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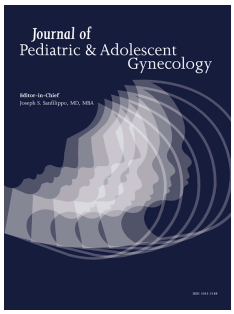

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Abstract

Study objective: To study the safety and efficacy of dienogest 2 mg in adolescents with suspected endometriosis.

Design: 52-week, open-label, single-arm study.

Setting: 21 study centers, six European countries.

Participants: Adolescents aged 12 to <18 years with clinically-suspected or laparoscopically-confirmed endometriosis.

Intervention: Dienogest 2 mg once-daily.

Main Outcome Measures: Primary endpoint was relative change in lumbar spine (L2-L4) bone mineral density (BMD) measured by dual-energy X-ray absorptiometry. A key secondary endpoint was change in endometriosis-associated pain assessed using a visual analog scale.

Results: Of 120 patients screened, 111 comprised the full-analysis set (i.e. patients who took ≥1 dose of study drug and had ≥1 post-treatment observation) and 97 (87.4%) completed the study. Mean lumbar BMD at baseline was 1.1046 (SD 0.1550) g/cm^2. At end of dienogest treatment (EOT, defined as at 52 weeks or premature study discontinuation), mean relative change in BMD from baseline was -1.2% (SD 2.3%) (n=103). Follow-up measurement 6 months after EOT in the subgroup with decreased BMD at EOT (n=60) showed partial recovery in lumbar BMD (mean change from baseline: -2.3% at EOT, -0.6% 6 months after EOT). Mean endometriosis-associated pain score was 64.3 (SD 19.1) mm at baseline and decreased to 9.0 (SD 13.9) mm by week 48.

Conclusions: In adolescents with suspected endometriosis, dienogest 2 mg for 52 weeks was associated with decrease in lumbar BMD, followed by partial recovery after treatment discontinuation. Endometriosis-associated pain was substantially reduced during treatment. As bone accretion is critical during adolescence, the VISADO study highlights the need for tailored treatment in this population, taking into account the expected efficacy on endometriosis-associated pain and an individual's risk factors for osteoporosis.

Key Words: Adolescent, Bone mineral density, Dienogest, Endometriosis, Pelvic pain

Clinical trial registration number: NCT01283724.

https://www.clinicaltrials.gov/ct2/show/NCT01283724

Introduction

Relative to adults, there are limited data on the frequency and symptoms of endometriosis in adolescents,[1,2] although many women first report symptoms in their teens or earlier.[3-5] Approximately 5% of girls aged 15 to 19 years report severe dysmenorrhea not alleviated by combined oral contraceptives (COC) and pain medication, a condition suggestive of endometriosis.[6,7] Endometriosis has been diagnosed by laparoscopy in young adolescents and young women (< 19–21 years) with dysmenorrhea and chronic pelvic pain at rates between 35% and 70%.[2,8-10]

The most common treatments for adults with endometriosis are medications to reduce pain (for example, nonsteroidal anti-inflammatory drugs [NSAIDs]), hormonal therapies, and laparoscopic surgery.[11] The rationale for hormonal therapies is to reduce circulating concentrations of estrogen, which decreases endometriotic lesion size and symptoms. Hormonal therapies available include COCs (unapproved by Regulatory Authorities for use in endometriosis), progestins, gonadotropin-releasing hormone (GnRH) agonists, androgens, and antiprogestagens.[11,12] Empirical use of hormonal therapy is an accepted, widely adopted approach to alleviating symptoms in women at high risk of endometriosis, without prior laparoscopic confirmation of the diagnosis.[13]

There is debate regarding whether early diagnosis and treatment of teenage endometriosis provides better long-term outcomes or simply increases the number of interventions without preventing disease progression.[14] Effective treatment of endometriosis in adolescents, however, has the potential to both reduce symptoms and improve quality of life.[4] Most adult treatments have not been tested in this age group. While oral contraceptives are reported to be effective in trials of adolescents,[15-17] hormone therapies used in adults, including GnRH agonists,[18-20] COCs,[21,22] and many progestins,[23-26] have safety profiles that are unsatisfactory for adolescents.[11,12] Specifically, the potential for bone mineral density (BMD) loss associated with hormonal treatments, through reduction in circulating estrogen levels, is of particular concern.[27] Further research is needed on the risk-benefit profile of treatments in adolescents.

Dienogest is a progestin indicated as monotherapy at an oral dose of 2 mg once-daily in endometriosis.[28] Dienogest is highly selective for the progesterone receptor, exhibiting strong progestational effects and moderate antigonadotrophic effects, with limited androgenic, glucocorticoid, or mineralocorticoid activity.[29,30] Dienogest suppresses estradiol levels only moderately[29,30] and, in a 6-month study in adults, did not alter mean lumbar spine BMD.[31,32] The safety and efficacy of dienogest for providing pain relief in the adult population have been confirmed in several clinical trials, differing in design and ethnicity of populations.[21,31,33-37]

During development of dienogest, the Paediatric Committee (PDCO) of the European Medicines Agency requested a Paediatric Investigational Plan (PIP) for the indication of endometriosis in symptomatic patients post-menarche (age 12 to <18 years). Bayer initiated the phase 2 safety study in 2011 (VISADO; ClinicalTrials.gov Identifier: NCT01283724). The primary objective of the VISADO study, agreed with the PDCO, was to evaluate the long-term (52-week) effects of dienogest 2 mg once-daily on BMD of the lumbar spine, measured by dual-energy X-ray absorptiometry (DEXA), in adolescents with confirmed or clinically suspected endometriosis.[38]

Materials and Methods

VISADO was a multicenter, single-arm, open-label study conducted at 21 study centers in 6 European countries (Austria, Czech Republic, Finland, France, Germany, and Spain) between March 2011 and June 2014. In discussion with the PDCO, it was agreed to conduct the study in an uncontrolled design because no other treatments have been approved for treatment of endometriosis in adolescents.[39] Furthermore, placebo treatment was excluded from an ethical perspective in this age group.

Adolescent girls post-menarche, aged 12 to < 18 years, with clinically suspected or laparoscopically diagnosed endometriosis were eligible for study inclusion. Appropriate definitions of the study population (age, diagnostic criteria) were discussed with the PDCO during development of the PIP. Laparoscopic confirmation of endometriosis was not made

mandatory because surgical procedures are commonly avoided in this age group.[39] Furthermore, empirical treatment is common in adolescents with pelvic pain and dysmenorrhea when other causes of pelvic pain symptoms are excluded.[13]

Inclusion criteria included dysmenorrhea of moderate to severe intensity, with or without chronic pelvic pain, for ≥2 cycles in the previous 4 months, and either (1) clinically suspected endometriosis (pelvic pain incompletely relieved by NSAIDs and/or OCs); (2) abdominal pain associated with ultrasound findings suggestive of endometriosis; or (3) failure of surgical treatment for endometriosis (with cyclic or chronic pelvic pain of ≥4 months' duration after confirmation of endometriosis). Patients were required to have an endometriosis-associated pelvic pain score ≥30 on a 100-mm unit visual analog scale (VAS), evaluated at screening retrospectively for the previous 4 weeks.

Patients were excluded from the study if laparoscopy had been performed in the past and endometriosis was absent; chronic pelvic pain may have been related to genitourinary or gastrointestinal disease; there was undiagnosed abnormal genital bleeding; or amenorrhea had been present in the previous 3 months. Patients were also excluded if they received hormonal therapies, including oral contraceptives within the previous 2 months, progestins or danazol within 3 months, or GnRH agonists within 6 months before the start of study. Patients with a clinically established need for surgical treatment of endometriosis were excluded. Diseases or conditions precluded study enrollment if they might worsen during study treatment, influence BMD, or result in altered absorption, accumulation, metabolism, or excretion of study drug. Investigators excluded any patient with clinically relevant findings at general physical or gynecological examination or with laboratory values outside the inclusion range.

Patients received oral dienogest 2 mg as a single daily dose. Tablets were taken with or without food, preferably at the same time each day, continuously through the 52-week study period. Information on medication intake and data for the evaluations described below were collected by patients using e-diaries. Patients were allowed NSAIDs for pain but no other medicines specific for endometriosis. Drugs or foods with potential to interact with

dienogest were prohibited during the study, in particular: anticoagulants (heparin or coumarin) and drugs known to influence the study medication (i.e. influence the CYP3A4 isoenzyme of the cytochrome P-450 pathway), such as barbiturates, primidone, carbamazepine, phenytoin, rifampicin, and possibly also oxcarbazepine, topiramate, griseofulvin, felbamate, nevirapine, and products containing St. John's wort, azole antifungals (e.g. ketoconazole, itraconazole, fluconazole), verapamil, macrolides (e.g. erythromycin, clarithromycin, roxithromycin), diltiazem, protease inhibitors (e.g. ritonavir, saquinavir, indinavir, nelfinavir), antidepressants (e.g. nefazodone, fluvoxamine, fluoxetine), or broad-spectrum antibiotics lasting more than 2 weeks.

The study was approved by the PDCO, pertinent national Competent Authorities, and each study site's independent ethics committee or institutional review board, and was conducted according to Good Clinical Practice guidelines, the Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population, Declaration of Helsinki, and local laws and regulations. Written informed consent was provided by patients and parents/other legal representative before the start of the study. If contraception was required, a non-hormonal barrier method (e.g. condom) could be used during the study.

Patients attended the clinic for screening (weeks -4 to -1), at baseline (week 0), every 4 weeks to end of treatment (EOT; week 52 or premature discontinuation from study medication), and at follow-up 4 weeks after EOT.

BMD of the lumbar spine (L2-L4) and whole-body was measured by DEXA at baseline and EOT. Patients with decreased lumbar spine BMD at EOT relative to baseline were invited to revisit 6 months later. For BMD of the lumbar spine, the mean of 2 measurements was calculated at each visit, while whole-body BMD was measured once per time point. BMD measurements were validated by Imaging Core Lab Services for Clinical Trials (SYNARC Inc., Portland, Oregon).

Endometriosis-associated pelvic pain on a 100-mm unit VAS was assessed by patients retrospectively for the previous 4 weeks at screening, baseline, and every 4 weeks ("Please indicate your subjective level of endometriosis pain looking back at the last 4

weeks"). The VAS is a validated measure of pain used previously in trials of dienogest in adults with endometriosis.[31,36,37,40]

The Biberoglu and Behrman (B&B) severity scale was used at screening, baseline, and every 4 weeks during treatment. The B&B severity profile for symptoms and signs (0 = none; 1 = mild; 2 = moderate; 3 = severe) is widely used to assess treatment response in endometriosis, including trials of dienogest in adults.[31,37] Clinical Global Impressions rating scale scores (1 = very much improved to 7 = very much worse) were assessed at weeks 12, 24, 36, and 52. Investigators rated total improvement, while patients rated satisfaction with treatment. The Endometriosis Health Profile (EHP-30) was self-administered by patients at baseline and weeks 12, 24, and 52, retrospectively for the prior 4 weeks. This quality of life questionnaire comprises 30 items covering 5 domains: pain, control and powerlessness, emotional well-being, social support, and self-image, and is validated in endometriosis.[41,42]

Adverse events (AEs) were reported throughout the study, including their nature, seriousness, intensity, and relationship to study drug. Vital signs and clinical laboratory variables (estradiol, bone metabolism markers, hematology, coagulation, blood chemistry, liver, diabetes mellitus, lipids, and urinalysis) were assessed at screening and preplanned intervals. Laboratory determinations were performed by a central laboratory (Laboratorium für Klinische Forschung GmbH, Germany). Uterine bleeding intensity (none, spotting, light, normal, or heavy) was recorded daily in an e-diary. Gynecological examination and transvaginal ultrasound (if patients consented) were performed to assess pelvic tenderness and induration at screening and preplanned intervals to week 52. Alternatively, abdominal ultrasound was offered. A complete physical examination was performed at screening and EOT.

A sample size of 80 evaluable subjects was agreed with the PDCO. Based on earlier studies,[31] a standard deviation of ~3 percentage points for the change in BMD was assumed. With a total of 80 subjects, a 95% confidence interval (CI) of width 1.3 percentage points could be provided.

Efficacy analyses were conducted on the full-analysis set (FAS) and per-protocol set (PPS), and safety was evaluated on the FAS. The FAS included all patients who took ≥ 1 dose of study drug and had ≥ 1 post-treatment observation. The PPS excluded patients from the FAS who had major protocol deviations affecting primary safety and efficacy endpoints.

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). Descriptive statistics were used for assessment of BMD, including arithmetic mean and standard deviation (SD), at baseline and EOT. Bleeding episodes were described over 90-day reference periods, as recommended by the World Health Organization.[43] Other data were evaluated by descriptive statistics for continuous variables and frequency tables for categorical data. There were no adjustments for covariates.

Results

Of 120 adolescents screened, 111 were eligible for study treatment and 97 (87.4%) completed the study (Fig. 1). Among 14 patients who discontinued study medication prematurely, the most common reason was withdrawal of informed consent (n=6). The FAS included 111 patients and the PPS 81 patients. Baseline demographics and characteristics of patients are shown in Table 1. Mean patient age was 15.4 years (range, 12 to <18 years) and mean age at menarche was 12.1 (SD 1.2) years. Ninety-seven patients (87.4%) were diagnosed by clinical symptoms and/or findings, 13 patients (11.7%) had imaging findings consistent with the diagnosis of endometriosis, and only 1 patient (0.9%) was diagnosed surgically. Compliance with study treatment, assessed by e-diary, was 87.3% (SD 16.6%; median 94.3%) in the FAS and 92.7% (SD 7.1%; median 94.8%) in the PPS.

Mean BMD of the lumbar spine (L2-L4) was 1.1046 (SD 0.1550) g/cm^2 at baseline (FAS). At EOT, mean percent change from baseline was -1.2% (SD 2.3%; 95% CI -1.70% to -0.78%; n=103) (Fig. 2). Lumbar spine BMD was lower at EOT than baseline in 73 of the 103 patients (70.9%) (mean change, -2.3%). Follow-up lumbar spine BMD measurements in 60 of these 73 patients 6 months after EOT showed partial recovery (mean change, -0.6% vs baseline, SD 2.4%; 95% CI -1.20% to 0.06%). For 22 (36.7%) of the 60 patients with

decreased BMD at EOT who attended measurement 6 months later, BMD had returned to baseline or had increased. Changes in lumbar spine BMD in the PPS were similar to the FAS (data not shown).

Lumbar spine BMD decreased in one patient by 6.2% at EOT, from a baseline of 1.269 g/cm^2; this was reported as a study drug–related serious AE (SAE). By 6 months after EOT, lumbar spine BMD decreased 8.7% versus baseline. Of note, this patient received medications between EOT and 6 months later that may have contributed to the further BMD decrease, including cyproterone acetate (50 mg) in combination with estradiol gel (0.1% daily, cutaneous) and chlormadinone acetate (10 mg). She had started smoking (5 cigarettes/day) 10 months before enrollment. Estradiol values in the patient were 311.7 pmol/L at baseline, 102.1 pmol/L at week 24, and 143.9 pmol/L at EOT.

Post hoc subanalyses, including regression analyses, were performed on relative BMD changes in different age groups, body mass index (BMI) levels, and smoking status at baseline. There was a small numerical tendency for greater decreases in lumbar BMD in "older" patients and smokers, with high variation (Supplemental file 1). Subanalyses of lumbar BMD change in patients grouped by time after menarche and pain symptoms indicated that greater BMD decrease was associated with longer time after menarche, but no correlation existed with intensity of pain (Supplemental files 2 and 3).

Mean whole-body BMD was 1.0932 (SD 0.0924) g/cm^2 at baseline (FAS). At EOT, mean percent change from baseline was +0.8% (SD 1.6%; 95% CI 0.50% to 1.14%). Whole-body BMD was at or above baseline in 101 patients (98.1%). In the 60 patients with decreased lumbar spine BMD at EOT, change in whole-body BMD at EOT was +0.5% (SD 1.3%). By 6 months post-EOT, change of whole-body BMD versus baseline in this subgroup was +0.8% (SD 1.5%; 95% CI 0.37% to 1.16%). In the patient who experienced 6.2% reduction in lumbar spine BMD (reported above), whole-body BMD decreased >6% at EOT. Changes in whole-body BMD in the PPS were similar to those in the FAS (data not shown).

Three biochemical markers of bone metabolism were assessed: type I collagen C-telopeptide (CTX-1) in serum and type II collagen C-telopeptide (CTX-2) in urine, markers of

bone resorption and cartilage degradation, respectively, and procollagen 1 N-terminal propeptide (P1NP) in blood, a marker of bone formation. All CTX-1, CTX-2, and P1NP concentrations in the adolescent patients exceeded upper reference values for adult premenopausal women. The adult reference ranges were applied because, at the time of starting the study, no reference data for adolescent populations were available. All analyzed markers showed a decrease from baseline to EOT, while not reaching the normal range for adult women. Age- and method-specific reference ranges have since become available for CTX-1, and post hoc analysis revealed that values exceeded the upper reference range in <10 samples; these increases were <10% above the normal range.

Mean endometriosis-associated pelvic pain at baseline assessed by VAS was 64.3 mm (SD 19.1 mm). By week 4, the VAS score decreased to 36.8 mm (SD 26.1 mm) and by week 48 to the lowest mean value of 9.0 mm (SD 13.9 mm) (Supplemental file 4). The proportion of responders (ie, ≥ 30% reduction in VAS score from baseline) was 81.0% (81 of 100 patients) at week 24. B&B scores showed increased proportions of patients without endometriosis symptoms between baseline and EOT: pelvic pain (from 9.1% to 71.2%, n=110), dysmenorrhea (3.6% to 78.8%, n=110), and dyspareunia (9.1% to 23.1%, n=21). Only 21 patients provided data on dyspareunia, probably because of the low frequency of intercourse in this population. There were accompanying decreases in the proportions of patients with moderate to severe symptoms of pelvic pain (from 67.2% to 4.8%) and dysmenorrhea (74.6% to 5.8%). At baseline and EOT, 33 and 56 patients, accordingly, underwent a gynecological investigation. The proportion of patients without gynecological signs of endometriosis increased between baseline and EOT: pelvic tenderness (from 63.6% to 80.4%) and induration (60.6% to 87.5%). The proportion of patients with moderate or severe pelvic tenderness decreased at EOT versus baseline (from 6.1% to 1.8%), while no patients had induration of moderate or severe severity at baseline or EOT.

Investigators rated patient status as “much improved” or “very much improved” in 85.6% at week 12, with a further increase to 89.9% at EOT. A total of 74.1% patients were “much satisfied” or “very much satisfied” at week 12, with a further increase to 84.5% at

EOT. Health-related quality of life assessed by EHP-30 showed improvements in all items assessed (Supplemental file 5).

AEs were reported by 92 (82.9%) patients. The most frequent AEs (>5% of patients) were headache (9.0%), breast discomfort (7.2%), weight increased (6.3%), and abdominal pain (5.4%). Frequencies of individual AEs were similar to those reported previously in adults (Supplemental file 6). In 40 patients (36.0%), AEs were judged related to study medication. Five patients experienced 7 SAEs during the 52-week study, of which 1 was considered related to study medication: a case of a ruptured ovarian cyst on the right side; the patient recovered fully 4 days later. Other SAEs included suspected adenomyosis and ovarian adhesions, right acute pyelonephritis, sprain of cervical spine, pyelonephritis, and depression. AEs in 5 patients (4.5%) led to study drug discontinuation: hypogastric pain and ruptured ovarian cyst (SAE; see above), major depression, cholecystitis, nausea, headache, and vomiting; 1 patient discontinued due to amenorrhea not acceptable for her. Two patients reported a SAE after the 52-week treatment period: right ovary dermoid cyst (this patient also had the SAE of acute pyelonephritis) and bone densitometry decrease (related to study medication, described above).

Mean body weight increased by 1.87 (SD 3.82) kg between screening and EOT. Weight increase was reported as an AE in 10 patients (9.0%) and weight decrease in 3 patients (2.7%). Blood pressure values were stable during study and no changes in clinical laboratory parameters were judged clinically relevant by investigators.

Estradiol concentrations ranged widely, as expected, at different phases of the menstrual cycle at screening (41.1-1388.0 pmol/L) and EOT (47.0-1848.0 pmol/L), while remaining within the normal range (46.0-1827.9 pmol/L). The mean serum estradiol concentration decreased from 374.8 (SD 278.6; median 275.0) pmol/L at baseline to 201.5 (SD 235.3; median 139.5) pmol/L at EOT.

The number of bleeding/spotting days decreased during study (Fig. 3). Similarly, the mean (SD) number of bleeding episodes in 90-day reference periods 1, 2, 3, to 4 decreased from 12.0 (12.0), 4.1 (7.0), 3.8 (7.5), to 2.4 (6.3), and the mean (SD) number of

bleeding/spotting episodes decreased from 3.1 (2.3), 1.9 (2.1), 1.5 (2.1), to 1.6 (2.0), respectively. With continued use of dienogest an increasing number of patients experienced amenorrhea (Fig. 3).

No pregnancies were detected during study treatment. One subject became pregnant shortly after the end of treatment. Her pregnancy test 20 days after the last study medication dose showed a positive result. Her pregnancy test at end of treatment had been negative. She underwent surgical abortion.

Discussion

In this 52-week multicenter study of adolescent patients, dienogest 2 mg once-daily was effective in relieving the symptoms (pelvic pain, dysmenorrhea, and dyspareunia) and signs (pelvic tenderness and induration) of endometriosis. Dienogest was generally well tolerated, consistent with previously reported trials of adults with endometriosis.

Change in mean lumbar spine BMD was the primary study endpoint. Dienogest was associated with a mean decrease in lumbar spine BMD of -1.2% at EOT. Follow-up assessment in 60 of the 73 patients with decreased lumbar spine BMD at EOT showed a partial recovery 6 months later. In contrast to the change in lumbar spine BMD, whole-body BMD increased 0.8% from baseline to EOT in the study population. Discordance in DEXA data between whole-body and regional (for example, spinal) sites is a well-recognized observation in osteoporosis and other studies, and is attributed to differences in the relative proportion of cortical versus cancellous bone.[44-46]

Post hoc subanalyses detected no clear correlations between BMD changes and patient age, time after menarche, or BMI, while current smokers showed a higher mean BMD decrease than nonsmokers.

In studies of adults with endometriosis, dienogest has shown limited effects on BMD. Strowitzki et al,[31] in a 24-week trial, observed a 0.25% increase in mean lumbar spine BMD with dienogest 2 mg, versus a decrease of 4.04% with leuprolide acetate (*P*=.0003, treatment comparison). In a 24-week trial by Harada et al,[33] reduction in BMD during

dienogest 1 mg twice-daily was significantly lower than with buserelin acetate (BA): -1.0 ± 2.3% versus -2.6 ± 2.3% (*P*=.003). In a 52-week trial, Momoeda et al[35] reported the long-term effect of dienogest 1 mg twice-daily on lumbar spine BMD, with a mean change from baseline of -1.7% (SD 2.2%). These results are similar to those of the VISADO study.

Other hormonal treatments for endometriosis, including GnRH agonists and other progestins, demonstrate substantial adverse effects on BMD in adults.[11,21,23,25-27] GnRH agonists, in particular, induce low levels of circulating estrogens,[47] which can reduce BMD by 4%-5% after 6 months.[48] Among the progestins, medroxyprogesterone acetate is noted to have an adverse effect on BMD.[25] While COCs are commonly prescribed, their effect on bone metabolism and impact on peak bone mass in adolescents remain unclear.[49-51]

When interpreting the BMD data in the VISADO study, it is important to note that decreased BMD is a surrogate marker to identify osteoporosis and assess fracture risk, particularly in postmenopausal women. In addition, BMD addresses bone quantity, not bone quality.[52] While loss of BMD is of concern during adolescence and early adulthood—a critical period of bone accretion—measurement of BMD in premenopausal women should be interpreted with caution.[52] In particular, it is unknown whether a decrease of BMD in adolescents will reduce peak bone mass and increase risk for fracture in later life.

Baseline concentrations of biochemical markers of bone turnover assessed in the VISADO study exceeded the upper reference range for adult premenopausal women. This may be partially explained by the effects of ongoing bone formation in adolescents. Post hoc analysis of CTX-1 data using newly available reference ranges for adolescents indicated that almost all values in the VISADO study were within the expected range or exceeded it minimally. Due to the lack of established reference ranges for other markers in the healthy adolescent population, no final conclusions can be drawn on the clinical relevance of these findings.

Dienogest 2 mg substantially decreased endometriosis-associated pelvic pain evaluated by the VAS. By week 4, pain was nearly one half the level at baseline, and pain continued to decrease, with the lowest mean value at week 48. Consistent with VAS

outcomes, B&B scores improved substantially and global assessments by physicians and patients showed marked improvements. Efficacy assessments were accompanied by improvements in quality of life reported by the EHP-30.

The efficacy findings for dienogest 2 mg in this adolescent population are consistent with data in adults with endometriosis, where the reductions in pain score were similar at equivalent time points.[31,37] Also consistent with adult studies,[32,36,37] dienogest 2 mg demonstrated favorable tolerability in the adolescent population, with a predictable adverse event profile. The VISADO study showed modest suppression of estradiol levels, with median values (139.5 pmol/L, FAS) that remain within the therapeutic window suggested for endometriosis treatment.[53]

A progressive reduction in bleeding/spotting days and episodes over time, and an amenorrhea rate of 35.3% during dienogest treatment in 90-day reference period 2, are consistent with a study in adults (amenorrhea rate 38.9% in reference period 2[31]). By reference period 4 in the VISADO study, the amenorrhea rate had increased to 40.9%.

Limitations of the VISADO study include the open-label design with lack of a control group. An uncontrolled study design was agreed with the PDCO, as there is no comparator treatment appropriately tested in the adolescent population and a placebo-controlled study was considered unethical. The study allowed inclusion of patients with suspected endometriosis in the absence of definitive diagnosis by laparoscopy. In this regard, VISADO is representative of routine clinical practice, where laparoscopy (particularly in adolescents) is frequently avoided and empirical treatment is standard. Third, the study was not primarily designed to identify predictive factors for BMD decrease during dienogest treatment, which would help the treating physician considering dienogest treatment. Subgroup analyses based on age, BMI, and smoking status were performed, but did not permit clear conclusions for treatment decisions due to limited sample sizes. Fourth, the study included patients with limited racial diversity. Finally, follow-up BMD data after EOT were available only in patients with decreased BMD at EOT, not in those with unchanged or increased BMD.

In conclusion, the treatment of endometriosis in adolescents with 2 mg of dienogest once-daily for 52 weeks was associated with a decrease in lumbar spine BMD, followed by partial recovery after treatment discontinuation. Individual patients may show more substantial changes in lumbar spine or whole-body BMD than observed in the VISADO study. As bone accretion is critical during adolescence, the physician would need to weigh the benefits of dienogest 2 mg against potential risks in individual adolescent patients, as well as take into account any significant risk factors for osteoporosis.

The efficacy of dienogest in relieving endometriosis-associated symptoms and signs and the profile of common AEs were comparable to those in adult populations.

The VISADO study constitutes a rare resource for evidence-based treatment of endometriosis in adolescents and highlights the need for individualized treatment in these patients.

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Table legend

Table 1. Demographics and Baseline Patient Characteristics (FAS)

Figure legends

Fig. 1. Flow diagram of patients through the VISADO study.

Fig. 2. Box and whisker plots of (A) lumbar spine (L2-L4) bone mineral density (BMD) (g/cm^2) and (B) relative change in L2-L4 BMD in all patients (gray boxes) and in the subgroup of patients who had a decrease in L2-L4 BMD at end of treatment (EOT) (white boxes). Boxes show median values (horizontal rules) and 25% and 75% quartiles (borders of boxes); whiskers indicate 2.5% and 97.5% quantiles; and crosses indicate individual outliers.

* For 1 subject a BMD measurement from the lumbar spine at 6 months after EOT is available, although the relative change in L2-L4 BMD from baseline to EOT showed an increase. The reason why this subject had a second BMD measurement at 6 months after EOT is that eligibility for this BMD examination was based on adjusted but not yet corrected BMD values. The adjusted results for the relative change of L2- L4 BMD from baseline to EOT showed a decrease, while the adjusted and corrected results—which are relevant for reporting—showed an increase.

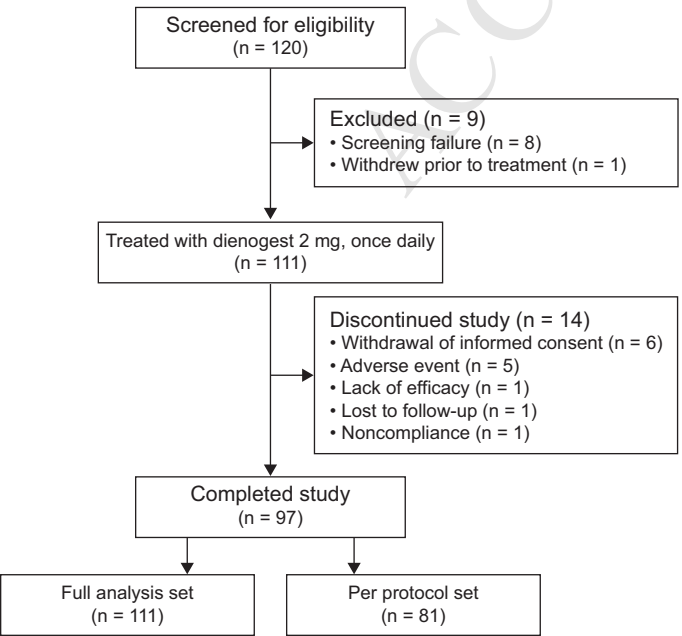
Fig. 3. Uterine bleeding/spotting days and amenorrhea rate in World Health Organization 90-day reference periods 1 to 4 (full-analysis set).

Table 1

Demographics and Baseline Patient Characteristics (FAS)

	Dienogest 2 mg (n=111)
Age, years	
Mean (SD)	15.4 (1.3)
Median	16.0
Range	12-17
Race, n (%)	
White	105 (94.6)
Black/African American	1 (0.9)
Not reported	5 (4.5)
Weight, kg	
Mean (SD)	61.8 (11.2)
Range	41.0-97.0
BMI, kg/m^2	
Mean (SD)	22.5 (3.7)
Range	16.0-34.8
Country, n (%)	
Czech Republic	50 (45.0)
Finland	19 (17.1)
Germany	16 (14.4)
Austria	13 (11.7)
Spain	8 (7.2)
France	5 (4.5)
Diagnosis of endometriosis, n (%)	
Clinical suspicion	97 (87.4)
Laparoscopy	1 (0.9)
Imaging findings consistent with endometriosis	13 (11.7)

BMI, body mass index; FAS, full-analysis set; SD, standard deviation



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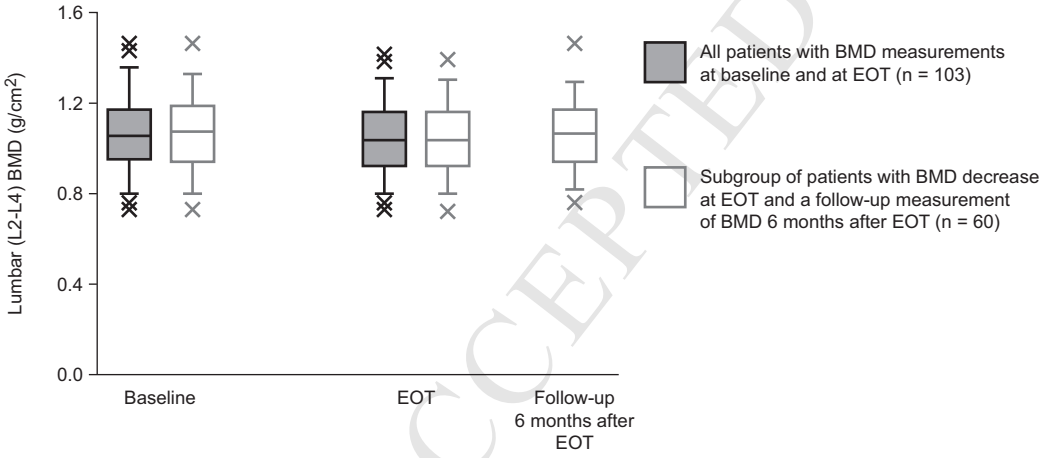

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