DR DIETMAR TRUMMER (Orcid ID : 0000-0001-9643-0109)

Received Date : 19-Sep-2016

Revised Date : 27-Jan-2017

Accepted Date : 30-Jan-2017

Article type : Original Research Article

Efficacy, safety and tolerability of the CCR1 antagonist BAY 86-5047 for the treatment of endometriosis-associated pelvic pain: a randomized controlled trial

Running title: Efficacy of BAY 86-5047 in endometriosis

Dietmar Trummer[1], Anja Walzer[2], Esther Groettrup-Wolfers[3] and Heinz Schmitz[2]

[1]R&D Statistics, [2]Global Clinical Development and [3]Global Pharmacovigilance,

Bayer Pharma AG, Global Development, Berlin, Germany

Corresponding author

Dietmar Trummer

R&D Statistics, Bayer Pharma AG, Global Development, Müllerstr. 178, 13353 Berlin, Germany

E-mail: dietmar.trummer@bayer.com

Conflicts of interest notification

The authors are employees of Bayer Pharma AG**.**

Abstract

Introduction: Antagonism of CC chemokine receptor type 1 (CCR1) may provide a novel treatment approach for women with symptomatic endometriosis. Studies of CCR1 antagonists in these patients have not been reported. *Materials and methods:* Women (n = 110; 18–45 years) with symptomatic endometriosis were randomized to BAY 86-5047 or placebo for 12 weeks. Pelvic pain was assessed using the visual analogue scale (VAS) and women recorded the intake of pain medication in a diary. The primary efficacy outcome was a composite of the absolute change in VAS score and the cumulative change in consumption of analgesics between baseline and the end of treatment. Safety assessments included adverse events, blood and urine evaluation and electrocardiography. *Results:* Mean VAS scores decreased from 64.8 mm at baseline to 49.2 mm at week 12 in the BAY 86-5047 group and from 67.2 mm to 47.8 mm in the placebo group. The proportion of women using analgesics decreased from 33.9% to 11.5% and from 44.4% to 15.4% for patients who received BAY 86-5047 or placebo, respectively. There was no significant difference between the two treatment groups in terms of change in VAS scores (P = 0.45) or intake of analgesics (P = 0.82). A three-step sensitivity analysis failed to show superiority of BAY 86-5047 over placebo (P = 0.67). BAY 86-5047 was well tolerated and no significant safety concerns arose during the study. *Conclusions:* Based on these results, BAY 86-5047 is unlikely to have utility in the treatment of women with endometriosis-associated pelvic pain.

Key words

endometriosis / pelvic pain / BAY 86-5047 / CCR1 antagonist / placebo

Abbreviations

AE	adverse event
B&B	Biberoglu and Behrman
CCR1	CC chemokine receptor type 1
EAPP	endometriosis-associated pelvic pain
RANTES	regulated upon activation, normal T cell expressed and secreted cytokine
rASRM	revised American Society for Reproductive Medicine
VAS	visual analogue scale

Key message

The potent, selective CC chemokine receptor type 1 (CCR1) antagonist BAY 86-5047 is ineffective for the treatment of women with endometriosis-associated pelvic pain when administered for 12 weeks.

Introduction

Endometriosis is sex hormone-dependent inflammatory disease defined by the presence of endometrium-like tissue (endometriotic lesions) outside the lining of the uterus, predominantly in the pelvic region (1). The growth of this ectopic tissue induces a chronic inflammatory reaction, and women with endometriosis may experience dysmenorrhea, chronic pelvic pain, dyspareunia, chronic fatigue and sub-fertility (2). Endometriosis is estimated to affect up to 10% of women during their reproductive years, with disease severity varying between individuals (1).

Endometriotic lesions can be removed by laparoscopic surgery, which may relieve pain and enhance fertility in some cases (3). Current pharmacological therapies for endometriosis treat disease-associated pelvic pain and comprise primarily non-steroidal anti-inflammatory drugs

and hormonal treatments that suppress endogenous estradiol levels, including combined oral contraceptives, progestins and gonadotropin-releasing hormone agonists (4). There is evidence that these therapies can provide some symptomatic relief, but findings from patient surveys suggest that, overall, their efficacy is unsatisfactory in many women (5). Neither surgical nor medical therapies have confirmed superior efficacy in treating endometriosis-associated pelvic pain (EAPP) and current guidelines do not recommend either treatment modality over the other (2).

Over the past decade, there has been increased interest in developing non-hormonal therapies that target the pain and inflammatory pathways fundamental to endometriosis (6). However, regulatory approval has yet to be obtained for any non-hormonal treatment for the disease. Of particular interest are immunomodulatory strategies aimed at reducing disease-associated chronic inflammation (7). Such therapies are based on observations that the pathogenesis of endometriosis is characterized by excessive leukocyte numbers, principally macrophages and T cells, in both endometriotic implants and within the surrounding peritoneal fluid (8). The recruitment of leukocytes to inflammatory sites is mediated through the binding of chemokines (low molecular weight cytokines) to their cognate receptors (9), a process that propagates the inflammatory state. One of the principal chemokines present in the peritoneal fluid of women with endometriosis, accounting for 70% of its monocyte chemotactic activity (10), is RANTES (regulated upon activation, normal T cell expressed and secreted cytokine; also known as CCL3) (8). CC chemokine receptor type 1 (CCR1) is a chemokine receptor with high affinity for RANTES (9), which is present at increased levels on the peritoneal macrophages of women with endometriosis (8). Binding of chemokines to CCR1 is associated with pro-inflammatory actions, including leukocyte migration and upregulation of integrins, such as CD11b, to promote leukocyte adherence to the endothelium (11). For this reason, CCR1 has been proposed as a contributory factor to endometriosis-associated inflammation, and may constitute a novel non-hormonal target for the development of new drugs to treat this disease.

Several CCR1 antagonists have already been developed, with the intention of reducing pain symptoms in chronic inflammatory diseases (11). The small molecule antagonist BAY 86-5047 has been shown to bind selectively to CCR1 with high affinity (12), which consequently prevents binding of the proinflammatory chemokines CCL3, CCL5 and CCL7 to this receptor (13). BAY 86-5047 has been studied in several chronic inflammatory conditions, including

multiple sclerosis (13) and renal fibrosis (14). This study aimed to evaluate the efficacy, safety and tolerability of BAY 86-5047 given orally over 12 weeks for the treatment of women with EAPP.

Material and methods

The study was a multicenter, randomized, placebo-controlled, parallel-group, double-blind trial. A total of 28 centers took part, across seven countries. Women of reproductive age (18–45 years) were eligible for inclusion in the study if they fulfilled the following criteria:

- endometriosis, as determined by diagnostic laparoscopy or laparotomy between 24 months and 6 weeks prior to screening (visit 1)
- a minimum pelvic pain score of 40 mm on the visual analogue scale (VAS) at screening and at baseline
- willingness to use a barrier contraceptive method (unless bilateral tubal ligation had been performed previously), but no hormonal contraception
- willingness to use only ibuprofen (up to 3 × 400 mg tablets per day) to treat pain associated with endometriosis.

Participants were assigned to BAY 86-5047 or placebo by means of a blocked randomization list generated by the sponsor's central randomization service. Both participants and investigators were blinded to treatment allocation. Both treatments were administered as two tablets (taken three times daily). The treatment was taken continuously with no medication-free days.

The study period comprised a screening phase of 4–8 weeks prior to treatment and a 12-week treatment phase, in which BAY 86-5047 was titrated up to a dose of 1800 mg per day over the first 10 days. Participants visited the study site at screening, start of treatment (baseline) and at weeks 1, 2, 4, 8 and 12 of treatment. A follow-up visit took place at week 16. Participants were given a diary to record their intake of treatment and analgesics (ibuprofen), pain severity using the VAS and the occurrence of adverse events (AEs).

Pelvic pain was assessed using the VAS at baseline (visit 2, the first day of treatment) and at weeks 4, 8, 12 and 16. Patients were asked to make a single mark on the line indicating her pain associated with endometriosis during the time window of the preceding 4 weeks. Biberoglu and Behrman (B&B) scores (15) were measured at baseline and at weeks 12 and 16 in order to assess the severity of symptoms, based on participants' self-assessment of pain and gynecological palpation by the attending clinician. Safety outcomes were monitored throughout the study, including AEs, electrocardiogram, bleeding patterns and laboratory evaluations.

The primary efficacy variable was a composite comprising the individual absolute change in EAPP, measured by VAS score (mm), and the cumulative change in consumption of analgesics between baseline and the end of treatment. The secondary efficacy variables were change in VAS score between baseline and week 12 or premature discontinuation, change in intake of analgesics from baseline to week 12, change in B&B scores from baseline to week 12 and global assessment of efficacy by the patient and investigator at week 12. AEs, including clinically relevant changes in safety parameters (e.g. standard laboratory parameters or vital signs), were summarized by treatment group according to the Medical Dictionary for Regulatory Activities.

Competent authorities and the responsible ethics committees/institutional review boards of the participating centers approved the study protocol between 23 Sept 2004 and 09 Mar 2006 (Supporting Table S1) and all participants provided written informed consent. The study (ClinicalTrials.gov identifier: NCT00185341; EudraCT number: 2004-000630-37) was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation.

Statistical analyses

Sample size was determined based on an expected difference in VAS score reduction of 25 mm between the BAY 86-5047 and placebo arms, with a standard deviation of approximately 35 mm for both groups. Using an error margin for one-sided test ($\alpha = 0.025$) and a power of 0.9 ($\beta = 0.1$), it was calculated that 43 patients would be required in each treatment arm to detect superiority of BAY 86-5047 over placebo. Given an anticipated drop-out rate of 25%, at least 58 patients were required in each treatment group.

The primary efficacy variable was tested using Tamhane and Logan's approximate likelihood ratio test (16) and a sensitivity analysis, using a three-step hierarchical testing procedure (designed to demonstrate the superiority of at least one component within the composite primary endpoint while both components are non-inferior) according to Röhmel *et al.* (17).

Superiority analysis was used to test change in VAS and B&B scores between baseline and week 12. Descriptive statistics were used to analyze VAS scores, intake of analgesic medication at baseline and week 12, and safety parameters. B&B scores were assessed using descriptive statistics and responder analysis at baseline, week 12 and follow-up. Global assessment of efficacy was assessed at the end of treatment using the Clinical Global Impression scale (18).

Results

Participant characteristics

The participant flow diagram is shown in Figure 1. Following screening, 110 participants were eligible for study during the period February 2005 to February 2007. Participants (54 receiving placebo, 56 receiving BAY 86-5047) were randomized and comprised the full analysis set for the study.

Participant demographic and baseline clinical data are displayed in Table 1. Almost all the women enrolled (98.2%) were Caucasian. Where data were available, the majority of women were categorized as disease stage III or IV (according to the revised American Society for Reproductive Medicine [rASRM] classification). The two groups were similar in terms of age, ethnicity, body mass index and rASRM stage of endometriosis.

Efficacy variables after 12 weeks of treatment

Primary efficacy variables

Within the full analysis set, there was no significant difference in the primary endpoint between the placebo and BAY 86-5047 groups (P = 0.75) after 12 weeks of treatment using the approximate likelihood ratio test. Similarly, the three-step sensitivity analysis failed to demonstrate superiority of BAY 86-5047 over placebo (P = 0.67).

For participants who received BAY 86-5047, mean VAS scores decreased from 64.8 mm at baseline to 49.2 mm at week 12, a reduction of 15.6 mm (Figure 2). For women treated with placebo, mean VAS scores decreased by 19.4 mm over the same period, from 67.2 mm to 47.8 mm. These changes were not significantly different between the BAY 86-5047 and placebo groups (P = 0.45).

The proportion of participants taking analgesics decreased from 33.9% at baseline to 11.5% at week 12 in the BAY 86-5047 group, and from 44.4% to 15.4% over the same period in the placebo group (Figure 3). There was no significant difference between the two treatment groups in terms of analgesic intake (P = 0.82). Moreover, for both groups of participants, there was little change in the intake of rescue medication from baseline. Overall, there was no clear relation between the change in VAS scores and the change in rescue medication intake (Figure 4).

Secondary efficacy variables

Analysis of B&B scores showed similar trends in the two treatment groups (Figure 5). There was no significant difference in total B&B scores for women treated with BAY 86-5047 or placebo (P = 1.0). There was also no significant difference between the groups for the individual components of B&B assessment, namely non-cyclic pelvic pain, dysmenorrhea and dyspareunia. Similarly, there was no significant difference between the treatment groups in terms of change in analgesic intake. At the end of the study, the proportion of patients treated with BAY 86-5047 whose condition was categorized by investigators as being 'much improved' was 33.3%, compared with 28.5% of patients taking placebo.

Safety

No safety concerns were identified from physical examination, vital signs, laboratory safety tests or electrocardiograms. AEs leading to dose reduction were principally of a gastrointestinal nature and occurred mainly in the BAY 86-5047 group (11 participants/20 AEs vs one participant/one AE in the placebo group). Study medication was prematurely discontinued due to AEs in 11 participants (17 AEs) who received BAY 86-5047 and in four participants (four AEs) given placebo. Nausea and vomiting were the most common reasons for withdrawal (four and three patients, respectively, who received BAY 86-5047).

There were seven serious AEs, of which two were assessed by the investigators as possibly related to BAY 86-5047 treatment: one event of vertigo with no pathological findings on cerebral computed tomography scans, and one case of squamous epithelial cancer of the cervix *in situ* (cervical intraepithelial neoplasia III) with underlying human papilloma virus infection. The remaining five serious AEs, unrelated to treatment, consisted of three events of severe dysmenorrhea requiring hospitalization, one ankle fracture and one pregnancy that ended in miscarriage in the 6th gestational week. No safety concerns were identified from evaluation of these serious AEs.

Discussion

New therapies for endometriosis are needed, in particular novel drugs that target the pain and inflammatory pathways fundamental to the disease. Many potential drugs have shown promise in preclinical studies, but few have been tested in clinical trials (6). Moreover, those that have reached this stage of development have so far yielded disappointing results. Many clinical studies of endometriosis treatments have been registered in clinical trial registries, but the results are often not published (19, 20). These issues have limited progress in improving the treatment of women suffering from EAPP.

There is a growing body of evidence to support a role of inflammation in the pathophysiology of endometriosis. Indeed, it has been proposed recently that endometriosis-associated pain is largely attributable to activation of the innate immune system in response to tissue degeneration within endometriotic lesions (7). Therefore, drugs that block inflammatory response pathways may enable direct targeting of a key source of endometriosis-associated pain. Blockade of the chemokine receptor, CCR1, in endometriosis is an attractive concept, based on its high expression levels both on peritoneal macrophages and within endometriotic lesions (8, 21). Pre-clinical studies have demonstrated the ability of small-molecule antagonists to block the binding of ligands to CCR1 *in vitro* (22). Such compounds have also been shown to inhibit CCL5/RANTES-mediated monocyte migration (23) and chemokine-induced upregulation of the integrin, CD11b, on macrophages (22) (24). However, despite these promising findings, clinical investigations of CCR1 antagonists have, thus far, yielded disappointing results (11).

The present study assessed the efficacy of the novel CCR1 antagonist, BAY 86-5047, when administered orally three times daily over 12 weeks in women with endometriosis. During the treatment of patients with multiple sclerosis, this dosing regimen was shown to result in plasma drug concentrations of BAY 86-5047 exceeding 100 mg/mL and receptor blockade of at least 90% (13). A previous study suggested that this level of CCR1 receptor blockade may be necessary to observe efficacy in pre-clinical models (24). Despite this, the present study failed to demonstrate the efficacy of BAY 86-5047 to treat EAPP. Although treatment with BAY 86-5047 resulted in a reduction in VAS score and analgesic intake, similar reductions were also seen in women who received placebo, and there was no significant difference between the two treatment groups.

Several factors may underlie the lack of efficacy of BAY 86-5047 in this study. The failure of previous trials has been attributed to the selected drug doses being too low to achieve adequate CCR1 inhibition *in vivo* (24). However, many of these clinical trials have presented evidence of the pharmacodynamic activity of their selected CCR1 antagonists. Administration of the CCR1 antagonist, CP-481 715, to patients with rheumatoid arthritis resulted in decreased monocyte infiltration into synovial tissue (25) and the drug exhibited dose-dependent CCR1 inhibition in a phase 1 evaluation of the compound (22). Despite these promising results, a subsequent phase 2 study showed no benefit of CP-481,715 on disease progression when compared with placebo (11). Similarly, while administration of BAY 86-5047 to patients with multiple sclerosis decreased monocyte activation *in vivo* (13), there was no reduction in the cumulative number of newly active lesions in patients treated with the drug vs placebo after 16 weeks.

These pharmacodynamic findings suggest that the lack of clinical efficacy of CCR1 antagonists cannot be attributed to sub-optimal dosing, and other explanations must be considered. The disease pathophysiology of endometriosis may be too complex to be modulated by CCR1 antagonism alone. While our pre-clinical studies demonstrated the efficacy of BAY 86-5047 in animal disease models (unpublished data), such models are not always representative of disease in humans (26). In the treatment of endometriosis, and in other inflammatory conditions, it may be that additional pathological mechanisms act to counter-balance CCR1 antagonism. This could involve the compensatory up-regulation of other chemokine receptors (11), which maintains inflammatory signalling during disease

pathogenesis. Thus, a multi-targeted approach may be warranted, for example, combining CCR1 antagonists with inhibitors of other chemokine receptors or drugs targeted at other components of the inflammatory immune response.

A further possibility is that aspects of the study population and clinical trial design may not have been appropriate for evaluating the efficacy of BAY 86-5047. Information on the stage of endometriosis was not known with certainty for all women so we cannot exclude the possibility that the two study groups might have been heterogeneous in this regard and that this masked any beneficial effects of the compound. Moreover, the methods used to detect EAPV might not have been sufficiently sensitive to detect differences between the treatments. In our opinion both of these possibilities are unlikely, given that there was no ambiguity in the effects on the efficacy outcomes seen with both placebo and BAY 86-5047 treatments.

It should also be considered that the disease stage at which drug intervention is initiated may have impacted on the response to treatment; clinical interventions may be effective only at particular points in the natural history of a given disease (27). Our findings are based on a short-term study in a small number of patients; however, the trial was adequately powered to detect clinically relevant differences between the treatment groups.

One interesting finding from this study was the observation of a significant placebo effect, which has also been observed in other clinical trials of endometriosis therapies. The study was designed to detect a minimally important clinical difference between the treatment and placebo groups of 25 mm, based on literature showing mean reductions in 12-week VAS scores in the range of 0–20 mm for placebo groups (28-30). This non-inferiority margin is notably higher than the 10 mm difference validated by Gerlinger *et al.* on the basis of findings from two placebo-controlled studies in endometriosis (18). In the present study, the absolute reduction in VAS score observed for women receiving placebo was considerable (19.4 mm or 29%), and numerically higher than the reduction in the BAY 86-5047 group. This highlights the importance of conducting placebo-controlled studies in the evaluation of novel therapies for the treatment of endometriosis.

Conclusion

The results of this study indicate that BAY 86-5047 (600 mg three times daily) is ineffective for the treatment of women with EAPP. A greater incidence of AEs was observed among patients treated with BAY 86-5047 than those who received placebo, but overall the study drug was considered to be well tolerated. Subsequent to this study, the development of BAY 86-5047 was discontinued. The lack of efficacy of CCR1 antagonists in other indications may suggest that CCR1 antagonism is insufficient as a standalone therapy for the treatment of inflammatory diseases. New targets for treatment of the underlying pain and inflammatory pathways fundamental to endometriosis, and increasing knowledge of these pathological mechanisms, remain an important priority for future research.

Acknowledgements

Medical writing support was provided by Lucy Ambrose DPhil and William Gattrell PhD of Oxford PharmaGenesis, Oxford, UK with funding from Bayer Pharma AG.

Funding

This study was funded by Bayer Pharma AG.

References

1. Vercellini P, Vigano P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10(5):261–75.
2. Dunselman GAJ, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al. ESHRE guideline: management of women with endometriosis. Human Reprod. 2014;29(3):400–12.
3. Johnson NP, Hummelshoj L. Consensus on current management of endometriosis. Hum Reprod. 2013 28(6):1552–86.
4. Quaas AM, Weedin EA, Hansen KR. On-label and off-label drug use in the treatment of endometriosis. Fertil Steril. 2015;103(3):612–25.

5. Bernuit D, Ebert AD, Halis G, Strothmann A, Gerlinger C, Geppert K, et al. Female perspectives on endometriosis: findings from the uterine bleeding and pain women's research study. J Endometr Pelvic Pain Disord. 2011;3(2):73–85.

6. Soares SR, Martinez-Varea A, Hidalgo-Mora JJ, Pellicer A. Pharmacologic therapies in endometriosis: a systematic review. Fertil Steril. 2012;98(3):529–55.

7. Laux-Biehlmann A, d'Hooghe T, Zollner TM. Menstruation pulls the trigger for inflammation and pain in endometriosis. Trends Pharmacol Sci. 2015;36(5):270–6.

8. Wieser F, Dogan S, Klingel K, Diedrich K, Taylor RN, Hornung D. Expression and regulation of CCR1 in peritoneal macrophages from women with and without endometriosis. Fertil Steril. 2005;83(6):1878–81.

9. Horuk R. Molecular properties of the chemokine receptor family. Trends Pharmacol Sci. 1994;15(5):159–65.

10. Hornung D, Bentzien F, Wallwiener D, Kiesel L, Taylor RN. Chemokine bioactivity of RANTES in endometriotic and normal endometrial stromal cells and peritoneal fluid. Mol Hum Reprod. 2001;7(2):163–8.

11. Gladue RP, Brown MF, Zwillich SH. CCR1 antagonists: what have we learned from clinical trials. Curr Top Med Chem. 2010;10(13):1268–77.

12. Liang M, Mallari C, Rosser M, Ng HP, May K, Monahan S, et al. Identification and characterization of a potent, selective, and orally active antagonist of the CC chemokine receptor-1. J Biol Chem. 2000;275(25):19000–8.

13. Zipp F, Hartung HP, Hillert J, Schimrigk S, Trebst C, Stangel M, et al. Blockade of chemokine signaling in patients with multiple sclerosis. Neurology. 2006;67(10):1880–3.

14. Anders HJ, Vielhauer V, Frink M, Linde Y, Cohen CD, Blattner SM, et al. A chemokine receptor CCR-1 antagonist reduces renal fibrosis after unilateral ureter ligation. J Clin Invest. 2002;109(2):251–9.

15. Biberoglu KO, Behrman SJ. Dosage aspects of danazol therapy in endometriosis: short-term and long-term effectiveness. Am J Obstet Gynecol. 1981;139(6):645–54.

16. Tamhane AC, Logan BR. Accurate critical constants for the one-sided approximate likelihood ratio test of a normal mean vector when the covariance matrix is estimated. Biometrics. 2002;58(3):650–6.

17. Röhmel J, Gerlinger C, Benda N, Lauter J. On testing simultaneously non-inferiority in two multiple primary endpoints and superiority in at least one of them. Biom J. 2006;48(6):916–33.

18. Gerlinger C, Schumacher U, Faustmann T, Colligs A, Schmitz H, Seitz C. Defining a minimal clinically important difference for endometriosis-associated pelvic pain measured on a visual analog scale: analyses of two placebo-controlled, randomized trials. Health Qual Life Outcomes. 2010;8:138.
19. Guo S. An overview of the current status of clinical trials on endometriosis: issues and concerns. Fertil Steril. 2014;101(1):183–90.
20. Guo S, Olive DL. Two unsuccessful clinical trials on endometriosis and a few lessons learned. Gynecol Obstet Invest. 2007;64(1):24–35.
21. Yang Y, Zhang X, Zhou C, Huang X, Lin J, Xu H. Elevated immunoreactivity of RANTES and CCR1 correlate with the severity of stages and dysmenorrhea in women with deep infiltrating endometriosis. Acta Histochem. 2013;115(5):434–9.
22. Clucas AT, Shah A, Zhang YD, Chow VF, Gladue RP. Phase I evaluation of the safety, pharmacokinetics and pharmacodynamics of CP-481,715. Clinical Pharmacokinet. 2007;46(9):757–66.
23. Lebre MC, Vergunst CE, Choi IY, Aarrass S, Oliveira AS, Wyant T, et al. Why CCR2 and CCR5 blockade failed and why CCR1 blockade might still be effective in the treatment of rheumatoid arthritis. PLoS One. 2011;6(7):e21772.
24. Dairaghi DJ, Zhang P, Wang Y, Seitz LC, Johnson DA, Miao S, et al. Pharmacokinetic and pharmacodynamic evaluation of the novel CCR1 antagonist CCX354 in healthy human subjects: implications for selection of clinical dose. Clin Pharmacol Ther. 2011;89(5):726–34.
25. Haringman JJ, Kraan MC, Smeets TJ, Zwinderman KH, Tak PP. Chemokine blockade and chronic inflammatory disease: proof of concept in patients with rheumatoid arthritis. Ann Rheum Dis. 2003;62(8):715–21.
26. Tirado-Gonzalez I, Barrientos G, Tariverdian N, Arck PC, Garcia MG, Klapp BF, et al. Endometriosis research: animal models for the study of a complex disease. J Reprod Immunol. 2010;86(2):141–7.
27. Schall TJ, Proudfoot AE. Overcoming hurdles in developing successful drugs targeting chemokine receptors. Nat Rev Immunol. 2011;11(5):355–63.
28. Koninckx PR, Craessaerts M, Timmerman D, Cornillie F, Kennedy S. Anti-TNF-treatment for deep endometriosis-associated pain: a randomized placebo-controlled trial. Hum Reprod. 2008;23(9):2017–23.
29. Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2008;90(5):1583–8.

30. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2010;151(2):193–8.

Supporting Information legend

Table S1. Details of ethical approval in study centers.

Table legend

Table 1 Participant demographics and baseline characteristics. Data are presented as mean (SD) or number (%).

[a]Data presented only for patients in whom endometriosis was histologically confirmed.

rASRM, revised American Society for Reproductive Medicine; SD, standard deviation.

Figure legends

Figure 1 Study design flowchart. AE, adverse event.

Figure 2 Participants' pain, scored using the VAS, at screening, during treatment (baseline to week 12) and at follow-up (week 16). Data are presented as mean ± SD. SD, standard deviation; VAS, visual analogue scale.

Figure 3 Intake of analgesics at baseline, at the end of treatment (week 12) and at follow-up (week 16).

Figure 4 Scatterplot for changes in VAS score and rescue medication intake relative to baseline for participants taking placebo or BAY 86-5047. Data for participants in the placebo group are indicated by red circles and for participants in the BAY 86-5047 group by blue squares. Three outlying data points were excluded. VAS, visual analogue scale.

Figure 5 Biberoglu & Behrman scores of symptom severity at baseline and at the end of treatment (week 12) for (a) pelvic pain, (b) dysmenorrhea and (c) dyspareunia.

Table 1 Participant demographics and baseline characteristics.

	Placebo	**BAY 86-5047**	**Total**
Age, years	33.3 (6.3)	31.5 (6.0)	32.4 (6.2)
Ethnicity			
Caucasian	53 (98.1%)	55 (98.2%)	108 (98.2%)
Black	1 (1.9%)	0 (0.0%)	1 (0.9%)
Hispanic	0 (0.0%)	1 (1.8%)	1 (0.9%)
Body mass index, kg/m^2	23.6 (4.0)	22.8 (3.8)	23.2 (3.9)
rASRM stage[a]			
I	0 (0.0%)	1 (1.8%)	1 (0.9%)
II	3 (5.6%)	0 (0.0%)	3 (2.7%)
III	5 (9.3%)	6 (10.7%)	11 (10.0%)
IV	7 (13.0%)	6 (10.7%)	13 (11.8%)
Data missing	22 (40.7%)	20 (35.7%)	42 (38.2%)
Sub-fertility			
No	35 (64.8%)	48 (85.7%)	83 (75.5%)
Yes	19 (35.2%)	8 (14.3%)	27 (24.5%)

Data are presented as mean (SD) or number (%).

rASRM, revised American Society for Reproductive Medicine; SD, standard deviation.

[a]Data presented only for patients in whom endometriosis was histologically confirmed.