Vilaprisan for the treatment of symptomatic endometriosis: results from a terminated phase 2b randomized controlled trial

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Objective: To evaluate the efficacy and safety of 2 doses of vilaprisan vs. placebo in participants with symptomatic endometriosis.
Design: Multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 2b trial (NCT03573336). The initially planned sample size was 315 patients. Recruitment was paused to assess long-term toxicity findings in rodents; although the findings were assessed as likely to be of limited clinical relevance in humans, the study was closed by the sponsor. During the pause, enrolled patients completed 3 or 6 months of treatment per their assigned regimen.
Setting: University hospitals, a regional hospital, and a private clinic.
Patients: Premenopausal adults with confirmed endometriosis and moderate-to-severe pelvic pain ($\geq$4/10 on a numerical rating scale) were enrolled. Inclusion required protocol adherence, including $\geq$24 diary entries, and an average pain score of $\geq$3.5.
Intervention: Participants were randomly assigned 1:1:1 to receive vilaprisan (2 mg), vilaprisan (4 mg), or placebo.
Main Outcome Measures: The primary outcome was a change in the 7-day mean "worst pain" (per the endometriosis symptom diary item 1) from baseline to month 3. All analyses were descriptive only.
Results: Eight participants were randomly assigned to treatment before the study pause: 6 received vilaprisan (4 mg, n = 4 and 2 mg, n = 2), and 2 received placebo. The 6 vilaprisan recipients experienced an improvement in endometriosis-associated pelvic pain, whereas the 2 placebo recipients experienced no change or increased pain; all 8 participants had decreased use of pain medication. Bleeding intensity decreased from baseline in the vilaprisan group.
Conclusion: The study findings suggest that vilaprisan may improve outcomes in patients with endometriosis. Further studies in larger populations would be needed to accurately assess treatment effects.
Clinical Trial Registration Number: NCT03573336 (F S Rep® 2024;5:189–96. ©2024 by American Society for Reproductive Medicine.)
Key Words: Vilaprisan, endometriosis, pelvic pain, dysmenorrhea, selective progesterone receptor modulator

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The availability of the data underlying this publication will be determined later, according to Bayer's commitment to the EFPIA/PhRMA "Principles for Responsible Clinical Trial Data Sharing." This pertains to the scope, time point, and process of data access. As such, Bayer commits to sharing, on request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014. Interested researchers can use https://vivli.org/ourmember/bayer/ to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.
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Endometriosis is a chronic, estrogen-dependent, inflammatory disorder that is complex in etiology, pathogenesis, and presentation (1). It is classically defined as the presence of endometrial-like tissue outside of the uterus, although it is increasingly being considered a systemic disease (2). The condition can be progressive, stable, or regressive in nature (3–6), and not all patients are symptomatic (7). Endometriosis is estimated to affect 2%–10% of women of reproductive age and up to 50% of infertile women (8); however, because of misdiagnosis and diagnostic delay, the exact prevalence may be higher (9).

Symptomatic endometriosis is frequently characterized by debilitating pain, heavy menstrual bleeding, fatigue, and infertility (10). Pain symptoms can include dysmenorrhea, noncyclic pelvic pain, dyspareunia, and pain during urination or bowel movements (10); other symptoms associated with endometriosis include mood disorders, systemic inflammation, constipation, and diarrhea (2, 11). These symptoms can considerably impact women's quality of life.

Endometriosis requires long-term management, and guidelines and general consensus have moved toward clinical diagnosis along with noninvasive, empirical treatments to avoid repeated surgical procedures (8, 12–14). Current first- and second-line medical treatments available for endometriosis-related pain include nonsteroidal anti-inflammatory drugs, hormonal therapies (such as oral contraceptives), gonadotropin-releasing hormone (GnRH) agonists, and, more recently, GnRH antagonists (15–18). However, GnRH agonists and antagonists are not always effective and may be associated with hypoestrogenic side effects, such as hot flashes, decreased bone mineral density, and depression (8, 18, 19). In patients whose symptoms are refractory to pharmacologic treatment, surgical treatment options may be advised; however, these are also not always effective and may be associated with symptom recurrence and surgical complications (12, 14, 20). Therefore, substantial unmet needs remain in the management of endometriosis, and new treatment options are required.

Selective progesterone receptor modulators (SPRMs) are a class of synthetic compounds targeting the progesterone receptor with agonist and antagonist properties. Selective progesterone receptor modulators have demonstrated efficacy in treating uterine fibroids, which have been linked to aberrant progesterone signaling (21, 22). Disrupted progesterone signaling has been implicated also in the development of endometriosis, and it has, therefore, been hypothesized that SPRMs may have therapeutic potential in treating endometriosis (21, 22). Although data from 2 randomized controlled trials suggest potential benefits of the SPRM mifepristone in the management of endometriosis symptoms, the available data on other SPRMs (such as asoprisnil and ulipristal acetate) are not conclusive regarding their long-term efficacy and/or safety (20, 23).

Vilaprisan is a novel, investigational SPRM that has an antiprogestogenic effect that is fivefold more potent than that of ulipristal acetate (24), and it has been shown to induce amenorrhea and reduce the volume of uterine fibroids (25–29). In phase 1 studies conducted in healthy women and phase 2 and 3 studies in women with uterine fibroids, treatment with vilaprisan 0.5–4 mg for up to 3 months or vilaprisan 2 mg for up to 6 months was well tolerated, and the expected progesterone receptor modulator-associated endometrial changes were reversible after the end of vilaprisan treatment followed by one to 2 menstrual bleedings (25, 26, 28, 29).

On the basis of these findings in uterine fibroids—a disease with some treatment overlap with endometriosis—a regimen of repeated 6-month treatment periods (TPs) using vilaprisan, with 2 menstrual bleeding episodes between TPs, was selected for investigation in the treatment of endometriosis, and the results of this phase 2b trial are reported here. The vilaprisan clinical development program, including this phase 2b trial, was placed on hold in 2018 to allow for a thorough evaluation of preneoplastic and neoplastic endometrial and adrenal findings and cutaneous sarcomas in rodent species. Although investigations later indicated that these findings were likely of limited clinical relevance in humans, the study sponsor—after discussion with the regulatory authorities—elected to close the studies. Initially, patients were allowed to complete their ongoing 3-month treatment courses (at the time, it was assumed that the studies would later resume). However, it was subsequently decided to close the studies, and additional follow-up procedures were introduced for patients who had been treated. Data from the TP and the follow-up of these participants are reported here.

MATERIALS AND METHODS

Study design

The study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 2b trial that assessed the efficacy and safety of 2 different doses of vilaprisan vs. placebo in participants with symptomatic endometriosis. Study participants were randomly assigned 1:1:1 to receive vilaprisan 2 mg, vilaprisan 4 mg, or placebo. Randomization to treatment was stratified by country (Austria, Canada, and Finland) and using the method of endometriosis diagnosis (surgery or imaging). Patients were registered into the interactive voice response system and interactive web response system at screening and assigned a unique multidigit subject identification number by the site for unambiguous identification. The study employed a double-blind design with nondistinguishable vilaprisan and placebo tablets. Unblinding was permitted in the event of a suspected serious adverse reaction or emergency.

The planned study design included the following phases: a screening phase, a placebo-controlled dose-finding phase, a drug-free interval encompassing 2 menstrual bleeding episodes, a placebo-controlled extension phase, and a follow-up phase (Fig. 1). Endometriosis symptoms and their impact on participants' daily lives were to be documented throughout the study. The planned primary objective was to assess the efficacy of 2 doses of vilaprisan compared with placebo in participants with symptomatic endometriosis, and the planned secondary objective was to evaluate the safety and tolerability of each dose. The planned primary outcome was the change in participants' 7-day mean "worst pain" from baseline to month 3 of the first 24-week TP measured on a daily numerical rating scale (NRS). The study design was approved by each of the

participating study centers' institutional review boards, and the study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. The study is registered on clinicaltrials.gov (Clinicaltrials.gov identifier: NCT03573336).

Early study closure

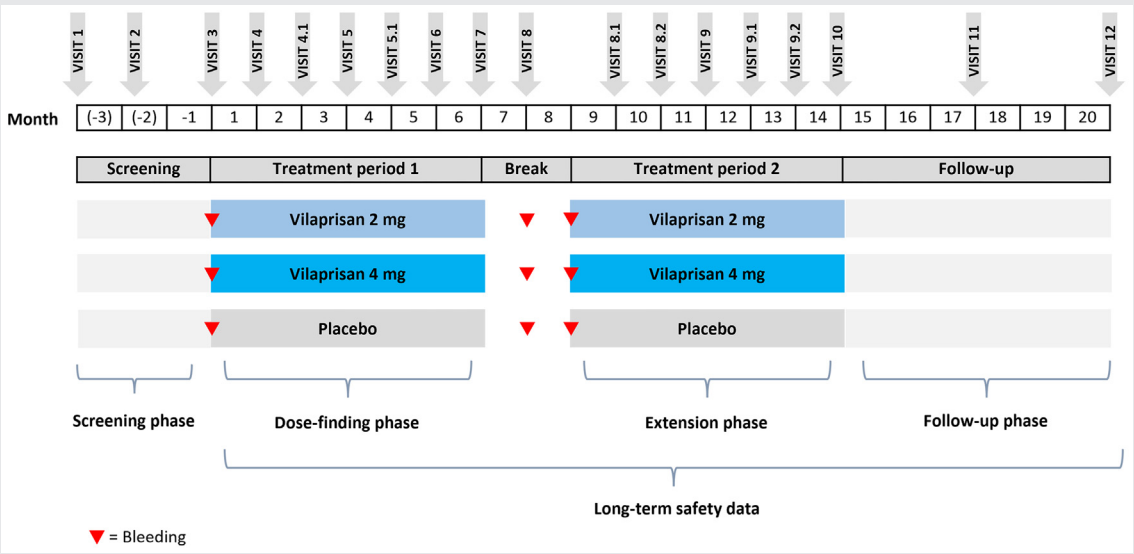
All the required and relevant preclinical studies were performed before the first-in-human trials of vilaprisan. As per usual practice, further preclinical studies were conducted and evaluated in parallel with clinical development. Recruitment for all clinical trials of vilaprisan and the start of new TPs were stopped in December 2018 to allow a thorough evaluation of preliminary findings from a long-term (2-year) rat and mouse carcinogenicity study with vilaprisan that showed abnormalities of the adrenals, uterus, and skin. Initially, it was planned to restart the vilaprisan clinical trials at a later date. Although investigations revealed that the preclinical findings were likely to be rodent-specific and of limited clinical relevance in humans, the study sponsor, after discussion with the regulatory authorities, elected to close all studies after completion of an additional, comprehensive safety follow-up with particular focus on endometrial, adrenal, and skin safety, to ensure the safety of the women enrolled and to thoroughly assess the potential relevance of the preclinical findings to humans (comprehensive publications on these safety data are in development).

Recruitment for the present phase 2b study started in July 2018 with an initial planned sample size of 315 patients (including a minimum of 210 surgically diagnosed endometriosis cases for primary efficacy and up to 105 imaging-diagnosed cases). At the time of the study pause in December 2018, participants taking study treatment were instructed to complete 3 months of treatment if they were in the first 3 months of their TPs, or to complete 6 months of treatment if they were in the second 3 months (i.e., months 4–6) of their TPs. Participants were instructed not to start a new TP. In addition, a safety close-out visit, including comprehensive safety follow-up measures for all study participants who received at least one dose of vilaprisan, was implemented as soon as possible after the decision on study closure. After the sponsor decided to close the study, treatment blinding was removed for all participants to prevent unnecessary follow-up procedures in patients exposed to placebo only.

Study population

The study enrolled premenopausal participants who were at least 18 years of age and had a confirmed diagnosis of endometriosis. The diagnosis was confirmed using laparoscopy or laparotomy within the last 10 years but not <8 weeks before the first study visit, or on the basis of imaging, visualized using transvaginal ultrasound at the screening visit or diagnosed with magnetic resonance imaging within 12 months of the first study visit. Eligible participants had moderate-to-severe endometriosis-associated pelvic pain (EAPP) of ≥4 out of 10 in the last 28 days before the first study visit, measured on the NRS; demonstrated adherence to the study procedures during the screening period (at least 24 diary entries of the Endometriosis Symptom Diary [ESD] item 1 ["worst pain" on the daily NRS] during the first 28 consecutive days after the first study visit; and an average score of ≥3.5 for the available ESD item 1 entry during this period). Key exclusion criteria included: pregnancy or lactation; any

FIGURE 1



Planned study design. One month = 28 days.

Taylor. Vilaprisan treatment for endometriosis. F S Rep 2024.

disease or condition compromising organ system function, including impaired kidney function or abnormal liver parameters; undiagnosed abnormal genital bleeding; regular use of pain medication because of other underlying diseases; or concomitant treatment with any hormonal contraceptive or contraceptive device, progesterone receptor modulator GnRH agonist, raloxifene (or similar selective estrogen receptor modulators), fluoride, calcitonin, or an agent affecting bone metabolism.

Assessments

Efficacy. Participants were asked to complete the ESD and the Endometriosis Impact Scale, both newly developed patient-reported outcomes instruments, which assess patients' experience of endometriosis symptoms and the impact of these symptoms of endometriosis on patients' lives, respectively (30). The ESD was completed daily, and the Endometriosis Impact Scale was completed weekly, using an electronic hand-held device (eDiary). Participants were also asked to rate their EAPP from "no pain" to "unbearable pain" using a visual analogue scale on the eDiary every 4 weeks, using a 4-week recall period.

Further efficacy assessments were planned but not performed because of the early termination of the study. For details of all planned assessments, please refer to the Supplemental Material (available online).

Pharmacokinetics. Blood samples were taken to measure the pharmacokinetic plasma concentrations of vilaprisan. Population pharmacokinetic analysis of vilaprisan and evaluation of pharmacokinetic and pharmacodynamic relationships were planned but never performed because of the early termination of the trial.

Safety. Adverse events (AEs) and serious AEs (SAEs) were recorded. Adverse events of special interest included drug-induced liver injury; endometrial disorders (all subcategories of endometrial hyperplasia, according to the World Health Organization 2014 classification); endometrial histology and thickening (assessed using a transvaginal ultrasound); adrenal neoplasms (benign and malignant); cutaneous sarcoma; heavy menstrual bleeding (HMB) or worsening of EAPP; and relevant loss of bone mineral density (BMD; measured using a dual-energy X-ray absorptiometry [DEXA] scan). Liver parameters, including alanine aminotransferase and aspartate aminotransferase levels, were monitored monthly during treatment. After the decision to terminate the study, a safety close-out visit was implemented where participants who received at least one dose of vilaprisan underwent safety evaluations, including a DEXA scan for BMD, as well as endometrial, adrenal, and skin evaluations.

Statistical analyses

The sample size was initially determined through a simulation-based analysis using previous phase 2 data. On the basis of the analysis, to achieve an any-pair power of 0.90 with a family-wise error rate of 0.05, 59 patients with data after the 3-month treatment interval in each treatment arm and a total sample size of 210 patients were required (70 patients per treatment arm) to account for a 15% drop-out rate. To achieve 100 active vilaprisan-treated subjects with a treatment duration of 1 year, taking into account a drop-out rate of 50%, a further 105 subjects were planned to be added to the calculated sample size of 210, resulting in an initially planned sample size of 315.

A one-sided Dunnett test to compare each of the investigated doses of vilaprisan with placebo in a confirmatory manner at an overall significance level of 2.5% was planned for the primary efficacy analysis. However, because of the early termination of the study, the intended sample size was not reached. All data were analyzed descriptively, and no statistical analysis was performed on the collected data.

RESULTS

Before the study pause and subsequent closure, 48 participants were enrolled in the study. Forty participants failed the screening process, with the most frequent reasons for screening failure being inclusion and exclusion criteria not met (n = 21), "other" reasons (often relating to the study pause), and participant withdrawal (Supplemental Fig. 1, available online). Eight participants were randomly assigned to treatment in 6 study centers in 3 countries (Supplemental Table 1, available online). Six participants were assigned to vilaprisan treatment (4 to vilaprisan [4 mg] and 2 to vilaprisan [2 mg]), and 2 participants were assigned to placebo treatment.

Treatment duration was between 19 and 168 days for the 4 participants who took vilaprisan 4 mg per day (i.e., 76–672 mg total vilaprisan exposure) and 82 or 162 days for the 2 participants on vilaprisan 2 mg per day (164 mg or 324 mg total vilaprisan exposure). Placebo treatment lasted for 82, or 168, days. The participants randomly assigned to treatment were all white and were aged between 24 and 37 years (Supplemental Table 1). One participant in the vilaprisan 4 mg group discontinued the study medication prematurely after 19 days in TP1 because of withdrawal from the study (no specific reason was provided). All other participants were treated for 3 or 6 months.

The planned study objectives could not be met with the data available from participants enrolled before the study pause and subsequent closure; however, the available data are described below.

Efficacy

All 6 participants who received vilaprisan treatment experienced an improvement in EAPP from baseline (first 28 days of the screening period) to month 3 (third cycle of 28 days of treatment), whereas participants who received the placebo experienced no change or even an increase in EAPP (Fig. 2). From baseline to month 3 of the first 24-week TP, the mean worst daily pelvic pain improved by 2.90 and 4.46 NRS points (per ESD item 1) in the 2 participants who received vilaprisan 2 mg, and by 4.08, 2.07, 2.82, and 1.16 NRS points in the 4 participants who received vilaprisan 4 mg. For the 2 participants who received a placebo, the mean worst daily pelvic pain was unchanged for one and worsened for the other (by 0.96 NRS points) from baseline to the end of TP1.

Pain medication use decreased from baseline in the treatment phase in participants treated with vilaprisan (Fig. 3), from a mean of 1.01–0.16 tablets per day in the 4 mg group to 0.61–0.09 tablets per day in the 2 mg group. In the placebo group, mean pain medication use was 1.03 tablets per day at baseline and 0.81 tablets per day in the treatment phase.

A decrease in bleeding intensity was observed in participants treated with vilaprisan, in accordance with its mode of action (Fig. 4). All 6 vilaprisan-treated participants had a maximum bleeding intensity reported as normal to heavy at baseline. During month 3 of the study drug treatment, 3 out of these 6 participants had no vaginal bleeding at all, 2 participants reported maximum bleeding intensity as light, and one participant who had maximum bleeding intensity of heavy during the baseline period reported heavy bleeding again during the last 28 days of treatment. It should be noted, however, that this patient discontinued treatment after 19 days. The 2 placebo-treated participants had a maximum vaginal bleeding intensity of light and heavy at baseline and normal and heavy vaginal bleeding at the end of treatment.

Safety

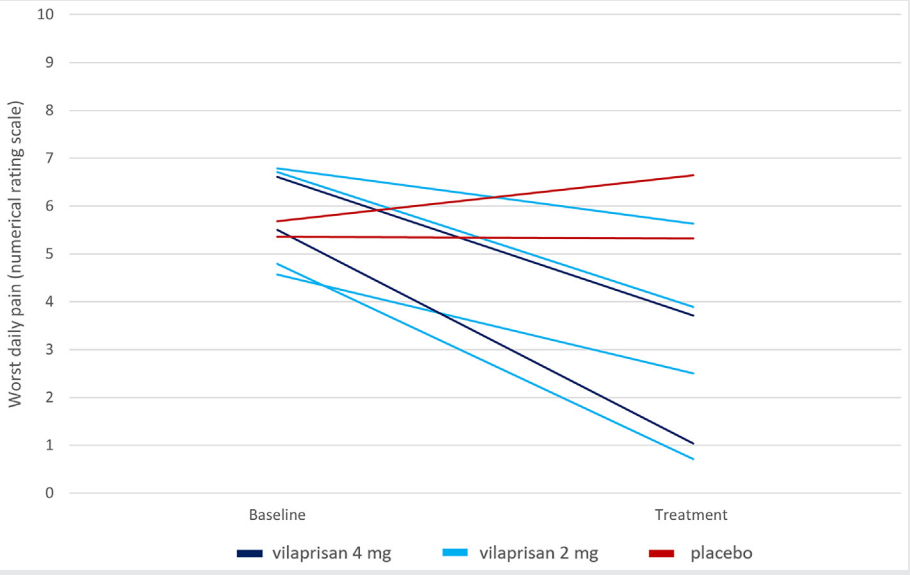
The total amount of active drug intake ranged from 76–672 mg in the vilaprisan 4 mg group (days with treatment between 19 and 168) to 164–324 mg in the vilaprisan 2 mg group (days with treatment between 82 and 162). No deaths were reported throughout the study. Six SAEs were reported in 4 participants: one SAE was reported in each of the 3 participants in the vilaprisan 4 mg group (gastroenteritis, adrenal adenoma, and endometriosis [leading to hospitalization 300 days after the end of treatment; event reported as endometriosis-related pelvic pain]), and 3 SAEs were reported in one participant in the vilaprisan 2 mg group (2 events of retinal detachment in the left eye and one event of endometriosis ablation). The case of adrenal adenoma was diagnosed approximately 1.5 years after completion of a 12-week treatment with the study drug on the basis of a local reading of a magnetic resonance imaging scan, and the case was assessed as related to the study drug by the investigator. However, the centrally blinded expert reading did not detect any adrenal masses. Because of the patient's relatively short treatment duration (12 weeks only) and the fact that the centrally blinded read did not confirm the presence of an adrenal mass, the case was assessed as unrelated to the study drug by the sponsor. All other SAEs were assessed as unrelated to the study drug by both the investigator and the sponsor and were resolved shortly afterward or during the follow-up period. At the safety close-out examination, >22 months after the end of treatment, one participant who had received vilaprisan 2 mg for >5 months had a mild intensity AE of BMD decrease that was assessed as unrelated to the study drug. The relative change of BMD from baseline was −5.78% for the lumbar spine, +0.42% for the hip, and +2.22% for the femoral neck.

No abnormalities in endometrial biopsy evaluation (including any subcategory of endometrial hyperplasia, according to the World Health Organization 2014 classification, or endometrial thickening), or cases of HMB, liver disorders (including alanine aminotransferase and aspartate aminotransferase levels increasing to >3 times the upper limit of normal), or relevant skin disorders (i.e., cutaneous sarcoma), were reported in the vilaprisan-treated participants.

DISCUSSION

Symptomatic endometriosis is associated with a considerable disease burden that can affect many aspects of women's lives

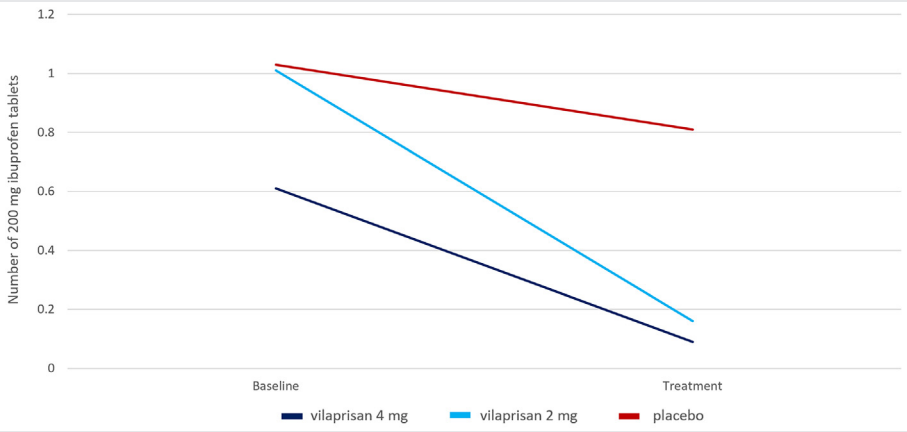
FIGURE 2



Mean worst daily pelvic pain for each of the 8 participants in the first 28 days of the screening period (baseline) and during month 3 (third cycle of 28 days) of the 12-week or 24-week study drug treatment period.

Taylor. Vilaprisan treatment for endometriosis. F S Rep 2024.

FIGURE 3



The mean worst daily pain medication use by each of the 8 study participants in the first 28 days of the screening period (baseline) and during month 3 (third cycle of 28 days) of the 12-week or 24-week study drug treatment period.

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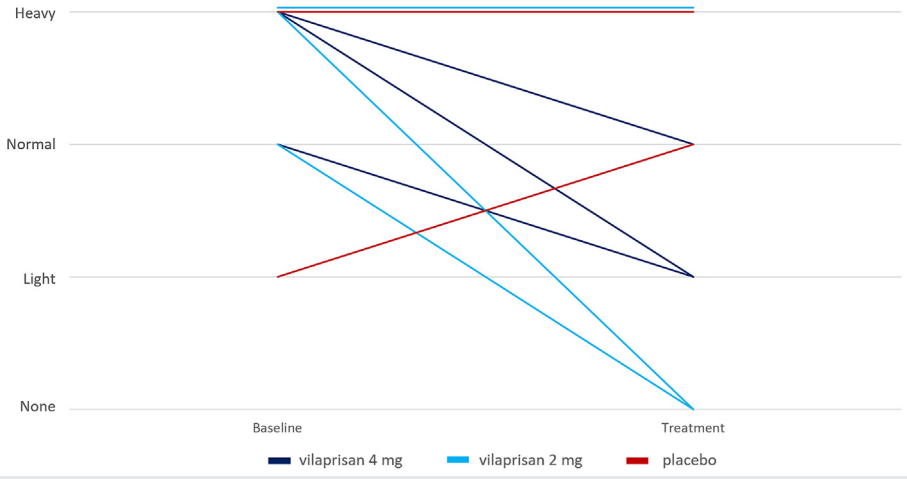
(31). Although several treatment options are available, they are not always effective and may be associated with side effects; therefore, there is a substantial need for new treatment options. This study aimed to assess the efficacy and safety of 2 different doses of vilaprisan vs. placebo in participants with symptomatic endometriosis. However, because of the early termination of the study and the significant impact this had on the number of participants enrolled and treated, only limited conclusions can be drawn from the study findings. Nevertheless, the available data from this study suggest that vilaprisan warrants further evaluation as a potential treatment for endometriosis.

The 6 participants treated with vilaprisan experienced an improvement in symptoms of EAPP. In contrast, of the 2 participants who received placebo treatment, one experienced no change and the other reported an increase in EAPP. Pain medication use decreased in those treated with vilaprisan accordingly. Furthermore, a decrease in bleeding intensity

FIGURE 4



The maximum intensity of vaginal bleeding for each of the 8 participants in the first 28 days of the screening period (baseline) and during month 3 (third cycle of 28 days) of the first 12-week or 24-week study drug treatment period.

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was observed in participants treated with vilaprisan, in accordance with vilaprisan's mode of action. No reason for a serious safety concern was identified, and there were no deaths in the study. Serious AEs were reported in 4 participants, with one case of adrenal adenoma assessed by the investigator as related to the study drug but not by the sponsor, as the central blinded read of the adrenal magnetic resonance imaging did not confirm the presence of adrenal masses. All other SAEs were assessed as unrelated to the study drug by the investigators and the sponsor. No abnormalities in endometrial biopsy evaluation or cases of HMB, liver disorders, or skin disorders were reported in the participants treated with vilaprisan.

Given the early study closure, the number of study participants was far lower than planned; however, the available data suggest that vilaprisan may be effective in the treatment of endometriosis. Moreover, these findings provide supporting evidence for the potential clinical utility of SPRMs as a drug class in endometriosis. Because there remains a need for effective treatments without the side effects observed with currently available treatments, further investigation of SPRMs in endometriosis could be a promising avenue for research.

CONCLUSION

Findings from this study suggest that vilaprisan may improve outcomes in patients with endometriosis. However, early study termination limited the amount of data collected and precluded statistical analysis of any observed treatment effect. Further studies in larger populations would be needed to accurately assess the treatment effects of vilaprisan.

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CRediT Authorship Contribution Statement

Hugh S. Taylor: Data interpretation, Writing—original draft, Writing—review. Liying Dong: Study design, Data analysis, Data interpretation, Writing—original draft, Writing—review. Johanna Haikonen: Data interpretation, Writing—original draft, Writing—review. Peter Oppelt: Data interpretation, Writing—original draft, Writing—review. Karl Tamussino: Data interpretation, Writing—original draft, Writing—review. Rene Wenzl: Data interpretation, Writing—original draft, Writing—review. Thomas Faustmann: Study design, Data analysis, Data interpretation, Writing—original draft, Writing—review. Esther Groettrup-Wolfers: Study design, Data analysis, Data interpretation, Writing—original draft, Writing—review. Xiaowei Ren: Study design, Data analysis, Data interpretation, Writing—original draft, Writing—review. Christian Seitz: Study design, Data analysis, Data interpretation, Writing—original draft, Writing—review.

Declaration of Interests

H.S.T. reports having served as an investigator for previous Bayer-sponsored studies and also reports funding from Abbvie and consulting fees from Organon outside the submitted. L.D. reports having served as a full-time employee of Bayer at the time of the study and also reports funding from Bayer for the submitted work and funding and stock options from Bayer outside the submitted work. J.H. reports having served as an investigator for previous Bayer-sponsored studies and also reports funding from Bayer for the submitted work. P.O. reports having served as an investigator for previous Bayer-sponsored studies and also reports to the advisory board for Ryeqo outside of the submitted work. K.T. reports having served as an investigator for previous Bayer-sponsored studies and reports stock options to the Austrian Society of OBGYN outside the submitted work. R.W. reports having served as an investigator for previous Bayer-sponsored studies and also reports consulting fees from Gedeon Richter; honoraria from Gedeon Richter and Intuitive; patents for noninvasive diagnosis of endometriosis; and stock options from Novartis outside the submitted work. T.F. reports having served as a full-time employee of Bayer at the time of the study. E.G.W. reports being a full-time employee of Bayer. X.R. reports being a full-time employee of Bayer. C.S. reports being a full-time employee of Bayer. C.S. also reports funding from Bayer AG Berlin, Germany, for the submitted work; patents on use issued by vilaprisan; and stock options issued by Bayer AG outside the submitted work.

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