
	13	31.0 (27.4), n=462	N/A
LNG (pg/mL)	2	1202 (1003), n=921	2386 (1871), n=319
	6	1753 (1505), n=629	2611 (1933), n=221
	13	1590 (1502), n=462	N/A

Sponsor made a claim comparing the exposure of AG200-15 and OC based on the single blood draw in each cycle. The reviewer found that any meaningful comparison of exposure based on single measurement could not be made considering the different PK profiles of AG200-15 (relatively flat) and OC (rapid absorption and elimination).

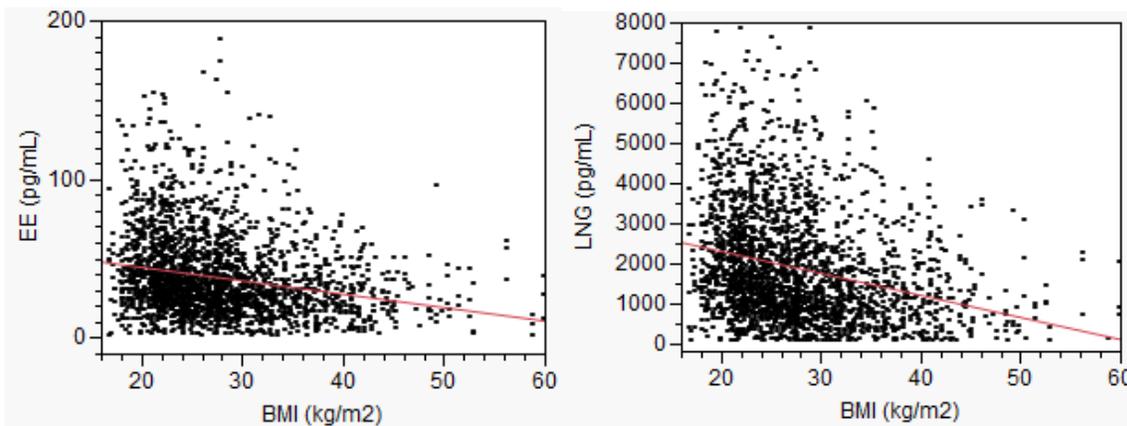


Figure 18 The concentrations of EE and LNG obtained before the 3rd application of the AG200-15 at the 2nd, 6th, and 13th cycles (PK population); ATI-CL12

Based on the both EE and LNG concentrations obtained before the 3rd application of AG200-14 at the 2nd, 6th, and 13th cycles, there has been statistically significant trend (P value <0.001 for both EE and LNG) of decreasing concentrations of both EE and LNG with increasing BMI (BMI at screening) ranging from 16 to 60.

Table 45 Comparison of EE, LNG, and BMI in subjects who became pregnant vs. not pregnant in AG200-15 group (PK population); ATI-CL12

	Pregnant, n=45	Not pregnant, n=1032
EE (pg/mL)	35.0 (27.1)	38.3 (25.9)
LNG (pg/mL)	1806 (1481)	1916 (1455)
BMI (kg/m ²)	27.9 (7.1)	27.7 (7.1)

In study ATI-CL12, there were 45 subjects who became pregnant during the study while on AG200-15. The differences in mean EE, LNG, BMI in subjects who became pregnant vs. not pregnant were smaller than 10% and within the error range (differences are less than SD).

Table 46 Distribution of patch application site

-----AG200-15 (N=1273)-----			
Cycle	Application Site	Number of Cycles	Number of Patches
Cycles 1-13 combined	Abdomen	4103/10180 (40.3%)	12597/32508 (38.8%)
	Buttock	4825/10180 (47.4%)	15503/32508 (47.7%)
	Upper Torso (Excluding Breasts)	1187/10180 (11.7%)	3842/32508 (11.8%)
	No data	65/10180 (0.6%)	566/32508 (1.7%)

The most common site of patch application for AG200-15 treatment group was the buttock (in 47.4% of the cycles in which 1 or more patches were applied), followed by the abdomen (40.3%) and the upper torso (11.7%).

- **Conclusions**

Due to the high variability (CV ranging 76 – 94%) and limited PK data available from the study, any meaningful comparison of EE and LNG exposures from AG200-15 with OC could not be made. However, there were trends of decreasing both EE and LNG concentration with increasing BMI within 200-15 group.

ATI-CL13

- **Title**

An open-label, randomized, phase 3 study of the contraceptive efficacy and safety of AG200-15 in comparison to an OC containing 0.03 mg EE and 0.15 mg LNG

- **Objectives**

To provide comparative evaluation of AG200-15 vs. OC with regard to safety, contraceptive efficacy (as evaluated by pregnancy rates), hormone related adverse events, lipid profile, cycle control (bleeding pattern), subject compliance and plasma concentrations of EE and LNG

- **Study design**

This was an open-label, randomized, comparative, parallel group, multi-center, contraceptive efficacy and safety study. The 400 sexually active women were enrolled in this study. The subjects were randomized in 1:1 ratio, with 201 subjects assigned to AG200-15 and 206 subjects assigned to an OC (Levora containing 0.03 mg EE and 0.15 mg LNG, ANDA 073592 approved in December 1993). The subjects were treated for 6 cycles. A treatment cycle was defined as a 28-day period: 21 days on treatment (consecutive administration of the three 7-day patches or 21 days of active pill-taking) followed by 7 days off treatment (i.e., no patch was applied or no active pills were taken).

The patch was applied to the abdomen, the buttock or the upper torso excluding the breasts. During the visits scheduled before application of the last patch at the third and sixth cycles, blood was drawn to evaluate plasma concentrations of LNG and EE.

- Inclusion criteria

- Sexually active women requesting contraception;
- 17 to 40 years old;
- Regular menses every 24 - 35 days; if current continuous use of hormonal birth control historical data will be used to determine qualification;
- In good general health, confirmed by medical history, physical (including gynecologic) examination and screening laboratory values;
- Willing to sign the informed consent form to participate in the study and refrain from using condoms on a regular basis and any other steroid hormonal therapy (other than topical corticosteroids) for the duration of the study.

- Exclusion criteria

- Known or suspected pregnancy;
- Lactating women;
- Breast-feeding within 42 days prior to the start of study medication;
- Women who smoked and were ≥ 35 years old or turned 35 anytime during the study;
- Uncontrolled hypertension (blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) in women with BMI <32 kg/m²;
- History or presence of hypertension (blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) in women with BMI ≥ 32 kg/m²;
- Valvular heart disease with complications;
- Diabetes Mellitus with vascular disease in women with BMI <32 kg/m²;
- Diabetes Mellitus type I and II in women with BMI ≥ 32 kg/m²;
- History of headaches with focal neurological symptoms;
- Uncontrolled thyroid disorder;
- Sickle cell anemia;
- Current or history of clinically significant depression in the last year;
- Known disturbance of lipid metabolism (triglycerides >300);
- Acute or chronic hepatocellular disease with abnormal liver function;
- Hepatic adenoma or carcinoma;
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use;
- Positive HIV and/or hepatitis at screening
- Plans for major surgery with anticipated prolonged immobilization;
- History of or existing thromboembolic disorder, vascular disease, cerebral vascular or coronary artery disease;
- Undiagnosed abnormal genital bleeding;
- Known or suspected breast carcinoma, endometrial carcinoma, or estrogen-dependent neoplasia;
- History or presence of dermal hypersensitivity in response to topical applications (bandages, surgical tape, etc.) or known hypersensitivity to any components of this product;
- Use of an injectable hormonal contraceptive within the past 6 months prior to the screening visit;
- Used a contraceptive implant or hormone-medicated intrauterine device (IUD) within the 2 months prior to the screening visit;
- Other contraceptive methods such as sterilization, tubal ligation or IUD (must be removed prior to randomization);
- Status post-partum or post-abortion within a period of 42 days prior to the start of study medication;

- Chronic use of any medication that might interfere with the efficacy of hormone contraceptives (including barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's Wort, topiramate, and HIV protease inhibitors);
- Administration of any investigational drug and/or experimental device within 30 days prior to the screening visit, or current participation in any observational studies;
- A recent history (within prior 12 months) of drug or alcohol abuse;
- Deemed by the investigator to have questionable ability to comply with the protocol and provide accurate information;
- Positive for chlamydia and gonorrhea;
- Same sex relationship.

- Subject disposition, data sets analyzed and demographics

- Subject disposition and data sets analyzed

Disposition Status	Category	Total	OC	AG200-15
Screened (total)		626	---	---
Randomized		407	206	201
Safety Population			188 (91.3%)	177 (88.1%)
Intention to Treat (ITT) 1 Population			186 (90.3%)	170 (84.6%)
ITT 2 Population			182 (88.3%)	158 (78.6%)
PK Population			147 (71.4%)	117 (58.2%)
Completed Study			145 (70.4%)	112 (55.7%)
Did not Complete Study			61 (29.6%)	89 (44.3%)
Reason for Premature Discontinuation	Any Reason		61 (29.6%)	89 (44.3%)
	Adverse Event(s)		4 (1.9%)	14 (17.0%)
	Death		0	0
	Non-Compliance		5 (2.4%)	2 (1.0%)
	Lost to Follow-up		32 (15.5%)	44 (21.9%)
	Subject's Decision		13 (6.3%)	21 (10.4%)
	Pregnancy ^a		1 (0.5%)	4 (2.0%)
	Protocol Violation		3 (1.5%)	2 (1.0%)
	Investigator's Decision		1 (0.5%)	1 (0.5%)
	Sponsor's Decision		0	0
	Other		2 (1.0%)	1 (0.5%)

- Safety population: all subjects who received the study drug
- PK population: all subjects with available PK data
- Intent to treat (ITT)1 population: all subjects in complete or incomplete on-therapy cycles
- ITT2 population: all subjects in complete or incomplete on-therapy cycles with intercourse and no other birth control methods were used. This was the pre-specified primary efficacy dataset.

It is notable that there are high discontinuation rates (44.3%: AG200-15 vs. 29.6%: OC) of this study.

- Demographics (safety population)

Parameter	Category	Statistic	OC N=188	AG200-15 N=177
Age (years)		n	188	177
		Mean	26.7	25.9
		Median	26.0	25.0
		SD	5.7	5.4
		CV (%)	21.5	21.0
		Min, Max	(18.0, 40.0)	(18.0, 40.0)
Weight (kg)		n	188	177
		Mean	66.2	65.9
		Median	65.0	65.9
		SD	10.9	11.1
		CV (%)	16.4	16.8
		Min, Max	(46.0, 99.0)	(43.2, 94.1)
Height (cm)		n	188	177
		Mean	163.0	163.7
		Median	162.6	163.8
		SD	6.2	6.8
		CV (%)	3.8	4.1
		Min, Max	(149.0, 180.3)	(147.3, 182.8)
BMI (kg/m ²)		n	188	177
		Mean	24.8	24.6
		Median	24.6	24.5
		SD	3.6	4.0
		CV (%)	14.4	16.1
		Min, Max	(17.0, 32.0)	(17.2, 31.9)
Race/Ethnicity	White (Not Hispanic)	n (%)	111 (59.0%)	106 (59.9%)
	Hispanic (White)	n (%)	37 (19.7%)	28 (15.8%)
	Black	n (%)	30 (16.0%)	34 (19.2%)
	Asian	n (%)	2 (1.1%)	6 (3.4%)
	Other	n (%)	8 (4.3%)	3 (1.7%)
Age Category (years)	≤ 35 years	n (%)	172 (91.5%)	164 (92.7%)
	> 35 years	n (%)	16 (8.5%)	13 (7.3%)
Previous Contraceptive Use Status	New User	n (%)	100 (53.2%)	107 (60.5%)
	Current User	n (%)	65 (34.6%)	44 (24.9%)
	Recent User	n (%)	23 (12.2%)	26 (14.7%)

Each treatment groups are comparable in terms of the demographic parameters.

- Results

Table 47 Mean (SD) concentration of EE and LNG by treatment cycle (PK population); ATI-CL12

Analyte	Cycle	AG200-15 N=933	OC N=326
EE (pg/mL)	3	44.5 (30.8), n=111	50.6 (45.9), n=140
	6	34.7 (23.0), n=96	54.7 (55.2), n=123
LNG (pg/mL)	3	2244 (1896), n=111	3474 (2572), n=140
	6	1743 (1299), n=95	3682 (3060), n= 123

Sponsor made a claim comparing the exposure of AG200-15 and OC based on the single blood draw in each cycle. The reviewer found that any meaningful comparison of exposure based on single measurement could not be made considering the different PK profiles of AG200-15 (relatively flat) and OC (rapid absorption and elimination).

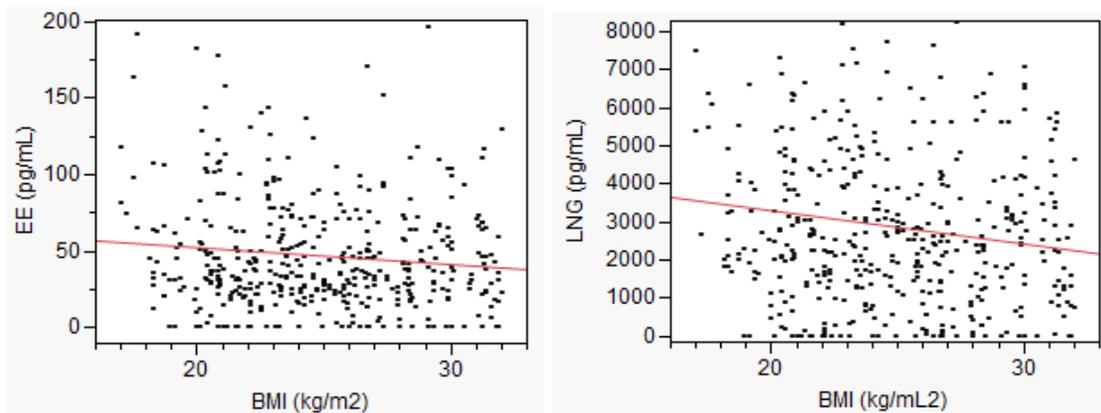


Figure 19 The concentrations of EE and LNG obtained before the 3rd application of the AG200-15 at the 3rd and 6th cycles (PK population); ATI-CL13

Based on the both EE and LNG concentrations obtained before the 3rd application of AG200-14 at the 3rd and 6th cycles, there has been statistically significant trend (P value = 0.034 (EE) and 0.004(LNG)) of decreasing concentrations of both EE and LNG with increasing BMI (BMI at screening) ranging from 17 to 32.

Table 48 Comparison of EE, LNG, and BMI in subjects who became pregnant vs. not pregnant (PK population); ATI-CL12

	Pregnant, n=3	Not pregnant, n=114
EE (pg/mL)	14.5 (16.2)	40.5 (27.8)
LNG (pg/mL)	1179 (1395)	2029 (1666)
BMI (kg/m ²)	28.0 (1.9)	24.7 (4.0)

In study ATI-CL13, there were only 3 subjects (out of who 117 PK population) who became pregnant during the study while on AG200-15. Therefore, any meaningful comparison of BMI, exposure of EE and LNG between pregnant subjects and non-pregnant subjects are not possible.

- **Conclusions**

Due to the high variability (CV ranging 66.1 – 101%) and limited PK data available from the study, any meaningful comparison of EE and LNG exposures with OC could not be made. However, there were trends of decreasing both EE and LNG concentration with increasing BMI within 200-15 group.

4.2 Cover Sheet and OCP Filing

APPEARS THIS WAY ON ORIGINAL



**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA/BLA or Supplement**

NDA Number: 204017

Applicant: Watson

Stamp Date: 4/12/2012

Drug Name: AG200-15

NDA Type: Original

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction (DDI) information?			X	Based on the literatures; There is no clinical DDI study conducted.
Criteria for Assessing Quality of an NDA					
Data					
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X			
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			X	
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Request for pediatric study
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA/BLA or Supplement**

13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
17	Was the translation from another language important or needed for publication?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

- **Drug Product:** AG200-15, a 15 cm² Transdermal Contraceptive Delivery System (TCDS), containing 2.6 mg levonorgestrel (LNG) and 2.3 mg ethinyl estradiol (EE)
- **Dosage and Administration:** Once every 7 days for 3 weeks to buttock, abdomen, or upper torso followed by a 1-week “patch-free” period
- **Indication:** Prevention of pregnancy

Background

AG200-15 is a thin transdermal system containing LNG and EE to prevent the pregnancy. The application contains 19 clinical studies (13 studies with earlier formulations evaluating safety and/or PK AND 6 studies with to-be-marketed formulataion). Of these, 6 studies were performed with the final formulation, AG200-15, and include 4 pharmacokinetic (PK) studies and 2 phase 3 safety and efficacy studies. The following table summarizes the 6 studies:

Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Duration of Treatment
PK/PD ATI-CL11	Evaluation of ovulation suppression, cycle control, PK profile and safety of TCDSs containing 2 different doses of LNG and 3 different doses of EE	Multicenter, open-label, randomized, parallel group study followed by multicenter, open-label, single-arm extension	<u>AG200</u> : 2.17 mg LNG/ 1.92 mg EE / 12.5 cm ² <u>AG200LE</u> : 2.17 mg LNG/ 1.28 mg EE / 12.5 cm ² <u>AG200-15</u> : 2.60 mg LNG/ 2.30 mg EE / 15 cm ² 1 patch/7 day period; Transdermal	<u>AG200</u> : Enrolled: 45 Completed: 41 <u>AG200-LE</u> : Enrolled: 45 Completed: 41 <u>AG200-15</u> : Enrolled: 33 Completed: 25	3 cycles of 28-days (21 days on treatment, 7 days off treatment)
PK ATI-CL14	Evaluation of the EE PK profile of AG200-15 compared to a marketed oral contraceptive tablet, PK and safety of AG200-15	Single-center, open-label, randomized, crossover, 2 part	<u>AG200-15</u> : 2.60 mg LNG/ 2.30 mg EE / 15 cm ² ; 1 patch/7 day period; Transdermal <u>Ortho-Cyclen® (OC)</u> : 250 µg NGM/ 35 µg EE; Once daily; Oral	<u>Enrolled/ completed</u> : Part I: 36/36 Part II: AG200-15/ Ortho-Cyclen®: 18/18 Ortho-Cyclen®/ AG200-15: 16/16	84 days (2 cycles with patch followed by 1 cycle with OC, each cycle = 3 weeks treatment and 1 week no treatment)
PK ATI-CL15	Evaluation of EE/LNG PK profile and safety of AG200-15 application to three different anatomical sites (lower abdomen, upper torso, buttock)	Open-label, randomized, 3-period crossover	<u>AG200-15</u> : 2.60 mg LNG/ 2.30 mg EE / 15 cm ² ; 1 patch/7 day period; Transdermal	Enrolled: 24 Completed: 22	3 periods of at least 7 days each; Treatment periods separated by 1 week washout periods

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA/BLA or Supplement**

PK ATI-CL16	Evaluation of EE/LNG PK profile, wearability and safety of AG200-15 following application under normal use conditions and under various extreme external conditions specified (dry sauna, whirlpool, treadmill exercise, and cold water immersion)	Open-label, randomized, 3-period, 5-treatment, incomplete block, crossover	<u>AG200-15:</u> 2.60 mg LNG/ 2.30 mg EE / 15 cm ² ; 1 patch/7 day period; Transdermal	Enrolled: 24 Completed: 24	Three 7-day treatment periods with 7-day washout periods in between treatment periods
Efficacy, Safety ATI-CL12	Comparative evaluation of contraceptive efficacy, safety, cycle control; subject compliance and PK of EE/LNG of AG200-15 compared to a low dose OC; patch wearability	Multicenter, open-label, randomized, comparative, parallel group	<u>AG200-15:</u> 2.60 mg LNG/ 2.30 mg EE / 15 cm ² ; 1 patch/7 day period; Transdermal <u>Lessina® (OC):</u> 0.100 mg LNG/ 0.020 mg EE Once daily; Oral	<u>AG200-15:</u> 1378 enrolled (includes 249 who switched to patch from OC at Cycle 7)/ 635 completed <u>Lessina® (OC):</u> Enrolled: 375 Completed: 249	<u>AG200-15:</u> Thirteen 28-day cycles (cycle=3 weekly patches, 7 days patch-free) <u>OC:</u> Lessina® once daily for 6 cycles (28 days) and then switched to AG200-15 for seven 28-day cycles
Safety, Efficacy ATI-CL13	Comparative evaluation of safety, contraceptive efficacy, lipid profile, cycle control, subject compliance and PK of EE/LNG of AG200-15 compared to a low-dose OC; patch wearability	Multicenter, open-label, randomized, comparative, parallel group	<u>AG200-15:</u> 2.60 mg LNG/ 2.30 mg EE Patch area: 15 cm ² ; 1 patch/7 day period; Transdermal <u>Levora® (OC):</u> 0.150 mg LNG/ 0.030 mg EE; Once daily; Oral	<u>AG200-15:</u> Enrolled: 201 Completed: 112 <u>Levora® (OC):</u> Enrolled: 206 Completed: 145	AG200-15 for six 28-day cycles (cycle=3 weekly patches, 7 days patch free) or Levora® daily for six 28-day cycles

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

Formulation

Sponsor originally developed several formulations of TCDS containing different amounts of LNG and EE. The final drug formulation of AG200-15 contains 2.60 mg of LNG and 2.30 mg of EE. The active matrix core is 15 cm² surrounded by the perimeter adhesive. The to-be-marketed formulation of AG200-15 was used in the phase 3 studies and the phase 1 PK and PK/PD studies listed in the table above.

Communication with the Division in regards to the clinical pharmacology prior to the NDA submission:

September 22, 2008

The Division recommends that the Sponsor conduct the following studies prior to initiation of the phase 3 studies:

- 1) A relative bioavailability (BA) study comparing the to-be-marketed formulation of the transdermal contraceptive delivery system (TCDS; i.e., AG200-15) and an oral contraceptive (OC) product
Phase 3 studies, ATI-CL12 and ATI-CL13, may not yield meaningful PK comparison data between AG200-15 and OC products because there was single PK sampling within one cycle. However, ATI-CL14 contains intensive (up to 168 hours for AG200-15 AND up to 72 hours for OC product, ortho cyclen) PK samplings for both AG200-15 and OC product, which can yield meaningful PK comparison data.
- 2) A study to assess the effect of different application sites on the pharmacokinetics (PK) of AG200-15, if phase 3 studies will allow application of AG200-15 to more than one body site (e.g., abdomen, buttock, upper arm)
In the study, ATI-CL15, EE/LNG PK profile was evaluated when AG200-15 was applied to the different application sites (lower abdomen, upper torso, and buttock).

In addition, the Division recommends modifying the proposed PK study for the TCDS to add additional seven-day intensive PK measurements following the fourth and sixth applications (i.e., the first and third applications during the second cycle) of the TCDS, in addition to the proposed intensive PK measurement following the first patch application. This would help to assess the carryover effect between cycles and the accumulation within each cycle.

The 7-day (hour 0 – 168) PK samples were collected on cycle 1, 3, 4, 6 in the study ATI-CL14 as the Division recommended.

Finally, the NDA should include one or more PK study(ies) assessing the PK profiles of the to-be-marketed formulation of the TCDS under different external conditions (e.g., sauna, exercise, cold water).

In the study, ATI-CL16, EE/LNG PK profile was evaluated under daily exposure to different external conditions.

- *Dry Sauna Period- The subject was exposed to dry sauna conditions for a period of 10 minutes (temperature between 76°C and 82°C [168.8°F – 179.6°F]).*
- *Whirlpool period- The subject sat in the whirlpool for a period of 10 minutes (temperature between 39°C and 41°C [102.2°F – 105.8°F]).*

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA/BLA or Supplement**

- *Treadmill Period*-The subject walked on the treadmill for 20-30 minutes at 60%-80% maximum heart rate (HRmax), calculated as 220 minus the age of the subject.
- *Cold Water Immersion Period*- The subject sat in a cold water bath for 5 to 15 minutes (temperature maximum of 22°C [71.6 °F]).

-March 9, 2010

- It is recommended to use a standardized adhesion scale to address patch wearability in the proposed phase 3 study (ATI-CL12).
The patch wearability was assessed in the two phase 3 studies (ATI-CL12 and ATI-CL13).

Request for waiver of pediatric studies

The sponsor has requested a waiver for the requirement of pediatric studies to be conducted in females < 17 years.

-Sponsor's justification: The studies in pediatric females for the indication of prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception is not applicable to premenarcheal subjects and not required in postmenarcheal subjects because safety and efficacy data for this subpopulation can be extrapolated from adult studies.

Reviewer's comments

The sponsor is claiming similar safety and efficacy in women with a body mass index of (b) (6). The relationship between the safety/efficacy and the drug exposure will be reviewed.

Comments to be conveyed to the sponsor in a 74-day letter:

Any comparative claims including oral equivalent dose and systemic exposure comparison of levonorgestrel and estradiol will be a review issue.

Hyunjin Kim

Reviewing Pharmacologist

Date

Myong-Jin Kim

Team Leader/Supervisor

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HYUNJIN KIM
01/10/2013

MYONG JIN KIM
01/10/2013

HAE YOUNG AHN
01/11/2013