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Long-term use of dienogest in the treatment of painful symptoms in adenomyosis

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Abstract

Aim: We aimed to investigate the safety and efficacy of dienogest (DNG), a progestational 19-norsteroid, administered for 52 weeks in patients with symptomatic adenomyosis.

Methods: A total of 130 patients with adenomyosis received 2 mg of DNG orally each day for 52 weeks. In cases of complicated anemia, patients were treated for anemia prior to receiving the medication. Adverse events and adverse drug reactions were evaluated. The patients' pain symptoms (dysmenorrhea and pelvic pain from adenomyosis) were assessed using a pain-scoring tool. This was a verbal rating scale comprising a 0–3-point pain-severity score measuring disability to work, and an analgesics-usage score measuring need for analgesics.

Results: The most common adverse drug reactions included metrorrhagia (96.9%) and hot flush (7.7%). However, in most cases, metrorrhagia was tolerable and no clinically significant changes were observed concerning the incidence or severity of reactions during the 52-week treatment period. There were no serious adverse events. Both the pain-severity score and analgesics-usage score decreased after the start of treatment with DNG. The mean ± standard deviation changes from baseline for the pain score were −3.4 ± 1.8 at 24 weeks and −3.8 ± 1.5 at 52 weeks, respectively.

Conclusion: The long-term use of DNG was well-tolerated and effective in patients with symptomatic adenomyosis.

Key words: adenomyosis, dienogest, long-term adverse effects, progestin analogs, safety.

Introduction

Adenomyosis is a common gynecological disease in which endometrium-like tissue grows ectopically within the myometrium. Adenomyosis often significantly reduces quality of life (QOL) due to severe painful symptoms, such as dysmenorrhea and pelvic pain. The conservative medical treatment for these symptoms has been hormone therapies for endometriosis, based on the biological similarity of adenomyosis to endometriosis.[1] Although hormone therapies, such as gonadotropin-releasing hormone (GnRH) analogs, may be effective in controlling the symptoms of adenomyosis, the frequency of associated adverse events (AE) due to hypoestrogenism, such as hot flush and decrease in bone mass, makes it difficult to continue GnRH analogs therapy over the long term.[1] In particular, an increasing tendency towards late childbearing in recent years has created a need for extended conservative therapy in patients with adenomyosis. Therefore, an effective and well-tolerated option for long-term treatment of adenomyosis symptoms is highly desirable.

Dienogest (DNG), a 19-nortestosterone derivative, is a progestin with high selectivity for progesterone receptors.[2] DNG exhibits antiovulatory activity[3] and antiproliferative effects on endometrial cells.[4] Based on this hormonal profile, DNG at a dose of 2 mg/day is used as a treatment for painful symptoms in patients with endometriosis, without causing any severe hypoestrogenic adverse effects.[5,6] It is also expected to

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be an effective treatment for painful symptoms associated with adenomyosis. On the other hand, irregular genital bleeding due to the progestational action of DNG on the endometrium is a well-known AE in patients with endometriosis.[7] In patients with adenomyosis, this occasionally results in severe anemia.[8]

The purpose of the present study was to investigate the safety and efficacy of DNG, administered for 52 weeks, in the treatment of symptomatic adenomyosis.

Methods

Study design and patients

This was an open-label, multicenter, long-term treatment study. It was conducted from July 2014 through January 2016 at 29 study sites in Japan. The protocol was approved by the institutional review boards of all participating sites.

Inclusion criteria were as follows: (i) aged 20 years or older; (ii) regular menstrual cycles; (iii) adenomyosis diagnosed by imaging analysis (both magnetic resonance imaging and transvaginal sonography);[9] and (iv) pain symptoms during the menstrual cycle (lower abdominal pain and/or lumbago) scoring 3 points or more on the verbal pain-rating scale developed by Harada *et al.*[10] (Table 1).

Exclusion criteria were as follows: (i) submucous leiomyoma diagnosed by imaging analysis (both magnetic resonance imaging and transvaginal sonography); (ii) severe anemia (hemoglobin concentrations lower than 8.0 g/dL); (iii) marked uterine enlargement (maximum dimension of more than 100.0 mm or myometrial thickness of more than 40.0 mm), *etc.* In cases of mild or moderate anemia (hemoglobin levels between 8.0 and 11.0 g/dL), patients were given anemia treatment so that hemoglobin concentrations reached at least 11.0 g/dL before starting administration of DNG.

Written informed consent was obtained from all patients and patient anonymity was preserved.

Table 1 Grading, scoring, and definitions for components of the pain score

Grade	Score	Definition
Pain-severity score (lower abdominal pain and/or lumbago)		
None	0	None
Mild	1	Low efficiency for work and/or study
Moderate	2	Needing to rest in bed and/or loss of work
Severe	3	In bed for 1 day or more
Analgesics-usage score		
None	0	None
Mild	1	Taking analgesics for 1 day
Moderate	2	Taking analgesics for 2 days
Severe	3	Taking analgesics for 3 days or more

Study treatments and measurements

DNG was administered orally (1 mg twice daily), starting between the 2nd and 5th day of the menstrual cycle. For the duration of the study, patients were required to use reliable contraception other than hormonal agents and were allowed to take analgesics.

The primary safety end-point was evaluation of AE. An AE is any unfavorable and unintended sign, symptom, or disease that does not necessarily have a causal relationship with the investigational product. The secondary safety end-point was adverse drug reactions (ADR). An ADR is an AE that the investigator judged could not be ruled out from having a causal relationship with the investigational product. The severity of AE was evaluated as mild, moderate, or severe by the physician. Given that a high incidence of irregular genital bleeding was expected due to the progestational effects of DNG on the endometrium,[7] the number of days and severity of genital bleeding were assessed using a patient diary form. If there was a concern over severe anemia due to persisting severe genital bleeding, then washout up to 14 doses for 7 days was allowed at the discretion of the physician. The re-entry after washout was judged by the physician. Laboratory-hematology tests were performed at baseline, every 4 weeks from the start until the end of treatment (EOT: 52 weeks or when discontinued), and after patients resumed menstruation. Laboratory biochemical and urinalysis tests were conducted at baseline, every 8 weeks during the treatment period, and at EOT.

To evaluate efficacy, patients were assessed using a pain score and the visual analog scale (VAS) at baseline, every 4 weeks from the start until EOT, and after resuming menstruation. Uterine size and serum estradiol concentrations were measured at baseline, every 8 weeks during the treatment period, and at EOT. Uterine size was determined based on the diameters of three angles (D1, D2, and D3 mm), including the maximum diameter of the uterus by transvaginal ultrasonography. The uterus was evaluated as a spheroid. The maximum diameter of the uterine corpus (from the internal cervical os to the fundus serosa) was measured as the maximum diameter of the uterus. QOL was rated using the 36-Item Short-Form

Health Survey (SF-36 QOL score)[11] at baseline, after 24 weeks of treatment, and at EOT.

This study complies with the policies and/or procedures of *The Journal of Obstetrics and Gynaecology Research*. Monitoring and auditing procedures confirmed that the clinical study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice.

Statistical analysis

The safety analysis set consisted of patients who received the study drug at least once during the treatment period and had safety data collected after the treatment period. The efficacy analysis set was the full analysis set (FAS). The FAS consisted of enrolled patients who received the study drug at least once during the treatment period and had a pain score evaluation after the start of the treatment period.

AE were summarized by preferred term using the Medical Dictionary for Regulatory Activities Version 18.0.

SAS 9.2 was used for statistical analysis. To ensure that at least 100 patients took DNG for 52 weeks without discontinuing, the sample size was determined with reference to the discontinuation rate in a clinical study evaluating long-term use of DNG in the treatment of endometriosis.[12] We set 135 as the target with respect to the number of enrolled patients.

Results

A total of 130 patients were given DNG at least once and were assessed for both safety and efficacy. Of the 130 cases, 12 patients during the treatment period and two patients during the post-treatment observation period discontinued from the study (Fig. 1). Of the 12 discontinuations during the treatment period, six cases were due to AE (all of which were ADR), three cases were consent withdrawals for personal reasons, and three cases were due to other reasons (deviation from inclusion and exclusion criteria, deviation concerning prohibited treatment and non-compliance). The mean ± standard deviation (SD) during the DNG treatment period in this study was 347.1 ± 77.6 days. The patient characteristics are summarized in Table 2.

Safety

The incidence of AE after the start of the treatment period was 99.2% (129/130 cases); the incidence of ADR was 97.7% (127/130 cases). No serious AE were observed during this study.

The primary AE were: metrorrhagia (96.9%, 126/130 cases), nasopharyngitis (46.2%, 60/130 cases), hot flush

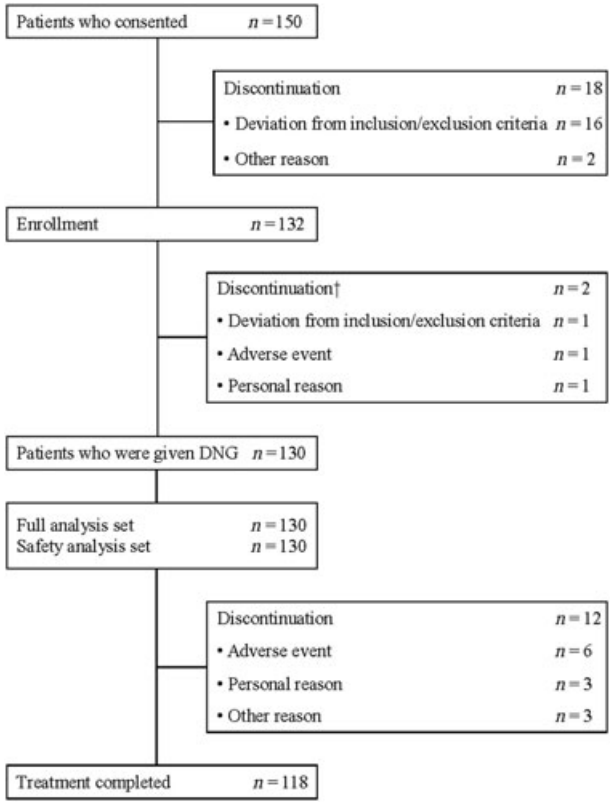

Figure 1 Flow chart. †Multiple options are allowed as reasons for discontinuation. DNG, dienogest.

Table 2 Demographic data (safety analysis set)

Characteristic	*n* = 130
Age (years)†	39.2 ± 6.3
Weight (kg)†	57.3 ± 8.7
Body mass index (kg/m^2)†	22.4 ± 3.4
Cycle length (days)†	29.1 ± 6.0
Number of partus (%)	
0	47 (36.2)
≥1	83 (63.8)
Complications with endometriosis and/or uterine leiomyoma (%)	
Without endometriosis or uterine leiomyoma	51.5
With endometriosis	18.5
With uterine leiomyoma	18.5
With endometriosis and uterine leiomyoma	11.5

†Each value represents the mean ± standard deviation.

(8.5%, 11/130 cases), urticaria (6.2%, 8/130 cases), candida infection (6.2%, 8/130 cases), eczema (5.4%, 7/130 cases), and nausea (5.4%, 7/130 cases). The primary ADR were: metrorrhagia (96.9%, 126/130 cases) and hot flush (7.7%, 10/130 cases) (Table 3). Discontinuation due to ADR occurred in six cases (i.e., metrorrhagia in three cases, uterine polyp in one case, menopausal symptoms in one case, and Basedow's disease in one case).

Focusing on the most frequent ADR observed during the treatment period, metrorrhagia was mostly mild (123/125 cases) and was moderate in two cases; there were no severe cases of metrorrhagia. Both of the two moderate cases (one of which also included severe anemia due to metrorrhagia) had short-term washouts during the treatment period and successfully controlled their irregular genital bleeding. Fifty of the 125 cases of metrorrhagia resolved during the treatment period and 75 of them resolved within 2 months of EOT. Anemia-related ADR considered to be associated with metrorrhagia occurred in three out of 130 cases, including the above case of severe anemia, but none of the patients withdrew from the study. All of the cases resolved during the treatment period.

The incidence of metrorrhagia during the first 12 weeks of the treatment period was 93.8% (122/130 cases); from 12 weeks to EOT, there were only three cases. We therefore focused on the occurrence and intensity of genital bleeding during the treatment period. During the treatment period, 125/129 cases experienced genital bleeding at least once. Of the 130 cases, one case was excluded from the analysis due to a significant deviation from the proper administration method specified in the protocol. The mean number of days of genital bleeding per 28 days of treatment reached a maximum of 18 days at 8 weeks, 11 days at 24 weeks, and 6 days at 52 weeks, indicating a decreasing trend in genital bleeding as the treatment period progressed (Fig. 2). In terms of intensity, the proportion of cases with no genital bleeding per 28 days of treatment period was 9.4% (12/128 cases) at 8 weeks, 30.9% (38/123 cases) at 24 weeks, and 56.8% (67/118 cases) at 52 weeks, indicating an increasing trend in the proportion of cases with no genital bleeding as the treatment period progressed (Fig. 3).

Resumption of menses after EOT was confirmed in 127 cases. In those 120 cases where menstrual data could be evaluated, the mean ± SD for the number of

Table 3 Adverse drug reactions reported frequently (≥2%) during the entire observation period (safety analysis set)

	Observation period			
	Week 0 to 24		Entire period	
Adverse drug reaction	*n*	%	*n*	%
Metrorrhagia	123	94.6	126	96.9
Hot flush	9	6.9	10	7.7
Menopausal symptoms	5	3.8	6	4.6
Nausea	5	3.8	5	3.8
Uterine leiomyoma	2	1.5	4	3.1
Breast discomfort	2	1.5	4	3.1
Anemia	1	0.8	4	3.1
Headache	3	2.3	3	2.3
Palpitations	3	2.3	3	2.3
Malaise	3	2.3	3	2.3
Insomnia	2	1.5	3	2.3
Urticaria	2	1.5	3	2.3
Hyperhidrosis	1	0.8	3	2.3
Edema	1	0.8	3	2.3

Adverse drug reactions were summarized by preferred term using the Medical Dictionary for Regulatory Activities Version 18.0.

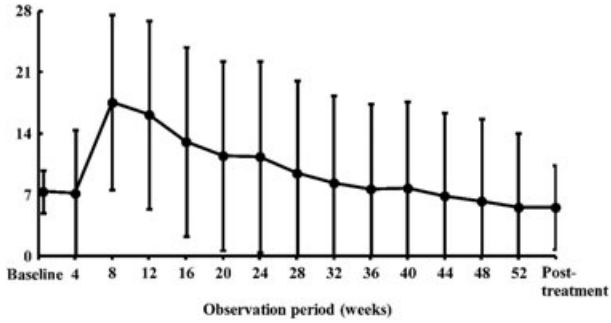

Figure 2 Number of days of genital bleeding observed every 28 days during the study period. Each point represents the mean ± standard deviation.

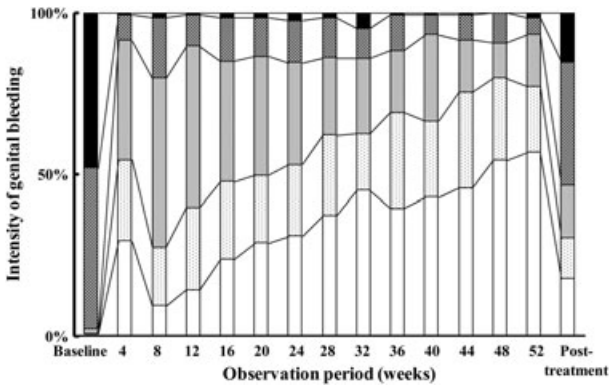

Figure 3 Proportional incidence of genital bleeding, classified into five categories as follows: (■) More than menstrual. (▩) Menstrual. (▤) Breakthrough. (▥) Spotting. (□) None. The highest individual incidence of genital bleeding per 28 days of observation is also shown.

days from EOT to the first day of menstruation was 28.5 ± 7.3 days. For the duration of the menstrual period, the mean ± SD was 6.6 ± 1.4 days at baseline and 6.2 ± 1.4 days at resumption of menses, respectively.

Abnormal changes in laboratory tests were judged to be ADR in 3.8% of cases (5/130). One of these was in the patient with severe anemia. In this case, abnormal levels of red blood cells, hemoglobin, and hematocrit resolved during the treatment period after short-term washout and supplemented with an iron preparation. Another was urine sugar positive caused by Basedow's disease and was resolved after discontinuation of treatment. The other cases resolved without intervention during the treatment period or after EOT. Bodyweight showed a statistically significant increase from baseline after 16 weeks of treatment and up to EOT. One mild ADR (weight increased) was observed during the treatment period and resolved after EOT. The mean values and median values for all clinical-laboratory parameters were within the normal ranges throughout the study period. Changes in laboratory hematology are shown in Table 4.

Efficacy

Table 5 shows that the mean pain score and its component parts (the pain-severity score and analgesics-usage score) decreased over the course of the treatment period. The mean ± SD for the decrease in the pain score was −3.4 ± 1.8 at 24 weeks and −3.8 ± 1.5 at 52 weeks of treatment. The mean VAS values also decreased over the course of the treatment period. The mean ± SD for the decrease in VAS values was −52.7 ± 25.7 mm at 24 weeks and −56.7 ± 24.2 mm at 52 weeks of treatment.

Of the eight subscales, the SF-36 QOL score showed typical changes in the Bodily Pain subscale. The mean ± SD for the Bodily Pain subscale score was 36.5 ± 17.5 at baseline, markedly worse than the standard value for age-matched Japanese women (76.1 ± 21.3).[13] During the treatment period, the mean ± SD of the values for the Bodily Pain subscale score was 71.5 ± 24.8 at 24 weeks and 79.6 ± 23.5 at

Table 4 Changes in laboratory hematology (safety analysis set)

Item	Unit	Baseline (n = 130)	Week 24 (n = 121)	Week 52 (n = 118)
Red blood cell count	(×10 000/μL)	437.5 ± 35.2	446.1 ± 34.3	442.7 ± 31.4
Hemoglobin	(g/dL)	12.8 ± 1.2	13.5 ± 0.9	13.5 ± 0.9
Hematocrit	(%)	38.8 ± 3.2	40.5 ± 2.6	40.7 ± 2.4

Each value represents the mean ± standard deviation.

Table 5 Efficacy data (full analysis set)

Characteristic	Baseline (n = 130)	Change in week 24† (n = 122)	Change in week 52† (n = 118)
Pain score	4.6 ± 1.1	−3.4 ± 1.8 [−3.7, −3.1]	−3.8 ± 1.5 [−4.1, −3.5]
Complication with endometriosis and/or uterine leiomyoma‡			
Without endometriosis or uterine leiomyoma	4.5 ± 1.2	−3.5 ± 1.6 [−3.9, −3.1]	−3.8 ± 1.4 [−4.1, −3.4]
With endometriosis	4.6 ± 1.1	−3.6 ± 2.2 [−4.6, −2.6]	−4.1 ± 1.8 [−4.9, −3.3]
With uterine leiomyoma	4.6 ± 0.8	−3.0 ± 2.1 [−3.9, −2.1]	−3.8 ± 1.6 [−4.5, −3.1]
With endometriosis and uterine leiomyoma	4.6 ± 1.2	−3.4 ± 1.8 [−4.4, −2.3]	−3.5 ± 1.9 [−4.7, −2.4]
Pain-severity score	2.4 ± 0.6	−1.7 ± 1.0 [−1.9, −1.5]	−1.9 ± 0.8 [−2.1, −1.8]
Analgesics-usage score	2.2 ± 0.9	−1.7 ± 1.2 [−1.9, −1.5]	−1.9 ± 1.1 [−2.1, −1.7]
Visual analog scale (mm)	65.9 ± 20.3	−52.7 ± 25.7 [−57.3, −48.1]	−56.7 ± 24.2 [−61.2, −52.3]
Uterine size (cm^3)	105.4 ± 62.7	20.6 ± 30.3§,¶ [15.1, 26.0]	26.0 ± 27.9¶ [20.9, 31.1]

Each value represents the mean ± standard deviation. †Two-sided 95% confidence intervals of the mean are shown in square brackets. ‡Number at baseline: without endometriosis or uterine leiomyoma, n = 67; with endometriosis, n = 24; with uterine leiomyoma, n = 24; with endometriosis and uterine leiomyoma, n = 15. Number at week 24: without endometriosis or uterine leiomyoma, n = 65; with endometriosis, n = 21; with uterine leiomyoma, n = 22; with endometriosis and uterine leiomyoma, n = 14. Number at week 52: without endometriosis or uterine leiomyoma, n = 64; with endometriosis, n = 21; with uterine leiomyoma, n = 20; with endometriosis and uterine leiomyoma, n = 13. §n = 121. ¶Percent reduction in uterine size compared with the baseline (%).

52 weeks of treatment, thus showing an improvement of 35.1 ± 26.7 at 24 weeks and 43.0 ± 26.7 at 52 weeks of treatment over the baseline score (Table 6).

The mean ± SD for uterine size was 105.4 ± 62.7 cm^3 at baseline. The mean ± SD of reductions for uterine size was 20.6 ± 30.3% at 24 weeks and 26.0 ± 27.9% at 52 weeks of treatment, which was statistically significant, but was not clinically insignificant (Table 5). Serum-estradiol concentrations (mean ± SD [median], pg/mL) at baseline, 24 weeks, and 52 weeks of treatment were 131.0 ± 97.7 (104.0), 50.5 ± 47.7 (35.0), and 53.2 ± 53.2 (34.0), respectively, showing mild suppression of estradiol levels over the course of the treatment period (Fig. 4).

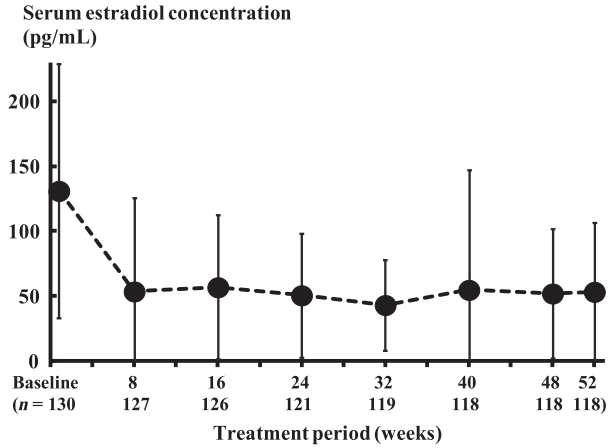

Figure 4 Serum estradiol concentrations during the study period. Each point represents the mean ± standard deviation.

Discussion

The intended outcome of treating symptomatic adenomyosis is the alleviation of symptoms and improvement in the patient's QOL. There is therefore a need for drug therapy that can be used for long-term treatment of symptomatic adenomyosis.

DNG is approved as a medical treatment for endometriosis, although reports of serious ADR have linked DNG to metrorrhagia as well as serious anemia. In all of these cases, patients also had complications of adenomyosis or leiomyoma. In some cases, patients have had uterine enlargement or severe anemia before DNG has been administered.[8] On the other hand, as there is no drug currently approved for adenomyosis, DNG is regarded as a potential treatment for symptomatic adenomyosis based on the similarity of the hormonal responses in endometriosis and adenomyosis.

We investigated the safety and efficacy of long-term administration of DNG for 52 weeks in patients with adenomyosis, some of whom also had complications of endometriosis and/or leiomyoma.

Metrorrhagia was a particularly frequent ADR during the DNG treatment period, although prolonged treatment showed a decrease in the occurrence and intensity of genital bleeding. Discontinuation due to metrorrhagia occurred in three cases. Two of the three cases had short-term washouts and wanted to withdraw from the study. Fourteen cases had short-term washouts due to metrorrhagia. These patients resumed medication after short-term washout as the episodes of genital bleeding either decreased or cleared up. All of the metrorrhagia cases resolved during the treatment period or after EOT. Genital bleeding with DNG was considered to arise from breakthrough bleeding in the pseudodecidua due to the study drug's progestational effects.[7] A short-term washout period was reported to be effective in controlling the progestational breakthrough bleeding.[14]

We also set exclusion criteria for patients with severe anemia (hemoglobin concentrations lower than 8.0 g/dL) and marked uterine enlargement. In cases of mild or moderate anemia (hemoglobin levels between 8.0

Table 6 Changes in the SF-36 QOL score (full analysis set)

Subscale	Baseline (n = 130)	Week 24 (n = 121)	Week 52 (n = 118)	Change in week 52† (n = 118)
Physical Functioning	90.3 ± 12.9	92.4 ± 9.8	94.0 ± 9.3	3.7 ± 11.6 [1.6, 5.8]
Role-Physical	69.8 ± 36.7	91.7 ± 21.7	88.4 ± 29.5	19.1 ± 41.4 [11.5, 26.6]
Bodily Pain	36.5 ± 17.5	71.5 ± 24.8	79.6 ± 23.5	43.0 ± 26.7 [38.2, 47.9]
General Health	60.1 ± 16.7	65.9 ± 16.0	66.2 ± 16.4	5.9 ± 14.5 [3.3, 8.6]
Vitality	56.6 ± 17.9	61.3 ± 19.2	62.5 ± 21.0	5.3 ± 20.9 [1.5, 9.2]
Social Functioning	80.3 ± 21.3	90.5 ± 16.8	91.4 ± 19.0	10.2 ± 26.8 [5.3, 15.1]
Role-Emotional	79.0 ± 34.8	92.3 ± 23.9	93.2 ± 21.2	12.4 ± 38.4 [5.4, 19.4]
Mental Health	72.0 ± 14.9	74.1 ± 17.9	76.2 ± 17.6	3.6 ± 17.3 [0.4, 6.7]

Each value represents the mean ± standard deviation. †Two-sided 95% confidence intervals of the mean are shown in square brackets. SF-36 QOL, 36-Item Short-Form Health Survey.

and 11.0 g/dL), the patients were given anemia treatment so that hemoglobin concentrations reached at least 11.0 g/dL before starting administration of DNG. Under these conditions, and with adequate observation of genital bleeding episodes by the investigators throughout the study period, the above safety results show the tolerability of genital bleeding during long-term treatment with DNG. This study does not provide any support for use of DNG in patients with risk factors for serious genital bleeding or anemia. A detailed consideration of the risk–benefit ratio is important before using DNG in patients with adenomyosis.

Sugimoto *et al.* retrospectively investigated endometriosis patients who received DNG for 53 weeks or longer, and reported that metrorrhagia was not the main reason for discontinuation of DNG, although minor decreases in the myometrial thickness were observed from weeks 53 to 120 and the main ADR was metrorrhagia. These results coincided with the results of this study. The results of a study on the intention for continued treatment with DNG using questionnaires showed that 29 of 33 patients responded that they wanted to continue DNG and one patient responded that she did not want to continue DNG due to high medication cost.[15]

We evaluated the effects of DNG on pain symptoms associated with adenomyosis by using the verbal rating scale established for assessing pain symptoms associated with endometriosis.[5] The decrease in the pain score was −3.4 at 24 weeks and −3.8 at 52 weeks of treatment, showing a clinically identifiable impact of DNG administration, as the mean reduction in pain score was significantly larger than that for placebo (−1.4, unpublished observation), as measured by more than two rating scales. These effects were also confirmed by patient evaluations based on the VAS and the SF-36 QOL score. Specifically, the Bodily Pain subscale score in the SF-36 QOL rating after 52 weeks of treatment (79.6) was nearly identical to the reference value for Japanese women (76.1).[13]

The hypoestrogenic effect of DNG is reported to be less frequent than with GnRH analogs, delivering a therapeutic effect with minimal changes to bone metabolism in patients with estrogen-dependent diseases.[5,6] In this study, mean serum estradiol concentrations were 50.5 pg/mL at 24 weeks and 53.2 pg/mL at 52 weeks of treatment, comparable to the levels seen in those reports.

Comparing this study with research evaluating DNG as a long-term treatment for endometriosis,[12] both studies show that the most frequent ADR associated with DNG is metrorrhagia, while there is no trend towards increased incidence of metrorrhagia over an extended administration period.

In conclusion, given that DNG was well tolerated and effective in treating painful symptoms due to adenomyosis, it has the potential to become a best-in-class drug for long-term hormonal therapy for this condition.

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Disclosure

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