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CLINICAL ARTICLE

Estradiol valerate plus dienogest versus ethinylestradiol plus levonorgestrel for the treatment of primary dysmenorrhea

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ABSTRACT

Objective: To demonstrate the superiority of estradiol valerate plus dienogest (E_2V/DNG) over ethinylestradiol plus levonorgestrel (EE/LNG) in reducing the number of days with dysmenorrheic pain among women with primary dysmenorrhea. *Methods:* In a phase IIIb trial conducted at 44 centers worldwide between April 2009 and November 2010, otherwise healthy women aged 14 − 50 years requesting contraception were randomized to daily oral administration of E_2V/DNG (n = 253) or EE/LNG (n = 254) for three 28-day cycles. The primary efficacy variable was number of days with dysmenorrheic pain, the category of which (none, mild, moderate, severe) was self-assessed on a daily basis (irrespective of menstrual bleeding status) and recorded on diary cards. Notably, the women documented their pain as they experienced it before taking any (permitted) rescue medication. *Results:* Overall, 217 and 209 women receiving E_2V/DNG and EE/LNG, respectively, completed the study. The mean ± SD change from baseline in number of days with dysmenorrheic pain was −4.6 ± 4.6 days and −4.2 ± 4.2 days for the E_2V/DNG and EE/LNG groups, respectively ($P = 0.34$). *Conclusion:* Both E_2V/DNG and EE/LNG led to considerable relief of dysmenorrheic complaints among women with primary dysmenorrhea, decreasing the number of days with dysmenorrheic pain from baseline to a similar extent.
ClinicalTrials.gov: NCT00909857

1. Introduction

Primary dysmenorrhea has been defined as recurrent cramping pain in the lower abdomen and/or pelvis that occurs immediately prior to or during menstruation in the absence of any identifiable pelvic pathology [1,2]. The incidence of primary dysmenorrhea varies considerably by geographic location, but it is nonetheless widespread and considered a highly prevalent condition, affecting an estimated 30%–50% of young women [1–3]. At its most severe, primary dysmenorrhea results in work or school absenteeism for 15% of young women [1].

Primary dysmenorrhea is considered to be associated with increased prostanoid secretion from the endometrium during menstruation, which in turn induces abnormal uterine contractility [1]. Therefore, currently available treatments, typically non-steroidal anti-inflammatory drugs (NSAIDs), target prostaglandin synthesis to relieve dysmenorrheic complaints, and are recommended as a first-line medical treatment to relieve pain and to improve daily activity among women suffering from primary dysmenorrhea [2]. Concerns about the gastrointestinal safety of NSAIDs [4] or the cardiovascular safety of COX-2 inhibitors [5], however, indicate the need for a treatment for dysmenorrhea with an improved risk–benefit profile.

Although NSAIDs are specifically suited for the treatment of acute dysmenorrheic pain, combined oral contraceptives (COCs) are often used off-label to prevent the development of primary dysmenorrhea symptoms. Their efficacy, however, has not been adequately demonstrated in clinical trials [6], and symptoms sometimes reoccur during the hormone-free interval (HFI), which is 7 days for most COC regimens.

The 26/2-day dynamic dosing regimen of a COC containing estradiol valerate and dienogest (E_2V/DNG) administered via an estrogen step-down and progestogen step-up approach (E_2V 3 mg on days 1–2, E_2V 2 mg/DNG 2 mg on days 3–7, E_2V 2 mg/DNG 3 mg on days 8–24, E_2V 1 mg on days 25–26, and placebo on days 27–28) includes a shortened HFI compared with conventional 21/7-day regimen COCs. This ensures that stable levels of estradiol are maintained throughout the 28-day cycle, including during the HFI [7]. Furthermore, the short serum half-life of DNG (approximately 10 hours) [8] results in only a limited accumulation of DNG during the 28-day E_2V/DNG regimen and, as such, its rapid systemic clearance from the circulation during

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the HFI does not seem to have a negative impact on symptoms associated with hormonal withdrawal, such as headache and pelvic pain. As a result, it was hypothesized that E_2V/DNG might have a more favorable effect on primary dysmenorrhea compared with established 21/7-day monophasic regimen COCs.

Therefore, the primary objective of the present study, CALM, was to demonstrate superiority of E_2V/DNG over an established COC (ethinylestradiol 0.02 mg, levonorgestrel 0.1 mg; EE/LNG) with respect to the number of days with dysmenorrheic pain (defined as pelvic pain during the menstrual or withdrawal bleeding episode and the 2 days before this episode) in a defined period (i.e. 2 treatment and 2 baseline cycles).

2. Materials and methods

In a phase IIIb, double-blind, double-dummy, parallel-group study conducted at 44 centers across Canada, Chile, Germany, Italy, the Philippines, and the United States, women suffering from primary dysmenorrhea were recruited between April 15, 2009, and November 18, 2010. The study was performed in keeping with the ethical principles of the International Conference on Harmonization–Good Clinical Practice guidelines, which have their origin in the Declaration of Helsinki. The study was approved by local ethics committees and institutional review boards, and written informed consent was obtained from all women before study enrollment.

Otherwise healthy women aged 14 — 50 years (smokers ≤35 years) requesting contraception and suffering from primary dysmenorrhea were eligible for inclusion in the study. At the screening visit, the gynecologic, menstrual, and surgical history of patients was recorded, and a gynecologic examination of every patient was performed. Pregnant or breastfeeding women, women with a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) of more than 32, and women with pelvic pathology were excluded from the study.

Regarding sample size, it was calculated that 164 evaluable subjects per treatment group would be required to detect a standardized effect size of 0.36 between the 2 treatment groups with 90% power assuming a 2-sided *t* test at an α level of 0.05. Experience in similar studies among patients with primary dysmenorrhea suggested that there might be a dropout rate of 40%–50% over the treatment period. Assuming a 45% dropout rate, it was determined that 290 women per treatment group (i.e. 580 women in total) would be required for the study.

Eligible women underwent 2 observation baseline cycles to confirm the occurrence of dysmenorrhea. The women rated their pelvic pain on a daily basis on diary cards using the following 4-point scale: 0, none (no pain); 1, mild (mild dysmenorrheic pain with no need for the intake of painkiller); 2, moderate (moderate dysmenorrheic pain with need for the intake of painkiller); and 3, severe (severe dysmenorrheic pain with need for the intake of painkiller). Dysmenorrhea was defined as a total score of 8 or more points per cycle for pelvic or lower abdominal pain that started up to 2 days before the onset of the menses or during menstrual flow, and ended before or at cessation of menstrual flow.

Women who met the inclusion criteria were randomized to daily oral administration of E_2V/DNG (Qlaira; Bayer HealthCare, Berlin, Germany) plus placebo, or placebo plus EE/LNG (Miranova; Bayer HealthCare, Berlin, Germany) for 3 cycles of 28 days each. The investigational and reference product were packed for a double-dummy design that included the study product plus matching placebo in 1 wallet containing 2 blisters of 28 tablets each. Women were randomly assigned to the 2 treatments in a 1:1 ratio via a centralized computer-generated randomization list provided by the sponsor. Study medication was assigned in blocks via an interactive voice response system according to the randomization list; randomization numbers were allocated in ascending order based on the sequence of arrival of patients to the study center. Both patients and investigators remained blind to the medication assigned. Women were permitted to use rescue medication (ibuprofen, maximum 1200 mg on any single day) to relieve, but not to prevent, menstruation-related pelvic pain.

To assess treatment compliance, the women were required to complete a diary card on a daily basis to determine their intake of study and rescue medication. Missed tablets and use of back-up contraception (excluding natural methods, as documented in the diary cards) were also included in the compliance assessment. Compliance to study treatment was calculated as the actual number of tablets taken divided by the scheduled number of tablets for the respective duration of treatment.

The primary efficacy variable was the number of days with dysmenorrheic pain (defined as pelvic pain during the menstrual/withdrawal bleeding episode and the 2 days before this episode) in a defined period (i.e. 2 treatment and 2 baseline cycles). Dysmenorrheic pain represented any spasmodic pelvic or lower abdominal pain with possible radiation toward the back or thighs. Pain severity (none, mild, moderate, severe) was self-assessed by the women on a daily basis (irrespective of menstrual bleeding status) throughout the study and recorded on diary cards. Notably, the women had to document their pain as they experienced it before taking any permitted rescue medication.

Secondary efficacy variables included the total points score for dysmenorrheic pain, number of days with pelvic pain independent of the occurrence of vaginal bleeding, rescue medication consumption (standardized intake of ibuprofen), interference of dysmenorrheic pain with work or school and social or other activity, bleeding pattern and cycle control parameters, and sick leave taken, as noted in the absenteeism questionnaire (data not shown) [9,10]. In addition, the following questionnaires were used: the Resource Use Questionnaire, the General Health and Well-Being Questionnaire Short Form 36 version 1 (SF-36v1) [11], and Global Clinical Impression [12]. The Resource Use Questionnaire was completed at screening before the start of the first baseline cycle. The SF-36v1 and absenteeism questionnaires were completed at screening, during days 12–19 of the second baseline cycle and the second treatment cycle, and during days 12–19 after the end of treatment or at end of the study for those who discontinued prematurely. The Global Clinical Impression scale assessment was completed during days 12–19 of the second treatment cycle or on premature discontinuation.

Safety assessments included physical and gynecologic examinations (cervical smear), monitoring vital signs (heart rate and blood pressure), body weight and BMI, and reporting of adverse events (AEs).

The primary efficacy variable was assessed on the basis of the full analysis set, defined as all women who took at least 1 dose of study medication and who had at least 1 observation recorded after starting the study treatment. Statistical analyses were done via SAS for Windows version 9 (SAS Institute, Cary, NC, USA). The 2-sample *t* test was used to determine the superiority of E_2V/DNG over EE/LNG. A *P* value of less than 0.05 was considered statistically significant.

3. Results

During the study period, 507 women were randomized to treatment: 253 women to E_2V/DNG, and 254 to EE/LNG. In total, 464 women received study medication and were included in the full analysis set: 234 in the E_2V/DNG group, and 230 in the EE/LNG group (Fig. 1). Overall, 217 women receiving E_2V/DNG and 209 women receiving EE/LNG completed the treatment; 38 women prematurely discontinued study medication across the 2 treatment groups. The women's demographic and baseline characteristics were similar in the 2 groups (Table 1).

Overall, 231 of 234 (98.7%) women in the E_2V/DNG group and 227 of 230 (98.7%) women in the EE/LNG group showed at least 75% compliance with the allocated study treatments.

For the primary efficacy variable, the change from baseline in the number of days with dysmenorrheic pain was similar in both treatment groups: the mean ± SD change from baseline was –4.6 ± 4.6 days in the