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The PK/PD Relationship of Ethinyl Estradiol and Unscheduled Bleeding or Spotting for an Ascending-dose, Estrogen/Progestin Combination Oral Contraceptive (OC)

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ABSTRACT

Introduction: The estrogen component of OCs provides stability to the endometrium so that irregular shedding and unwanted breakthrough bleeding are minimized. An ascending-dose, extended-regimen ethinyl estradiol/ levonorgestrel (EE/LNG) combination OC (ADER) has been developed to provide better protection against unscheduled bleeding (UB) or spotting (US). It is hypothesized that gradual increases in EE may be more effective in preventing UB/US than sustained low levels of estrogen. This analysis characterizes the profile of US/UB with ADER.

Methods: Data were combined from several clinical studies in which ADER (LNG, 150 mcg for 84 days with EE 20 mcg Days 1-42, 25 mcg Days 43-63, 30 mcg Days 64-84; 10 mcg EE Days 85-91), constant-dose EE/LNG-OC (CDS; LNG 150 mcg/EE 30 mcg Days 1-84; 10 mcg EE Days 85-91), or low-constant-dose EE/LNG-OC (CDloS; LNG 100 mcg/EE 20 mcg Days 1-84; 10 mcg EE alone Days 85-91) were administered to non-pregnant women of childbearing age.

Results: The % of subjects on ADER experiencing UB/US increased over the initial 42 days and then stabilized for the remainder of the cycle (Days 43-84). Analysis of the % of patients experiencing UB/US over time consistently shows less UB/US during the second half of each cycle (Days 43-84) with ADER vs CDS and CDloS (observed in each extended cycle studied up to 4). During the initial 42-day period, the PK model predicted a steady-state trough EE plasma concentration of 9.67 pg/mL during dosing with EE 20 mcg. Days 43-63, 25 mcg EE begins the UB stabilization period, which coincides with a predicted increase in trough EE plasma concentration to 12.08 pg/mL. A second EE dose increase to 30 mcg, Days 64-84, is predicted to result in a trough EE plasma concentration of 14.50 pg/mL. Conversely, the predicted EE trough concentrations with CDS and CDloS remained constant at 16.97 and 9.67 pg/mL through Day 84.

Conclusions: The gradual increase in dose of EE in ADER during Days 43-84 of the 91-day treatment cycle resulted in increasing steady-state EE plasma concentrations that correlated with a lower percentage of subjects experiencing UB/US compared to the sustained constant plasma levels of EE in CDS or CDloS.

INTRODUCTION

- While extended oral contraceptive (OC) regimens reduce the frequency of scheduled monthly bleeding episodes,[1] unscheduled breakthrough bleeding and spotting is a common side effect of these regimens, particularly during the early cycles of therapy.[2-4]
- Because unscheduled bleeding and spotting can lead to poor adherence and early OC discontinuation,[1] different strategies have been proposed to reduce their incidence.
  - Using low-dose estrogen instead of placebo during the last 7 days of the cycle has been associated with greater ovarian suppression, a reduced incidence of unscheduled bleeding, and a more rapid decrease in the occurrence of unscheduled bleeding compared to OCs with a traditional pill-free interval.[1,5,6]
  - A second strategy is to increase the estrogen dose immediately prior to the period in which unscheduled bleeding typically occurs. Multiple studies have demonstrated that unscheduled bleeding with extended regimens tends to occur between days 43 and 56 in the cycle, usually at approximately Day 49.[2,7] Increasing the estrogen dose at this time may stabilize the endometrium and reduce breakthrough bleeding.
- A novel ascending-dose, extended-regimen (ADER) ethinyl estradiol (EE)/ levonorgestrel (LNG) OC provides the convenience of fewer scheduled withdrawal periods per year, yet contains a lower total hormonal content relative to some currently approved extended-regimen OCs.
  - The 91-day ADER consists of a gradually increasing estrogen dose (20 mcg from days 1 through 42; 25 mcg from days 43 through 63; 30 mcg from days 64 through 84) combined with a continuous low progestin (LNG) dose (150 mcg) for 84 days followed by a low dose of EE for 7 days.
  - This design provides a ratio of estrogen to progestin that becomes relatively more estrogenic across the extended regimen, with the estrogen increasing at specific times in the cycle prior to the time when breakthrough bleeding tends to be experienced by the greatest proportion of women using extended-regimen OCs.
- Gradual increases in EE may be more effective in preventing unscheduled bleeding and spotting than sustained low levels of estrogen.
- It is hypothesized that the stepwise increase may also be better suited to preventing unscheduled bleeding compared to the persistent higher levels of EE in extended OC regimens with consistent EE dosing because higher estrogen levels have been proposed to desensitize or downregulate endometrial estrogen receptors.[8,9] Moreover, using ascending EE doses reduces total EE exposure compared to using sustained higher doses, and using the lowest effective dose to achieve the desired effect is a guiding principle of any therapy.
- The objectives of this report are to characterize the PK/PD profile of the ADER and compare it to other marketed extended-regimen branded OCs using data collected during its clinical development program and similar data from other marketed extended-regimen brands of OCs.
- Because the PK of and systemic exposure to LNG 150 mcg following single doses of 150 mcg within extended-dose regimens was comparable, this analysis focuses on the PK/PD of EE within the included regimens.

METHODS

- A population PK model was developed using pooled data obtained following administration of ADER EE/LNG as well as three marketed extended-regimen OCs containing EE and LNG in several studies described in **Table 1**.

Table 1. Studies included in the PK model

Product	Dosing regimen	Subjects*	Patients
ADER	Days 1-42: EE 20 mcg/LNG 150 mcg Days 43-63: EE 25 mcg/LNG 150 mcg Days 64-84: EE 30 mcg/LNG 150 mcg Days 85-91: EE 10 mcg	n=18	• Healthy, non-tobacco using adult female patients with normal menstrual cycle • 18-45 years old • BMI 18-30 kg/m^2
Seasonale	Days 1-84: EE 30 mcg/LNG 150 mcg Days 85-91: placebo	n=29	• Healthy female adult patients • 18-35 years old • Within 15% of their ideal body weight
Seasonique	Days 1-84: EE 30 mcg/LNG 150 mcg Days 85-91: EE 10 mcg	n=30†	• Healthy female adult patients with normal menstrual cycle • 19-51 years old • 119-191 lb
Seasonique	Days 1-84: EE 30 mcg/LNG 150 mcg Days 85-91: EE 10 mcg	n=29	• Healthy, non-tobacco using, female adult patients with normal menstrual cycle • 19-51 years old • BMI 18-30 kg/m^2
Seasonique	Days 1-84: EE 30 mcg/LNG 150 mcg Days 85-91: EE 10 mcg	n=17	• Healthy female patients • 18-47 years old • 53-87 kg
LoSeasonique	Days 1-84: EE 20 mcg/LNG 100 mcg Days 85-91: EE 10 mcg	n=30	• Healthy, adult female patients with regular menstrual cycle • 18-35 years old • 48-75 kg

*All studies assessed single-dose pharmacokinetics with the exception of 1 Seasonique study†, which included both multidose and single-dose assessments.

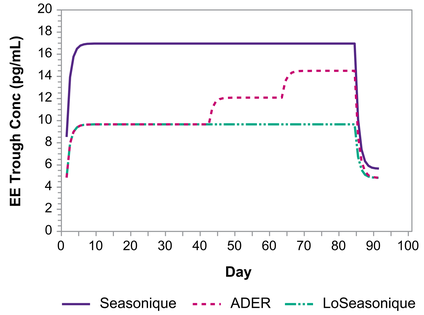
- This PK model was used to predict plasma EE exposure over time for the entire 91-day period of the extended-regimens. The predicted trough concentrations were then used for graphical displays of EE exposure.
- The pharmacodynamic (PD) analysis evaluated the timing and frequency of episodes of unscheduled bleeding or spotting that were recorded by study subjects in a daily diary over 4 cycles of 91 days in the Phase 3 studies for each product, all of which were similarly designed.
- Finally, the PK/PD analysis compared the predicted plasma EE concentration by time profile over the 91-day extended cycle for each treatment to the unscheduled bleeding and spotting profile for that treatment.

RESULTS

PK Profile

- Results of the PK model for ADER demonstrated stepwise increases in systemic exposure to EE with each increase in dose over the first 84 days of the cycle as assessed by steady-state C_{max}, C_{min}, and AUC prior to each EE dose change (**Figure 1**).
- These increases are followed by lower concentrations of EE during the 7-day period of low-dose estrogen (10 mcg) that replaces the typical hormone-free interval at the end of the cycle.

Figure 1. Model-predicted trough concentrations of EE following administration of extended regimens of ascending dose EE/LNG, EE 30 mcg/LNG 150 mcg, and EE 20 mcg/LNG 100 mcg

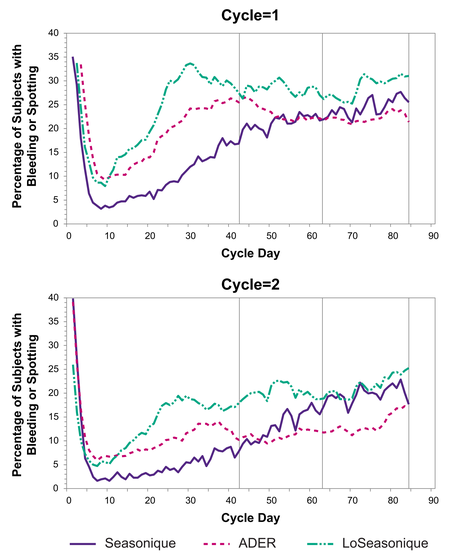


- In contrast, predicted EE trough concentrations with Seasonique and LoSeasonique were constant during the first 84 days of the cycle. Predicted EE trough concentrations during the last 7 days of the cycle were consistent among all products.

PD Profile

- Plots of unscheduled bleeding and spotting data indicate that, in early cycles, the percentage of subjects experiencing bleeding or spotting while taking ADER EE/LNG tends to increase over the initial 42 days then stabilize for the remainder of the cycle.

Figure 2a and b. Incidence of unscheduled bleeding or spotting during the first 2 extended cycles of ascending dose EE/LNG, EE 30 mcg/LNG 150 mcg, and EE 20 mcg/LNG 100 mcg



- In contrast, the percentage of subjects experiencing unscheduled bleeding or spotting following administration of EE 30 mcg/LNG or EE 20 mcg/LNG for 84 days plus EE 10 mcg for 7 days (Seasonique or LoSeasonique) continues to climb throughout the entire extended cycle.
- As a result of these conflicting trends, the percent of subjects experiencing either bleeding or spotting is lower with ADER EE/LNG during the second half of the cycle than it is with either EE 30 mcg/LNG or EE 20 mcg/LNG for 84 days plus EE 10 mcg for 7 days (Seasonique or LoSeasonique).
- In subsequent cycles (cycles 3 and 4), the percentage of subjects experiencing unscheduled bleeding or spotting is relatively constant over the full extended cycle. The trends relative to EE 30 mcg/LNG or EE 20 mcg/LNG for 84 days plus EE 10 mcg for 7 days (Seasonique or LoSeasonique) in cycles 3 and 4 are comparable to those previously noted.

PK/PD Profile

- The observed bleeding/spotting trends (**Figures 2a** and **2b**) are partially explained by the differences in exposure to EE and the EE trough concentrations over the course of the extended cycle following administration of the 3 products (**Figure 1**).

CONCLUSIONS

- Systemic exposure to EE increases in a step-wise fashion with increasing EE doses following the administration of the ADER OC and then decreases when the low EE dose is administered at the end of the cycle.
- This pooled analysis of similarly designed trials suggest that unscheduled bleeding with ADER EE/LNG is comparable to that seen with extended regimen EE 30 mcg/LNG 150 mcg, despite a 20% lower dose, and less than extended regimen EE 20 mcg/LNG 100 mcg in Cycle 1, and less than both regimens by the end of Cycle 2.
- The gradually increasing dose of EE within the ADER EE/LNG may provide better protection against breakthrough bleeding or spotting than the sustained low levels of EE in the low-dose EE 20 mcg/LNG extended regimen.
- Additional studies are needed to confirm the association between the pharmacokinetics of ascending dose and monophasic extended OC regimens and the incidence of unscheduled bleeding.

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