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Efficacy and safety of a 21/7-active combined oral contraceptive with continuous low-dose ethinyl estradiol☆,☆☆,★,★★,☆☆☆

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Abstract

Objective: Substituting low-dose ethinyl estradiol (EE) for the hormone-free interval in combined oral contraceptives (COCs) may enhance ovarian suppression and improve tolerability. This noncomparative phase 3 study evaluated the efficacy and safety of a 21/7-active COC regimen including 21 days of desogestrel (DSG)/EE followed by 7 days of EE.

Study design: This multicenter, open-label, phase 3, single-arm study enrolled sexually active women aged 18–40 years at risk for pregnancy. Women received up to 1 year, or 13 consecutive 28-day cycles, of DSG 150 mcg/EE 20 mcg for 21 days and EE 10 mcg alone for 7 days. Participants kept diaries to record compliance, bleeding/spotting and other contraceptive use. Efficacy was measured using the Pearl Index (PI) and life-table approach. Safety and tolerability were assessed primarily through reported adverse events (AEs).

Results: A total of 2858 women enrolled and 1680 completed the study. Forty-six pregnancies in 2401 women aged 18–35 years occurred after COC initiation and up to 7 days after last DSG/EE or EE-only tablet was taken. When cycles in which another contraceptive method was used were excluded, the PI was 2.68 [95% confidence interval (CI), 1.96–3.57]. The cumulative pregnancy rate after 1 year of treatment was 2.47% (95% CI, 1.85–3.29) for all users aged 18–35 years. When only cycles during which women considered compliant were included, the PI was 2.00 (95% CI, 1.39–2.80). AEs were similar to those seen with other oral contraceptives.

Conclusions: This 21/7-active DSG/EE COC with 7 days of low-dose EE was efficacious and well tolerated for pregnancy prevention.

Implications statement: This phase 3 open-label study demonstrated that a 21/7-active COC regimen including 21 days of DSG 150 mcg/EE 20 mcg and 7 days of EE 10 mcg was efficacious and well tolerated for pregnancy prevention.

Keywords: Contraception; Birth control pill; Hormone-free interval; Phase 3 trial

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1. Introduction

Since their introduction, combined oral contraceptive (COC) regimens have undergone a variety of changes to improve safety, efficacy and tolerability profiles. Estrogen doses have decreased to reduce side effects as well as thrombotic risks associated with COCs. Modifications to the biochemical structure of progestins have also been introduced to help improve COC tolerability and acceptability [1]. For example, COCs with desogestrel (DSG) have high progestational activity and reduced androgenicity and have been found to have good tolerability [2–5].

Evidence also suggests that modifications to the 7-day hormone-free interval (HFI) in 28-day COC regimens may enhance both efficacy and tolerability [6–8]. One such modification is to use low-dose ethinyl estradiol (EE) (10 mcg) instead of placebo or no treatment during the last 7 days of the cycle.

Studies comparing 28-day regimens with and without low-dose EE during the traditional HFI demonstrate that low-dose EE during the last week of the cycle suppresses pituitary–ovarian activity and ovarian follicular activity [6,9,10].

COCs that incorporate both newer progestins and changes to the traditional HFI may provide useful and well-tolerated options for women seeking pregnancy prevention. One such regimen contains 21 days of DSG 150 mcg and EE 20 mcg followed by 7 days of low-dose EE (10 mcg). A previous 6-month study of this formulation demonstrated its efficacy and tolerability in women seeking pregnancy prevention [11].

The primary objective of this study was to further assess the efficacy and safety of this 21/7-active DSG/EE COC regimen taken for 1 year to prevent pregnancy.

2. Methods

2.1. Study design and population

This multicenter, open-label, phase 3, single-arm trial (ClinicalTrials.gov identifier: NCT01178125) was conducted between August 11, 2010 and January 31, 2013 at 53 centers in the United States and 9 centers in Israel. It was designed and conducted according to the laws, regulations and administrative provisions associated with Good Clinical Practice in the conduct of clinical trials on medical products for human use, as applicable by national legislation and as required by major regulatory authorities and in accordance with the Declaration of Helsinki and its updates. Institutional review board or Ethics Committee approval was obtained by all study sites. Participants gave written informed consent before enrollment.

Eligible participants included sexually active females who were at risk for pregnancy, were aged 18–40 years at the time of the screening visit and agreed to routinely use DSG/EE as their only birth control method.

Key exclusion criteria included a history or the presence of any condition that contraindicated the use of COCs, current or recent history of chronic use of any medication that may have interfered with the efficacy of COCs or history of a clinically significant adverse experience with COC use. There were no weight or body mass index (BMI) restrictions. Full inclusion and exclusion criteria are listed in the supplementary material.

2.2. Study procedures

The trial consisted of a 4-week screening period, a 1-year treatment period and a posttreatment period of approximately 3 weeks. Following the screening period, eligible women were enrolled into the study and received up to 1 year of the DSG/EE COC (13 consecutive 28-day cycles), with each 28-day cycle including DSG 150 mcg/EE 20 mcg for 21 days, followed by EE 10 mcg for 7 days. All women were instructed to take one tablet daily at approximately the same time each day. Women had the choice of starting DSG/EE on the first day of their menses (i.e., first-day start) or on the first Sunday following the first day of their menses (i.e., Sunday start).

Women returned to the clinic for a study visit on Weeks 4–6, then for visits approximately every 12 weeks (Weeks 16, 28 and 40). At all visits, urine pregnancy tests were performed, vital signs were assessed, concomitant medications were reviewed and adverse events (AEs) were recorded. During the trial, all women completed electronic patient-reported outcomes diaries to record DSG/EE administration, bleeding/spotting, use of other contraceptives and DSG/EE compliance. Treatment compliance was also assessed by tablet counts at scheduled study visits. At all follow-up visits, women were asked if they remained at risk for pregnancy; women who said no were discontinued from the study.

At a subset of study centers, women had the option to participate in an endometrial biopsy substudy to explore the effect of the study drug on changes in endometrial tissue.

For all women who took at least one dose of DSG/EE, a posttreatment study visit was conducted approximately 3 weeks after the last dose of DSG/EE. In addition, women who took DSG/EE for at least 3 months, withdrew from the study and did not initiate a contraceptive method that regulated or altered the menstrual cycle after the study discontinued were monitored via telephone monthly for 3 months after the last dose for occurrence of pregnancy and/or return of menses.

2.3. Efficacy assessment

Pregnancy was determined by urine and/or serum tests. Transvaginal ultrasound was used to document pregnancy and determine conception date.

2.4. Cycle control assessment

Women recorded the incidence of vaginal bleeding/spotting in daily electronic diaries.