

Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial

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BACKGROUND: Dienogest is a selective progestin that has been investigated in a clinical trial programme for the treatment of endometriosis. The current non-inferiority trial compared the efficacy and safety of dienogest against leuprolide acetate (LA) for treating the pain associated with endometriosis.

METHODS: Patients with confirmed endometriosis were randomized to treatment with dienogest (2 mg/day, orally) or LA (3.75 mg, depot i.m. injection, every 4 weeks) for 24 weeks. The primary efficacy variable was absolute change in pelvic pain from baseline to end of treatment, assessed by visual analogue scale (VAS). Safety variables included adverse event profile, laboratory parameters, bone mineral density (BMD), bone markers and bleeding patterns.

RESULTS: A total of 252 women were randomized to treatment with dienogest ($n = 124$) or LA ($n = 128$); 87.9 and 93.8% of the respective groups completed the trial. Absolute reductions in VAS score from baseline to Week 24 were 47.5 mm with dienogest and 46.0 mm with LA, demonstrating the equivalence of dienogest relative to LA. Hypoestrogenic effects (e.g. hot flushes) were reported less frequently in the dienogest group. As expected, bleeding episodes were suppressed less with dienogest than with LA. Changes in mean lumbar BMD between screening and final visit were +0.25% with dienogest and -4.04% with LA subgroups ($P = 0.0003$). Markers of bone resorption increased with LA but not dienogest.

CONCLUSIONS: Dienogest 2 mg/day orally demonstrated equivalent efficacy to depot LA at standard dose in relieving the pain associated with endometriosis, although offering advantages in safety and tolerability.

Key words: dienogest / progestins / endometriosis / pelvic pain / GnRH agonists

Introduction

Endometriosis is a prevalent and chronic condition in women of child-bearing age (National Institutes of Health, 2007). There is currently no cure for endometriosis and reported recurrence rates after surgical therapy are high (Guo, 2009). The aim of most medical therapies is to alleviate the severity of symptoms, which typically include pelvic pain, dysmenorrhoea and dyspareunia, combined with an acceptable safety profile that together offers an improvement in the woman's quality of life (Kennedy *et al.*, 2005; Gao *et al.*, 2006).

Commonly used medical therapies that are approved in the treatment of endometriosis include: gonadotrophin-releasing hormone (GnRH) agonists; the androgen danazol; and progestins. Although these agents represent standard therapies in endometriosis, they are frequently associated with suboptimal safety and tolerability that impact on long-term use and adherence. For example, GnRH agonists such as leuprolide acetate (LA), whereas accepted as highly efficacious therapy, are associated with symptoms of estrogen deprivation (including hot flushes, vaginal dryness, headache and decreased libido) and bone demineralization that limits treatment to 6 months

in the absence of add-back therapy (Prentice *et al.*, 2000; Winkel and Scialli, 2001; Mounsey *et al.*, 2006). Danazol is characterized by adverse changes in lipid metabolism and androgenic adverse effects, including weight gain, oedema, acne, hirsutism and oily skin, which lead to low compliance with therapy (Winkel and Scialli, 2001; Selak *et al.*, 2007).

Progestins offer long-term efficacy in endometriosis, but a number of these agents are associated with weight gain and androgenic effects when administered at the high doses required for efficacy (Mahutte and Arici, 2003; Vercellini *et al.*, 2003). Depot medroxyprogesterone acetate (MPA; 104 mg, subcutaneous injection, every 3 months) has demonstrated an efficacy equivalent to LA, but long-term use of depot MPA preparations is shown to impact adversely on bone mineral density (BMD), while the delay in resumption of ovulation that may follow discontinuation of this therapy is a contraindication to use in women wishing to conceive in the near future (Vercellini *et al.*, 2003; Crosignani *et al.*, 2006; Schlaff *et al.*, 2006). Combined oral contraceptives, whereas widely used to manage symptoms of endometriosis, are not approved for this indication in most countries and lack a solid body of supportive clinical trial evidence (Davis *et al.*, 2007).

Dienogest is a selective progestin that combines the pharmacological properties of 19-norprogestins and progesterone derivatives, offering a pronounced progestogenic effect at the endometrium with an absence of androgenicity and moderate suppression of ovarian activity (Oettel *et al.*, 1999; Schindler *et al.*, 2006; Sasagawa *et al.*, 2008).

In clinical trials, including a dose–response study (Köhler *et al.*, 2010), a placebo-controlled study (Seitz *et al.*, 2008), an active-controlled study versus triptorelin after laparoscopic surgery (Cosson *et al.*, 2002) and a long-term safety study (Seitz *et al.*, 2009), dienogest was shown to be an effective and well-tolerated treatment for endometriosis. The dose–response study indicated that 2 mg/day is the optimal dose for dienogest in the treatment of endometriosis (Köhler *et al.*, 2010).

The aim of the current clinical trial was to investigate the efficacy and safety of dienogest 2 mg orally once daily in the treatment of pelvic pain associated with endometriosis in a direct comparison using a non-inferiority design against a current standard therapy consisting of depot LA.

Materials and Methods

Patients

Women aged 18–45 years were eligible for study enrolment if they experienced pain associated with histologically proven endometriosis in revised-American Fertility Society (r-AFS, 1985) stages I–IV. Endometriosis had to be confirmed by diagnostic laparoscopy within 3 months of study commencement or by therapeutic laparoscopy within 12 months of study commencement with a subsequent recurrence of pain.

Exclusion criteria included pregnancy or breast feeding, amenorrhoea within 3 months of screening, a primary need for surgical treatment of endometriosis, previous use of hormonal agents (e.g. GnRH agonists ≤ 6 months, progestins or danazol ≤ 3 months or oral contraceptives ≤ 1 month before screening), abnormal findings at gynaecological examination, an abnormal cervical cytological smear in the last 3 months or risk factors for decreased BMD (e.g. a family history of osteoporosis or use of anticonvulsants or corticosteroids).

Study design

The study was a 24-week, multicentre, randomized, open-label, parallel-group study of dienogest versus LA. Patients were randomized in a 1:1 distribution to receive dienogest at a dose of 2 mg, given orally at the same time once daily, or LA at a standard dose of 3.75 mg as a depot i.m. injection every 4 weeks. Randomization was done using randomization blocks, with a randomization list generated by Corporate Biometry, Schering AG. The first dienogest tablet was taken on the first day after onset of menstrual bleeding and the first LA injection was given during the first 3 days of menstrual bleeding.

Compliance with dienogest treatment was monitored by diary records completed by patients. On the basis of their modes of action, contraceptive coverage could be expected for dienogest and LA; however, women were advised to use barrier methods during the study period if they required reliable contraception.

The study was conducted at 17 centres in Germany (nine centres), Austria (two centres), Spain (two centres), Poland (two centres), Italy (one centre) and Portugal (one centre), between December 1998 and April 2001. The study protocol was approved by the local independent ethics committees and all participants provided written, informed consent before study enrolment. The study was conducted in accordance with the amended version of the Declaration of Helsinki and in compliance with the principles of Good Clinical Practice.

Efficacy variables

The primary efficacy variable was the absolute change in endometriosis-associated pelvic pain from baseline to the end of treatment, assessed by a visual analogue scale (VAS; 0 mm = absence of pain, 100 mm = unbearable pain). The VAS score was selected as the primary efficacy variable in this study because the VAS is an appropriate and well-established tool for the measurement of pelvic pain associated with endometriosis (Fauconnier *et al.*, 2009).

Secondary efficacy variables included rates of improvement in pelvic pain measured by VAS score change, responder rates based on a range of VAS score definitions, and changes in the physician-administered modified Biberoglu and Behrman (B&B) severity profile, encompassing symptoms (pelvic pain, dysmenorrhoea and dyspareunia) and physical findings (pelvic tenderness and induration; Biberoglu and Behrman, 1981).

Quality of life variables

Changes in quality of life from baseline to the end of treatment were assessed using the Short Form-36™ (SF-36) Health Survey (Ware and Kosinski, 2001).

Safety variables

Spontaneously reported adverse events were recorded at pretreatment, Week 12 and Week 24 (during the final visit) and were classified using the Hoechst Adverse Reaction Terminology System (HARTS). Adverse events were rated treatment-related at the discretion of investigators. Episodes of hot flushes were documented daily by women using diary cards. BMD and markers of bone metabolism were measured in a patient subgroup from three study centres. BMD of the lumbar spine (L1–L4) was assessed at screening and at the final visit using dual energy X-ray absorptiometry. Bone metabolism markers were assessed at baseline and at the final visit and included serum bone specific alkaline phosphatase, serum N-mid osteocalcin, urinary calcium and urinary CrossLaps®.

Clinical laboratory parameters were analysed on blood and urine specimens from women in a non-fasting state at pretreatment and Week 24. In addition, serum estradiol was analysed at baseline and Week 24 in a patient subgroup from three study centres.

The presence and intensity of bleeding were documented by women on a diary card each day. Physical examination, including blood pressure and bodyweight measurement, was performed at pretreatment and Week 24.

Statistical analysis

The primary study aim was to demonstrate the non-inferiority of dienogest compared with LA for the treatment of pelvic pain associated with endometriosis, measured by the change in VAS score from baseline. On the basis of available data for other conditions characterized by chronic pain (Wells *et al.*, 1993; Todd and Funk, 1996), a non-inferiority margin of 15 mm on the VAS was prespecified. As is appropriate for non-inferiority studies (Piaggio *et al.*, 2006), the primary analysis was based on the per protocol set (PPS), which included all randomized patients except those with major protocol deviations that affected the primary efficacy variable. The full analysis set (FAS), which included all randomized patients receiving at least one unit of study medication and providing at least one observation after dosing, was also investigated in support of analyses on the PPS.

A secondary efficacy analysis was the proportion of women who experienced an improvement in pain score by study end. The null hypothesis that dienogest is inferior to LA with respect to the proportion of women improving during treatment was tested against its alternative that dienogest is not inferior to LA, using the normal approximation for binomially distributed data. The prespecified non-inferiority margin was 20% points, which coincides with the margin for response rates used in earlier approvals of endometriosis therapies by the US Food and Drug Administration (2005). The test was performed at a one-sided significance level of $\alpha = 2.5\%$. Responder rates using various definitions of response were compared between treatments using the same methodology.

The sample size was calculated on the assumption of equal efficacy for dienogest and LA and a common standard deviation (SD) of 30 mm for the primary efficacy variable. A total of 88 evaluable patients were required in each treatment group to yield a power ($1-\beta$) of 90% to demonstrate the non-inferiority of dienogest relative to LA. Assuming a withdrawal rate of 30%, a total of 252 patients was therefore required for enrolment.

Safety analyses were performed on the FAS, unless otherwise specified. The percent change from baseline in BMD was a secondary target variable subject to statistical testing. In order to show that the loss in BMD was lower when dienogest rather than LA was administered, the null hypothesis:

$$H_0 : \mu_{LA} \geq \mu_{DNG}$$

was tested against the alternative hypothesis:

$$H_1 : \mu_{LA} < \mu_{DNG}$$

where μ_{DNG} and μ_{LA} denote the expected values for the percentage change from baseline in BMD in the dienogest and LA groups, respectively. The null hypothesis was tested using the one-sided *t*-test for two independent samples under the assumption of a common SD. The test was performed at a one-sided significance level of $\alpha = 2.5\%$. The number of patients whose BMD had to be measured was calculated under the assumption of a 4% point difference in BMD change between the treatments and a common SD of 4% points. By this approach, 22 evaluable patients per group were needed to achieve the power ($1-\beta$) = 90%.

The uterine bleeding pattern was analysed according to Gerlinger *et al.* (2007). By this method, uterine bleeding patterns were analysed in two reference periods, each of 90 days' duration, in accordance with recommendations by the World Health Organization (Belsey *et al.*, 1986).

Efficacy and safety variables are reported using means and either the SD or standard error of the mean (SEM), or absolute and relative frequency counts.

Results

Patient characteristics

Of 269 women screened, 252 were randomized to treatment with either dienogest ($n = 124$) or LA ($n = 128$; Fig. 1). A total of 109 (87.9%) women in the dienogest group and 120 (93.8%) women in the LA group completed the study (Fig. 1). The FAS analysis included 248 patients ($n = 120$, dienogest; $n = 128$, LA), while the PPS analysis included 186 women ($n = 90$, dienogest; $n = 96$, LA). BMD was assessed in a subgroup of 57 women ($n = 26$, dienogest; $n = 31$, LA), and estradiol levels were measured in 70 women ($n = 32$, dienogest; $n = 38$, LA).

Women were of comparable age, height, weight and body mass index in the two groups (Table I). There were no relevant group differences in gynaecological or laparoscopic history (Table I). The use of concomitant medications recorded in patient-maintained diaries, including analgesic medication for endometriosis, did not differ relevantly between the groups at baseline or during the trial.

Efficacy variables

Primary efficacy variable

Both dienogest and LA were associated with substantial reductions in VAS score between baseline and Week 24. At baseline, the mean (\pm SD) VAS score was 60.2 (± 24.2) mm in the dienogest group and 57.9 (± 21.0) mm in the LA group. By Week 24, mean VAS scores had decreased to 12.7 (± 20.3) mm in the dienogest group and to 11.9 (± 16.9) mm in the LA group (PPS; Fig. 2). The absolute reduction in VAS score was 47.5 (± 28.8) mm with dienogest and 46.0 (± 24.8) mm with LA, representing a treatment difference of 1.5 mm in favour of dienogest [95% confidence interval (CI), -9.26 to 6.25]. The non-inferiority of dienogest relative to LA was therefore demonstrated, based on the prespecified non-inferiority margin of 15 mm ($P < 0.0001$).

Similar results demonstrating the non-inferiority of dienogest versus LA measured by VAS score change were observed in the FAS. Mean (\pm SD) VAS score reductions were 40.2 (± 32.0) mm in the dienogest group and 41.8 (± 28.6) mm in the LA group, representing a treatment difference of 1.6 mm (95% CI, -6.42 to 9.58; P for non-inferiority = 0.0004).

Secondary efficacy variables

The proportions of women who experienced an improvement in VAS score by study end were similar in the dienogest and LA groups. In the PPS, 96.7% of women in the dienogest group and 95.8% of women in the LA group experienced an improvement in pelvic pain after 24 weeks in comparison with baseline (P for non-inferiority < 0.0001).

Responder analyses showed similar proportions of responders in the two treatment groups for all response definitions that were investigated. These sensitivity analyses therefore supported the main analyses describing the non-inferiority of dienogest versus LA.

The intensity of pelvic symptoms and physical findings, summarized by the B&B total symptom and sign severity score profile, decreased

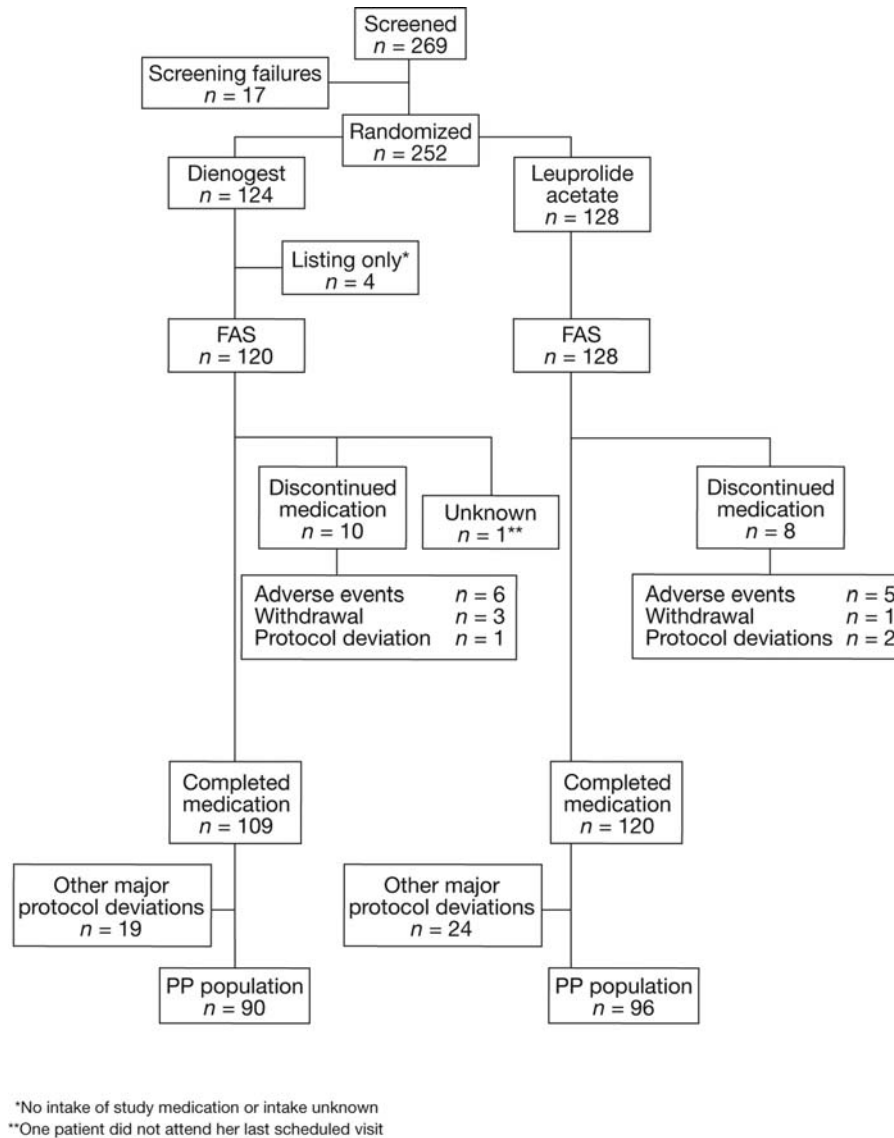


Figure 1 Patient disposition.

FAS, full analysis set; PP, per protocol.

similarly in the two treatment groups between screening and Week 24 (Fig. 3). Whereas 12.2% of women in the dienogest group and 6.3% of women in the LA group had very severe symptoms at screening, none had this symptom grade at final visit. The severity of the individual symptoms of pelvic pain, dysmenorrhoea and dyspareunia and the severity of the physical signs of pelvic tenderness and induration also decreased in both treatment groups between screening and final visit (data not shown).

Quality-of-life variables

Quality of life, assessed by the SF-36 Health Survey, improved in both treatment groups, with an indication of more pronounced benefit in the dienogest than LA group.

At 24 weeks, the mean (\pm SD) SF-36 physical health summary scale score improved relative to screening by 10.2 points (from 41.4 ± 8.5

to 51.6 ± 6.7 points) in the dienogest group and by 7.0 points (from 44.2 ± 8.0 to 51.2 ± 7.1 points) in the LA group (PPS). Over the same period, the mean SF-36 mental health summary scale score improved by 3.3 points (from 42.1 ± 11.5 to 45.4 ± 10.9 points) in the dienogest group and by 1.9 points (from 44.0 ± 11.6 to 45.9 ± 11.7 points) in the LA group.

Safety variables

Adverse events

Headache was the most common treatment-related adverse event in both groups (12.5%, dienogest; 19.5%, LA; Table II). Women treated with dienogest less frequently experienced events representing other hypoestrogenic symptoms (such as hot flushes, vaginal dryness, decreased libido and sleep disorder) than women treated with LA.

Table I Baseline characteristics of patients (FAS).

	Dienogest 2 mg (n = 120)	LA 3.75 mg (n = 128)
Age (years, mean ± SD)	30.6 ± 6.2	31.0 ± 5.8
Height (cm, mean ± SD)	166.1 ± 7.3	166.3 ± 6.6
Weight (kg, mean ± SD)	62.5 ± 10.8	62.7 ± 9.6
Body mass index (mean ± SD) ^a	22.6 ± 3.4	22.7 ± 3.2
Pelvic pain VAS (mm, mean ± SD) ^b	53.3 ± 29.1	55.4 ± 24.2
r-AFS stage (n, %)		
I: minimal	28 (23.3)	39 (30.5)
II: mild	35 (29.2)	34 (26.6)
III: moderate	39 (32.5)	35 (27.3)
IV: severe	18 (15.0)	20 (15.6)

^aWeight (kg)/height (m²).

^bn = 118, dienogest; n = 127, leuprolide acetate.

FAS, full analysis set; LA, leuprolide acetate; r-AFS, revised American Fertility Society; SD, standard deviation; VAS, visual analogue scale.

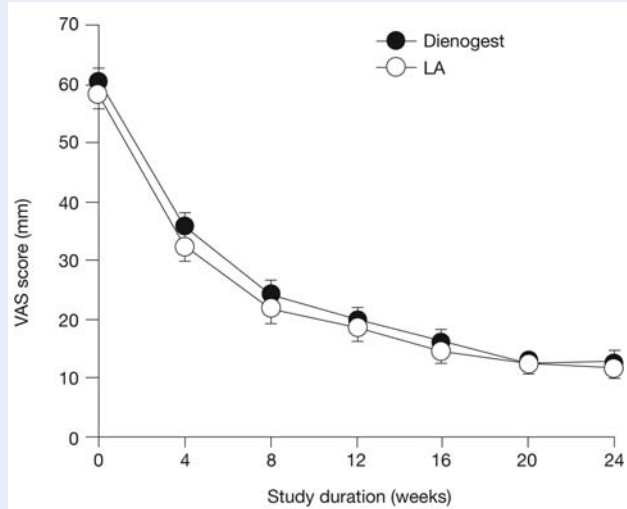


Figure 2 Mean (± SEM) VAS scores at baseline and Weeks 4, 8, 12, 16, 20 and 24 in dienogest 2 mg and leuprolide acetate 3.75 mg treatment groups (PPS).

LA, leuprolide acetate; PPS, per protocol set; VAS, visual analogue scale.

The majority of adverse events were of mild or moderate intensity in both groups. Seven serious adverse events were reported in six women during the study. In the dienogest group, one woman suffered severe depression, which was considered possibly related to the study drug. Other serious adverse events reported in the dienogest group included one case of planned hysterectomy and three hospitalizations for pelvic pain, abdominal pain or kidney calculus (twice), which were considered unlikely to be related to the study drug. One serious

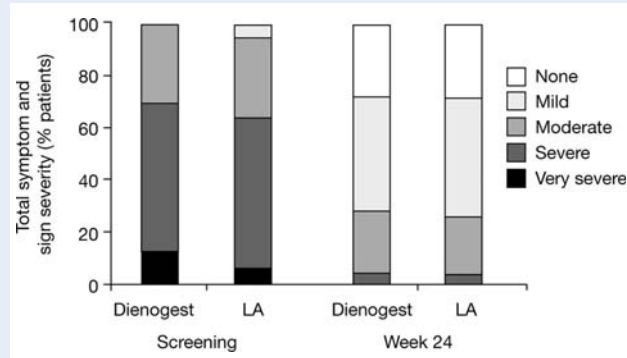


Figure 3 Total symptom and sign severity score profile (B&B) at baseline and Week 24 in the dienogest and LA groups (PPS).

B&B, Biberoglu and Behrman; LA, leuprolide acetate; PPS, per protocol set.

Table II Numbers and proportions of women with adverse events at least possibly treatment related in dienogest and leuprolide acetate groups (≥4% of women in either treatment group; FAS).

HARTS code	Dienogest 2 mg (n = 120)		Leuprolide acetate 3.75 mg (n = 128)	
	n	%	n	%
Headache	15	12.5	25	19.5
Weight gain	8	6.7	5	3.9
Depression	6	5.0	11	8.6
Decreased libido	5	4.2	8	6.3
Acne	5	4.1	6	4.7
Alopecia	4	3.3	7	5.5
Migraine	3	2.5	6	4.7
Sleep disorder	2	1.7	10	7.8
Vaginal dryness	2	1.7	9	7.0
Hot flushes	0	0.0	9	7.0

FAS, full analysis set; HARTS, Hoechst adverse reaction terminology system.

adverse event of disc prolapse requiring hospitalization was reported in the LA group, which the investigator rated as unlikely to be related to the study drug.

Six women (5.0%) in the dienogest group and five women (3.9%) in the LA group discontinued the study prematurely due to adverse events. Events leading to discontinuation included hypertension, tinnitus, ovarian cyst, nausea and (in two women) depression in the dienogest group, and hot flushes, arthritis, depression, allergic reaction and sleep disorder in the LA group.

Clinical laboratory parameters

No changes in standard laboratory parameters between screening and final visit in either treatment group were considered to be clinically significant by the investigators.

Mean levels of serum estradiol remained stable in the dienogest subgroup ($n = 32$; from 256.3 to 249.9 pmol/l) and showed a pronounced decrease in the LA subgroup ($n = 38$; from 299.0 to 68.5 pmol/l; Fig. 4a).

Hot flushes

In the LA group, the mean number of days/week with hot flushes increased from 0.78 in Week 1 to 4.70 in Week 24 (FAS; Fig. 4b). The mean number of days/week with hot flushes was stable in the dienogest group over the same period (1.04 in Week 1 and 0.82 in Week 24).

Bone mineral density

Mean BMD of the lumbar spine (L1–L4) was 1.062 g/cm² in the dienogest subgroup ($n = 26$) and 1.070 g/cm² in the LA subgroup ($n = 31$) at screening, and was 1.036 g/cm² ($n = 23$) and 1.014 g/cm² ($n = 30$), respectively, at final visit (FAS). In women whose measurements were available at both screening and final visit, mean lumbar BMD increased by 0.0022 g/cm² in the dienogest subgroup ($n = 21$) and decreased by 0.0415 g/cm² in the LA subgroup ($n = 29$), representing mean (\pm SD) percentage changes of +0.25 (\pm 2.77) and -4.04 (\pm 4.84) for dienogest and LA, respectively ($P = 0.0003$ for superiority of dienogest; Fig. 4c).

Markers of bone metabolism

Markers of bone resorption. Mean (\pm SD) urine calcium levels decreased by 137.4 (\pm 295.5) mmol/mol creatinine in the dienogest group and increased by 111.3 (\pm 227.9) mmol/mol creatinine in the LA group during the study (FAS). Mean (\pm SD) urinary Cross-Laps[®] levels increased by 7.6 (\pm 261.8) μ g/mmol creatinine in the dienogest group and by 189.4 (\pm 231.0) μ g/mmol creatinine in the LA group (FAS).

Markers of bone formation. Mean (\pm SD) serum bone-specific alkaline phosphatase levels increased at 24 weeks relative to baseline by 0.2 (\pm 2.5) μ g/l in the dienogest group and by 3.2 (\pm 3.0) μ g/l in the LA group (FAS). Mean (\pm SD) serum osteocalcin levels decreased by 0.4 (\pm 1.5) nmol/l in the dienogest group and increased by 0.5 (\pm 1.4) nmol/l in the LA group (FAS).

Bleeding patterns

A total of 80.8% of women in the dienogest group and 87.5% in the LA group reported regular bleeding cycles within the year prior to screening, whereas 16.7 and 18.8% of women, respectively, described intracyclic bleeding.

Bleeding profiles differed between the treatment groups during the trial. In general, the number of bleeding/spotting episodes and the number of bleeding/spotting days over time decreased in both groups, with a stronger trend in the LA group than in the dienogest group (Table III).

Comparison of bleeding patterns during the first 90-day reference period showed that infrequent bleeding was the predominant pattern (80.6%) in the LA group, while the highest incidences in the dienogest group were prolonged bleeding (45.1%) and irregular bleeding (44.2%). During the second 90-day reference period, there was a shift from infrequent bleeding to amenorrhoea (75.9%) in women

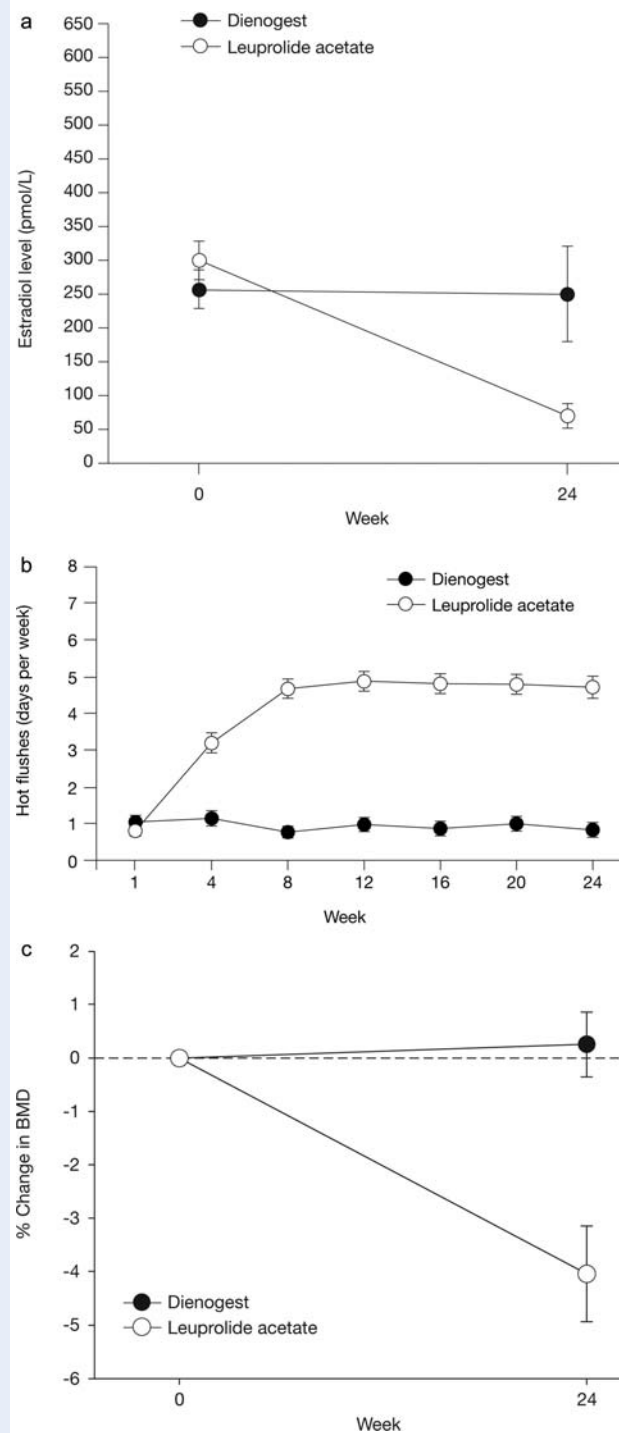


Figure 4 (a) Change in mean (\pm SEM) estradiol concentrations in dienogest ($n = 32$) and leuprolide acetate ($n = 38$) subgroups. (b) Mean (\pm SEM) number of days/week with hot flushes in dienogest ($n = 120$) and leuprolide acetate ($n = 128$) groups (FAS). FAS, full analysis set. (c) Percent change in mean (\pm SEM) BMD in dienogest ($n = 21$) and leuprolide acetate ($n = 29$) subgroups (i.e. women with measurements available at both screening and final visit). BMD, bone mineral density.

Table III Bleeding patterns during 90-day reference periods 1 and 2 in dienogest and LA groups (FAS).

	Dienogest 2 mg		Leuprolide acetate 3.75 mg	
	n	Mean ± SD	n	Mean ± SD
Number of bleeding/spotting episodes				
Reference period 1	110	3.33 ± 1.82	115	2.02 ± 1.20
Reference period 2	101	1.87 ± 2.01	113	0.47 ± 1.13
Number of bleeding/spotting days				
Reference period 1	110	25.61 ± 18.50	115	11.61 ± 7.01
Reference period 2	104	11.81 ± 15.10	114	2.00 ± 4.90
Length of bleeding/spotting episodes				
Reference period 1	108	8.82 ± 7.99	115	6.54 ± 3.90
Reference period 2	63	5.82 ± 4.29	28	4.30 ± 3.20
Number of spotting-only episodes				
Reference period 1	110	1.22 ± 1.38	115	0.55 ± 0.85
Reference period 2	101	0.95 ± 1.37	113	0.17 ± 0.52
Number of spotting-only days				
Reference period 1	110	15.08 ± 14.90	115	4.90 ± 4.19
Reference period 2	104	7.06 ± 10.09	114	0.75 ± 1.74
Length of spotting-only episodes				
Reference period 1	68	4.66 ± 5.10	45	2.37 ± 1.29
Reference period 2	44	3.73 ± 2.49	15	2.27 ± 1.03

FAS, full analysis set; SD, standard deviation.

Reference period 1 was the first 90 days after the start of treatment. Reference period 2 was from Day 91 to the end of study.

receiving LA. Continued use of dienogest was also associated with shift in incidence toward amenorrhoea (from 1.8% in period 1 to 38.9% in period 2), with reductions in irregular and prolonged bleeding (16.7 and 7.4%, respectively, in period 2).

No patients withdrew prematurely from the study due to a changed bleeding pattern or adverse bleeding events.

Vital signs and weight

There were no clinically relevant changes in mean blood pressure or heart rate during the study in either treatment group. Mean (\pm SD) body weight increased marginally and to a similar extent in the dienogest group (1.21 ± 4.12 kg) and the LA group (1.15 ± 3.46 kg; FAS).

Discussion

This 24-week, randomized, multicentre, head-to-head comparison of dienogest and LA in women with histologically proven endometriosis demonstrated that dienogest 2 mg/day orally is as effective as i.m. LA for relieving endometriosis-associated pelvic pain. This finding is of high clinical relevance, as pelvic pain is one of the most important symptoms of endometriosis and because agents in the GnRH agonist class are widely considered a reference standard treatment for improving these symptoms (Dlugi *et al.*, 1990; Ling, 1999; Prentice *et al.*, 2000; Crosignani *et al.*, 2006; Schlaff *et al.*, 2006).

The comparable efficacy of dienogest and LA for reducing pelvic pain measured by VAS score (the primary efficacy variable) was supported by secondary analyses. The secondary analyses identified equivalence between the dienogest and LA groups in the proportions of women experiencing improvements in pelvic pain, responder rates and improvements in physician-assessed B&B severity profiles. In quality of life analysis, the improvements associated with dienogest appeared superior to those accompanying LA therapy.

The outcomes from this study support previous studies which investigated the efficacy of dienogest in relieving symptoms of endometriosis (Cosson *et al.*, 2002; Schindler *et al.*, 2006; Momoeda and Taketani, 2007; Seitz *et al.*, 2008; Harada *et al.*, 2009; Köhler *et al.*, 2010). In a phase II dose-finding study, dienogest 2 mg daily offered improvements in patient-reported symptoms and in second-look laparoscopic assessments of pathology after 24 weeks. In that study, a reduction of endometriotic lesions occurred in approximately two-thirds of women in the dienogest 2 mg group based on r-AFS scores (Köhler *et al.*, 2010).

Compared with depot LA, which has well-characterized hypoestrogenic effects that limit long-term use, dienogest was associated with a favourable safety profile in this randomized, controlled trial. Women treated with LA for 24 weeks experienced substantial decreases in serum estradiol levels, compared with relatively stable serum estradiol levels associated with dienogest. Dienogest at a dose of 2 mg once daily was similarly associated with only moderate decreases in estradiol levels in a 12-week placebo-controlled study and in a 1-year extension study (Seitz *et al.*, 2008, 2009). The higher frequency of hot flushes observed with LA than dienogest is readily explained by the between-group differences in serum estradiol levels in the current trial. Other hypoestrogenic effects, such as headache, vaginal dryness, decreased libido and sleep disorder, were also reported more frequently by women treated with LA than those treated with dienogest. The observed combination of equivalent efficacy and different levels of hypoestrogenic effects between dienogest and LA supports the hypothesis of an optimal 'estrogen window' for endometriosis therapy, which was proposed a number of years ago (Barbieri, 1992, 1998).

Adverse events were of mild or moderate intensity in most women and overall rates of study discontinuation due to adverse events were low in both groups. Weight gain, which is a characteristic of a number of other progestins used in endometriosis, was minimal in dienogest-treated women. Mean lumbar BMD was unchanged over the study period in dienogest-treated women, but decreased by approximately 4% in the LA group, with statistically significant differences in mean BMD between the treatment groups. Markers of bone metabolism indicated increased bone resorption in the LA but not dienogest group. This may also indicate an advantage of dienogest compared with depot MPA, which has been associated with a significant loss of BMD resulting in a 'black box warning' by the US Food and Drug Administration (Physician Information, 2009).

The safety and tolerability findings from the current trial support the findings of previous studies of dienogest in endometriosis (Köhler *et al.*, 1989, 2010; Schindler *et al.*, 2006; Seitz *et al.*, 2008; Harada *et al.*, 2009).

Characteristic differences in safety and tolerability profile between agents used in endometriosis may influence medication choice, alongside considerations of efficacy in reducing symptoms. Consistent with

observations in the current trial, GnRH agonists such as LA are associated with hypoestrogenic effects and related adverse effects on BMD (Winkel and Scialli, 2001), which limits treatment to 6 months in the absence of add-back therapy. The European Society for Human Reproduction and Embryology (ESHRE) guideline recommends, in particular, careful consideration in the use of GnRH agonists in younger women who have not reached maximum bone density (Kennedy et al., 2005). Although add-back therapy can reduce the hypoestrogenic effects of GnRH agonists, the optimal add-back regimen has not yet been established and this approach adds to the cost of therapy (Mounsey et al., 2006). Danazol, although remaining a standard therapy for endometriosis in some countries, is associated with adverse effects on lipid metabolism and androgenic adverse effects. Dienogest, in contrast, appears to have no relevant effect on lipids (Köhler et al., 1989; Schindler et al., 2006; Seitz et al., 2008) and lacks androgenic side effects (Oettel et al., 1999; Schindler et al., 2003).

Irregular uterine bleeding is a known adverse effect of treatment with progestins, including depot preparations of MPA, which have been compared in trials against LA (Vercellini et al., 2003; Crosignani et al., 2006; Schlaff et al., 2006). As expected in the current study, amenorrhoea rates were higher in the LA than dienogest group due to the substantial depletion in estrogen levels in the former. In the dienogest group, there was a shift from predominantly prolonged or irregular bleeding in the first 90-day reference period toward amenorrhoea in the second reference period. The mean number of bleeding/spotting episodes and bleeding/spotting days decreased over time in both groups. The absence of discontinuations due to abnormal bleeding patterns in either group suggests that bleeding events may have minimal influence on adherence in light of the reduction in symptoms associated with therapy. Informing women on the likely effects of dienogest therapy may enhance adherence further. Other studies that examined bleeding patterns during dienogest treatment, including the 1-year extension study, also reported progressive reductions in bleeding irregularity over time (Cosson et al., 2002; Seitz et al., 2008, 2009; Köhler et al., 2010).

Limitations associated with the current study include the open-label design, which was chosen because blinding would require a double-dummy design with placebo injections. Even with such a design, successful blinding would be questionable because of the characteristic adverse event profile of LA (i.e. occurrence of hot flushes) that is readily recognized by patients and investigators. As VAS scoring for pain is a subjective measure, the process of obtaining patients' scores by investigators could have introduced bias. In addition, as this study was not placebo controlled, proof of efficacy for dienogest rested on evidence of non-inferiority relative to an active control. This type of design requires a priori acceptance of the efficacy of LA on endometriosis-associated pain and specification of an appropriate non-inferiority margin. The non-inferiority margin of 15 mm on the VAS pain scale was chosen based on data from other conditions characterized by chronic pain (Wells et al., 1993; Todd and Funk, 1996). A recent analysis of data from patients with endometriosis showed that a non-inferiority margin of 10 mm may be more appropriate (Gerlinger et al., 2009). As the CI for the treatment difference excluded 10 mm in both the PPS and FAS in this study, the non-inferiority of dienogest is confirmed even when applying this stricter margin.

A further potential limitation of the study relates to a treatment duration that was restricted to 24 weeks, which was necessary because GnRH agonists are approved in the treatment of endometriosis for up to 6 months only, due to their deleterious effects on BMD. The study therefore does not address the long-term efficacy and safety of dienogest.

Despite these potential limitations, dienogest provided consistent improvements in a range of patient- and physician-assessed symptoms at 24 weeks similar to LA, indicating that these outcomes are robust and clinically relevant in the treatment of endometriosis.

In conclusion, this head-to-head study demonstrated that dienogest 2 mg daily has equivalent efficacy to depot LA for relieving endometriosis-associated pelvic pain. In addition, dienogest was associated with acceptable safety and tolerability, offering advantages when compared with LA including a substantially lower incidence of hot flushes and minimal change in BMD and bone metabolism. The efficacy and safety profile of dienogest characterized in this study suggests that dienogest may offer an effective and well-tolerated treatment in endometriosis.

Authors' Roles

T.S.: Substantial contributions to conception, design, interpretation of data and drafting and critical revision of article. J.M. and C.G.: Substantial contributions to design, analysis, interpretation of data and drafting and critical revision of article. T.F. and C.S.: Substantial contributions to interpretation of data and drafting and critical revision of article.

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