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A phase 2b multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of vaginal rings containing nomegestrol acetate or etonogestrel and 17β-estradiol in the treatment of women with primary dysmenorrhea☆,☆☆,★,★★

Michelle C. Fox [a,*], Christine Klipping [b], Allison Martin Nguyen [a], Tara L. Frenkl [a], Sandra M. Cruz [a], Yinna Wang [a], Tjeerd Korver [c]

[a] Merck & Co., Inc., 2000 Galloping Hill Road, Kenilworth, NJ, 07033, USA
[b] dinox bv, Hanzeplein 1 /INGANG53, 9713, GZ, Groningen, The Netherlands
[c] Reprovision Clinical Consultancy, Beethovengaarde 111, 5344, CE, Oss, The Netherlands

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ABSTRACT

Objective: To evaluate the effect of investigational vaginal rings containing nomegestrol acetate (NOMAC) plus 17β-estradiol (E2) or etonogestrel (ENG) plus E2 in women with moderate to severe primary dysmenorrhea.
Study design: This was a Phase 2b randomized, placebo-controlled, multicenter, double-blind study. We randomized participants to one of five treatment groups: four hormonal rings and one placebo ring. The investigational vaginal rings released 300 μg of E2 daily along with 700 μg or 900 μg of NOMAC or 100 μg or 125 μg of ENG. Each participant received 2 identical rings and was to insert each for 21 days followed by a 7-day ring-free period. The primary endpoint, as assessed by a daily electronic diary (e-Diary), was the change in menstrual pain score from baseline to the second in-treatment withdrawal bleeding episode (Cycle 2). The pain score was the mean of the three highest scores for menstrual cramping pain (0–4 point scale) recorded from the day before menses to the third day of bleeding. The primary hypothesis was that at least one investigational vaginal ring would demonstrate a statistically significant larger reduction from baseline in pain score compared to placebo. Secondary endpoints included total mean impact score (which assessed the negative impact on work/school, physical activities, leisure/social activities) and the amount and days of rescue medication (ibuprofen) used. Clinical trial registration number: NCT01670656.
Results: We randomized 439 participants. The mean pain score decreased from baseline to Cycle 2 in all groups; the decrease in all four treatment groups compared to placebo was statistically significant (p-values ≤0.002). All treatment groups had greater reductions than placebo in ibuprofen intake and greater improvement in impact scores; these differences were statistically significant for both endpoints for the ENG-E2 100/300 μg/day group, while the other groups were not statistically significant for one or both endpoints.
Conclusion: All four investigational rings produced a statistically significantly larger reduction from baseline in mean menstrual pain score compared to placebo while pain medication use decreased.
Implications: This placebo-controlled study provides evidence that vaginal contraceptive rings containing NOMAC-E2 or ENG-E2 improve moderate to severe dysmenorrhea, across all of doses studied. This adds to the evidence that hormonal contraceptives are effective treatments for dysmenorrhea.

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* Corresponding author. Tel.: +1 732 594 2312.
E-mail addresses: michelle.fox2@merck.com (M.C. Fox), c.klipping@dinox.umcg.nl (C. Klipping), allison_martin@merck.com (A.M. Nguyen), tara_frenkl@merck.com (T.L. Frenkl), sandra_cruz@merck.com (S.M. Cruz), yin.na.wang@merck.com (Y. Wang), tjeerd.korver@gmail.com (T. Korver).

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1. Introduction

Primary dysmenorrhea, affecting up to 91% of females under age 20 and up to 67% over 18 [1], is defined as cramping pain in the pelvis occurring just before or during menstruation, in the absence of underlying reproductive tract pathology. Among women with primary dysmenorrhea, approximately half experience moderate to severe pelvic pain, which may last 8 to 72 hours (h) after menses begins. Dysmenorrhea symptoms may interfere with normal daily activities [2,3], such that 10–30% of all working women and students in the United States miss 1–2 days of work or school per month [1].

Hormonal contraceptives (HCs) prevent or lessen primary dysmenorrhea by inhibiting ovulation, thereby limiting estrogen-induced endometrial growth and decreasing prostaglandin production. Although combined oral contraceptives (COC) are commonly used for treatment [4], and the etonogestrel (ENG) – ethinyl estradiol (EE) contraceptive vaginal ring has been associated with a reduction in menstrual pain [5–9], few randomized placebo-controlled trials have been performed to evaluate HCs for dysmenorrhea treatment [4,10–12]. No studies to date have used adequate methodology to capture both daily pelvic pain ratings and rescue medication use to accurately assess efficacy.

This double-blind, randomized trial evaluated efficacy and safety of four investigational vaginal rings for treatment of moderate to severe primary dysmenorrhea, using an electronic diary (e-Diary) to capture daily pain ratings, rescue medication use and the impact of pelvic pain on daily life. The rings released 300 μg of E2 daily along with 700 μg or 900 μg of nomegestrol acetate (NOMAC) (hereafter referred to as NOMAC-E2 700/300 and NOMAC-E2 900/300), or along with 100 μg or 125 μg of etonogestrel (ENG) (hereafter referred to as ENG-E2 100/300 and ENG-E2 125/300). The daily release rates of NOMAC and ENG were chosen based on prior studies demonstrating ovulation inhibition, cycle control and tolerability during development of oral NOMAC-E2 and the ENG-EE vaginal ring. Physiologic E2 was selected rather than EE as it is theorized to be less thrombogenic and have less adverse effects on the cardiovascular profile. The E2 release rate was selected to restore physiologic levels (i.e., mean 60–100 pcg/mL) to avoid hypoestrogenic effects of progestin induced ovarian suppression.

2. Methods

2.1. Study participants

We conducted the study at 38 sites throughout the EU, Australia, New Zealand, South America, Mexico and South Africa in accordance with guidelines on good clinical practice and ethical standards established by the Declaration of Helsinki. We obtained approvals from all appropriate ethical review committees and institutional review boards. All participants provided written informed consent. The study was registered as ClinicalTrials.gov number NCT01670656 [Protocol no. PO8257/MK-8175A/MK-8342B-057].

We enrolled otherwise healthy women 18 to 50 years of age with regular menstrual cycles (cycle length 23–35 days) who reported moderate to severe primary dysmenorrhea. We excluded women with secondary amenorrhea (as determined or suspected by medical history or physical examination) and those requiring diagnostic imaging. Participants had to discontinue HCs and intrauterine devices and use condoms for the study duration unless sterilized. Key exclusion criteria were as follows: standard contraindications to COCs (e.g., severe hypertension); secondary dysmenorrhea; pregnant or lactating; self-reported unsatisfactory response to previous hormonal treatment of dysmenorrhea; allergy/sensitivity to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs; HC injection within 6 months of screening; medicines affecting steroid bioavailability within the past 2 months.

Additionally, participants recorded menstrual bleeding and cramping pain score on a daily electronic diary (e-Diary) throughout a screening menstrual cycle to confirm existing moderate to severe dysmenorrhea. We used the cramping pain question from the Menstrual Distress Questionnaire – Today version (MDQ-T) which asks women to rate the most severe cramping pain experienced in the last 24 h (0-'no cramping', 1-'mild', 2-'moderate', 3-'strong', 4-'severe') [13]. We averaged the three highest scores during the time from the day before menses onset to menstrual cycle day 3 (hereafter, this interval is designated the "cramping window") to determine the mean menstrual pain score. Subjects with a mean score <2 during the screening menstrual cycle were excluded.

2.2. Study design

Figure S1 (Supplemental Material) shows the study design. This was a randomized, placebo-controlled, multicenter, double-blind study with five groups: NOMAC-E2 700/300, NOMAC-E2 900/300, ENG-E2 100/300, ENG-E2 125/300 and placebo vaginal rings. After confirming eligibility during the screening cycle, subjects were randomized using an interactive voice response system (IVRS). Randomization was performed in a 1:1:1:1:1 ratio with a block size of 5 by a computer generated sequence not accessible to the study team or site staff. To protect blinding (due to slight color difference between active and placebo rings), the rings were dispensed in identical opaque sachets and were not shown to the investigators or staff.

Each participant received two rings of the same formulation. The participant inserted the first ring in clinic during the first week of their menstrual cycle, marking treatment Cycle 1/ Day 1. Participants were instructed to leave the ring in place for 21 days and then remove it at home on Day 22. After 7 ring-free days (Days 22 through 28), participants were to insert the second ring at home (Cycle 2/ Day 1), and this ring was to remain in place for 21 days and be removed on Day 22. Ibuprofen (400 mg tablets) was provided for rescue treatment for dysmenorrhea (maximum of 3200 mg allowed daily). The investigators instructed participants to use no other analgesics without first contacting the site.

Our primary objective was to identify at least one ring that showed efficacy for primary dysmenorrhea, as demonstrated by a statistically significant larger reduction in mean menstrual pain score from baseline to Cycle 2 compared to placebo.

2.3. Patient reported outcome measures

The daily e-Diary included a new patient-reported outcome measure, the Dysmenorrhea Daily Diary (DysDD), which captured vaginal bleeding, cramping pain score, rescue pain medication use, and the impact of pelvic pain on daily life [14]. Validation of the DysDD using data from this trial has been published [15].

2.4. Efficacy endpoints

The primary endpoint was the change from baseline to Cycle 2 in mean menstrual pain score (mean of three highest pain scores during the cramping window). The cramping window focused data collection and analyses when the most severe dysmenorrhea was expected based on qualitative patient interviews and quantitative data collected during development of the DysDD [14] and e-Diary. If no bleeding occurred, cycle Days 21 to 28 were used in place of the cramping window for analysis.

Secondary endpoints included change from baseline versus placebo to Cycle 2 in mean total impact score, number of ibuprofen tablets used for menstrual pain, and number of days of ibuprofen intake. Additionally, the responder rate per cycle was determined; a responder was defined as a participant with at least a 1-point reduction in pain score, as compared to baseline.

2.5. Safety assessments

Safety assessments included monitoring of adverse events (AEs) and vital signs. Venous and arterial thrombotic/thromboembolic events were pre-specified as Tier 1 events subject to inferential testing for statistical significance.

2.6. Sample size determination

Based on assumptions from previous studies and an estimated 15% drop out rate, we estimated sample size to be 450 to achieve more than 90% power to demonstrate that at least one investigational ring had a statistically significant reduction from baseline with respect to the primary endpoint. For further details, see the study protocol (Supplemental Material).

2.7. Statistical analysis

The Full Analysis Set (FAS), consisting of all randomized participants who inserted a vaginal ring with at least one baseline or one post-baseline efficacy assessment was the primary population used for efficacy analyses. We analyzed primary and secondary efficacy endpoints using a constrained longitudinal data analysis (cLDA) method [16] in which least squares (LS) mean change from baseline was estimated from a linear model. The cLDA model included terms for treatment, time, and the interaction of time by treatment. All analyses were restricted to data from the cramping window. Each group's change from baseline was compared to placebo. Dunnett's procedure was applied for multiplicity adjustment in the primary hypotheses [17]. The All Subjects as Treated (ASaT) population, consisting of all participants who inserted a vaginal ring, was used for the safety data analysis.

3. Results

Fig. 1 shows participant disposition; 840 participants were screened beginning in January 2013, and 439 participants were randomized. Due to an unexpected increase in screen failures just prior to ending recruitment, we randomized slightly less than 450 subjects. The last subject was randomized in July 2013 and completed follow-up in September 2013. All but one randomized participant (assigned to ENG/E2 100/300) received treatment. Thirty-five participants discontinued; the most common reasons for discontinuation were AEs and non-compliance with the protocol or treatment (Fig. 1). Over 90% of participants completed the study.

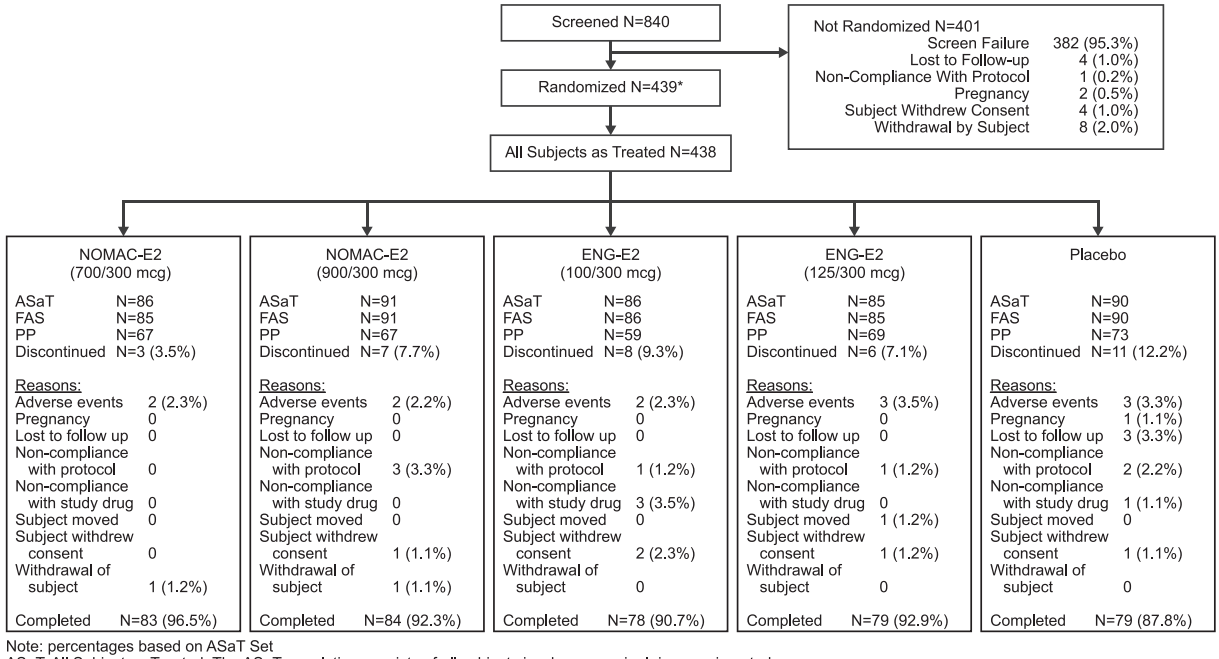
The demographics of the groups were similar (Table 1). The mean age of the combined population was 28.6 years. Most (75.6%) of the participants were white, and 20% were multi-racial. The mean body mass index of the population was 23.6 kg/m^2.

Compliance, assessed as the percentage of cycles with both a ring use period of 21±2 days and a ring-free period of 7±1 days, ranged between 72.1% and 87.1% per cycle. Over 75% of patients kept the ring *in situ* throughout the entire ring-use period.

3.1. Efficacy

Table 2 provides outcomes for the FAS analyses; however, per-protocol analyses had similar results (data not shown). For those on active treatment, mean pain scores at baseline ranged from 2.8 to 2.9 (i.e., moderate to strong pain) and from 0.9 to 1.3 (i.e., mild pain) during Cycles 1 and 2. The active groups had LS mean reduction in pain score from baseline of 1.7 or more at Cycle 2. In the placebo group, mean baseline pain score was 3 and mean reduction from baseline was 1.2. As shown in Table 2, changes from baseline to Cycle 2 in the active ring groups were all statistically significantly greater than with placebo ($p \leq 0.002$).

Across active treatment groups, mean rescue ibuprofen use decreased from 9 to 10 tablets at baseline to 3 to 4 tablets at Cycle 2; a smaller decrease occurred in the placebo group (10 tablets at baseline to 5 at Cycle 2). The difference in change from baseline in tablets reported per day in investigational treatment groups compared to placebo ranged between −1.2 and −2.3 tablets (Table 2). When adjusted for multiple comparisons, the decrease in tablet intake



Note: percentages based on ASaT Set
ASaT: All Subject as Treated. The ASaT population consists of all subjects in whom a vaginal ring was inserted.
FAS: Full Analysis Set. The FAS population consists of all randomized subjects, in whom a vaginal ring was inserted, with at least one baseline or post-baseline efficacy value.
PP: Per Protocol. The PP Set is defined as a subset of the FAS and consists of subjects who were compliant to the protocol, ie, those subjects who did not have any protocol violation that may interfere with the assessment(s) of efficacy.
*1 subject did not insert a vaginal ring.

Fig. 1. Disposition of participants.

Table 1
Demographics and baseline characteristics of participants* in a Phase 2b clinical trial of vaginal rings containing nomegestrol acetate or etonogestrel and 17β-estradiol.

Parameter	NOMAC-E2 700/300 μg N=86	NOMAC-E2 900/300 μg N=91	ENG-E2 100/300 μg N=86	ENG-E2 125/300 μg N=85	Placebo N=90
Age					
Mean ± SD	28.7±7.5	28.7±8.1	29.1±7.7	28.3±7.8	28.4±8.2
Range	18 to 47	18 to 44	18 to 46	18 to 49	18 to 48
Race, n (%)					
American Indian or Alaska Native	2 (2.3)	3 (3.3)	2 (2.3)	2 (2.4)	2 (2.2)
Asian	0	1 (1.1)	0	1 (1.2)	0
Black or African American	1 (1.2)	0	0	1 (1.2)	1 (1.1)
Multi-racial	17 (19.8)	16 (17.6)	17 (19.8)	18 (21.2)	19 (21.1)
Native Hawaiian or Other Pacific	0	2 (2.2)	0	2 (2.4)	0
White	66 (76.7)	69 (75.8)	67 (77.9)	61 (71.8)	68 (75.6)
Ethnicity, n (%)					
Hispanic or Latino	28 (32.6)	29 (31.9)	31 (36.0)	24 (28.2)	28 (31.1)
Not Hispanic or Latino	58 (67.4)	62 (68.1)	55 (64.0)	61 (71.8)	62 (68.9)
BMI, kg/m^2					
Mean ± SD	23.4±3.9	23.6±3.7	23.5±3.9	23.5±4.1	23.9±4.6
Range	17.7 to 34.9	18.1 to 33.6	18.0 to 33.9	16.8 to 34.8	18.0 to 42.9

BMI = body mass index; NOMAC-E2 = nomegestrol acetate/17β-estradiol; ENG-E2 = etonogestrel/17β-estradiol.
* Includes all randomized subjects who inserted a vaginal ring and thus excludes one subject assigned to ENG-E2 100/300 who was randomized but never treated.

reached statistical significance for the ENG/E2 100/300 group only (adjusted p=0.006). The LS mean change from baseline in number of days that ibuprofen was taken was greater in the active groups (−1.4 to−1.7 days) compared to placebo (1.1 days) (Table 2); this difference was statistically significant for ENG/E2 100/300 and NOMAC/E2 900/300 (p≤0.01).

Table 2
Primary (menstrual pain score) and secondary (total mean impact score, total number of ibuprofen tablets consumed, number of days of ibuprofen tablets taken, and secondary responder rate) efficacy endpoints by vaginal ring treatment group (Full Analysis Set; N=437[1]).†

Endpoint	NOMAC-E2 700/300 μg N=85	NOMAC-E2 900/300 μg N=91	ENG-E2 100/300 μg N=86	ENG-E2 125/300 μg N=85	Placebo N=90
Primary: Menstrual Pain Score					
Baseline, Mean ± SD	2.9±0.7	2.8±0.7	2.8±0.7	2.9±0.6	3.0±0.5
Cycle 1, Mean ± SD	1.3±0.9	1.3±1.0	1.3±1.1	1.3±1.0	1.8±1.0
Cycle 2, Mean ± SD	1.1±0.9	1.1±1.0	0.9±0.9	1.2±1.0	1.8±1.0
LS Mean (95% CI) Change from Baseline at Cycle 2[1]	−1.7 (-2.0, −1.5)	−1.7 (−1.9, −1.5)	-1.9 (-2.1, −1.7)	−1.7 (-1.9, −1.5)	−1.2 (-1.4, −0.9)
Difference (95% CI) versus Placebo in LS Mean Change from Baseline at Cycle 2	−0.6 (-1.0, −0.2)	−0.6 (-0.9, −0.2)	−0.8 (-1.1, −0.4)	−0.5 (-0.9, −0.2)	
Adjusted p-value for Difference versus Placebo	<0.001	<0.001	<0.001	0.002	
Secondary: Total Mean Impact Score in the Dysmenorrhea Daily Diary (DysDD)					
Baseline, Mean ± SD	8.6±3.9	8.4±3.6	8.4±3.8	8.7±3.6	9.1±3.6
Cycle 2, Mean ± SD	3.7±3.2	3.6±3.6	3.9±3.3	4.5±3.8	5.8±3.8
LS Mean (95% CI) Change from Baseline at Cycle 2[1]	−4.8 (-5.6, −4.0)	−5.0 (-5.7, −4.2)	−4.7 (-5.5, −3.9)	−4.3 (-5.1, −3.5)	−3.1 (-3.9, −2.4)
Difference (95% CI) versus Placebo in LS Mean Change from Baseline at Cycle 2	−1.7 (-3.0, −0.4)	−1.9 (-3.1, −0.6)	−1.6 (-2.9, −0.3)	−1.2 (-2.5, 0.1)	
Adjusted p-value for Difference versus Placebo	0.006	0.001	0.012	0.084	
Secondary: Total Number of Ibuprofen Tablets Consumed					
Baseline, Mean ± SD	9.8±6.9	9.2±5.6	10.3±7.0	9.3±6.4	10.3±11.3
Cycle 2, Mean ± SD	3.4±3.8	3.3±5.8	2.8±4.5	3.6±4.8	5.1±5.1
LS Mean (95% CI) Change from Baseline at Cycle 2[1]	−6.4 (-7.5, −5.3)	−6.3 (-7.4, −5.2)	−7.1 (-8.2, −6.0)	−6.0 (-7.1, −4.9)	−4.8 (-6.0, −3.7)
Difference (95% CI) versus Placebo in LS Mean Change from Baseline at Cycle 2	−1.6 (-3.4, 0.2)	−1.5 (-3.3, 0.2)	−2.3 (-4.1, −0.5)	−1.2 (-3.0, 0.6)	
Adjusted p-value for Difference versus Placebo	0.089	0.123	0.006	0.343	
Secondary: Number of Days Ibuprofen Tablets Taken					
Baseline, Mean ± SD	2.7±0.9	2.8±0.9	2.8±0.9	2.7±1.0	2.8±0.8
Cycle 2, Mean ± SD	1.5±1.3	1.1±1.1	1.1±1.2	1.3±1.2	1.7±1.1
LS Mean (95% CI) Change from Baseline at Cycle 2[1]	−1.3 (-1.5, −1.0)	−1.7 (-2.0, −1.4)	−1.7 (-2.0, −1.4)	−1.4 (-1.7, −1.1)	−1.1 (-1.4, −0.9)
Difference (95% CI) versus Placebo in LS Mean Change from Baseline at Cycle 2	−0.1 (−0.6, 0.3)	−0.6 (-1.0, −0.1)	-0.6 (-1.0, −0.1)	−0.3 (-0.7, 0.2)	
Adjusted p-value for Difference versus Placebo	>0.999	0.009	0.010	0.535	
Secondary: Responder[2] Rate per Cycle					
Cycle 1, n/m (%)	61/83 (73.5)	64/85 (75.3)	57/78 (73.1)	61/81 (75.3)	36/66 (54.5)
Cycle 2, n/m (%)	60/80 (75.0)	63/82 (76.8)	64/79 (81.0)	58/77 (75.3)	39/70 (55.7)

NOMAC-E2 = nomegestrol acetate/17β-estradiol; ENG-E2 = etonogestrel/17β-estradiol; SD = Standard Deviation; CI=Confidence Interval; LS Mean = Least-Squares Mean; 95% CI for difference in LS Means was adjusted for Dunnett correction.
† N=437; 2/439 randomized patients (one treated and one who never inserted a ring) contributed no efficacy endpoint data.
[1] Based on a longitudinal data analysis model with terms for treatment time (cycle) and the interaction of time by treatment. The total mean impact score from the DysDD was calculated by summing the scores across four impact scores (impact on work/school, social/leisure activities, physical activities, and sleep). Each item was rated on a 5-point scale: total impact score ranged from 0 to 16.
[2] A responder was defined as a participant with at least 1 point reduction in the mean menstrual pain score for the cycle. N=Number of participants in full analysis set; m = within group total number of participants (number of evaluable cycles).

At Cycles 1 and 2, approximately 75% receiving investigational rings compared to over 50% receiving placebo were responders, defined as participants achieving a reduction of at least 1 point in pain score (Table 2). The decrease from baseline to Cycle 2 in total impact score was statistically significantly greater for all active rings compared to placebo, except for ENG/E2 125/300.

3.2. Safety

There were no notable differences among the groups in the AE rates (Table S1, Supplemental Material). Three serious AEs were reported in two participants, with none assessed by the investigator as treatment-related. These included appendicitis, drug toxicity (not to study medication), and impulse disorder. There were no arterial or venous thrombotic events. AEs reported by ≥5% of participants in any group included breast pain, headache, and acne. Similar proportions of participants across all groups, including placebo, reported headaches. Breast pain was reported more frequently in the NOMAC-E2 700/300 group and acne was reported more frequently in the placebo group.

4. Discussion

This study adds to data from randomized trials on the efficacy of using HCs to treat primary dysmenorrhea and is the first to use a daily e-Diary containing the DysDD to evaluate treatment of dysmenorrhea. All active rings demonstrated a statistically significantly larger reduction in mean menstrual pain score vs. placebo. The investigational rings also reduced the impact of dysmenorrhea on daily activities as compared to placebo. While the ENG-E2 100/300 ring may be considered the most effective ring in this study because it was the only ring to achieve statistical significance compared with placebo for all primary and secondary endpoints, differences between groups were small and no statistical testing was performed to compare treatment response between rings. The high placebo response (i.e., 40% decrease from baseline pain score) may have limited the ability to find statistically significant differences in secondary outcomes; however, the benefit of treatment is evident with statistically significant greater pain score reductions than placebo and a 1-point improvement in pain for over 75% of subjects in all active treatment groups while rescue medication use decreased. A major strength of the study is the randomized placebo-controlled design, which decreases the chance of bias. Only three of ten past placebo-controlled studies were ranked as having high-quality methods by the Cochrane systematic review published in 2009 [18]; the others were noted to have major flaws in randomization or blinding or did not report data in ways conducive to meta-analysis. While meta-analysis of these 10 studies (n=497) demonstrated treatment efficacy of COCs for dysmenorrhea vs. placebo (OR 2.1, 95% CI 1.2.-3.1), there was significant heterogeneity in results due to differences in severity of dysmenorrhea and outcome measures. The first of the high-quality studies, Culberg et al. (1972) [12], used higher-dose COCs containing 50 mcg EE that are rarely used today. Davis et al. (2005) [11] published the effect of a low dose COC on adolescents with moderate to severe dysmenorrhea (n=74) and found that COCs were a more effective than placebo with decrease in total MDQ pain score and in use of pain medication. As this study used total MDQ pain score (rather than the cramping score alone), results cannot be directly compared to our study. Hendrix and Alexander (2002), in a placebo-controlled study of a low dose COC for dysmenorrhea, noted the most significant changes in MDQ results were seen in the cramping pain score (mean change −1.4 with COC and −0.3 with placebo; p<.0001) [10].

Similar to Hendrix and Alexander (2002), we focused on the cramping pain score of the MDQ; however, we used e-Diaries and prospectively assessed baseline pain in the same manner prior to and during treatment [10]. All other studies assessed baseline pain via retrospective recall. This study is the first to use an e-Diary that prevented late (>48 h delay) data and thus is less affected by recall bias, resulting in more accurate assessment of treatment response.

We also used a novel approach to assess efficacy by limiting analyses to the most relevant days within the cycle (i.e., 4-day cramping window). This prevents pain experienced during non-menstrual days from confounding the analysis. As informed by patient interviews in women with moderate to severe dysmenorrhea, the majority experience most severe pain for 1–2 days during the first days of bleeding and some experience pain prior to menses onset [14,15]. Thus, treatment is expected to have the greatest impact during this time. In the rare cases that higher pain ratings were recorded after day 3 of menses, those missed 'peak' pain ratings would be randomly distributed across treatment groups and not expected to impact overall results.

This study is the only study to determine the effect of HC on dysmenorrhea with an adequate control for use of over the counter (OTC) pain medication. No other study restricted rescue medication use to one formulation with daily reporting of tablet intake. Due to uniform use of rescue medication (as well as the randomized, placebo-controlled design), we may conclude that the effect is due to treatment and not confounded by increased pain medication use or other factors.

A key limitation is exclusion of women who reported inadequate response to prior hormonal therapy. This exclusion was used to maximize the potential for showing treatment response in this Phase 2 study. Further confirmation of effect is needed in a larger study open to all women with primary dysmenorrhea.

Though all investigational rings were associated with a decrease in pain and impact scores compared to placebo, results were often not statistically significant. This is in part due to a large placebo effect. Past studies have demonstrated a placebo effect as well; though differences in methods of data collection and analysis make comparisons difficult to interpret [10,11]. In Hendrix and Alexander (2002), the placebo effect appears lower than our study [10]. This may be due to numerous factors including use of paper diaries, assessment of pain score on Cycle Day 2 only, or differences in study populations and assessment of treatment outcome at Cycle 4 (versus Cycle 2). It is possible, but unlikely, that the use of a vaginal ring versus COC contributed due to unknown differences between users of each method.

Additional limitations are as follows. The short study precludes assessment of whether the treatment effect will decrease over time. Slight differences in color between the placebo and active rings could have unblinded the study; however, participants, investigators and staff did not have the opportunity to compare the rings. Participants with prior COC or vaginal ring use may have been alerted to treatment assignment (i.e., active vs. placebo) depending on how closely their menses/withdrawal bleeding correlated with ring removal; however, this is unlikely given that discordance may be expected in the first few cycles of use. There were no known incidents of potential unblinding.

Further study of ENG-E2 and NOMAC-E2 rings is needed to confirm treatment efficacy in larger randomized trials of women with primary dysmenorrhea as well as to explore treatment in women with underlying pathology (e.g., endometriosis, fibroids).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2018.10.009.

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