Effective treatment of heavy and/or prolonged menstrual bleeding with an oral contraceptive containing estradiol valerate and dienogest: a randomized, double-blind Phase III trial

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Submitted on October 26, 2010; resubmitted on May 19, 2011; accepted on June 6, 2011

BACKGROUND: This double-blind trial investigated the efficacy and safety of estradiol valerate/dienogest (E2V/DNG) for the treatment of heavy menstrual bleeding without recognizable organic pathology.

METHODS: Otherwise healthy women with idiopathic heavy, prolonged or frequent menstrual bleeding, confirmed during a 90-day run-in phase, were randomized (2:1) according to a permuted-block, computer-generated schedule to E2V/DNG or placebo for 196 days at 34 centres in Europe and Australia. The primary efficacy end-point was the proportion of women with a 'complete' response (i.e. a return to 'menstrual normality') during a 90-day efficacy phase. Secondary end-points included changes in measured menstrual blood loss (MBL) and iron metabolism parameters.

RESULTS: The intention-to-treat population comprised 231 women. The E2V/DNG response rate was much higher than with placebo (P < 0.0001). The mean reduction in MBL volume in E2V/DNG recipients was 69.4% (median 79.2%) versus 5.8% (median 7.4%) in placebo recipients. The between-treatment difference in MBL volume was 373 ml in favour of E2V/DNG (95% confidence interval 490, 255 ml; P < 0.0001). Significant improvements in iron metabolism parameters were observed with E2V/DNG but not placebo. Overall, 14 women (9.7%) treated with E2V/DNG and 5 (6.2%) treated with placebo prematurely discontinued treatment because of adverse events, headache being the most prevalent. Serious adverse events occurred in both the E2V/DNG and placebo groups (each n = 2).

CONCLUSIONS: E2V/DNG is an effective treatment in women with heavy and/or prolonged menstrual bleeding without organic pathology. Further study of E2V/DNG compared with an active comparator is warranted. ClinicalTrials.gov identifier: NCT00307801.

Key words: dienogest / estradiol valerate / oral contraceptive / heavy and/or prolonged menstrual bleeding / RCT

Introduction

A novel oral contraceptive (OC) comprising estradiol valerate and dienogest (E2V/DNG) has recently become available in the majority of countries in Europe. E2V/DNG is an effective and well-tolerated OC (Ahrendt et al., 2009; Palacios et al., 2010). Moreover, it is the first widely available OC to provide natural 17ß-estradiol (E2) and thus represents a new class of OC.

Data indicate that E2V/DNG is associated with a vaginal bleeding profile that is more acceptable than that of other E2-containing OCs that have been investigated in clinical studies (Serup et al., 1979; Koetsawang et al., 1980; Schubert and Cullberg, 1987; Wenzl et al., 1993;...
Kivinen and Saure, 1996). A recent clinical trial in 798 healthy women aged 18–50 years has shown that, when administered as a contraceptive, E2V/DNG delivers acceptable cycle control, with shorter and lighter bleeding and a higher rate of absent withdrawal bleeding (defined as a cycle in which no scheduled withdrawal bleeding occurred) compared with an OC containing ethinyl estradiol 20 μg and levonorgestrel 100 μg (Ahrendt et al., 2009). The acceptable bleeding profile of E2V/DNG is attributed to (i) the incorporation of the progestogen DNG, which has a pronounced endometrial effect (Oettel et al., 1999a,b; Sasagawa et al., 2008) and (ii) a dynamic dosing regimen consisting of a 26-day treatment phase (which includes a stepwise progressive reduction in the dose of E2V and an increase in the dose of DNG) followed by a 2-day placebo phase.

Because E2V/DNG was launched relatively recently, information on its clinical properties is still being gathered. Data from trials investigating the efficacy and bleeding profile of E2V/DNG, undertaken in populations of healthy contraceptive users, suggest that the preparation might be a suitable treatment for women with abnormal uterine bleeding, the most common symptom of which is heavy menstrual bleeding (HMB) (Istre and Qvigstad, 2007) [objectively defined as a menstrual blood loss (MBL) volume of 80 ml or more per cycle] (Hallberg et al., 1966). HMB may be the result of underlying uterine pathology or other organic causes; however, ~50% of cases lack a recognizable organic pathology (Fraser et al., 2009). It is thought that such cases are primarily the result of disturbances of the molecular control of endometrial mechanisms that regulate the volume of blood lost during menstruation (Livingstone and Fraser, 2002). Approved treatments for HMB include progestogens, antifibrinolytic agents and non-steroidal anti-inflammatory drugs (NSAIDs) (Fraser and McCarron, 1991; Irvine et al., 1998; Reid and Virtanen-Kari, 2005; Kaunitz et al., 2010). Combined OCs have generally been recognized as reducing MBL, and have been used to treat HMB (Nilsson and Rybo, 1971; Fraser and McCarron, 1991; Larsson et al., 1992; Milman et al., 1998; Endrikat et al., 2009; Sabaan et al., 2011), including in women with underlying organic pathology (Sayed et al., 2011); however, the evidence basis for their efficacy in the treatment of HMB is limited and most preparations have not received regulatory approval for this condition.

The current study was carried out to determine the efficacy and tolerability of E2V/DNG in women with objectively confirmed heavy and/or prolonged menstrual bleeding without organic cause.

Materials and Methods

Study design and participants

This randomized, double-blind, placebo-controlled Phase III trial investigated the efficacy and tolerability of E2V/DNG for the treatment of women with a verified complaint of heavy and/or prolonged menstrual bleeding. The study was conducted between February 2006 and May 2008 at 34 centres in Australia and Europe (Czech Republic, Finland, Germany, Hungary, the Netherlands, Poland, Sweden, the UK and Ukraine). The clinical trial registration number was NCT00307801. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization-Good Clinical Practice. The study protocols (and any amendments) were approved by each site’s Institutional Review Board/Independent Ethics Committee. Written informed consent was obtained from all study participants prior to study entry.

The study consisted of four parts: a screening phase of up to 28 days, a 90-day run-in phase, a 196-day treatment phase (which concluded with a 90-day efficacy phase that had to start on the first day of a treatment cycle) and a follow-up phase of 30 days. To be eligible for inclusion into the treatment phase, women were required to display symptoms of HMB (two or more menstrual bleeding episodes each with a measured MBL volume of 80 ml or more), prolonged menstrual bleeding (two or more menstrual bleeding episodes each lasting 8 days or more), and/or frequent menstrual bleeding (more than five menstrual bleeding episodes with a minimum of 20 bleeding days overall) during the 90-day run-in phase. The use of medications intended to relieve women of their HMB (e.g. sex steroids, NSAIDs, tranexamic acid) was not allowed throughout the whole study.

To be eligible to participate in the study, women had to be aged 18 years or older and have symptoms of heavy, prolonged and/or frequent menstrual bleeding (confirmed during the 90-day run-in phase). Women had to have been used to use a barrier method of contraception and to use and collect sanitary protection items (pads and tampons) provided by the sponsor for the duration of the study. Women were required to have a normal result after endometrial biopsy or, at most, mild, simple endometrial hyperplasia in the 6 months prior to study entry. Women were excluded from entering the study if they had an abnormal transvaginal ultrasound or abnormal values for any laboratory examination that were considered to be clinically significant, if they had a history of endometrial ablation, or if they had undergone dilatation and curettage in the 2 months preceding the study. Women were also excluded if they had a bleeding disorder that was determined during the 90-day run-in phase to be the result of organic pathology (including chronic endometritis, adenomyosis, endometriosis, endometrial polyps, leiomyomas or uterine malignancy). Women who were unwilling to discontinue the use of tranexamic acid or NSAIDs during menses were excluded, as were women with a BMI of more than 32 kg/m² or those aged 35 years or older who smoked more than 10 cigarettes per day (or any number of cigarettes in Australia and the UK). Other exclusion criteria consistent with other contraindications for the use of combined OCs were also applied. For ethical reasons, use of iron supplementation in this placebo-controlled study was allowed if considered necessary by the attending physician.

Study treatment

Following the 90-day run-in phase, women with at least one qualifying menstrual bleeding symptom were randomized (2:1) to 196 days of treatment (which comprised seven consecutive treatment cycles of 28 days each) with orally administered E2V/DNG (Qlaira®/Natazia®; Bayer HealthCare Pharmaceuticals, Berlin, Germany) or placebo. E2V/DNG was administered using an estrogen step-down and progestogen step-up approach (E2V 3 mg on Days 1–2, E2V 2 mg/DNG 2 mg on Days 3–7, E2V 2 mg/DNG 3 mg on Days 8–24, E2V 1 mg on Days 25–26 and placebo on Days 27–28; E2V 1 mg = E2 0.76 mg). Study medication was initiated on the first day of bleeding after randomization, and there were no tablet-free days between treatment cycles.

Both patients and investigators were blinded to treatment. To maintain blinding, E2V/DNG and placebo tablets were administered in identical 28-day blister packs.

Randomization was performed according to a permuted-block (using a block size of six), computer-generated schedule (RANDO SAS Macro) that was designed to achieve balanced treatment allocation in each block. The blocks of randomization numbers were distributed to each centre. Investigators assigned patients to the next randomization number available from the block assigned to their study site.
Study assessments

Throughout the study (including during the 90-day run-in phase), women were required to complete an electronic diary on a daily basis. The diary was used to document women’s perceptions of menstrual bleeding presence and intensity, the number and type of items of sanitary protection used, and study drug intake during the treatment phase. Women rated their bleeding intensity on a daily basis as none, spotting, light bleeding, normal bleeding or heavy bleeding. If MBL was rated of greater intensity than spotting, the women were to select one of the three ‘bleeding’ categories; the choice of whether bleeding intensity was light, normal or heavy was made by individual women based on the characteristics of the bleed relative to their normal menses. A bleed-free day was defined as a day with no bleeding or only spotting. Spotting was defined as bleeding that was less than that associated with normal menstruation (relative to the patient’s experience), with no need for sanitary protection other than panty liners. If bleeding intensity data were missing on non-consecutive days, the intensity on the missing day was considered to be the higher intensity on the bordering days. No more than nine non-consecutive days were replaced in a 90-day interval. Consecutive days with missing bleeding intensity data were not replaced.

In addition to completing an electronic diary, women were required to collect and ship all used sanitary protection (pads and tampons) so that MBL could be objectively quantified. Care was taken to counsel women about maximizing the collection of their total menstrual loss, including blood ‘clots’. MBL was measured using a modified version of the alkaline haematin method (Hallberg and Nilsson, 1964; Shaw et al., 1972) to quantify haemoglobin in menstrual fluid after detergent extraction. A central laboratory (Laboratorium für Klinische Forschung GmbH, Kiel, Germany) was used to process and analyse all sanitary protection items.

Study end-points

Efficacy

The primary efficacy outcome was the proportion of women who showed a complete response to treatment (i.e. a complete return to ‘menstrual normality’) during the 90-day efficacy phase (versus the 90-day run-in phase). A complete response to treatment was defined as a composite of the following components: no bleeding episodes lasting more than 7 days; no more than four bleeding episodes overall; no bleeding episodes with a blood loss volume of 80 ml or more; no more than one bleeding episode increase from baseline; no more than 24 days of bleeding overall; and no increase from baseline in the total number of bleeding days. In addition, patients recruited because of the presence of prolonged bleeding were required to demonstrate a decrease of at least 2 days in the maximum duration of a bleeding episode. Similarly, in patients recruited because of the presence of heavy bleeding, the blood loss volume per bleeding episode had to be <80 ml and had to represent a decrease of at least 50% relative to the average blood loss volume per episode during the study recruitment phase (where the qualifying bleeding episodes were those with an MBL volume of at least 80 ml).

Secondary efficacy variables included changes in MBL volume, the number of bleeding days and episodes, the number of sanitary protection items used and iron metabolism parameters. Other secondary end-points included the proportion of patients with an improvement in menstrual bleeding symptoms according to an investigator’s global assessment scale and a patient’s overall assessment scale. Both assessment scales were administered on Days 84 and 196 when investigators and women were still blinded to treatment. The seven-point scales ranged from very much improved to very much worse compared with symptoms at study admission.

Safety and tolerability

All women were given the opportunity to report adverse events associated with treatment; complaints were to be spontaneously volunteered rather than directly elicited. Adverse events were coded using an internationally recognized dictionary (MedDRA version 10.0), meaning that categories were mandated by standard adverse event reporting requirements. Additional safety assessments included analyses of vital signs and physical and gynaecological examinations.

Statistical analysis

It was assumed that the overall drop-out rate would be 30% and that the difference in the overall success rate between the E2V/DNG and placebo groups would be 30%. Based on these assumptions, a total of 180 subjects was considered necessary (E2V/DNG, n = 120; placebo, n = 60) to provide a power of 90% to test the null hypothesis that the rate of success in the two treatment groups would be equal at a 5% significance level. Statistical analyses were performed using SAS for Windows (Cary, NC, USA). All variables were analysed using descriptive statistical methods. The number of data available, mean, SD, minimum, quartiles, median and maximum were calculated for metric data. Frequency tables were generated for categorical data.

For the primary efficacy variable (complete response rate), each subject was allocated to one of the following three categories: (i) complete responder (absence of any menstrual bleeding symptoms and achievement of all relevant success criteria during the 90-day efficacy phase); (ii) partial or non-responder (failure to achieve all relevant success criteria during the 90-day efficacy phase) or (iii) subject with missing data. The category of subjects with missing data encompassed women who never received study medication, who did not complete a minimum of 90 days of treatment (early drop-outs), or who had too many missing bleeding data to define a valid 90-day efficacy phase (i.e. more than 1 day in sequence with missing bleeding information or more than nine non-consecutive days in a 90-day phase with missing bleeding information). The primary efficacy outcome was assessed in the intention-to-treat (ITT) population (i.e. all randomized subjects) and the per protocol population (i.e. all randomized women who met the inclusion/exclusion criteria and who did not take any prohibited medication, had at least 75% overall study drug compliance, had no major protocol violations, and completed seven treatment cycles). Additionally, an analysis based on women with an evaluable response was performed, which excluded those subjects with missing data. The primary efficacy variable was analysed by the difference of proportions and the corresponding unconditional two-sided 95% confidence interval (CI).

All secondary variables were analysed based on the ITT population, regardless of responder status. Subjects for whom a 90-day efficacy phase could not be defined (i.e. subjects with missing data) were excluded from any analyses that compared data from the 90-day run-in phase and the 90-day efficacy phase. Such women, however, were included in any analyses that referred to per-treatment cycle data. Dichotomous secondary efficacy variables were analysed by differences of proportions and the corresponding CIs. Continuous secondary efficacy variables were analysed with an analysis of variance (ANOVA) or an analysis of covariance model (ANCOVA).

Safety outcomes were assessed in all randomized subjects who took at least one dose of study medication.

Results

Figure 1 shows the flow of women through the study. A total of 575 women were screened; of these, 344 were classified as screening failures, with the major reason being failure to meet the strict inclusion or exclusion criteria. The ITT population comprised 231 women. A low
A drop-out rate was observed in both the E2V/DNG (n = 32) and placebo (n = 17) groups, respectively. More than three-quarters of women who were randomized to treatment completed the study.

Demographic and baseline characteristics of women included in the study are shown in Table I. The mean age of subjects was ≏39 years. More than 95% of women enrolled were of Caucasian origin. The most common menstrual bleeding symptom at baseline was heavy bleeding, followed by prolonged bleeding. Some women had both heavy and prolonged bleeding. No subjects presented with frequent menstrual bleeding at baseline.

**Complete response rate**

An overview of the responder status (and the conditions for a partial or non-response) in each treatment group is shown in Table II. The proportion of complete responders was higher in the E2V/DNG group than in the placebo group (29.5 versus 1.2%, respectively), both in the ITT population as well as in the population of women with evaluable data (i.e. excluding those subjects with missing data); these differences were highly significant (Fig. 2). In the strict responder analysis of women with an evaluable response (according to the complete response criteria), the responder rate for E2V/DNG was 40.7% (95% CI 31.4–50.6%) and for placebo 1.6% (95% CI 0.0–8.7%).

More than 90% of subjects [i.e. 136/149 (91.3%) in the E2V/DNG group and 76/82 (92.7%) in the placebo group] were recruited with HMB. When the response criterion was restricted to subjects cured from HMB (defined as 80 ml MBL volume for each episode), 86/136 (63.2%) of subjects in the E2V/DNG group were considered a response (i.e. did not present with HMB at the end of study) versus only 11/76 (14.5%) of women in the placebo group.

**MBL volume**

The percentage reduction in MBL volume from baseline to end of study in the group of subjects defined as heavy bleeders (i.e. >90% of ITT population) is presented in Fig. 3. This analysis shows that a 20, 50 and 80% reduction in MBL was achieved by 94, 84 and 50% of women, respectively, in the E2V/DNG group, compared with a much smaller proportion of women in the placebo group (40, 12 and 0% of women, respectively). An increase in MBL during treatment was observed in 5% of subjects who received E2V/DNG and more than 30% of subjects who received placebo.

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**Table I** Demographic and baseline characteristics of subjects assigned to treatment with E2V/DNG or placebo (ITT population).

<table>
<thead>
<tr>
<th></th>
<th>E2V/DNG (n = 149)</th>
<th>Placebo (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>39.5 ± 6.6</td>
<td>38.5 ± 7.5</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>144 (96.6)</td>
<td>80 (97.6)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (1.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.8 ± 11.8</td>
<td>71.6 ± 10.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.6 ± 3.5</td>
<td>25.7 ± 3.0</td>
</tr>
<tr>
<td>Bleeding symptoms, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>20 (13.4)</td>
<td>10 (12.2)</td>
</tr>
<tr>
<td>Frequent bleeding</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heavy bleeding</td>
<td>136 (91.3)</td>
<td>76 (92.7)</td>
</tr>
</tbody>
</table>

All data are presented as mean ± SD or absolute (and relative) frequency. Some women presented with multiple symptoms.
MBL volume by treatment cycle in women treated with E2V/DNG and with placebo (ITT population) is shown in Fig. 4. An analysis of data in the ITT population showed that subjects who received E2V/DNG showed a reduction in MBL volume from the first cycle of treatment onwards (the first E2V/DNG tablet was taken on Day 1 of menstrual period 1; therefore, menstrual period 2 occurred at the end of treatment cycle 1); in contrast, MBL volume in subjects who received placebo showed relatively little change and remained consistently higher than that observed in women treated with E2V/DNG. This was not only observed in the ITT population, but also in the subgroup of women categorized as non- or partial responders (Fig. 5).

For the complete responder analysis, MBL volume data during the 90-day run-in phase and during the 90-day efficacy phase were available in 108 women who received E2V/DNG and in 60 women who received placebo. Mean MBL volume during the run-in phase was comparable in women who received E2V/DNG and placebo [639 ml (median 476 ml; range 88–3472 ml) and 645 ml (median 498 ml; range 162–1994 ml), respectively (Table III)]. The mean reduction in total MBL volume for the whole of the 90-day efficacy phase compared with the whole of the 90-day run-in phase was 458 ± 410 ml (median 353 ml; range 2637 ml decrease to 348 ml increase) in E2V/DNG recipients and 93 ± 268 ml (median 48 ml; range 1121 ml decrease to 354 ml increase) in placebo recipients (Table III). Total mean MBL volume was reduced by 69.4% (median 79.2%) with E2V/DNG, compared with 5.8% (median 7.4%) for placebo. The mean adjusted between-treatment difference in MBL volume was 373 ml in favour of E2V/DNG (95% CI 490, 255 ml; \( P < 0.0001 \)).

### Number of sanitary protection items used
The observed decrease in MBL volume was associated with a decrease in the number of sanitary protection items used. The mean number of sanitary protection items used decreased from 29 ± 15 in treatment cycle 1 to 13 ± 13 in treatment cycle 7 in E2V/DNG recipients and from 27 ± 13 to 20 ± 9 in placebo recipients (\( P = 0.8245 \)). Data on the number of total sanitary protection items used during both the 90-day run-in phase and during the 90-day efficacy phase were available in 108 subjects who received E2V/DNG and in 60 who received placebo. The mean reduction in the number of sanitary protection items used was 38 ± 30 items in

### Table II: Responder status in women who received E2V/DNG or placebo in the ITT population.

<table>
<thead>
<tr>
<th></th>
<th>E2V/DNG (ITT, ( n = 149 ), ( n(%) ))</th>
<th>Placebo (ITT, ( n = 82 ), ( n(%) ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete responder</td>
<td>44 (29.5)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Partial or non-responder</td>
<td>64 (43.0)</td>
<td>61 (74.4)</td>
</tr>
<tr>
<td>Missing data</td>
<td>41 (27.5)</td>
<td>20 (24.4)</td>
</tr>
<tr>
<td>Criteria not achieved in partial or non-responders( ^a )</td>
<td>35 (23.5)</td>
<td>11 (13.4)</td>
</tr>
<tr>
<td>No bleeding episodes lasting more than 7 days</td>
<td>6 (4.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>No more than four bleeding episodes overall</td>
<td>36 (24.2)</td>
<td>61 (74.4)</td>
</tr>
<tr>
<td>No bleeding episodes with a MBL volume of 80 ml or more</td>
<td>2 (1.3)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>No more than one bleeding episode increase from baseline</td>
<td>11 (7.4)</td>
<td>5 (6.1)</td>
</tr>
<tr>
<td>No more than 24 bleeding days overall</td>
<td>24 (16.1)</td>
<td>18 (22.0)</td>
</tr>
<tr>
<td>If enrolled with prolonged bleeding</td>
<td>( n = 20 )</td>
<td>( n = 10 )</td>
</tr>
<tr>
<td>Decrease of at least 2 days from the run-in phase to the efficacy phase in the maximum duration of bleeding</td>
<td>2 (10.0)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>If enrolled with HMB</td>
<td>( n = 136 )</td>
<td>( n = 76 )</td>
</tr>
<tr>
<td>MBL associated with each episode less than 80 ml and decreased by at least 50% from the average of the qualifying bleeding episodes during the run-in phase</td>
<td>42 (30.9)</td>
<td>58 (76.3)</td>
</tr>
</tbody>
</table>

\( ^a \)Women could have been classified as non-responders for multiple reasons.

**Figure 2** Rate of complete response overall (ITT population, two columns on the left) and in subjects with an evaluable response (i.e. in subjects with no missing data) following treatment with E2V/DNG and placebo. \( ^* P < 0.0001 \) versus placebo.
the E2V/DNG group and 17 ± 32 in the placebo group (Table III). The mean percentage reduction in the number of sanitary protection items used was 46.8% (median 49.6%) with E2V/DNG, compared with 13.7% (median 18.0%) for placebo. The mean adjusted between-treatment difference in sanitary protection items used was significantly in favour of E2V/DNG [22 items fewer (95% CI 30, 14; \( P < 0.0001 \)].

**Iron metabolism parameters**

Mean levels of haemoglobin, haematocrit and ferritin at baseline and the change from baseline in these parameters on Day 196 of treatment in women who received E2V/DNG and placebo are shown in Table IV. There was a marked improvement from baseline in all three iron metabolism parameters in the E2V/DNG group that was not observed in subjects receiving placebo. The between-treatment difference in these changes was significant. The concomitant use of medications containing iron was permitted in this placebo-controlled study and was reported in 28/149 (18.8%) of E2V/DNG recipients and in 27/82 (32.9%) of placebo recipients.

**Investigators’ and patients’ global assessment**

The proportion of investigators who noted an improvement in their subjects’ bleeding symptoms at study end (rating of very much improved, much improved or improved) was significantly
greater with E2V/DNG (84.7%) compared with placebo (39.5%) (P < 0.0001). The proportion of subjects who assessed themselves as having had an overall improvement in bleeding symptoms at study end was also significantly larger in the E2V/DNG group (77.9%) compared with the placebo group (45.1%) (P < 0.0001).

**Table III** Characteristics of menstrual bleeding during the 90-day run-in phase and the 90-day efficacy phase in women treated with E2V/DNG or placebo.

<table>
<thead>
<tr>
<th></th>
<th>E2V/DNG 90-day run-in phase</th>
<th>E2V/DNG 90-day efficacy phase</th>
<th>Placebo 90-day run-in phase</th>
<th>Placebo 90-day efficacy phase</th>
<th>Change from 90-day run-in to 90-day efficacy phase</th>
<th>P-values for between group difference following treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBL (ml)</td>
<td>639.4 ± 513.5 (n = 149)</td>
<td>175.8 ± 200.8 (n = 108)</td>
<td>645.1 ± 391.2 (n = 79)</td>
<td>553.6 ± 308.0 (n = 62)</td>
<td>−93.2 ± 268.0 (n = 60)</td>
<td>P &lt; 0.0001**</td>
</tr>
<tr>
<td>Bleeding and spotting (days)</td>
<td>23.0 (n = 149)</td>
<td>21.3 (n = 108)</td>
<td>−1.6 (n = 108)</td>
<td>21.0 (n = 82)</td>
<td>19.1 (n = 62)</td>
<td>−1.9 (n = 62)</td>
</tr>
<tr>
<td>Bleeding only (days)</td>
<td>17.3 ± 6.7 (n = 149)</td>
<td>13.7 ± 7.0 (n = 108)</td>
<td>16.6 ± 6.7 (n = 82)</td>
<td>14.9 ± 5.7 (n = 62)</td>
<td>−2.1 ± 7.2 (n = 62)</td>
<td>P = 0.0186**</td>
</tr>
<tr>
<td>Spotting only (days)</td>
<td>5.7 ± 5.6 (n = 149)</td>
<td>7.6 ± 7.8 (n = 108)</td>
<td>4.4 ± 5.1 (n = 82)</td>
<td>4.2 ± 5.5 (n = 62)</td>
<td>−0.2 ± 6.0 (n = 62)</td>
<td>Not available</td>
</tr>
<tr>
<td>Bleeding episodes</td>
<td>3.5 ± 0.6 (n = 149)</td>
<td>3.1 ± 0.9 (n = 108)</td>
<td>3.4 ± 0.7 (n = 79)</td>
<td>3.1 ± 0.6 (n = 62)</td>
<td>−0.4 ± 0.7 (n = 60)</td>
<td>P = 0.5095**</td>
</tr>
<tr>
<td>Sanitary protection (number of items)</td>
<td>81.6 ± 32.7 (n = 149)</td>
<td>43.3 ± 31.7 (n = 108)</td>
<td>−38.4 ± 30.0 (n = 108)</td>
<td>82.0 ± 39.3 (n = 79)</td>
<td>64.8 ± 26.3 (n = 62)</td>
<td>−16.5 ± 32.2 (n = 60)</td>
</tr>
</tbody>
</table>

Only subjects with evaluable data (i.e. no missing data) were included in this analysis.

Data are shown as mean ± SD.

*P-value from a rank ANOVA with terms for treatment and centre for the difference between adjusted means for E2V/DNG and placebo.

**P-value from a rank ANCOVA with terms for treatment and centre and baseline as covariate for the difference between adjusted means for E2V/DNG and placebo.
Safety

Safety outcomes were assessed in all randomized subjects who received at least one dose of study medication (E2V/DNG, n = 145; placebo, n = 81). A total of 145 women (64.2%) reported at least one adverse event [95 women treated with E2V/DNG (65.5%) and 50 women treated with placebo (61.7%)]. Adverse events occurring in ≥3% of women in either treatment group are shown in Table V. Overall, 14 women (9.7%) treated with E2V/DNG and 5 (6.2%) treated with placebo prematurely discontinued treatment because of adverse events. Treatment-related adverse events were reported in n = 59 (40.7%) of women who received E2V/DNG and in n = 16 (19.8%) of those who received placebo. Some of the adverse events occurred with equal frequency among both treatment groups, but were more often considered to be treatment-related with E2V/DNG than with placebo (e.g. headache, liver enzyme increase). Treatment-related adverse events occurring in ≥2% of women in either treatment group included (in alphabetical order) aspartate aminotransferase increased (E2V/DNG, 2.1%; placebo, 1.2%), breast discomfort (2.1%; 0.0%), breast pain (5.5%; 0.0%), breast tenderness (3.4%; 2.5%), dysmenorrhea (2.8%; 0.0%), γ-glutamyltranspeptidase increased (1.4%; 2.5%), headache (9.7%; 7.4%), ‘metrorrhagia’ (5.5%; 1.2%), migraine (2.1%; 2.5%) and nausea (4.1%; 0.0%). No deaths were reported during the study. The overall number of serious adverse events was low. Serious adverse events were reported by two subjects (1.4%) treated with E2V/DNG (chronic cholecystitis, n = 1; breast cancer in situ, n = 1) and two (2.5%) treated with placebo (vertigo and panic attack, n = 1; spontaneous abortion and suspicion of abnormal pregnancy, n = 1). The case of breast cancer in situ, a 4-cm lesion, was diagnosed 5 months after initiating treatment in a women aged 45 years. This event was considered to be possibly related to treatment.

Discussion

In addition to being an effective and well-tolerated OC (Palacios et al., 2010), E2V/DNG has been shown in this multinational, randomized, placebo-controlled trial to be an effective treatment in women with heavy and/or prolonged menstrual bleeding. The women recruited ‘needed’ to meet standard criteria for combined OC use, making it broadly applicable to typical combined OC users and, by including women aged over 40 years, making it applicable to a high proportion of women typically at high risk of heavy and/or prolonged menstrual bleeding. As with any clinical study, the results are generally applicable.
to the population under assessment and it is uncertain whether these results would be generalizable to women who did not meet the inclusion criteria. Overall, E2V/DNG was generally well-tolerated with <10% of women discontinuing treatment because of adverse events compared with 6% in the placebo group.

The reduction in MBL volume in recipients of E2V/DNG observed in the current study (69.4%) was sustained and was much greater than reductions observed in other studies that have investigated the efficacy of combined OCs for the treatment of HMB (Nilsson and Rybo, 1971; Fraser and McCarron, 1991; Shabaan et al., 2011). To date, only two randomized trials have investigated the efficacy of combined OCs for the treatment of HMB without organic cause using objectively quantified MBL (Fraser and McCarron, 1991; Shabaan et al., 2011). In the first trial, the mean reduction in MBL over two cycles of combined OC treatment in the 12 women who received treatment was 43% (Fraser and McCarron, 1991). In the second larger trial (n = 56), the mean reduction in MBL at 12 months of treatment was 35% (Shabaan et al., 2011). A non-randomized study of 164 women with HMB found that administration of a combined OC reduced MBL volume [measured using the alkaline haematin method described by Hallberg and Nilsson (Hallberg and Nilsson, 1964)] by 52.6% (Nilsson and Rybo, 1971). Other studies have been conducted using semi-quantitative assessments of MBL, such as pictorial blood loss assessment chart (PBAC) scores (Endrikat et al., 2009); however, such studies are limited in their usefulness as a comparator to the current one. Indeed, in the second larger randomized trial that objectively quantified MBL with combined OC use, there was a wide variation in the percentage reduction in mean MBL achieved with the combined OC as determined by the alkaline haematin method and by the PBAC score at 12 months (35 versus 2.5%; Shabaan et al., 2011).

The results of the present study are robust. The complete responder analysis selected as the primary efficacy variable was based upon stringent criteria; depending on their symptoms, complete responders had to satisfy a composite of up to eight individual criteria over 90 days. This required that, in addition to an absence of previous symptoms, women had to show a substantial defined improvement in their condition. For example, if a woman was recruited because of HMB, the response criteria required that her MBL volume per bleeding episode be <80 ml and be reduced by more than 50% relative to the average of the qualifying bleeding episodes. Therefore, a woman with a MBL volume of 130 ml at baseline and 70 ml at treatment end could not be considered a responder, as this was less than a 50% reduction in MBL. To the authors’ knowledge, no other studies have used response criteria as strict as those used in the current study. Indeed, in the response analysis conducted for the criterion ‘resolution of heavy bleeding from baseline’, a much higher response rate for E2V/DNG (63.2%) was observed compared with placebo (14.5%), rendering E2V/DNG a successful treatment option for this symptom.

Importantly, the clinical benefit of E2V/DNG was considerably larger than indicated by the results of the primary efficacy analysis. First, reductions in MBL volume were not solely restricted to those women deemed to be complete responders, but were also observed in the subgroup of women classified as partial or non-responders. In addition, the decrease in MBL in recipients of E2V/DNG was associated with a decrease in the number of sanitary protection items used and an improvement in iron metabolism parameters; the magnitude of these changes was significantly superior in E2V/DNG versus placebo recipients.

Although not substantial, placebo recipients did show some reduction in MBL volume and in the number of sanitary protection items used. This reduction in MBL with placebo has recently been shown in another study (Lukes et al., 2010). Rather than being a true reduction in blood loss, this finding may reflect ‘collection fatigue’. That is, the lack of a marked improvement in bleeding symptoms in a lengthy and demanding trial may have led to reduced motivation in some placebo recipients, resulting in a failure to collect and/or send in all of the sanitary protection items used towards the end of the trial. Nonetheless, ~40% of placebo recipients had a subjective improvement in their bleeding symptoms (as rated by both the investigators and the women themselves). Women who received placebo may simply have benefited from having their condition acknowledged, which may have contributed to this result. Another factor that may have contributed to an apparent placebo response is natural variation in menstrual bleeding with regression to the mean. Specifically, only those subjects that met the inclusion criteria were randomized to treatment and it is possible that the 90-day screening phase represented a ‘peak’ bleeding episode for some women. Conversely, those subjects with a ‘trough’ bleeding episode during the 90-day screening phase would not have been randomized.

There are several limitations of the study that should be considered. First, the primary end-point, which comprised a rigorous complete responder analysis, was designed to address regulatory requirements and is not particularly relevant to healthcare providers. The nature of the end-point meant that the gradual but substantial improvement many subjects experienced over the course of the study was concealed. For this reason, emphasis must be placed upon the secondary end-point of change in MBL volume, as this is likely the most relevant outcome for clinicians and women. A second limitation of the study was that the majority of women in this study were Caucasian, which limits the generalizability of the data to other racial and ethnic groups. However, in an identically designed study conducted in parallel in North America, similar results were observed in a population that included a substantial number of women of Black and Hispanic ethnicity (Jensen et al., 2009). Thirdly, there were no women with a complaint of frequent menstrual bleeding who reached randomization in the current study (despite being sought at initial recruitment). This is likely because of the high threshold set for frequent bleeders. That said, it is possible that frequent bleeders constitute a different population of women in whom bleeding is the result of underlying pathology and, in this case, such women would have been explicitly excluded from the study. Fourthly, many women with self-referred HMB, although being interested in participation, did not meet the strict inclusion criteria during the run-in period, principally because of measured MBL not meeting the threshold criteria. As such, it is uncertain whether women with MBL <80 ml but who perceive their bleeding as heavy would experience the same benefits as those with 80 ml or more. However, preliminary analysis of pooled data from our study and another similarly designed study showed that E2V/DNG was highly effective in reducing MBL irrespective of initial baseline MBL (Fraser et al., 2011). Lastly, the lack of an active comparator may be a
weakness of the study; however, the design of the current study was required for regulatory purposes since combined OCs are not recognized for the treatment of HMB owing to an absence of similar placebo-controlled studies.

In conclusion, this randomized controlled trial conducted in Europe and Australia shows that, in addition to providing reliable contraceptive efficacy (Palacios et al., 2010), an OC containing E₂V/DNG significantly reduces menstrual bleeding in women with heavy and/or prolonged menstrual bleeding.

Authors’ roles

All authors made substantial contributions to the conception and design and/or the acquisition/analysis/interpretation of the data. In addition, all authors were involved in the drafting of the manuscript and revising it critically for important intellectual content. All authors provided approval of the final version of the manuscript.

Acknowledgements

The authors would like to thank Lyndal Staples and Phil Jones (inScience Communications, a Wolters Kluwer business, Chester, UK) for medical writing support during the preparation of this manuscript.

Conflicts of interest

S.P., S.Z., U.M. and A.M. are employees of Bayer HealthCare Pharmaceuticals. I.F. is a consultant and speaker for Bayer HealthCare Pharmaceuticals, Schering Plough and Daiichi Sankyo Pharmaceuticals and has received research support from the National Institutes of Health (NIH), the Australian National Health and Medical Research Council, the Population Council, Bayer HealthCare Pharmaceuticals and Schering Plough. T.R. is a consultant and speaker for Bayer HealthCare Pharmaceuticals. J.T.J. is a consultant and speaker for Bayer HealthCare Pharmaceuticals, Wyeth Pharmaceuticals and Schering Plough and has received research funding from Bayer HealthCare Pharmaceuticals, Wyeth, Pharmaceuticals, Warner Chilcott, the International Committee for Contraceptive Research, and the NIH.

Funding

Funding for this study, including for the medical writing assistance, was provided by Bayer HealthCare Pharmaceuticals.

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