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Efficacy and safety of an ascending-dose, extended-regimen levonorgestrel/ethinyl estradiol combined oral contraceptive☆,☆☆,☆☆☆,☆☆☆☆,★,★★,★★★

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Abstract

Objective: To evaluate the efficacy and safety of an ascending-dose, extended-regimen (ADER) combined oral contraceptive consisting of levonorgestrel (LNG) 150 mcg/ethinyl estradiol (EE) 20 mcg for 42 days, LNG 150 mcg/EE 25 mcg for 21 days, LNG 150 mcg/EE 30 mcg for 21 days and EE 10 mcg for 7 days.

Study Design: This was a multicenter, open-label, phase 3, single-arm study. Sexually active women aged 18–40 years were enrolled and received ADER for up to 1 year (4 consecutive 91-day cycles). Participants kept diaries to record adherence, bleeding/spotting and other contraceptive use. Efficacy was measured using the Pearl Index and the life-table method; safety and tolerability were assessed through reported adverse events (AEs).

Results: A total of 3701 women were enrolled and 2144 completed the study. The Pearl Index was 3.19 [95% confidence interval (CI), 2.49–4.03], based on 70 pregnancies that occurred after ADER initiation and ≤7 days after the last LNG/EE or EE-only pill in women aged 18–35

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★★★ Implications statement: An extended-regimen oral contraceptive consisting of levonorgestrel 150 mcg combined with an ascending dose of ethinyl estradiol (20 mcg for 42 days, 25 mcg for 21 days, 30 mcg for 21 days) followed by ethinyl estradiol 10 mcg alone for 7 days provided safe and effective prevention of pregnancy with a favorable bleeding profile.

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years, excluding cycles in which another contraceptive method was used. Life-table pregnancy rate was 2.82% (95% CI, 2.23%–3.57%) for all users aged 18–35 years. Unscheduled bleeding/spotting decreased with increasing EE doses within each cycle and decreased after cycle 1. No unexpected AEs or changes in laboratory parameters were reported.

Conclusion: This study demonstrated that ADER effectively prevented pregnancy with a favorable safety and tolerability profile.

Keywords: Contraception; Low dose; Bleeding; Spotting

1. Introduction

Extended-regimen (ER) combined oral contraceptives (COCs) have increased in popularity among many women due to their desire to avoid monthly bleeding [1]. For some women, bleeding is an inconvenience that interferes with quality of life and productivity. In others, bleeding is associated with adverse health effects, such as premenstrual syndrome, endometriosis and anemia [2].

Numerous studies in various populations have indicated that many women are willing to consider menstrual suppression with ER COCs, citing a preference for 4 scheduled bleeding episodes per year or complete elimination of scheduled bleeding [1,3–6]. Many women's health care providers also agree: a survey of 301 female OB/GYN fellows reported that more than half of respondents had personally suppressed their menstruation with COCs [7].

ER COCs include 84 days of therapy with combined estrogen and progestin and 7 days of therapy with placebo or low-dose ethinyl estradiol (EE) [8–10]. Compared with traditional 28-day COCs, ER COCs reduce the incidence of menstrual-related symptoms, offer comparable efficacy and provide improved convenience for women who wish to avoid scheduled monthly bleeding [8,11]. However, unscheduled bleeding with ER COCs can occur during early COC cycles and may result in discontinuation [8,10,12,13]. In one study of a 20-mcg EE ER COC, 40% of patients experienced unscheduled bleeding for 7 days or more in cycle 1 and 9.6% discontinued due to bleeding and/or spotting [10]. These data suggest that ER COCs causing less unscheduled bleeding would be clinically useful.

Findings from multiple studies have demonstrated that unscheduled bleeding with ER COCs that include 20- or 30-mcg EE tends to occur between days 43 and 58, usually around day 49, independent of the type of progestin and estrogen used in the regimen [8,14,15]. One theoretical strategy for reducing the incidence of unscheduled bleeding with ER COCs is to increase the dose of estrogen before the time in the cycle in which unscheduled bleeding is most likely to occur. Another proposed strategy is to use a low-dose estrogen instead of placebo during the usual hormone-free interval (HFI) to suppress follicular development [10,16–18]. An ER COC incorporating both strategies may provide effective prevention of pregnancy with greater ovarian, hormonal and endometrial suppression and endometrial stabilization than traditional regimens [9,10,19,20].

A new 91-day ascending-dose, ER (ADER) COC combines levonorgestrel (LNG) and EE and was designed to reduce unscheduled bleeding while minimizing total estrogen exposure [21]. This regimen was approved by the United States (US) Food and Drug Administration in March 2013 as Quartette™. In this regimen, EE doses increase when unscheduled bleeding has been most frequently reported [8,12,21].

The primary objective of this phase 3, open-label clinical trial was to evaluate efficacy and safety of ADER taken for 1 year by healthy women seeking contraception.

2. Methods

2.1. Study design and population

This was a multicenter, open-label, phase 3, single-arm trial of ADER administered for up to 1 year (4 consecutive 91-day cycles). Each 91-day cycle included LNG 150 mcg for 84 days combined with EE 20 mcg for 42 days, EE 25 mcg for 21 days, and EE 30 mcg for 21 days, followed by EE 10 mcg for 7 days [22], a dosing schedule identified in an earlier clinical study that evaluated bleeding patterns with three different ascending EE dose ERs [21].

The study was conducted at 98 clinical sites in the US between October 8, 2009, and September 9, 2011 (ClinicalTrials.gov identifier: NCT00996580). It was designed and conducted according to the laws, regulations and administrative provisions relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medical products for human use, as applicable by national and European legislation and as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki and its updates. Institutional review board approval was obtained by all study sites. Participants gave written informed consent before entering the study.

Sexually active adult women aged 18 to 40 years who were at risk for pregnancy and agreed to routinely use the study COC as the only birth control method were enrolled. Women were excluded if they had a history or current evidence of any condition that contraindicated COC use, such as current smoking in women aged ≥ 35 years, and current or recent chronic use of medications that could affect COC efficacy, or use of drugs that required simultaneous use of contraceptives. There were no weight or body mass index (BMI) restrictions.

2.2. Study procedures

The current trial consisted of a 4-week screening period, a 1-year treatment period and a posttreatment period of approximately 3 weeks (Fig. 1).

After the screening visit, eligible women were enrolled into the study and instructed to take 1 pill daily at approximately the same time each day, with no interval between packs, for a total of 4 consecutive 91-day cycles. All participants were "Sunday starters" and remained Sunday starters throughout the duration of the trial.

After initiation of ADER, participants were monitored during multiple follow-up clinic visits (Fig. 1). Urine pregnancy tests, assessment of vital signs, review of concomitant medications and recording of adverse events (AEs) were performed at all visits. Participants also were contacted and monitored by telephone at selected time points.

During the trial, all women completed a paper diary to record their adherence with ADER, bleeding/spotting and weekly use of other contraceptives. Adherence was also assessed by pill counts at scheduled study visits and early termination visits. Women prematurely discontinuing from the trial were provided with an alternative contraceptive, if desired.

2.3. Efficacy assessment

Efficacy was evaluated using Pearl Index (PI) and life-table analyses based on pregnancies classified as having occurred while "on drug," defined as a date of conception after the initiation of ADER and up to and including 7 days after the last LNG/EE or EE-only pill. Pregnancy was determined by a urine and/or serum pregnancy test. Estimated date of conception and gestational age were determined by transvaginal or abdominal ultrasound.

2.4. Safety assessment

All women who received at least one dose of study medication were included in the safety analysis. Safety and tolerability were primarily assessed through AE reports and changes in vital signs and laboratory data.

2.5. Cycle control assessment

Participants recorded the incidence of vaginal bleeding or spotting in their daily diaries. Bleeding was defined as vaginal blood loss that required the use of sanitary protection; spotting did not require any form of sanitary protection [23]. Bleeding or spotting that occurred during days 85 through 91 was considered scheduled; bleeding or spotting during days 1 through 84 was considered unscheduled. Bleeding patterns were analyzed in women with at least 28 days of ADER exposure per cycle.

2.6. Statistical methods

Sample size determination was based on attaining a certain level of exposure to the investigational product rather than power considerations. Determination of efficacy was based on a minimum exposure of the equivalent of 20,000 28-day cycle equivalents, with a minimum of 1670 women completing the four 91-day cycles of ADER for the evaluation of safety. Data were pooled across centers.

Two populations were defined for the analyses of safety and efficacy data: the safety population, which included all women who received 1 or more doses of ADER, and the pregnancy intent-to-treat (PITT) population, which included all enrolled women aged 18–35 years at screening who completed $\geq$28 days of treatment (a complete cycle equivalent).

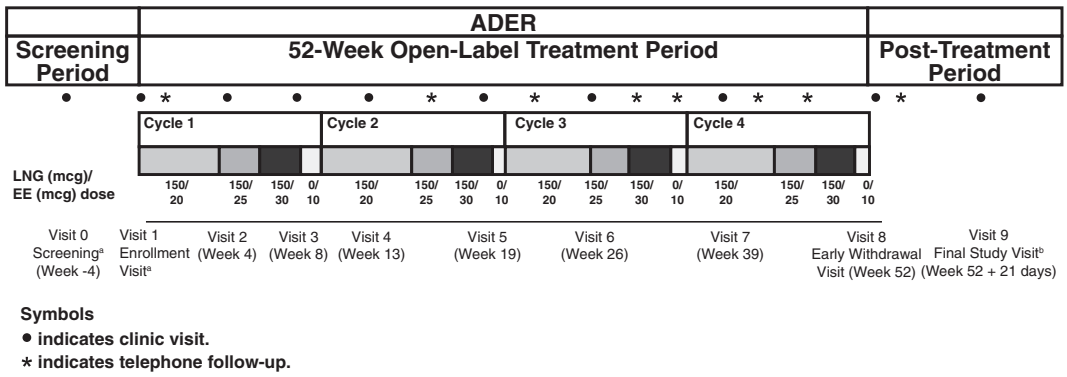

Fig. 1. Study design. [a]Results from tests done at the screening visit had to be reviewed by the investigator and be consistent with the inclusion and exclusion criteria. Eligible women were dispensed ADER at the enrollment visit. Women who were new starts or prior users had to have a spontaneous menses prior to initiating ADER. Women who were continuous users initiated ADER on the first Sunday following last day of active hormonal administration and the start of their withdrawal bleed, if applicable. Continuous users on an extended cycle COC did not have to complete an entire 91-day cycle. Women could not stop in the middle of any 28- or 35-day period of the extended cycle but could, for example, stop at the end of card 1 (28 days) or card 2 (56 days) and then start ADER. Week 1/Day 1 began on the day that the first dose of ADER was taken. [b]The final study visit occurred approximately 21 days (acceptable window was 21–28 days) following the last dose of ADER for all women, including those who completed the study and those who were withdrawn or discontinued the study early for any reason. Visit 9 had to be completed by all women who took ADER.

The primary efficacy end point was the pregnancy rate, reported as the PI. The PI was defined as the number of contraceptive failures per 100 woman-years of exposure. The formula was as follows: (100)×(total number of pregnancies)×(13)/(total number of 28-day cycles). PIs in the PITT population were calculated for all users, typical users and compliant users. The typical-user analysis included all complete 28-day cycles in which no other contraception was used. Women included in the compliant-user analysis had an overall adherence of ≥80%. All complete 28-day cycles in compliant users in which no other contraception was used, ≥2 consecutive pills were not skipped, and prohibited medication was not used were considered compliant-use cycles.

Cumulative pregnancy rates at 52 weeks in all users and in compliant users were also estimated using the life-table method. Two-sided 95% confidence intervals (CIs) were calculated for each PI and cumulative pregnancy estimate. Bleeding patterns, changes in vital signs and changes in laboratory values were summarized using descriptive statistics (mean, median, standard deviation, minimum and maximum values).

3. Results

Of the 4962 women screened, 3701 met the inclusion criteria and were enrolled (Fig. 2), 3597 were included in the safety population and 2144 women completed the study. The most common reasons for discontinuation in the safety population were lost to follow-up (13.3%) and AEs (13.0%).

Overall, the demographic characteristics of the analysis populations were comparable (Table 1). In the safety population, approximately 65% of all treated women were white, 19% were African American, and 11% were Hispanic. Mean age was 27.1 years; mean BMI was 27.4 kg/m^2. BMI was ≥30 kg/m^2 in 29% (1027/3597).

3.1. Efficacy

Seventy of the 2992 women in the PITT population were determined pregnant on drug (Table 2). The PI for all users, including all complete 28-day cycle equivalents in which women took drug, was 3.00 (95% CI, 2.34–3.79). The typical-use PI was 3.19 (95% CI, 2.49–4.03), and the compliant-use PI was 2.59 (95% CI, 1.94–3.37). Both the

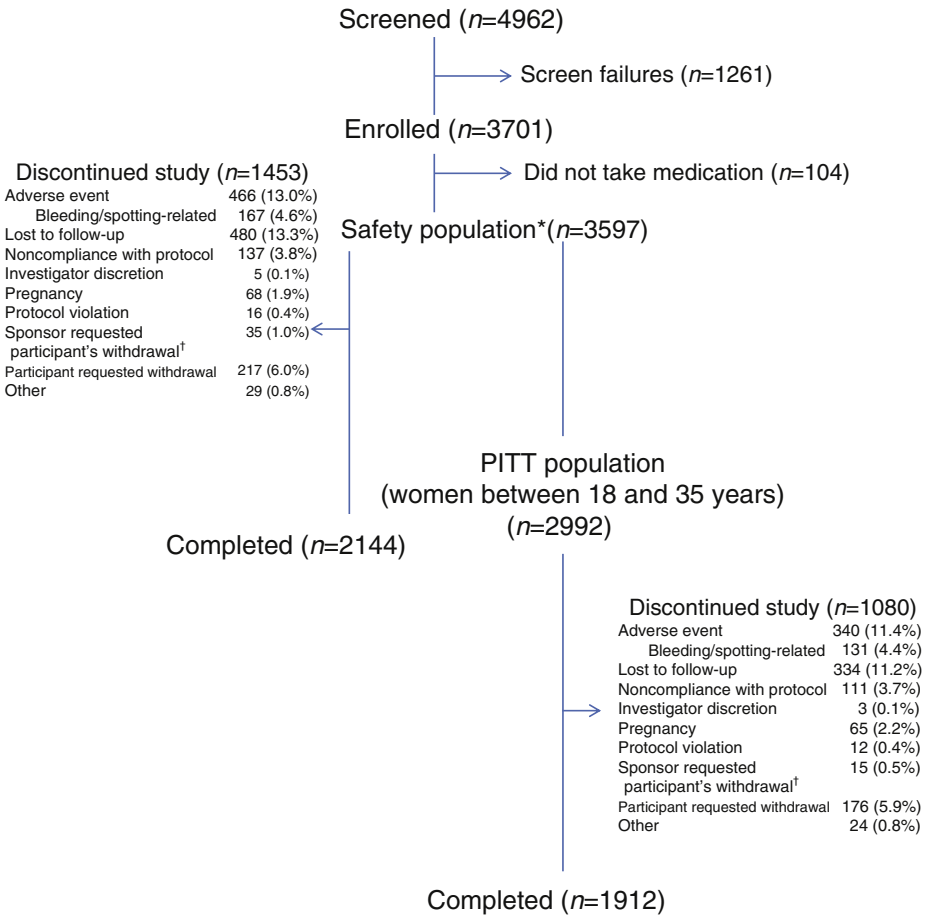

Fig. 2. Participant disposition. *Safety population includes women who took at least one dose of ADER. †Reasons for sponsor-requested withdrawal: need for chronic treatment with a medication prohibited by the protocol, consistent nonadherence with IP or diary completion, abnormal physical finding that required an intervention that would have confounded bleeding/spotting data or that made it unwise to continue hormonal contraception.

Table 1
Demographics and baseline characteristics in the safety and PITT analysis populations

Variable	Safety population (*N*=3597)	PITT population (*N*=2992)
Race/ethnicity, *n* (%)		
American Indian or Alaska native	14 (0.4)	12 (0.4)
Asian	78 (2.2)	70 (2.3)
Black or African American	696 (19.3)	548 (18.3)
Native Hawaiian or other Pacific Islander	10 (0.3)	10 (0.3)
White	2324 (64.6)	1952 (65.2)
Hispanic or Latina	404 (11.2)	335 (11.2)
Other	71 (2.0)	65 (2.2)
Height (in), mean (SD)	64.6 (2.7)	64.6 (2.7)
Age (y), mean (SD)	27.1 (5.7)	25.9 (4.6)
Weight (lb), mean (SD)	162.5 (43.2)	161.7 (43.3)
BMI (kg/m^2), mean (SD)	27.4 (7.0)	27.2 (7.0)
BMI category, *n* (%)[a]		
<25 kg/m^2	1683 (46.8)	1424 (47.6)
25–30 kg/m^2	886 (24.6)	720 (24.1)
30–40 kg/m^2	801 (22.3)	668 (22.3)
>40 kg/m^2	226 (6.3)	179 (6.0)
Smoking history		
Current	602 (16.7)	545 (18.2)
Former	636 (17.7)	527 (17.6)
Never	2359 (65.6)	1920 (64.2)
Contraceptive history		
Continuous user	1570 (43.6)	1326 (44.3)
New start	619 (17.2)	515 (17.2)
Prior user	1408 (39.1)	1151 (38.5)

SD, standard deviation.
[a] BMI data were missing for 1 patient (<1%).

typical-use and the compliant-use PIs excluded cycles in which another contraceptive was used. Life-table analyses estimated cumulative failure rates at the end of 1 year of 2.82% (95% CI, 2.23–3.57) for all PITT users and 3.06% (95% CI, 2.19–4.27) for compliant users, using 28-day cycles as the basis of the calculation intervals.

3.2. Cycle control

The pattern of scheduled bleeding or spotting days was stable across all 4 extended cycles (median of 4 days in cycles 1, 2 and 4 and 3 days in cycle 3). Amenorrhea (no bleeding or spotting at any time during the 91-day cycle) occurred in approximately 1.9% of women during cycle 1, 7.7% during cycle 2, 10.7% during cycle 3 and 10.1% during cycle 4.

The mean and median number of unscheduled bleeding or spotting days per cycle and unscheduled bleeding days consistently decreased from cycle 1 to cycle 4 (Fig. 3). For example, median unscheduled bleeding days decreased from 4 (1.0 day/woman-month) in cycle 1 to 0 in cycles 2 through 4. Fewer mean and median unscheduled bleeding or spotting days were reported with higher doses of EE (25 and 30 mcg) later in the cycle (Fig. 4).

3.3. Safety and tolerability

The types and incidence of reported AEs were consistent with those of other ER COCs. The most common treatment-emergent AEs (TEAEs) were headache (11.7%), nasopharyngitis (9.5%) and upper respiratory tract infection (9.0%) (Table 3). The most common treatment-related AEs were metrorrhagia (5.9%) and headache (4.5%).

The discontinuation rate over the 1-year course of exposure was 40.4%. Thirteen percent of the study population discontinued due to AEs, and 4.6% discontinued due to bleeding or spotting AEs. The most commonly reported AE leading to discontinuation was metrorrhagia (2.9%). Fifty-eight women experienced serious AEs. Of these events, 13 resulted in discontinuation from the trial and 7 were considered treatment related: deep vein thrombosis (*n*=2), outcome of pregnancies (*n*=2), gallbladder problems (*n*=2) and pulmonary embolism (*n*=1). There were no deaths in this trial. No unexpected changes in vital signs and laboratory test results for chemistry, lipids, hematology and urinalysis were noted over the course of the study.

4. Discussion

In this 1-year trial, the novel ADER demonstrated efficacy for the prevention of pregnancy comparable with that seen with other ER COCs [8,10,24,25]. Typical-use and compliant-use PIs were 3.19 and 2.59 pregnancies per 100 woman-years of use, respectively.

The life-table method confirmed the results of the PI analysis, indicating that the cumulative failure rate was 3.06% for compliant users and 2.82% for all users. Estimates of contraceptive failure may be slightly lower for all users because cycles in which additional birth control methods were used were excluded from the compliant- and typical-user analyses. Because variations in study design can affect PIs, comparisons of contraceptive efficacy from different studies should be made with caution [25]. Still, results from COC studies in recent decades suggest a trend toward

Table 2
Pregnancy rates reported as PI.

	No. of pregnancies	No. of completed 28-day cycles	PI (95% CI)
All use	70	30,366	3.00 (2.34–3.79)
Typical use	70	28,518	3.19 (2.49–4.03)
Compliant use	54	27,153	2.59 (1.94–3.37)

The all-user analysis included all complete 28-day cycles; typical-use analysis included all complete 28-day cycles during which no other birth control method was used; and compliant-use analysis included all complete 28-day cycles during which no other birth control method was used and the participant was deemed to be compliant during the cycle. A participant was considered noncompliant if she skipped two or more consecutive pills; had an overall adherence of <80%, based on a combination of diary data and pill counts; or used a prohibited medication.

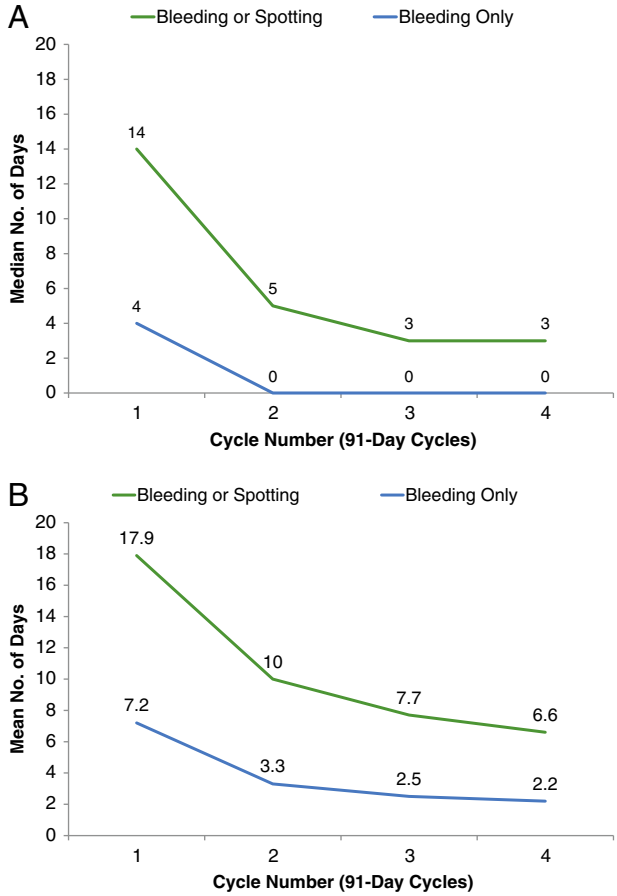

Fig. 3. Median (A) and mean (B) number of unscheduled bleeding or spotting and bleeding-only days in women with at least 28 days of exposure.

increasing — or creeping — PIs and life-table failure rates over time [25,26]. Numerous factors likely contribute to this trend, including more frequent and accurate pregnancy testing, differences in definitions of on-treatment pregnancies and lack of confirmation of COC adherence [9,10,13,25,27]. Standardization of COC study design and analyses are needed to facilitate study interpretation.

Although contraceptive efficacy and safety were the primary focus of this trial, its bleeding results were consistent with results from a phase 2 study comparing three experimental ADERs with a conventional LNG/EE extended regimen [21]. Bleeding patterns were similar between all of the experimental and conventional LNG/EE regimens, so the lowest-dose regimen was selected for further development.

Because of its ascending EE dose, ADER provides reduced exposure to estrogen compared to 30-mcg EE ERs, which may result in reduced estrogen-related AEs [28–30]. The AE incidences in this trial are consistent with those observed with low-dose COCs, confirming that ADER is safe and well tolerated [8,9].

Overall, TEAEs were few in number, unremarkable and consistent with those seen with other COCs. The rate of venous thromboembolism (n=3) was 11/10,000 woman-years, in line with the incidence of VTEs in other COC clinical trials [31,32]. Of the TEAEs recorded, only headache occurred with an incidence >10% (11.7%), a rate lower than those observed in other studies of LNG/EE ERs (21%–33%) [8,10].

Study limitations include its open-label design, the absence of a comparator and lack of objective measurement of adherence. Adherence was assessed by self-reported participant diaries and pill counts. Studies of COC adherence have shown a substantial discrepancy between participant self-reporting of adherence and actual adherence as revealed by electronic monitoring of pill packages [33] and pharmacokinetic assessments of contraceptive steroids analyzed in blood samples [34,35].

Nonetheless, this large clinical trial demonstrated that ADER is effective for the prevention of pregnancy. This 91-day ER results in four scheduled withdrawal bleeding episodes each year with a low and decreasing incidence of unscheduled

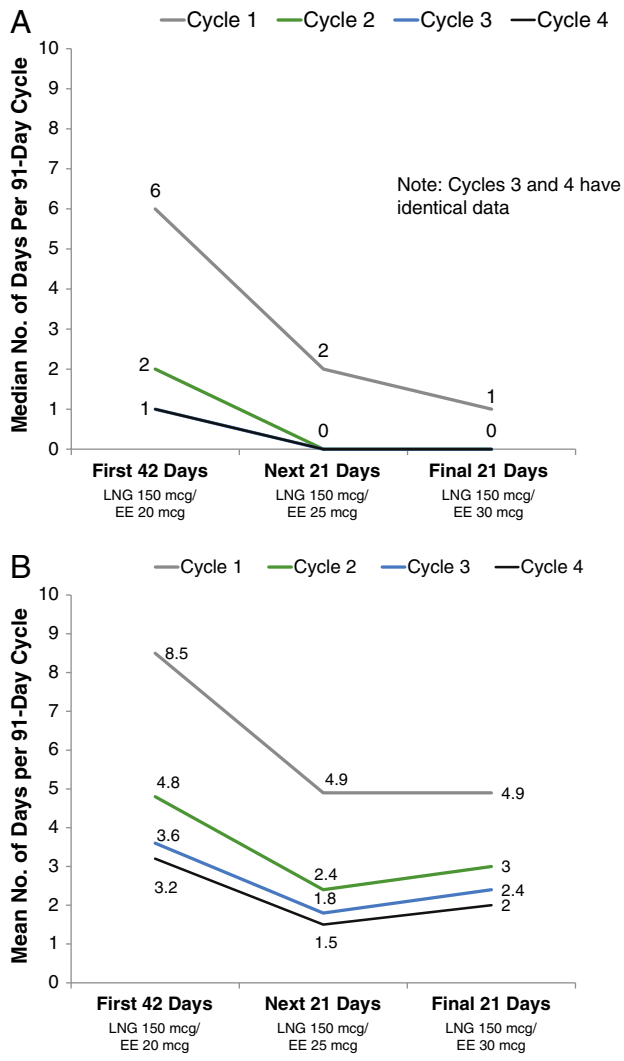

Fig. 4. Median (A) and mean (B) number of unscheduled bleeding or spotting days by dosing period in women with at least 28 days of exposure. Note: Unscheduled bleeding or spotting data recorded early in cycle 1 may have included scheduled bleeding/spotting from the cycle prior to the first dose of ADER.

Table 3
Safety and tolerability: TEAEs

AE	No. (%) (*N*=3597)
Headache	420 (11.7)
Nasopharyngitis	342 (9.5)
Upper respiratory tract infection	323 (9.0)
Sinusitis	246 (6.8)
Nausea	241 (6.7)
Metrorrhagia	216 (6.0)
Urinary tract infection	215 (6.0)
Acne	193 (5.4)
Dysmenorrhea	188 (5.2)
Weight increase	163 (4.5)
Back pain	153 (4.3)
Vaginal bleeding	112 (3.1)
Menorrhagia	18 (0.5)

bleeding/spotting after cycle 1. Moreover, ADER exposes women annually to less estrogen than 30-mcg ERs and similar estrogen to 21/7 regimens while minimizing unscheduled bleeding. ADER, a novel LNG/EE ER in which EE doses increase when unscheduled bleeding typically occurs and includes EE 10 mcg to modify the traditional HFI, provides the benefits of quarterly scheduled bleeding and offers a unique approach to minimizing unscheduled bleeding.

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