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Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain

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BACKGROUND: A clinical study compared efficacy and safety of depot medroxyprogesterone acetate (DMPA) with leuprolide for endometriosis-associated pain. METHODS: This multicentre, 18 month, evaluator-blinded, comparator-controlled trial randomized 300 women with laparoscopically diagnosed endometriosis to 6 month treatment with subcutaneous injection of 104 mg/0.65 ml DMPA (DMPA-SC 104) every 3 months or leuprolide (3.75 mg monthly or 11.25 mg every 3 months), with 12 months post-treatment follow-up. Endpoints included patient response to treatment in five signs/symptoms (dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness, induration) and changes in bone mineral density (BMD) and productivity at 6 and 18 months. RESULTS: DMPA-SC 104 and leuprolide produced equivalent ($P < 0.02$) reductions in at least four pain categories and significant ($P < 0.001$) improvements in composite score at months 6 and 18. At month 6, reductions in total hip and lumbar spine BMD were significantly less ($P < 0.001$) with DMPA-SC 104 versus leuprolide. BMD returned to pre-treatment levels 12 months post-treatment in the DMPA-SC 104 but not the leuprolide group. Total productivity also significantly ($P \leq 0.05$) improved in both groups at 6 and 18 months. CONCLUSIONS: DMPA-SC 104 reduces endometriosis-associated pain as effectively as leuprolide and improves productivity with significantly less BMD decline.

Key words: bone mineral density/depot medroxyprogesterone acetate/subcutaneous injection/endometriosis/leuprolide/pelvic pain

Introduction

Endometriosis, defined as the presence and proliferation of endometrial-like tissue outside the uterine cavity (Child and Tan, 2001), is thought to affect up to 10% of all women of reproductive age (Wheeler, 1989; Valle and Sciarra, 2003) and 25% of women who experience pelvic pain (Eskenazi and Warner, 1997). The generally cyclical nature of the pain associated with endometriosis probably results from the response of the endometrial-like tissue to cycling reproductive hormones (particularly estrogen) (Bulun *et al.*, 1999). As endometriosis lesions become inactive and gradually undergo regression during ovarian down-regulation, medical treatments attempt to produce these conditions hormonally (Valle and Sciarra, 2003).

Progestins have been used worldwide for decades as a treatment for endometriosis; they appear to stop proliferation in endometriotic implants and induce regressive changes (Schweppe, 2001). Given that endometriosis is a chronic, recurrent disorder, it is especially important that progestins are relatively well-tolerated, have only limited metabolic side-effects at low doses and are inexpensive, in order to make these agents suitable for longer term use (Schweppe, 2001). With the added benefit of a wide range of newer dosing and delivery options, currently available progestins or those in development represent a viable treatment option for endometriosis pain.

This study was undertaken to evaluate the use of a new, subcutaneous formulation of depot medroxyprogesterone acetate 104 mg/0.65 ml (DMPA-SC 104) as a treatment for endometriosis-associated pain. This unique formulation contains different excipients from the intramuscular formulation and was specifically designed for subcutaneous administration. As such, DMPA-SC 104 cannot be compounded from the intramuscular formulation. Contraceptive studies have demonstrated the safety and tolerability of DMPA-SC 104, which contains an ~30% lower dose than the intramuscular formulation (Jain *et al.*, 2004a; Jakimiuk, 2004).

The objectives of this study were to assess the equivalence (non-inferiority) of DMPA-SC 104 to leuprolide (a widely used and highly effective treatment for pain related to endometriosis) (Dlugi *et al.*, 1990; Rotondi *et al.*, 2002; Valle Sciarra, 2003) in the reduction of endometriosis-associated pain, as well as to evaluate differential effects of these treatments on bone mineral density (BMD) during 6 months of treatment and 12 months of post-treatment follow-up. Hypoestrogenic symptoms,

bleeding-pattern changes, adverse events, and the effects of treatment on quality of life were also assessed.

Materials and methods

Patients and study design

This was an 18 month, randomized, Phase III, evaluator-blinded, comparator-controlled clinical trial conducted in Europe, Asia, Latin America and New Zealand. The study period was from July 1, 2001, through August 11, 2003. Patients were randomized to 6 months of active treatment with DMPA-SC 104 or with leuprolide and were followed for an additional 12 months post-treatment during which neither drug could be used. Independent Ethics Committees approved the study protocol and all protocol amendments. Monitoring and auditing procedures before, during and upon completion of this study verified that it was conducted in accordance with the Declaration of Helsinki.

This study included pre-menopausal women aged 18–49 years with laparoscopically diagnosed endometriosis and persistent pain symptoms. Patients could be either recently diagnosed with signs and symptoms that fulfilled endometriosis pain criteria and with 3 months of persistent symptoms if surgery had been performed during laparoscopy, or they could have had a diagnostic laparoscopy within the past 42 months and persistent or recurrent symptoms for ≥3 months for which they had not received pharmacotherapy with medication. Symptoms were assessed using the modified scale of Biberoglu and Behrman (1981), in which pelvic symptoms/findings are rated on a scale of 0 (no discomfort) to 3 (severe pain) in the following five categories: dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration. Endometriosis-associated pain criteria included a total pelvic score of ≥6 (out of 15 possible), with a score of ≥2 in each of the pain categories of dysmenorrhoea, dyspareunia and pelvic pain. If a patient was sexually inactive for reasons other than endometriosis, the total score must have been ≥4, with scores of ≥2 for both dysmenorrhoea and pelvic pain. Women must also have had normal results from a Papanicolaou smear and normal mammogram (for women aged ≥35 years) within the past 12 months and be willing to use a non-hormonal contraceptive method for the duration of the study, as well as provide signed informed consent.

Staging of endometriosis patients was not done in this study. Although disease severity may be assessed by classification systems, there is no correlation between these systems and the severity of pain symptoms (Kennedy *et al.*, 2005).

Exclusion criteria included BMD below acceptable levels (both lumbar spine and total hip t score < -1.0) or a history of pathological or compression fractures; or any condition that might render a patient unable to comply with study instructions.

Study treatments and assessments

This study randomized patients in a 1:1 ratio to receive 6 months of treatment with either DMPA-SC 104 once every 3 months by subcutaneous injection or leuprolide acetate by subcutaneous injection (3.75 mg monthly or, in The Netherlands, 11.25 mg once every 3 months, depending on the labeling in the respective countries). In Peru, leuprolide was not approved for subcutaneous administration at the time of the study and was therefore administered intramuscularly in accordance with the local licence. Both treatments were initiated within the first 5 days of a normal menstrual cycle at visit 1 and a second injection was given 3 months (91±7 days) later (except for leuprolide 3.75 mg subcutaneously, which was administered monthly), for a total duration of 6 months of active treatment.

The DMPA-SC 104 injection was packaged and labelled by Pfizer (Pharmacia, Nerviano, Italy), which shipped it to each country for distribution to the study sites. Leuprolide was obtained by each country for distribution to the study sites.

Patients were followed on a monthly basis, at which time patient diaries were reviewed for evaluation of symptoms and bleeding-pattern changes; side-effects or other health concerns were also elicited. A pelvic examination was performed at most visits according to schedule. Patients entered the follow-up phase after completing 6 months of treatment. An endometriosis-impact patient diary was distributed every 3 months during follow-up. Bleeding-pattern information was not collected during the follow-up period. BMD was evaluated at pre-treatment, after 6 months of treatment and during the follow-up phase at 6 and 12 months post-treatment.

This was an evaluator-blinded study, in which the principal investigator and any designated sub-investigators and study coordinators at each centre were blinded to the randomization of each patient. For the purpose of maintaining the blinding, an independent person maintained the randomization code, received the study syringes and administered the study medication. This individual was instructed not to reveal the randomization code or to discuss the patient's route of administration with clinical study site personnel. In addition, patients were instructed not to discuss the route of administration.

Efficacy, outcomes research, and safety endpoints

The primary efficacy endpoint was the patient response to treatment in five individual endometriosis-associated pain categories (dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration) using the modified Biberoglu and Behrman symptom scale. For each category, a positive response was defined as an improvement from pre-treatment of ≥1 point in the score at the end of 6 months of treatment. For DMPA-SC 104 to demonstrate clinical equivalence to leuprolide in the reduction of endometriosis-associated pain, statistically equivalent improvement in at least four of the five symptoms would be required at month 6 (end of treatment). Additional (secondary) efficacy endpoints included improvement in symptom scores at 12 months follow-up (month 18 relative to pre-treatment).

Efficacy was also assessed using a composite score, the sum of all five individual symptom scores, which represents a global measurement of disease improvement. Clinically meaningful improvement was defined as a mean decrease of 4 points in the composite score within a treatment group after 6 months of treatment and after 12 months of follow-up. For patients who were not sexually active for reasons other than endometriosis-associated pain, a mean improvement of 3 points in the composite score (excluding dyspareunia) relative to pre-treatment was considered clinically meaningful.

Outcome research endpoints included seven pre-specified quality-of-life scales from validated disease-specific [Endometriosis Health Profile-30 (EHP-30)] and generic [Short Form-36 (SF-36)] instruments. Outcome data were also collected using additional subscales from these instruments: a Patient Satisfaction Questionnaire and an endometriosis-impact diary that included changes in productivity levels.

The primary safety endpoint was the decline in BMD after 6 months of treatment relative to pre-treatment and BMD recovery after 12 months of follow-up (month 18 relative to pre-treatment). Secondary endpoints included changes in the Kupperman Index (a composite measure of hypoestrogenic symptoms); the occurrence of hot flushes; changes in estradiol levels; adverse events; and changes in bleeding patterns, blood pressure, body weight and laboratory assay values. Bleeding patterns were collected from endometriosis-impact diaries and assessed using a 30 day bleeding-pattern analysis. For each 30 day period of treatment, the proportion of patients with amenorrhoea was summarized for months 1–6 for each treatment group. Coagulation tests and lipid profiles were performed only at selected study sites in Poland and Sweden. Coagulation tests included platelet count, prothrombin

time, activated partial thromboplastin time, fibrinogen, factor VII, factor X, antithrombin III, protein C and free-protein S. Lipid profiles included total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and very-low-density lipoprotein (VLDL)-cholesterol measurements.

Statistical methods

Patients who received at least one dose of study medication were included in the intent-to-treat population. Analyses for efficacy, outcomes research and safety endpoints were conducted using intent-to-treat observed-case analysis. In the observed-case analysis, only the collected data were used for analysis.

Statistical tests were two-sided and, except for the equivalence efficacy endpoints, a statistical test with $P \leq 0.05$ was considered statistically significant. For the difference in improvement rates for each of the five signs and symptoms of endometriosis, 96% two-sided confidence intervals were used. This reflects a multiple-endpoint adjustment to control the overall type I error rate at $\alpha = 0.05$ using the Hailperin–Ruger method of adjustment (Koch and Gansky, 1996). Equivalency (non-inferiority) was established for a sign or symptom if the lower bound of the confidence interval for the difference in the improvement rates between DMPA-SC 104 and leuprolide was > –20%. A *P* value was calculated that tested the null hypothesis that if DMPA-SC 104 percent improved minus leuprolide percent improved is ≤ –20%. Treatment equivalence was concluded when $P < 0.02$.

For the purpose of statistical analysis, variables were classified as either continuous or categorical. One-way analysis of variance was used to compare the treatment groups for selected pre-treatment continuous variables (e.g. age, weight, body mass index and composite score). For other continuous variables, treatment groups were compared at pre-treatment and in the change from pre-treatment using a Kruskal–Wallis test; within-group changes were analysed using a Wilcoxon-signed rank test. The χ^2-test was used for categorical variables. The evaluation of the seven pre-specified quality-of-life scales followed a gatekeeping approach to control the type I error rate at $\alpha = 0.05$. Statistical testing for quality-of-life scales was conducted using two-tailed *t* tests to evaluate within-treatment group changes from pre-treatment.

Results

Of 300 randomized patients, 299 received at least one dose of study medication and were included in the intent-to-treat population: 153 in the DMPA-SC 104 group and 146 in the leuprolide group. Continuation rates were similar between the treatment groups, with 90.2% of patients receiving DMPA-SC 104 and 93.2% of those receiving leuprolide completing the 6 month treatment period. Of the patients that completed the 6 month treatment period, 71.7 and 73.5% of patients in the DMPA-SC 104 and leuprolide groups completed the 12 month follow-up period respectively. Reasons for withdrawal are summarized in Figure 1.

The two treatment groups were similar with respect to all pre-treatment and demographic characteristics except race (the DMPA-SC 104 group had a higher percentage of Asian/Pacific Islander patients and the leuprolide group had a higher percentage of white patients, $P = 0.009$) (Table I). The mean ages were 31.8 and 30.9 years in the DMPA-SC 104 and leuprolide groups respectively, with a mean body mass index of 23.6 kg/m^2 in the DMPA-SC 104 group and 23.9 kg/m^2 in the leuprolide group. The two treatment groups were also similar with respect to the five individual signs and symptoms of endometriosis at pre-treatment, although the mean pre-treatment composite score was significantly higher ($P = 0.039$) in the leuprolide group compared with the DMPA-SC 104 group. Most patients in each group had moderate to severe pre-treatment pain. Ninety-eight patients met the protocol-specified criterion for a total pelvic score of ≥6 (or ≥4 if sexually inactive)

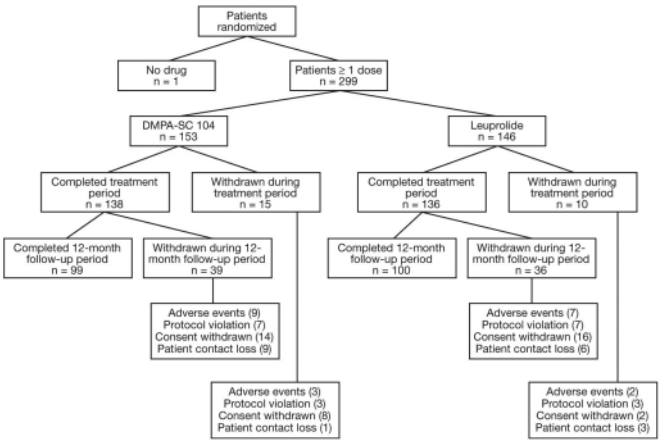

Figure 1. Disposition of patients in a randomized, evaluator-blinded, comparator-controlled trial comparing the efficacy and safety of depot medroxyprogesterone acetate 104 mg/0.65 ml subcutaneous injection vs leuprolide in the treatment of endometriosis-associated pain. Numbers of patients and reasons for withdrawal are given for both the 6-month treatment period and 12-month post-treatment follow-up phases.

Table I. Patient demographics and pre-treatment characteristics (intent to treat)

Characteristic	DMPA-SC 104 (*n* = 153)	Leuprolide (*n* = 146)
Age (years)		
Mean ± SD	31.8 ± 6.7	30.9 ± 6.1
Race (%)[a]		
White	56.2	64.4
Black	2.0	4.1
Asian/Pacific Islander	17.6	5.5
Mixed/multiracial	24.2	26.0
Weight (kg)		
Mean ± SD	61.5 ± 11.9	62.6 ± 12.6
BMI (kg/m^2)		
Mean ± SD	23.6 ± 3.9	23.9 ± 4.3
Range	16.1–35.0	15.2–37.6
Pre-treatment endometriosis composite score[bc]		
Mean ± SD	9.3 ± 2.4	9.8 ± 1.8
Range	3–14	6–14
Total hip BMD (g/cm^2)		
Mean ± SD	1.1 ± 0.1	1.1 ± 0.1
Lumbar spine BMD (g/cm^2)		
Mean ± SD	1.2 ± 0.1	1.2 ± 0.1

[a] Difference between treatment groups: $P = 0.009$.
[b] Sum of scores at randomization for dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and pelvic induration, where absent/none = 0, mild = 1, moderate = 2 and severe = 3.
[c] Difference between treatment groups: $P = 0.039$.
DMPA-SC 104 = depot medroxyprogesterone acetate 104 mg/0.65 ml subcutaneous injection; BMI = body mass index; BMD = bone mineral density.

at baseline but did not meet the criterion for a score of ≥2 in each of the categories of dysmenorrhoea, dyspareunia and pelvic pain (or if sexually inactive, a score of ≥2 in each of the categories of dysmenorrhoea and pelvic pain), at both baseline and randomization. This included 58 patients in the DMPA-SC 104 group and 40 patients in the leuprolide group.

Efficacy of DMPA-SC 104 versus leuprolide in the treatment of endometriosis-associated pain

In the observed-case analysis, 6 months of treatment with DMPA-SC 104 resulted in statistically equivalent ($P < 0.02$) reductions of all five signs and symptoms of endometriosis (dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration) compared with leuprolide treatment (as shown in Figure 2A). These results met the primary efficacy objective of the study, demonstrating that DMPA-SC 104 reduced endometriosis-associated pain as effectively as leuprolide.

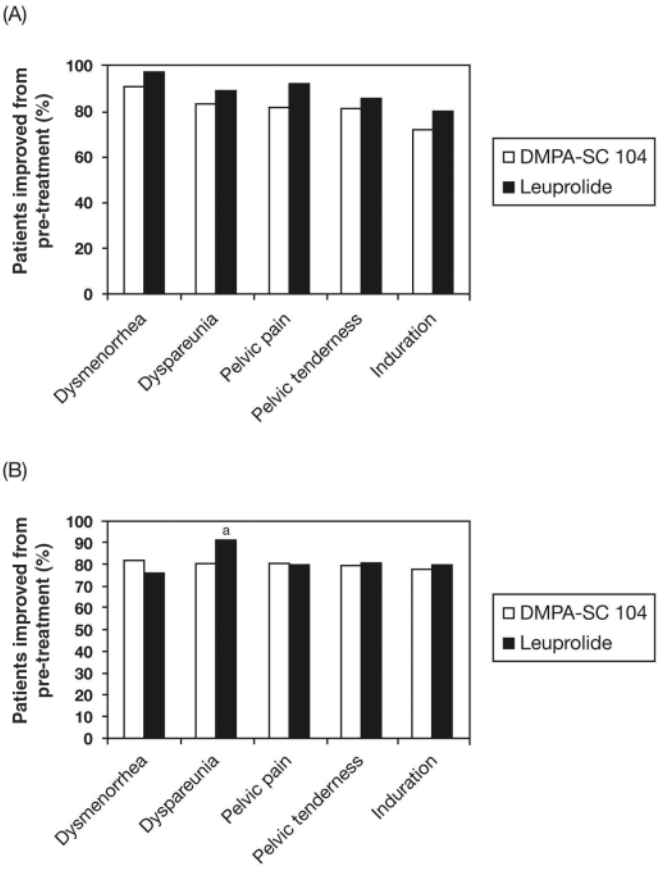

Figure 2. Percentages of patients treated with depot medroxyprogesterone acetate 104 mg/0.65 ml subcutaneous injection or leuprolide showing improvement in 5 individual signs and symptoms of endometriosis relative to pre-treatment, using observed-case analysis for the intent-to-treat population. Improvement was defined as a decrease of at least one point in the score relative to pre-treatment, using the modified Biberoglu and Behrman scale. Treatments were equivalent if $P < 0.02$, where the following null hypothesis was tested: Percent improvement with DMPA-SC 104 minus percent improvement with leuprolide is ≤–20%. (A) At month 6 end of treatment. (B) After 12 months of post-treatment follow-up (month 18 relative to pre-treatment). [a]Treatments not equivalent ($P = 0.049$).

After 12 months of post-treatment follow-up, the percentages of patients in each group continuing to show improvement from pre-treatment in these symptoms remained high (>75%), and treatment with DMPA-SC 104 demonstrated statistical equivalence to leuprolide for four of the five signs and symptoms (Figure 2B). Improvement of endometriosis-associated dyspareunia was also observed in both treatment groups, although the results did not meet statistical equivalence ($P < 0.049$).

Composite scores, calculated as the sum of the five individual scores for signs and symptoms of endometriosis, revealed that both DMPA-SC 104 and leuprolide resulted in statistically significant ($P < 0.001$) and clinically meaningful symptom improvements at month 6 (end of treatment) and at 12 months follow-up (month 18 relative to pre-treatment). In the DMPA-SC 104 group, mean improvement from pre-treatment was 6.3 at month 6 and 6.6 after 12 months of follow-up. Similarly, mean improvement from pre-treatment in the leuprolide group was 7.3 at month 6 and 6.1 after 12 months of follow-up.

Quality of life

As determined from patient reports, significant improvements in quality of life occurred in both the DMPA-SC 104 and leuprolide groups, as measured by EHP-30 and SF-36 scales. Mean scores for all four pre-specified EHP-30 scales (pain, emotional well-being, self-image and intercourse) as well as the two remaining scales (social support, control and powerlessness), significantly improved in both groups at month 6 compared with pre-treatment, and these improvements were maintained after 12 months of post-treatment follow-up (Figure 3). Similarly, scores for all three pre-specified scales of the SF-36 (physical function, role physical and social functioning) significantly improved at month 6 relative to pre-treatment in both treatment groups, with improvements maintained after 12 months of post-treatment follow-up ($P \leq 0.001$).

On the Patient Satisfaction Questionnaire, both groups experienced significant ($P \leq 0.006$) improvements in emotional and physical health at month 6 (end of treatment) relative to pre-treatment, based on patient reports. Patients in the DMPA-SC 104 group also experienced significant improvements in their sexual relationship at month 6 ($P = 0.039$); no significant improvement was observed in the leuprolide group ($P = 0.318$).

Productivity endpoints collected from the endometriosis-impact diaries revealed significant improvements in both groups with regard to the mean number of employed work and housework hours lost due to endometriosis symptoms (Table II). The hours of productivity that were lost due to absenteeism (planned work not attempted) and presenteeism (productivity lost due to reduced effectiveness caused by endometriosis symptoms) both significantly improved from pre-treatment to month 6, and these improvements were maintained throughout the 12 months of follow-up ($P \leq 0.05$). Total productivity losses for employed work and housework due to endometriosis also significantly ($P \leq 0.05$) improved in both groups from pre-treatment to month 6, and through the 12 months of follow-up (month 18 relative to pre-treatment).

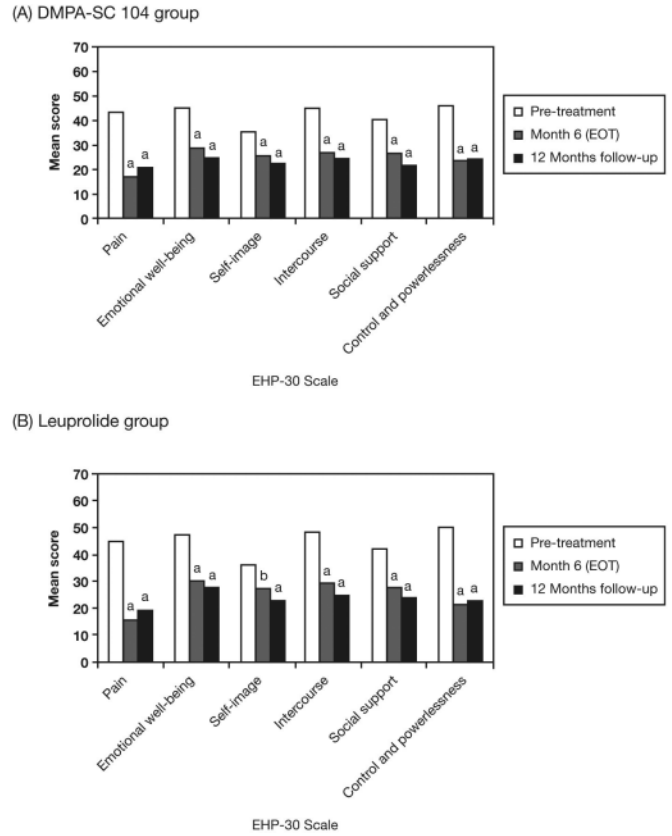

Figure 3. Impact of treatment on quality of life (intent-to-treat population): Mean scores on four pre-specified and two additional Endometriosis Health Profile-30 (EHP-30) scales at randomization, month 6 (end of treatment [EOT]) and after 12 months of post-treatment follow-up (month 18 relative to pre-treatment). Lower scores indicate improvement on each scale. *P* values for within-group differences from pre-treatment (*t* test): [a]$P < 0.001$. [b]$P = 0.002$.

Safety and tolerability

The primary safety endpoint in this trial was the change in BMD after 6 months of treatment, shown in Figure 4. In the leuprolide group, significant ($P < 0.001$) reductions from pre-treatment in both total hip and lumbar spine BMD (median percentage changes of –2.10 and –4.00, respectively) were observed at month 6. However, the DMPA-SC 104 group showed significant reduction from pre-treatment ($P < 0.001$) only in lumbar spine BMD (median percentage changes: total hip, –0.50; lumbar spine, –1.00). Compared with the leuprolide group, reductions in both total hip and lumbar spine BMD were significantly smaller ($P < 0.001$) in the DMPA-SC 104 group.

After 12 months of follow-up (month 18 relative to pre-treatment), the leuprolide group continued to show significant ($P \leq 0.002$) residual loss in median percentage change from pre-treatment in both total hip (–1.1%) and lumbar spine (–1.3%) BMD (Figure 4). In contrast, the DMPA-SC 104 group did not show statistically significant changes from pre-treatment after 12 months of follow-up for either total hip (–0.2%) or lumbar spine (–0.4%) BMD. As at month 6, the decreases after 12 months of follow-up were significantly less in the DMPA-SC 104 group than in the leuprolide group for total hip BMD ($P = 0.006$). For lumbar spine BMD, the median percentage change from pre-treatment was less in the DMPA-SC 104 group compared to the leuprolide group after 12 months of follow-up, although the difference was not statistically significant ($P = 0.08$).

Secondary safety and tolerability endpoints included measures of hormone-related effects. Median changes from pre-treatment in the Kupperman Index (Kupperman *et al.*, 1953) scores of hypoestrogenic signs and symptoms demonstrated statistically significant differences between treatment groups ($P < 0.001$) at each monthly visit throughout the 6 month treatment period (Figure 5). The leuprolide group experienced a significant median increase from pre-treatment ($P < 0.001$) at each month, while median scores changed very little in the DMPA-SC 104 group. At month 6 (end of treatment), the median change in Kupperman Index was 0 in the DMPA-SC 104 group and +6.0 in the leuprolide group.

The median average daily number of hot flushes (calculated by dividing the total number of hot flushes in the reference month by the number of days with data recorded in that month) was significantly lower ($P < 0.001$) in the DMPA-SC 104 group than in the leuprolide group during all 6 months of treatment. At month 6, the median average daily number of hot flushes was zero in the DMPA-SC 104 group and 2.0 in the leuprolide group. The maximum severity of hot flushes within a diary reference month was also significantly lower in the DMPA-SC 104 group than in the leuprolide group throughout the 6 month treatment period. At month 6 (Figure 6), severe hot flushes were reported in 7.6% of patients in the DMPA-SC 104 group compared with 35.2% in the leuprolide group ($P < 0.001$). At month 6, a significantly ($P < 0.001$) higher percentage of patients in the leuprolide group (90.3%) had estradiol levels below the limit of detectability (41 pg/ml), when compared to the DMPA-SC 104 group (61.8%).

Treatments also showed differences in bleeding-pattern profiles. Over the course of treatment, the incidence of amenorrhoea increased in each treatment group, although more patients in the leuprolide group experienced amenorrhoea. In the DMPA-SC 104 group, the percentage of patients having amenorrhoea increased from 19.5% in month 3 to 24% in month 6. In the leuprolide group, 83.7% of patients had amenorrhoea in month 3, and this percentage increased to 89.9% in month 6.

The percentage of patients who reported at least one adverse event during the treatment period was similar in the DMPA-SC 104 and leuprolide groups (69.7 and 65.0% respectively). Adverse events reported during the treatment period and considered by the investigator to be drug-related occurred in 50.7% of patients in the DMPA-SC 104 group and 39.2% of patients in the leuprolide group ($P = 0.047$). Drug-related adverse events in each treatment group (occurring in ≥5% of patients) are listed in Table III. A significantly higher ($P \leq 0.05$) percentage of patients in the DMPA-SC 104 group than in the leuprolide group reported drug-related intermenstrual bleeding, uterine haemorrhage and vaginal haemorrhage, while a significantly higher ($P = 0.003$) percentage of patients in the leuprolide group reported drug-related hot flushes. Serious adverse events occurred in 3.9% of patients in the DMPA-SC 104 group and 2.1% of patients in the leuprolide group during the

Table II. Endometriosis-impact diary: monthly mean (SD) responses from baseline for productivity (intent to treat)

Category	Pre-treatment[a]		Month 6 (end of treatment)		12 months follow-up (month 18 relative to pre treatment)	
	DMPA-SC 104	Leuprolide	DMPA-SC 104	Leuprolide	DMPA-SC 104	Leuprolide
Hours of employment lost due to absenteeism	19.14	14.19	4.88[b]	1.36[b]	3.59[b]	2.47[b]
	(35.95)	(28.62)	(17.11)	(6.54)	(18.21)	(7.92)
	n = 100	*n* = 101	*n* = 90	*n* = 89	*n* = 40	*n* = 43
Hours of employment productivity lost due to presenteeism	40.79	38.99	26.62[b]	26.90[b]	28.02[b]	17.32[b]
	(50.29)	(39.68)	(41.72)	(35.25)	(44.51)	(23.81)
	n = 95	*n* = 97	*n* = 86	*n* = 84	*n* = 40	*n* = 39
Total hours of productivity lost at employment	57.89	51.63	30.32[b]	26.75[b]	31.61[b]	18.18[b]
	(57.41)	(49.45)	(43.79)	(35.09)	(46.58)	(24.07)
	n = 100	*n* = 101	*n* = 90	*n* = 89	*n* = 40	*n* = 43
Hours of housework lost due to absenteeism	14.67	17.21	3.88[b]	2.80[b]	3.37[b]	1.42[b]
	(19.12)	(30.41)	(14.81)	(9.77)	(13.34)	(5.32)
	n = 132	*n* = 130	*n* = 101	*n* = 108	*n* = 51	*n* = 45
Hours of housework productivity lost due to presenteeism	18.34	18.15	7.32[b]	12.31[b]	5.25[b]	8.76[b]
	(28.04)	(30.07)	(12.68)	(21.48)	(7.00)	(15.18)
	n = 129	*n* = 126	*n* = 98	*n* = 99	*n* = 50	*n* = 40
Total hours of productivity lost at housework	32.59	34.80	10.98[b]	14.08[b]	8.52[b]	9.21[b]
	(34.02)	(44.90)	(20.12)	(22.38)	(15.76)	(15.67)
	n = 132	*n* = 130	*n* = 101	*n* = 108	*n* = 51	*n* = 45

[a]Includes all diary entries recorded before the start of treatment, averaged over 1 month.
[b]Statistically significant change from pre-treatment, *t*-test, significance defined at $P \leq 0.05$.
Absenteeism is defined as hours of planned work that was not attempted.
Presenteeism is defined as hours of lost productivity during work activity due to reduced effectiveness caused by endometriosis symptoms.
DMPA-SC 104 = depot medroxyprogesterone acetate 104 mg/0.65 ml subcutaneous injection.

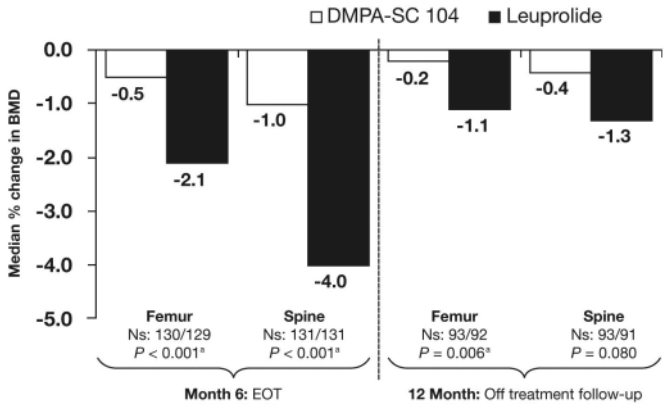

Figure 4. Median percent change in both total hip and lumbar spine bone mineral density (BMD) in each treatment group (intent-to-treat population) from pre-treatment to month 6 (end of treatment [EOT]) and after 12 months of post-treatment follow-up (month 18 relative to pre-treatment). [a]Statistically significant greater decrease observed in the leuprolide group vs the depot medroxyprogesterone acetate 104 mg/0.65 ml subcutaneous injection (DMPA-SC 104) group (Kruskal-Wallis test, $P \leq 0.05$). N = number of patients.

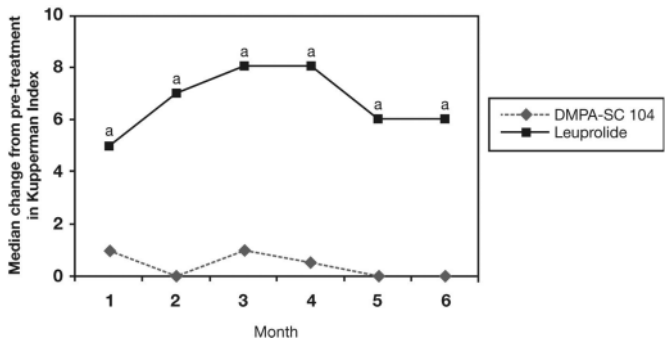

Figure 5. Median change from pre-treatment in Kupperman Index during 6 months of treatment with depot medroxyprogesterone acetate 104 mg/0.65 ml subcutaneous injection (DMPA-SC 104) or leuprolide, where increasing scores indicate an increase in hypoestrogenic symptoms (intent-to-treat [ITT] population). [a]*P* values for between-group differences (Kruskal-Wallis test): $P < 0.001$.

treatment period. The percentage of patients that discontinued treatment due to adverse events was 2.0% in the DMPA-SC 104 group and 1.4% in the leuprolide group. The percentage of patients who reported at least one adverse event during the follow-up period was also similar between groups (55.1% in the DMPA-SC 104 group and 50.0% in the leuprolide group). The most frequently reported adverse event during the follow-up period was breast pain, which was reported in 6.5% of the patients receiving DMPA-SC 104 and 5.1% of leuprolide-treated patients. Other adverse events occurring in >5% of patients in either group during follow-up were nasopharyngitis, headache, nausea, arthralgia, intermenstrual bleeding, and pregnancy.

The coagulation and fasting lipid sub-studies showed the expected small effect of DMPA-SC 104 on these parameters. No clinically relevant changes in haematology, chemistry assays or urinalysis were noted. Likewise, no clinically meaningful changes in blood pressure were observed. With regard to body weight, no clinically meaningful changes were noted. At month 6, the median increase in body weight was 0.70 kg in the DMPA-SC 104 group and 0.50 kg in the leuprolide group. After 12 months of follow-up, the median increase in body weight was 0.9 kg in the DMPA-SC 104 group and 0.85 kg in the leuprolide group.

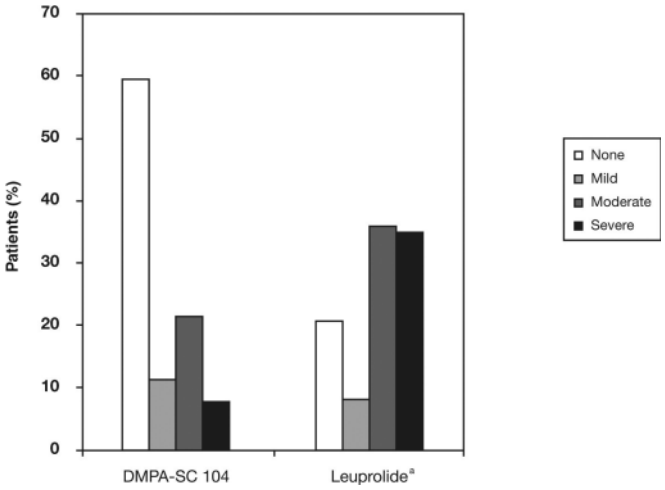

Figure 6. Percentages of patients in each treatment group with maximum severity of hot flushes recorded in endometriosis-impact diaries for month 6 rated as none, mild, moderate or severe (ITT population). [a]*P* value for between-group difference (chi-square test): $P < 0.001$.

Table III. Drug-related adverse events reported in ≥5% of patients during 6 months of treatment (intent to treat)

Adverse event	DMPA-SC 104 (*n* = 152)	Leuprolide (*n* = 143)
Nausea	17 (11.2)	10 (7.0)
Headache	5 (3.3)	9 (6.3)
Breast pain	8 (5.3)	5 (3.5)
Intermenstrual bleeding	19 (12.5)[a]	1 (0.7)
Hot flushes	9 (5.9)	24 (16.8)[a]

Values are *n* (%).
[a]Significantly different between groups, χ^2-test, $P \leq 0.05$.
DMPA-SC 104 = depot medroxyprogesterone acetate 104 mg/0.65 ml subcutaneous injection.

Discussion

In this randomized, evaluator-blinded, comparator-controlled clinical trial, DMPA-SC 104 was shown to be equivalent (non-inferior) to leuprolide in the reduction of endometriosis-associated pain after 6 months of treatment, as well as after 12 months of post-treatment follow-up. Both agents also produced statistically significant and clinically meaningful improvements in composite score after 6 months of treatment and after 12 months of follow-up. In addition, DMPA-SC 104 had significantly less impact on BMD than leuprolide during 6 months of treatment; BMD levels returned to pre-treatment within 12 months of discontinuation, while patients receiving leuprolide continued to show significant reductions from baseline in BMD at the end of follow-up. These data indicate that DMPA-SC 104 resulted in significantly less BMD decline than leuprolide after 6 months of treatment. Hypoestrogenic side-effects such as hot flushes were reported more frequently in the leuprolide group and were consistent with the decreased estradiol levels observed in this group, while more patients in the DMPA-SC 104 group reported bleeding changes. No clinically relevant weight changes between or within groups were observed during treatment or during the follow-up period. Importantly, treatment with either DMPA-SC 104 or leuprolide also significantly improved patients' quality of life. The higher quality of life noted by the patients at month 6 did not diminish or lessen during the 12 months of follow-up. These results highlight DMPA-SC 104 as a promising option for the management of endometriosis.

Current treatment options for endometriosis include surgery and medical therapies. Surgery is an invasive approach and may offer no improvement over medical therapy in terms of pain reduction (Sutton *et al.*, 1994; Hornstein *et al.*, 1997; Winkel, 2000, 2003; Shaw, 2003). Medical treatment options, which include combined oral contraceptives (Vercellini *et al.*, 2003a,b), danazol (Valle and Sciarra, 2003), progestins (Vercellini *et al.*, 1997) and GnRH agonists such as leuprolide (Winkel, 2000; Rotondi *et al.*, 2002; Rice, 2002; Valle and Sciarra, 2003), have demonstrated benefits in clinical trials. However, not all patients can use estrogen (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1997); moreover, the long-term treatment of endometriosis requires alternative strategies. More recently, potential treatments such as antiestrogens (Saito *et al.*, 2003; Viganò *et al.*, 2003) and aromatase inhibitors (Takayama *et al.*, 1998; Viganò *et al.*, 2003; Ailawadi *et al.*, 2004; Bulun *et al.*, 2004) have been considered, but larger clinical trials are required to assess their efficacy.

Progestins, which have been in use for many years, have been shown in several randomized controlled trials to provide equivalent efficacy to danazol or GnRH agonists for the relief of endometriosis-associated pain (Vercellini *et al.*,1997). Limited data have demonstrated the efficacy of oral medroxyprogesterone acetate (MPA) and depot medroxyprogesterone acetate intramuscular injection 150 mg/ml, in providing relief from endometriosis-related pain (Vercellini *et al.*, 1996; Harrison and Barry-Kinsella, 2000). However, use of the oral formulation necessitates daily dosing. This study demonstrated that DMPA-SC 104—a lower dose, SC formulation of depot medroxyprogesterone acetate—is equivalent to leuprolide in reducing endometriosis-associated pain. The additional advantages of DMPA-SC 104 include convenient dosing (once every 3 months) and high efficacy as a contraceptive (Jain *et al.*, 2004a,b). While the impact on BMD limits treatment with leuprolide to 6 months duration [Lupron Depot (package insert); Tap Pharmaceuticals, Lake Forest, IL, USA], DMPA-IM 150 has been used as a contraceptive for durations >6 months in women worldwide (Westhoff, 2003). Data on DMPA-IM 150 show that reversible declines in BMD occur during use, with increases in BMD observed following discontinuation (Kaunitz and Montgomery Rice, 2005; Montgomery Rice and Kaunitz, 2005; Scholes *et al.*, 2002, 2005). Compared with DMPA-IM 150, preliminary data show that DMPA-SC 104 users experience smaller median percentage declines in BMD after 1 and 2 years of treatment (Kaunitz and Kipersztok, 2005).

While weight changes may occur over time in women using hormonal contraception (Kaunitz, 2000; Stager and Cromer, 2000; Pelkman, 2002), this study did not observe an effect of DMPA-SC 104 on body weight. This is consistent with the

only rigorously designed study on DMPA-IM 150, which reported no significant effect of DMPA-IM 150 on body weight compared with placebo (Pelkman *et al.*, 2001). The data suggest that factors other than hormonal contraception may contribute to weight changes in women.

The impact of therapy on quality of life is yet another key issue to consider: women with chronic pelvic pain associated with endometriosis consistently report lower quality of life than women without this condition (Jones *et al.*, 2002; Marques *et al.*, 2004). Because endometriosis is a chronic condition, women frequently experience recurrences (Valle and Sciarra, 2003), and repeated use of invasive treatments or therapies associated with significant adverse events may also contribute to decreased quality of life. In a prospective randomized study of 48 women with endometriosis, treatment with both nafarelin (a GnRH agonist) and MPA resulted in significant improvements in factors associated with quality of life, including anxiety, depression and sleep disturbances (Bergqvist and Theorell, 2001). These documented improvements in quality of life, in addition to those found in the current study, are important to consider with regard to endometriosis treatments.

In conclusion, this randomized, evaluator-blinded, comparator-controlled clinical trial demonstrated that DMPA-SC 104, a unique formulation for subcutaneous administration, is as effective as leuprolide in reducing endometriosis pain after 6 months of treatment. Although further long-term studies are needed, the safety profile of DMPA-SC 104 and its use as a highly effective contraceptive worldwide suggest that this agent may be suitable for therapy of endometriosis-associated pain beyond 6 months. Coupled with the significant improvements in quality of life observed with treatment, these results suggest that DMPA-SC 104 may be suitable as first-line therapy for endometriosis-associated pain.

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