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Original Article

Update on the management of endometriosis-associated pain in France

Hervé Fernandez [a,b,c,*], Aubert Agostini [d], Hortense Baffet [e], Nathalie Chabbert-Buffet [f], Philippe Descamps [g], Jean-Philippe Estrade [h], Géraldine Giraudet [i], Claude Hocke [j], Bruno Salle [k], Florence Tremollieres [l], Charles Chapron [m]

[a] AP-HP, Gynecology and Obstetrics Department, Bicetre Hospital, GHU Sud, 78 avenue du Général Leclerc, Le Kremlin Bicetre F-94276, France
[b] Paris Saclay University, 63 rue Gabriel Péri, Le Kremlin Bicetre F-94276, France
[c] Centre of research in epidemiology and population health (CESP), UMR1018, Inserm, Paris Saclay University, Hôpital Paul Brousse, 16 avenue Paul Vaillant Couturier, Villejuif F-94816, France
[d] A Agostini, Service de Gynécologie Obstétrique, AP-HM, Assistance Publique-Hôpitaux de Marseille, Marseille, France
[e] H Baffet, Service de Gynécologie Médicale, Orthogénie et Sexologie, CHU de Lille, université de Lille, Lille, France
[f] N Chabbert-Buffet, Service de Gynécologie Obstétrique Médecine de la Reproduction, Centre expert en Endométriose C3E, Hôpital Tenon APHP Sorbonne Université, Paris, France
[g] P Descamps, Service de Gynécologie Obstétrique et Médecine de la Reproduction, CHU Angers, Centre expert en Endométriose Pays de Loire, Angers, France
[h] JP Estrade, Hôpital Privé de Provence, Aix en Provence, France
[i] G Giraudet, Hôpital Privé du Bois, Lille, France
[j] C Hocké, Service de Chirurgie Gynécologique et Médecine de la Reproduction, Centre expert régional Nouvelle Aquitaine, Centre Aliénor d'Aquitaine, Université Bordeaux, Bordeaux, France
[k] B Salle, Service de Médecine de la Reproduction, Hôpital Femme-Mère-Enfant, Hospices Civils de Lyon, Université Claude-Bernard Lyon 1, Bron, France
[l] F Trémollieres, Centre de Ménopause, Hôpital Paule de Viguier, CHU Toulouse, Université Toulouse III, Toulouse, France
[m] C Chapron, Service de Chirurgie Gynécologique II et Médecine de la Reproduction, AP-HP, Hôpital Universitaire Paris Centre (HUPC), Centre Hospitalier Universitaire (CHU) Cochin, Université Paris-Cité, Faculté de Médecine Paris-Centre, Paris, France

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ABSTRACT

The French National College of Obstetricians and Gynecologists (CNGOF) published guidelines for managing endometriosis-associated pain in 2018. Given the development of new pharmacological therapies and a review that was published in 2021, most national and international guidelines now suggest a new therapeutic approach.

In addition, a novel validated screening method based on patient questionnaires and analysis of 109-miRNA saliva signatures, which combines biomarkers and artificial intelligence, opens up new avenues for overcoming diagnostic challenges in patients with pelvic pain and for avoiding laparoscopic surgery when sonography and MRI are not conclusive.

Dienogest (DNG) 2 mg has been a reimbursable healthcare expense in France since 2020, and, according to recent studies, it is at least as effective as combined hormonal contraception (CHC) and can be used as an alternative to CHC for first-line treatment of endometriosis-associated pain. Since 2018, the literature concerning the use of DNG has grown considerably, and the French guidelines should be modified accordingly.

The levonorgestrel intrauterine system (LNG IUS) and other available progestins per os, including DNG, or the subcutaneous implant, can be offered as first-line therapy, gonadotropin-releasing hormone (GnRH) agonists with add-back therapy (ABT) as second-line therapy.

Oral GnRH antagonists are promising new medical treatments for women with endometriosis-associated pain. They competitively bind to GnRH receptors in the anterior pituitary, preventing native GnRH from binding to GnRH receptors and from stimulating the secretion of luteinizing hormone and follicle-stimulating hormone. Consequently, estradiol and progesterone production is reduced. Oral GnRH antagonists will soon be on the market in France. Given their mode of action, their efficacy is comparable to that of GnRH agonists, with the advantage of oral administration and rapid action with no flare-up effect. Combination therapy with ABT is likely to allow long-term treatment with minimal impact on bone mass. GnRH antagonists with ABT may thus be offered as second-line treatment as an alternative to GnRH agonists with ABT.

* Corresponding author at: CHU Bicêtre, Service Gynécologie Obstétrique, 78 rue du Général Leclerc, Le Kremlin Bicêtre 94270, France
E-mail address: herve.fernandez@aphp.fr (H. Fernandez).

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This article presents an update on the management of endometriosis-associated pain in women who do not have an immediate desire for pregnancy.

Introduction

Endometriosis, a chronic inflammatory disease characterized by lesions consisting of endometrial-like tissue outside the uterus, is associated with pelvic pain and infertility and affects 10% of women of reproductive age [1–3].

The symptoms associated with endometriosis include painful periods and chronic pelvic pain, painful ovulation, pain during or after sexual intercourse, heavy bleeding, fatigue, and infertility. Endometriosis can also impact general physical, mental, and social well-being [1,2].

The proliferation of endometriotic lesions requires estradiol (E2), which is proinflammatory [3], and all guidelines recommend hormonal, long-term treatment of patients to inhibit ovulation or to reduce estrogen production [2–4].

A review published in 2021 provided an overview of the therapeutic approaches recommended by eight widely used national and international guidelines [4]. Six are national guidelines — the French National College of Obstetricians and Gynecologists (CNGOF) guideline, the National German Guideline (S2k), the Society of Obstetricians and Gynecologists of Canada (SOGC) guideline, the American College of Obstetricians and Gynecologists (ACOG) guideline, the American Society for Reproductive Medicine (ASRM) guideline, and the National Institute for Health and Care (NICE) guideline — and two are international guidelines—the World Endometriosis Society (WES) guideline and the European Society of Human Reproduction and Embryology (ESHRE) guideline and are included in this review.

Most of these guidelines propose using combined hormonal contraception (CHC) as first-line empirical medical treatment for endometriosis-associated pain before performing diagnostic laparoscopy, although the reported level of evidence varies. Regarding the use of the LNG-IUS, no recommendations were made by NICE 2018 and ACOG 2010, whereas CNGOF 2018 and ASRM 2014 proposed it also as first-line treatment, and other guidelines proposed it as second-line treatment.

Dienogest (DNG) is positioned as a first-line treatment option, notably by the new ESHRE guidelines published in 2022 [5], but not by the CNGOF 2018, since it was not reimbursed at that time.

GnRH agonists are recommended as second-line treatment for patients with endometriosis-associated pain whose symptoms persist after treatment with a first-line therapy option, because of their limitations, including the delayed therapeutic impact secondary to the flare-up effect, to the profound suppression of E2 secretion with systemic concentrations below 20 pg/mL, and to the unpredictable reversibility of treatment when injectable depot forms are used [6,7]. Clinical side effects induced by hypoestrogenism, as well as the negative impact on bone mineral density (BMD), limit the duration of use or require additional, concomitant hormonal administration, which is usually referred to as add-back therapy (ABT) [4,8]. When combined with ABT, their use can be extended for up to 1 year without any significant impact on bone loss [8], provided that patients remain compliant with hormone replacement therapy.

All of the societies mentioned above agree that GnRH agonists effectively reduce endometriosis-associated pain. The CNGOF recommends that GnRH agonists with ABT should not be used for more than 1 year, the SOGC recommends a duration of no longer than 6 months, and the ESHRE highlights a lack of sufficient evidence regarding the optimal duration of GnRH agonists with ABT therapy. The S2k guideline indicates that GnRH agonists are not an appropriate treatment option for ovarian endometriomas.

In summary, with regard to pharmacological therapies for endometriosis-associated pain, most national and international guidelines included in the 2021 review by Kalaitzopoulos et al. suggest CHC and progestins, including DNG and LNG-IUS as first-line therapy, with a high level of evidence. GnRH agonists are considered as second-line option, reserved for patients with persistent symptoms after the use of first line therapy [4].

Nevertheless, regardless of the therapeutic approach, whether medical or surgical, about 50% of patients experience symptom recurrence after 5 years [3]. Since current medical treatments and/or surgical interventions may only offer incomplete pain relief, patients depend on the use of painkillers to control the pain, as well as repeated surgeries [9,10].

Nondrug treatments should also be considered. Acupuncture, osteopathy, relaxation, and yoga have been shown to improve quality of life and can be offered as a complementary approach to the medical and surgical management of endometriosis. In the case of chronic pain, interdisciplinary assessment (by gynecologists, algologists, sexologists, psychologists, and social workers) can be offered [11]. There are insufficient data to recommend dietary modification or vitamin supplements for patients with painful endometriosis [11].

Altogether, given the number of concerns with currently available treatments, there is a clear need for new therapeutic options. The aim of this review is to provide an update on the management of endometriosis-associated pain in women with no immediate desire of pregnancy in France, that includes new classes of drugs, based on recently published studies.

Medical treatment for the management of painful endometriosis – current French guidelines

The CNGOF–French National Authority for Health (HAS) guidelines were published in March 2018 [11]. These guidelines recommended CHC and the LNG-IUS as first-line hormonal therapies for the treatment of painful endometriosis (grade B). Second-line therapies included oral DNG or desogestrel, the etonogestrel-releasing implant, GnRH agonists (GnRHa) (grade C). The use of estrogen-containing ABT is strongly recommended in combination with GnRHa (grade B). At the time the CNGOF guidelines were drafted, DNG efficacy in treating endometriosis was well-evaluated and DNG had Marketing Authorization for this indication, but this drug DNG was not reimbursed in France.

After endometriosis surgery, hormonal treatment relying on CHC or the LNG-IUS is recommended to prevent pain recurrence (grade B). CHC is recommended to reduce the risk of endometrioma recurrence after surgery (grade B), but GnRHa is not recommended (grade C). Continuous CHC is recommended in the case of dysmenorrhea (DYS) (grade B). GnRHa is not recommended as a first-line treatment for endometriosis in adolescents because of the risk of bone demineralization (grade B). The management of endometriosis-induced chronic pain requires interdisciplinary evaluation. Physical therapies that improve quality of life, such as yoga, relaxation, or osteopathy, can be proposed (expert agreement).

Finally, the CNGOF highlighted that promising medical alternatives are currently undergoing preclinical and clinical evaluation. New treatment options are indeed needed, because one-third of patients are nonresponders to CHC or progestin-only medications due to progesterone resistance [12]. A systematic review evaluating patient response rates to medical therapies for endometriosis-associated pain highlighted that the average percentage of women who did not experience any pain reduction was 11%–19%, that 5%–59% of women had residual pain at the end of treatment, and that 17%–34% experienced recurrence of pain symptoms following treatment cessation [13]. After median study

durations of 2–24 months, the average discontinuation rates due to adverse events or lack of efficacy were 5%–16% [13]. Also, while GnRH agonists in combination with ABT as second-line therapy effectively relieve endometriosis-related symptoms, they have numerous limitations, including a delayed therapeutic impact (flare-up effect), a poor tolerability, and limitation use to a 1-year of treatment [12].

What's new since these guidelines were published?

Previous studies have highlighted the limited diagnostic value of clinical examinations and the added value of new validated screening method based on patient questionnaire [14,15]. Therefore, the challenge is not only to confirm advanced-stage disease by sonography or MRI, but also to address the diagnostic complexities of patients experiencing symptoms suggestive of endometriosis but with no confirmatory clinical and/or imaging examinations. If a tool for early, sensitive, and specific diagnosis of the disease were available, it would have the potential to improve the care of these women.

The advent in 2022 of the 109-miRNA saliva signature, which combines microRNA biomarkers and artificial intelligence, opens up new avenues for addressing diagnostic challenges in patients with pelvic pain. This diagnostic approach involves genome-wide miRNA expression profiling by performing next-generation sequencing of small RNAs. The overall diagnostic accuracy of the 109-miRNA diagnostic signature compared with the validation cohort was as follows: Sensitivity: 0.962 (95% CI: 0.937–0.973); Specificity: 0.951 (95% CI: 0.852–0.991); Positive Predictive Value: 0.987 (95% CI: 0.961–0.998), Negative Predictive Value: 0.867 (95% CI: 0.776–0.903); Positive Likelihood Ratio: 19.726 (95% CI: 6.310–108.826); Negative Likelihood Ratio: 0.040 (95% CI: 0.028–0.074); and Area Under the Curve: 0.98 (95% CI: 0.96–1.00). The high accuracy of the signature, which overcomes the limitations of currently available conventional diagnostic tools, justifies its immediate integration into conventional algorithms as a first-line tool for diagnosing pelvic pain and endometriosis to avoid diagnostic laparoscopy when sonography and MRI are normal or equivocal. This new era thus constitutes a true paradigm shift in clinical practice [16]. An interim analysis of a prospective multicenter external validation study confirmed that its utility as a diagnostic tool is continuing to be investigated [17]. In France, this test is not yet available in current practice.

Confirmation of the diagnosis of endometriosis in women with suggestive symptoms allows appropriate treatment to be implemented.

Dienogest

The approval of reimbursement for DNG 2 mg in France in April 2020 has allowed its wider use. About 80,000 women with endometriosis are currently being treated with DNG 2 mg each month in France vs. fewer than 800 before reimbursement was approved [18]. This rapid increase in the number of treated women since DNG reimbursement approval confirms that a real need existed of an efficient and accessible medical therapy. DNG, a so-called "*hybrid progestin*", has a unique pharmacological and pharmacodynamic profile combining the typical properties of the 19-nortestosterone compounds with those of progesterone derivatives [19]. DNG given orally has good bioavailability and a strong progestational effect due to its high selectivity for progesterone receptors [19]. When taken continuously, it inhibits systemic gonadotropin secretion and has local antiproliferative and anti-inflammatory effects on endometriotic lesions [19,20].

DNG is associated with partial inhibition of gonadotropin secretion, leading to a modest reduction in endogenous estradiol production. When given continuously, DNG induces a predominantly gestagenic endocrine environment, causing decidualization of endometrial tissue followed by atrophy of endometriotic lesions [21]. In volunteers given daily DNG doses of 0.5 to 3 mg, ovarian ovulation was effectively suppressed by the 2-mg and 3-mg doses, with a rapid return to ovulation after cessation [22].

In two randomized controlled trials (RCTs) cited in the CNGOF guidelines from 2018, DNG showed comparable efficacy to GnRH agonists, with better tolerability [23,24]. Since then, the literature concerning the use of DNG for treating endometriosis has grown considerably. A significant improvement in endometriosis lesions, pain symptoms, and quality of life was observed in women taking DNG compared to women who were given continuous CHC [25–27]. In two RCTs, the efficacy of DNG was comparable to that of CHC for endometriosis-associated pelvic pain relief and quality-of-life scores improvement [25,26]. DNG was associated with greater tolerability and a better safety profile versus continuous CHC containing ethinyl-estradiol and drospirenone [26]. In a prospective cohort study, Piacenti et al. compared two cohorts of women with endometriosis, 50 of whom were taking DNG and 50 of whom were taking continuous CHC combining ethinyl-estradiol and levonorgestrel [27]. Both treatments were effective and safe. Patient compliance and side effects were similar in both groups; however, there was a greater improvement of endometriotic lesions, pain symptoms, and quality of life in women taking DNG than in women taking CHC continuously [27].

A lasting improvement of quality of life and sexual function was reported by several studies including women with endometriosis who underwent up to 2 years of treatment with DNG [28,29].

No new RCTs evaluating the use of DNG for the relief of endometriosis-associated pain have been published since the VISADO study [30]. A recent narrative review including 14 studies non-randomized studies investigating the use of DNG for treating endometriosis in adolescents concluded that daily DNG 2 mg efficiently reduced the size of endometriotic lesions, decreased painful endometriosis symptoms, and improved quality-of-life scores. In most of these studies, DNG was shown to be safe and well tolerated, with predictable and moderate side effects, good patient compliance rates, and low withdrawal rates [31].

Several studies have reported a reduction in the size of endometriomas after treatment with DNG [27,32–34]. A reduction in the mean volume of 41%–75% was observed after 6 months [32–34], and of 76% after 12 months [34]. This effect was not seen in patients treated with a DNG and ethinyl-estradiol combination [32]. Piacenti et al. showed that treatment with DNG decreased the mean size of deep infiltrating endometriosis (DIE) lesions from 16 $\pm$ 5.2 mm (baseline) to 8.7 $\pm$ 2.8 mm at 6 months ($p < 0.014$) [27]. DNG was also effective for controlling DIE-associated pain, even when it does not reduce the volume of DIE nodules [35].

Concerning postoperative treatment, two systematic reviews and meta-analyses showed that patients treated with DNG after conservative surgery for endometriosis had a significantly lower risk of postoperative disease recurrence than those treated by the "watch-and-wait" approach or placebo [36,37]. DNG has therefore been recommended as maintenance therapy for patients with endometriosis to reduce the rate of recurrence after conservative surgery [38].

The general safety profile of DNG indicates that it is well tolerated in patients with endometriosis. In a pooled analysis of four clinical trials, DNG 2 mg showed a favorable safety profile for up to 65 weeks. The most frequently reported adverse events were headache, breast discomfort, depressed mood, and acne, each of which occurred in less than 10% of patients; the symptoms were generally mild to moderate in intensity and were associated with low discontinuation rates [39]. Administration of DNG for up to 5 years has also demonstrated a favorable safety profile [40,41]. An epidemiological study is currently in progress to determine if there is an increased risk of meningioma in women treated with DNG 2 mg, as it is with other progestins.

Treatment with DNG 2 mg, like other progestins, can lead to endometrial regression and bleeding irregularities. Bleeding can be constant during the first 3 months, with a decrease in intensity and frequency over time [29,39]. Analysis of bleeding patterns identified 37.8% of women as having irregular bleeding at 3 months [24], while this

percentage decreased to 15.2% and 5.8% at 6 and 24 months, respectively [29]. The rate of amenorrhea varied from 1% at 3 months to 46.5% and 70.8% at 6 and 24 months, respectively. Spotting can occur with long-term DNG treatment, although less than 1% of patients in clinical trials discontinued treatment for this reason [39]. Initiation of DNG 2 mg at the onset of menses may decrease initial bleeding. Treatment with a GnRH before beginning long-term DNG therapy might also reduce initial irregular bleeding [42,43]. Given the short half-life of DNG, continuous and regular intake is also necessary to maintain ovulation blockade.

Oral gonadotropin-releasing hormone antagonists

The oral nonpeptide GnRH receptor antagonists (Table 1) are promising new medical treatments for women with endometriosis-associated pain. They competitively bind to GnRH receptors in the anterior pituitary, preventing native GnRH from binding GnRH receptors and from stimulating the secretion of LH and FSH. Consequently, estradiol and progesterone production is reduced [12].

A systematic review and network meta-analysis of five studies and six RCTs including 2796 women and 10 different doses of oral GnRH antagonists concluded that oral GnRH antagonists are effective for treating endometriosis-associated pain with good overall patient satisfaction [44]. During short term use, there was a significant dose effect hypoestrogenism, particularly at the highest dose, when oral GnRH antagonists were not used in combination with ABT [44].

Elagolix

The first oral GnRH antagonist to be developed was elagolix, which is approved for used in the US as a once-daily low dose or a more effective twice-daily high dose. Elagolix has the shortest apparent terminal elimination half-life (approximately 4–6 h) among the currently available oral GnRH antagonists.

Two similar double-blind, 6-month phase 3 RCTs (Elaris Endometriosis I and II [EM-I and EM-II]) compared the effects of two doses of elagolix—150 mg once daily (lower-dose group) and 200 mg twice daily (higher-dose group)—with placebo in women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain [45]. In Elaris EM-I, the percentage of women who had a clinical response with respect to DYS was 46.4% in the lower-dose elagolix group and 75.8% in the higher-dose elagolix group, compared with 19.6% in the placebo group; in Elaris EM-II, the corresponding percentages were 43.4% and 72.4%, compared with 22.7% ($p < 0.001$ for all comparisons). In Elaris EM-I, the percentage of women who had a clinical response with respect to nonmenstrual pelvic pain (NMPP) was 50.4% in the lower-dose elagolix group and 54.5% in the higher-dose elagolix group, compared with 36.5% in the placebo group ($p < 0.001$ for all comparisons). In Elaris EM-II, the corresponding percentages were 49.8% and 57.8%, compared with 36.5% ($p = 0.003$ and $p < 0.001$, respectively). The lower dose of 150 mg once daily was less efficient and did not reduce dyspareunia [45]. Women who received elagolix had a higher incidence of hot flushes (mostly mild or moderate), higher levels of serum lipids, and a greater decrease in BMD from baseline versus placebo. The hypoestrogenism-induced reduction of BMD means that the maximum duration of treatment with elagolix is 24 months for the low dose (6 months in patients with moderate hepatic impairment) and 6 months for the high dose [46].

In July 2018, elagolix (Orilissa®) was officially approved in the US to treat women with moderate to severe endometriosis-related pain [47]. Elagolix is not approved in Europe, where no Marketing Authorization application has been submitted to date.

Linzagolix

Linzagolix is another oral GnRH receptor antagonist, with a half-life of approximately 15 h, that is currently under development for the treatment of uterine fibroid and endometriosis. At a dose of 75 mg, linzagolix was reported to maintain estradiol values within the range of 20–60 pg/mL [48]. At higher doses (200 mg), linzagolix pushed estradiol levels below 20 pg/mL, which is considered full ovarian suppression. The once-daily 200 mg dose of linzagolix requires ABT if administered for a long-term period, to offset side effects [48]. Due to the risk of BMD reduction with prolonged use, the 200 mg dose without concomitant ABT should not be used for longer than 6 months.

In 2019, the phase 2b EDELWEISS 1 clinical trial was completed in women with moderate to severe endometriosis-related pain [49]. At 12 weeks, doses ≥75 mg resulted in a significantly greater proportion of responders concerning overall pelvic pain compared to placebo (61.5%, 56.4%, and 56.3% for doses of 75, 100, and 200 mg, respectively versus 34.5% for placebo). A similar pattern was seen for DYS and NMPP. The effects were maintained or increased at 24 weeks. Serum estradiol was suppressed, quality of life improved, and the rate of amenorrhea increased in a dose-dependent manner. Mean BMD loss (spine) at 24 weeks was <1% at doses of 50 and 75 mg and increased in a dose-dependent manner up to 2.6% for 200 mg without ABT. Changes in BMD between baseline and week 52, evaluated by DXA scans, were in line with values recorded after 24 weeks of treatment. BMD loss in the 75 mg linzagolix group was within an acceptable range, while the decline with the 200/100 mg regimen was clinically relevant. For subsequent clinical development, the 200 mg dose was combined with estrogen/progestogen ABT (1 mg estradiol/0.5 mg NETA) to prevent significant BMD loss during continuous administration.

The phase 3 program initially involved two clinical trials: EDELWEISS 2, with approximately 450 subjects, and EDELWEISS 3, also with a similar sample size [48]. These two double-blind, placebo-controlled trials sought to assess two once-daily doses of linzagolix: 75 mg without ABT and 200 mg with ABT. After 24 weeks of treatment, women were able to opt for a treatment extension. Women who were initially allocated to placebo group were then randomly assigned to receive either 75 mg linzagolix without ABT or 200 mg with ABT, while those on active linzagolix regimens continued with their respective doses. Coprimary endpoints were responders' proportion for both DYS and NMPP after 12 weeks of therapy. Upon completion of treatment, all patients were followed-up for at least further 24 weeks.

In January 2021, ObsEva announced the discontinuation of the

Table 1
Comparison of oral GnRH antagonists in the treatment of endometriosis associated pain.

	Elagolix	Linzagolix	Relugolix
Half-life	4–6h	15h	25h
Dosage evaluated in phase 3 studies	150 mg once daily 200 mg twice daily	75 mg once daily 200 mg once daily+ABT*	40 mg once daily+ABT*
ABT* included in the same pill	No	No	Yes
ABT used in phase 3 studies	None	E2 1 mg / NETA 0.5 mg**	E2 1 mg / NETA 0.5 mg**
Development program in endometriosis	ELARIS 1 and 2 6 months	EDELWEISS 1 and 2*** 24 weeks	SPIRIT 1 and 2 24 weeks
Long term safety data (extension studies)	6-month extension for total treatment duration of up to 12 months	Ongoing: 24 weeks extension for total treatment duration of up to 52 weeks	Ongoing: 48 weeks extension for total treatment duration of up to 104 weeks
Publication phase 3 studies	Taylor et al. 2017[46]	Donnez et al. 2023 [49]	Giudice et al. 2022 [56]

* ABT: add back therapy.
** E2: estradiol; NETA: norethisterone acetate.
*** Discontinuation of the EDELWEISS 2 Phase III study and its extension in January 2021.

EDELWEISS 2 Phase III study and its clinical extension trial because of challenges related to patient screening and recruitment, as well as difficulties relating to the ongoing coronavirus pandemic.

In the phase 3 EDELWEISS 3 trial, responder thresholds were a drop of at least 1.1 points for DYS and 0.8 points for NMPP on a monthly pain rating scale ranging from 1 to 3 [48]. A *p*-value of <0.05 denoted a significant difference compared with placebo. At 6 months, DYS responders' rates were 80% with linzagolix 200 mg plus ABT ($p < 0.001$), 49.5% with linzagolix 75 mg ($p < 0.001$), and 23.5% with the placebo. NMPP responder rates were 57.1% with 200 mg linzagolix in combination with ABT ($p = 0.003$), 52.2% with 75 mg linzagolix ($p = 0.036$), and 38.5% with the placebo. By 52 weeks, both the 200-mg dose with ABT and the 75-mg dose yielded significant improvements in both coprimary efficacy endpoints (DYS and NMPP).

With regard to safety, the 6-month minimal BMD reduction in the lumbar spine was 0.79% with 200 mg linzagolix plus ABT and 0.89% with 75 mg linzagolix. Adverse events were noted in just over 5% of subjects in any active treatment arm. They included headaches (10.5%, 8.1%, and 8.0%), hot flushes (6.8%, 7.5%, and 2.5%), and fatigue (6.8%, 3.8%, and 2.5%) with 200 mg linzagolix plus ABT, 75 mg linzagolix, and placebo administration, respectively [48].

Linzagolix (Yselty®) was approved in June 2022 for the treatment of moderate to severe uterine fibroid symptoms in adult women of reproductive age in the EU [50]. It is currently not marketed in France, and, at the present date, no Marketing Authorization application has been submitted for the treatment of endometriosis.

Relugolix

Relugolix is an oral GnRH receptor antagonist with a half-life of about 25 h that was developped for uterine fibroid and endometriosis treatment.

In a phase 2 dose-ranging study in women with endometriosis-associated pain, daily treatment with 40 mg relugolix monotherapy for 24 weeks was generally well tolerated and associated with a significant reduction in pelvic pain compared to placebo, with efficacy similar to that of the GnRH agonist leuprorelin [51].

In a 24-week double-blind, double-dummy RCT comparing 40 mg relugolix monotherapy with the GnRH agonist leuprorelin (subcutaneous injection), relugolix was found to be noninferior to leuprorelin in reducing pelvic pain in women with endometriosis [52]. Menses returned earlier following the end of the trial in women who were given relugolix than in those who were given the GnRH agonist. Both drugs had a similar safety profile.

However, a dose-dependent reduction in BMD, as well as an increase in vasomotor symptoms, mean that relugolix monotherapy is not suitable for long-term use. Relugolix (40 mg) in combination with ABT (1 mg estradiol and 0.5 mg norethisterone acetate) was then developed as an once-daily treatment for uterine fibroids or endometriosis. This one-pill, once-a-day combined therapy was conceived to achieve efficacy and minimize vasomotor symptoms and BMD loss by maintaining estradiol serum concentration within a therapeutic range (20–50 pg/mL), what is comparable to that observed in the early follicular phase of the menstrual cycle [53,54].

SPIRIT 1 and 2 phase III trials were published in June 2022 in the Lancet Journal [55]. Giudice et al. investigated the efficacy of relugolix combination therapy (relugolix CT) for the treatment of endometriosis-associated pain. SPIRIT 1 and 2 were replicate phase 3, multicenter, randomized, double-blind, placebo-controlled trials performed in 219 research centers worldwide. Participants with surgically confirmed endometriosis and moderate or more severe DYS and with associated NMPP were randomized in a 1:1:1 ratio to 24 weeks of treatment with relugolix CT, 24 weeks of treatment with placebo, or delayed relugolix treatment (12 weeks of relugolix monotherapy followed by 12 weeks of combination therapy). The use of the ''delayed'' arm allowed evaluation of the impact of hypoestrogenism on efficacy, tolerability, and BMD.

The composite primary outcome in the trial was the proportion of participants who experienced a clinically meaningful improvement in DYS and NMPP (as rated on a 0–10 numerical rating score [NRS]). Secondary outcomes related to other efficacy parameters including a condition-specific quality of life questionnaire, the Endometriosis Health Profile (EHP-30), and safety. In total, 638 and 623 patients were randomized to SPIRIT 1 and 2, respectively. The study populations in each arm were comparable with regard to age, body mass index, and ethnicity.

After 24 weeks of treatment, significantly more participants had experienced a clinically meaningful improvement in DYS NRS (reduction of NRS score ≥ -2.8 points) with relugolix CT compared to placebo (SPIRIT 1: 75% vs. 27%, $p < 0.0001$; SPIRIT 2, 75% vs. 30%, $p < 0.0001$). Similarly, a greater proportion of participants experienced improvement in NMPP (reduction of NRS score ≥ -2.1 points) compared to placebo in both trials (SPIRIT 1: 59% vs. 40%, $p < 0.0001$; SPIRIT 2: 66% vs. 43%, $p < 0.0001$).

Of the key secondary outcomes, relugolix CT consistently demonstrated superiority compared to placebo regarding changes in DYS, NMPP, overall pain (NRS) scores, the pain domain score of the EHP-30, and dyspareunia relief. At the end of treatment, patients who received relugolix CT treatment were more prone not to require analgesics use compared to those who received placebo (SPIRIT 1, 56% vs. 31%, $p < 0.0001$; SPIRIT 2, 54% vs. 24%, $p < 0.0001$), and a greater number did not require opioids for pain management (SPIRIT 1: 86% vs. 76%, $p < 0.0001$, SPIRIT 2: 82% vs. 66%, $p < 0.0001$). About 75% of the women receiving relugolix CT had either no or infrequent bleeding. Many of the participants in SPIRIT 1 and 2 entered the ''extension arm'' of the trial, which allowed them to continue treatment for a further 80 weeks. Of those discontinuing relugolix, the median time to return to menses was 31 days, and by 2 months over 90% had menstruated. Adverse event rates were similar among the three arms. BMD change after treatment with relugolix CT was less than 1% and not deemed to be clinically significant. Participants who received delayed therapy exhibited similar changes in efficacy endpoints but were, unsurprisingly, more likely to experience hot flushes than those with combination therapy and exhibited a substantial reduction in BMD after 12 weeks of monotherapy.

These two RCTs demonstrate that relugolix CT effectively relieves moderate to severe endometriosis-associated pain. Delayed combined treatment did not exhibit higher efficacy compared to immediate combination therapy, suggesting that combination therapy is as effective as relugolix without ABT, while mitigating the negative impact on BMD and the hypoestrogenic side effects. Relugolix CT has the added benefit of improving compliance with ABT, as both medications are included in one pill, and thus potentially long-term bone health. While the extension study is still in progress, the year 1 data appear encouraging [56,57].

A *post hoc* analysis of the bleeding profiles of patients included in the SPIRIT 1 and 2 trials was presented at the ACOG conference held in Baltimore [58], Maryland in May 2023. Of the 1261 randomized patients, data were available for 501 patients at 2 years. The proportion of women who became amenorrheic with relugolix CT increased over time, from 74.4% at 24 weeks to 82.3% at 104 weeks. The number of bleeding days per cycle decreased from 5.8 at baseline to 1.2 at 104 weeks. The number of heavy or very heavy bleeding days decreased from 1.9 to 0. These data confirm that relugolix CT treatment in women with endometriosis-associated pain resulted in high rates of amenorrhea and complete elimination of heavy bleeding and demonstrated durable clinical benefits at 2 years [58].

Relugolix combination therapy (Ryeqo®) was approved in July 2021 in Europe for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age [59]. It is not marketed in France. A Marketing Authorization application for the treatment of pain associated with endometriosis was submitted to the European Medicines Agency in October 2022 [60].

Conclusion

DNG 2 mg has been a reimbursable healthcare expense in France since April 2020. According to recent studies, it is at least as effective as CHC for the treatment of endometriosis-associated pain. It is generally well tolerated, reduces the size of endometriotic lesions, and improves patients' quality of life. It also has the advantage of having Marketing Authorization for this indication. Therefore, it can be offered as first-line treatment as an alternative to CHC and other progestins in women of childbearing age. Data on the postoperative use of DNG also confirm its utility in preventing recurrences. There are few new data available regarding DNG use in adolescents, for whom it remains a second-line treatment.

The LNG-IUS can also be proposed as first-line treatment to women with endometriosis and adenomyosis who do not wish to become pregnant in the medium term.

Oral GnRH antagonists will soon be on the market in France. Given their mode of action, their efficacy as monotherapy is comparable to that of GnRH agonists, with the advantages of an oral administration route and rapid action with no flare-up effect.

Combination therapy with oral GnRH antagonist and ABT is likely to allow long-term treatment with minimal impact on bone mass. This approach may thus be offered as second-line treatment as an alternative to treatment with GnRH agonists with ABT.

Conflict of Interest

H Fernandez: Gedeon Richter, Theramex
A Agostini: Gedeon Richter, Theramex
H Baffet: pas de liens d'intérêt
N Chabbert Buffet: Bayer, Besins, Exeltis, Gedeon Richter, Organon, Theramex
P Descamps: Gedeon Richter, Theramex
JP Estrade: Gedeon Richter
G Giraudet: Gedeon Richter, Theramex
C. Hocké: Gedeon Richter, IBSA Pharma, Exeltis
B Salle: pas de liens d'intérêt
F Trémollieres: pas de liens d'intérêt
C Chapron: Gedeon Richter, Theramex

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