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ORIGINAL ARTICLE *Gynaecology*

Efficacy and safety of ASP1707 for endometriosis-associated pelvic pain: the phase II randomized controlled TERRA study

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STUDY QUESTION: Does the GnRH antagonist, ASP1707, reduce endometriosis-associated pelvic pain?

SUMMARY ANSWER: ASP1707 significantly reduced endometriosis-associated pelvic pain in a dose-related manner

WHAT IS KNOWN ALREADY: GnRH agonists are an effective therapeutic option for endometriosis that is refractory to non-steroidal anti-inflammatory drugs, oral contraceptives, and progestins. However, GnRH agonists cause complete suppression of estradiol (E2), resulting in hypoestrogenic side-effects such as bone loss that may increase the future risk of osteoporotic fractures.

STUDY DESIGN, SIZE, DURATION: This was a Phase II, multicenter, double-blind, randomized, parallel-group, placebo-controlled study conducted in 540 women from 04 December 2012 to 30 July 2015 in Europe and Japan. A sample size of 504 (84 subjects per group) was calculated to provide ≥80% power to detect a dose-related treatment effect among placebo and ASP1707 doses in change from baseline in pelvic pain, assuming different dose–response curves after 12 weeks of treatment.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Of 912 women with endometriosis-associated pelvic pain screened, 540 were enrolled, and 532 received ≥1 dose of study drug (placebo, $n = 88$; ASP1707 3 mg, $n = 86$; ASP1707 5 mg, $n = 91$; ASP1707 10 mg, $n = 90$; ASP1707 15 mg, $n = 88$; leuprorelin, $n = 89$) for 24 weeks.

MAIN RESULTS AND THE ROLE OF CHANCE: After 12 weeks of treatment with ASP1707, the mean (95% CI) changes in numeric rating score (NRS) for overall pelvic pain (OPP) were −1.56 (−1.91, −1.21), −1.63 (−1.99, −1.27), −1.93 (−2.27, −1.60), −2.29 (−2.64, −1.94), and −2.13 (−2.47, −1.79) for placebo, ASP1707 3 mg, ASP1707 5 mg, ASP1707 10 mg, and ASP1707 15 mg, respectively. Mean (95% CI) changes in NRS for dysmenorrhea were −1.50 (−2.00, −1.00), −2.72 (−3.22, −2.21), −2.85 (−3.33, −2.38), −3.97 (−4.46, −3.48), and −4.18 (−4.66, −3.70), respectively. Mean (95% CI) changes in NRS for non-menstrual pelvic pain (NMPP) were −1.53 (−1.88, −1.19), −1.51 (−1.87, −1.16), −1.80 (−2.14, −1.47), −2.03 (−2.37, −1.68), and −1.86 (−2.20, −1.52), respectively. Statistically significant dose-related treatment effects in reduction in NRS for OPP ($P = 0.001$), dysmenorrhea ($P < 0.001$), and NMPP ($P = 0.029$) were observed after 12 weeks among ASP1707 doses and were maintained through 24 weeks. Serum estradiol and bone mineral density decreased dose dependently with ASP1707 through 24 weeks, however, to a lesser extent than with leuprorelin.

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LIMITATIONS, REASON FOR CAUTION: This study was not powered for pairwise comparison of each ASP1707 group versus placebo.

WIDER IMPLICATIONS OF THE FINDINGS: All doses of ASP1707 reduced serum E2 levels to within the target range and to a lesser extent than leuprorelin. ASP1707 is a potential alternative treatment to leuprorelin for endometriosis-associated pelvic pain with lower impact on bone health.

STUDY FUNDING/COMPETING INTEREST(S): This study was funded by Astellas Pharma Inc. T.D'.H is Vice President and Head of Global Medical Affairs Fertility at Merck, Darmstadt, Germany since October 1, 2015. At the time that the TERRA study was conducted, he served as Principal Investigator in his role as Coordinator of the Leuven University Fertility Center. Since October 2015, T.D'.H has left Leuven University Hospital Gasthuisberg, but continues to serve as Professor in Reproductive Medicine and Biology at KU Leuven (University of Leuven) Belgium and at the Dept of Obstetrics, Gynecology and Reproduction at Yale University, New Haven, USA. T. Fukaya and Y. Osuga report personal consulting fees from Astellas Pharma Inc. during the conduct of the study and outside the submitted work. G.M. Holtkamp, and L. Skillern are employed by Astellas Pharma Europe B.V.; K. Miyazaki is employed by Astellas Pharma Inc.; B. López, was a biostatistician for Astellas Pharma Europe B.V. during conduct of the study; R. Besuyen was a contract Associate Director of Medical Science for Astellas during conduct of the study.

TRIAL REGISTRATION NUMBER: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01767090. EudraCT number 2012-002791-14.

TRIAL REGISTRATION DATE: 18 December 2012.

DATE OF FIRST SUBJECT'S ENROLLMENT: One subject signed informed consent on 04 December 2012; the first subject was randomized on 16 April 2013.

Key words: GnRH antagonists / endometriosis / pelvic pain / TERRA / dysmenorrhea

Introduction

Endometriosis is a gynecological disorder characterized by the presence of endometrial glands and tissue outside of the uterus, resulting in chronic inflammation, dysmenorrhea, dyspareunia, and chronic pelvic pain (Kennedy *et al.*, 2005). The worldwide prevalence of endometriosis among females ranges from 6 to 10% (Bulletti *et al.*, 2010). Gonadotropin-releasing hormone (GnRH) agonists are an effective therapeutic option for endometriosis that is refractory to non-steroidal anti-inflammatory drugs, oral contraceptives, and progestins (Carr *et al.*, 2014). However, GnRH agonists cause complete suppression of estradiol (E2), resulting in hypoestrogenic side-effects such as bone loss that may increase the future risk of osteoporotic fractures (Whitehouse *et al.*, 1990; Dawood *et al.*, 1995; Olive, 2008; Bowles, 2010). The European Society of Human Reproduction and Embryology guidelines recommend the use of estrogens and/or progestogens or tibolone as add-back therapy alongside GnRH agonists (Dunselman *et al.*, 2014). Despite this, bone loss remains a limiting factor for therapy duration, and continuous treatment is not recommended for longer than 6 months (Lupron Depot® Package Insert). Partial suppression of E2 with GnRH antagonists is thought to less impact bone health, while improving endometriosis-associated symptoms (Kupker *et al.*, 2002).

ASP1707 is an orally administered GnRH antagonist currently investigated for treatment of endometriosis-related pain. ASP1707 suppresses the pituitary–gonadal axis, suggesting a therapeutic potential to ameliorate pain associated with endometriosis. Phase I studies in healthy young females, in combination with pharmacokinetic/pharmacodynamic (PK/PD) modeling, suggest that by suppressing E2 levels, ASP1707 may reduce endometriosis symptoms with minimal impact on bone health. The phase II TERRA study evaluated the efficacy, safety and dose–response relationship of ASP1707 in subjects with endometriosis-associated pelvic pain.

Materials and Methods

Study design

TERRA was a phase II, multinational, multicenter, double-blind, randomized, parallel-group, placebo-controlled study conducted in Europe and Japan. An observational period lasting at least one menstrual cycle was followed by a 24-week treatment period consisting of two parts (Fig. 1). After subjects were screened for inclusion/exclusion criteria by the site investigator, randomization was conducted using an Interactive Response System. Eligible subjects were randomized 1:1:1:1:1:1 to placebo, one of four doses of ASP1707 (3, 5, 10 or 15 mg), or leuprorelin acetate (subcutaneous injection; 3.75 mg/month) (PROSTAP SR® Package Leaflet). Treatment allocation was stratified by region (Europe versus Japan) and country. All ASP1707 and placebo medication kits contained preprinted medication numbers. The study drug, except for open-label active-control, was packed using a double-blind method. All patients randomized to ASP1707 or placebo took 3 tablets once daily in the morning (ASP1707 15 mg group: 3 × 5 mg tablets; ASP1707 10 mg group: 2 × 5 mg tablets and 1 placebo tablet; ASP1707 5 mg group: 1 × 5 mg tablet and 2 placebo tablets; ASP1707 3 mg group: 3 × 1 mg tablets; placebo group: 3 placebo tablets). All tablets were identical in size, appearance and dimensions and all subjects and study personnel were blinded to treatment. During Part 1, subjects received daily oral placebo, daily oral ASP1707, or leuprorelin acetate for 12 weeks. During Part 2, subjects received daily oral ASP1707 (3, 5, 10 or 15 mg) or leuprorelin acetate (subcutaneous injection; 3.75 mg/month) for 12 weeks. Subjects randomized to placebo for Part 1 were also randomized to one of four ASP1707 doses for Part 2. The objective of Part 1 was to evaluate the efficacy of ASP1707 versus placebo, which was limited to 12 weeks due to ethical considerations associated with treating patients who are suffering from pain with placebo for a long duration. Part 2 was designed to confirm whether the efficacy observed in Part 1 was sustained over time and to provide longer duration of treatment to more accurately assess the impact of ASP1707 on bone mineral density (BMD). The dose range of 3–15 mg ASP1707 was selected to target a range of E2 levels from 20 to 50 pg/mL.

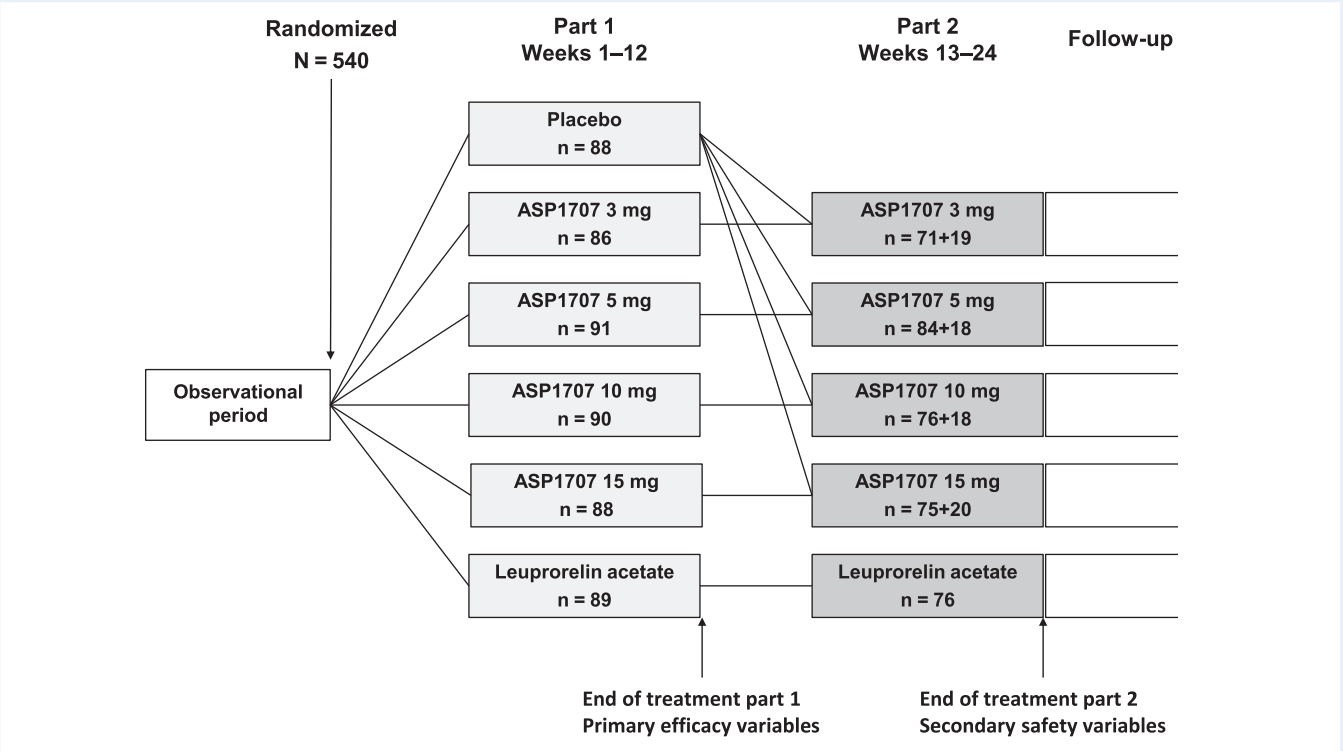

Figure 1 Study design. For Part 2, the number of subjects is presented as: *n* = subjects randomized to ASP1707 in Part 1 + subjects randomized to Placebo in Part 1 and ASP1707 in Part 2.

This range was assumed to impact bone health less than complete suppression of E2 levels typically observed with GnRH agonists while still improving endometriosis-associated symptoms (Kupker *et al.*, 2002). All treatment groups were double blind except for leuprorelin acetate, which was included with the purpose of providing a reference for potential effects of ASP1707 on bone health.

Study subjects

Eligible subjects were women aged 18–45 years with moderate-to-severe endometriosis-associated dysmenorrhea and non-menstrual pelvic pain (NMPP), a surgically confirmed diagnosis of endometriosis, and a confirmed regular menstrual cycle of 24–35 days. Exclusion criteria included treatments that alter gynecological endocrinology, surgery for endometriosis within 4 weeks of study initiation, and the presence of pelvic or gynecological abnormalities (Full eligibility criteria are included in the Supplementary materials).

This study was registered on ClinicalTrials.gov (NCT01767090) on 18 December 2012 and further information is also available on EU Clinical Trials Registrar (2012-002791-14). The Independent Ethics Committee or Institutional Review Board reviewed the ethical, scientific, and medical appropriateness of the study before initiation. The study was conducted in accordance with the protocol, Good Clinical Practice, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles in the Declaration of Helsinki. All subjects provided informed consent.

Study assessments

Subjects completed a daily electronic diary (e-diary) during the observational period and the 24 weeks of treatment. E-diary data included the endometriosis pain daily diary (EPDD) (van Nooten *et al.*, 2018), which included a daily numeric rating score (NRS; 0, no pain; 10, worst imaginable pain) score for pelvic pain, days and amount of bleeding, occurrence of sexual intercourse and dyspareunia, and the use of protocol-defined rescue medication (i.e. ibuprofen). Rescue with Ibuprofen (200-mg tablets) was permitted at the patient's discretion for endometriosis-related pain only, per instructions in the patient leaflet. Pelvic pain was scored of 1–3 ('mild pain'), 4–6 ('moderate pain') and 7–10 ('severe pain') (Bourdel *et al.*, 2015).

Study objectives

The primary objectives were to assess the efficacy and dose–response relationship of ASP1707 in reducing endometriosis-associated pelvic pain at the end of treatment (EoT) Part 1. Secondary objectives were to assess the safety, tolerability, PK, and the dose–response relationship of ASP1707 in reducing serum E2 levels.

Primary efficacy variables

The primary efficacy variables were change from baseline to EoT Part 1 in the mean NRS (0, no pain; 10, worst imaginable pain) for overall pelvic pain (OPP), dysmenorrhea, and NMPP. OPP was calculated as the mean NRS from the last 28-day period (including menstrual and non-menstrual bleeding days). Dysmenorrhea was calculated as the mean of OPP scores from menstrual bleeding days within the 28-day period. NMPP was calculated as the mean of OPP scores from all days except menstrual bleeding days within the 28-day period.

Secondary efficacy variables

Secondary efficacy variables include change from baseline to EoT Part 2 in mean NRS for OPP, dysmenorrhea, and NMPP in subjects who were

treated with the same dose for the full 24-week study. Secondary efficacy variables also included change from baseline to EoT (for Parts 1 and 2) in: mean NRS relating to interference of pain with daily activities; mean NRS for dyspareunia; mean scores of the modified Biberoglu and Behrman symptom (i.e. dysmenorrhea, NMPP, and dyspareunia) and sign (i.e. pelvic tenderness and induration) domains (Biberoglu and Behrman, 1981; Vincent et al., 2010); use of rescue medication; mean pain interference score of the Brief Pain Inventory; Endometriosis Health Profile-5 score; Female Sexual Function Index (FSFI) score; Beck Depression Inventory-II (BDI-II) score; the European quality of life 5-dimension 5-level scale (EQ-5D-5L) score, and Patient Global Impression of Change. The FSFI, BDI-II, and EQ-5D-5L were performed only at European sites. Patient Global Impression of Change was measured at EoT Parts 1 and 2.

Pharmacokinetics, pharmacodynamics, and safety

Total plasma ASP1707 concentration was analyzed by Astellas Pharma Europe B.V. at Week 2 and between Week 4 and EoT Part 2 using validated liquid chromatography-tandem mass spectrometry methods. The lower limit of quantification for ASP1707 in plasma was 50 pg/mL. Compliance was measured for subjects in ASP1707 dose groups and the placebo group as the amount of study drug dispensed and returned per subject. Pharmacodynamic assessments included E2 (Weeks 2, 4, 8, 12, 14, 16, 20, 24, and 26), bone alkaline phosphatase (bALP) and collagen type 1 cross-linked N-telopeptide (NTX; at baseline and at Weeks 12 and 24), follicle-stimulating hormone and luteinizing hormone, and progesterone (at baseline and at Weeks 4, 8, 12, 16, 20, and 24). The lower limit of quantification for E2, luteinizing hormone, follicle-stimulating hormone, progesterone, and bALP in plasma were 12.0 pg/mL, 1 IU/L, 1.7 IU/L, 0.25 ng/mL, and 4.9 µg/mL, respectively. Safety was assessed by evaluation of adverse events (AEs), safety laboratory tests, vital signs, weight, 12-lead electrocardiograms, physical and gynecological examination, bleeding patterns, hot flashes, and return of menstruation. Bone health was assessed by dual-energy X-ray absorptiometry (DXA) scan (GE-Lunar: Prodigy, iDXA, and DPX models; Hologic: QDR4500, Delphi, Discovery, and Explorer models) at baseline and at EoT Parts 1 and 2. BMD and trabecular bone score (TBS; a measure for bone microarchitecture, post-hoc) were derived from the DXA scan.

Statistical analysis

A sample size of 504 subjects (84 subjects per treatment group) was calculated to provide at least 80% power to detect a dose-related treatment effect among placebo and ASP1707 doses in change from baseline of mean OPP score, assuming different dose–response curves after 12 weeks of treatment. Specifically, we evaluated whether the pattern (trend) for change in overall pain score for placebo was comparable with those for ASP1707. In the dose–response curves considered, a maximum effect was assumed to be ~0.50, and the dose of ASP1707 showing half of this maximum effect was estimated to be 2–5 mg. The study was 80% powered to detect a difference in BMD of 2% between ASP1707 dose groups and leuprorelin. Power was calculated with a two-sided significance level of 0.05 unless otherwise noted.

The full analysis set was used for all efficacy analyses, consisting of all subjects who took at least one dose of placebo, ASP1707 or leuprorelin, had a primary NRS for OPP at baseline, and had at least one evaluable post-baseline NRS for OPP (i.e. at least 14 days of pain score). An NRS of 0 was imputed for dysmenorrhea in subjects who became amenorrheic and, therefore, reported no dysmenorrhea. The safety analysis set consisted of all randomized subjects who took at least one dose of study medication. Statistical analyses for safety and efficacy were performed on the full analysis and safety sets accordingly. The primary test for a treatment effect was a linear trend for placebo and all ASP1707 doses. The test for linear trend was applied by using the linear contrast based on the ordinal dose. Results were described by two-sided *P*-value, least square-means (LS-means) estimate of the contrast with 95% CI. Comparisons of individual doses of ASP1707 with placebo were secondary, and not powered, using Dunnett's adjustment for multiple comparisons.

Efficacy

For Part 1, the change from baseline to EoT in the mean NRS for OPP, dysmenorrhea, and NMPP was analyzed using an analysis of covariance model. Results were described using a two-sided *P*-value; LS-means of the linear contrast with 95% CI. Pairwise comparison of each ASP1707 group versus placebo was performed using Dunnett's test. Use of rescue medication was analyzed using a Cochran–Mantel–Haenszel test including treatment group and region.

Safety

The percentage change of BMD from baseline to EoT Part 2 by location (hip–total hip, spine-adjusted total spine, and hip–femoral neck) for all ASP1707 doses and leuprorelin was analyzed by location using an analysis of covariance model. The two-sided 90% CI of the mean was calculated. Pairwise comparison of each ASP1707 group versus the leuprorelin group was performed using Dunnett's test. Analyses were performed on subjects who remained within the same treatment for 24 weeks. Change in TBS from baseline was defined for each subject and converted to a percentage. Bivariate inter-group comparisons were performed between groups using Student's *t*-test analysis.

Results

Of 912 subjects screened for inclusion between 04 December 2012 and 31 July 2014, 372 were screen failures (Fig. 2). The most common inclusion criteria that were violated were confirmed menstrual cycle of 24–35 days ($n = 78$) and moderate-to-severe endometriosis-associated dysmenorrhea and NMPP ($n = 77$). The most common exclusion criteria that were violated were clinically relevant gynecological abnormalities at screening ($n = 44$), concurrent or previous osteoporosis ($n = 36$), QT interval corrected for heart rate by < 450 ms ($n = 38$). Of the remaining 540 subjects who were enrolled, eight did not receive study drug. In total, 532 subjects received ≥1 dose of study medication (safety analysis set) and 494 reported evaluable NRS data post-baseline (full analysis set). Protocol violations included concurrent or previous conditions that could affect BMD measurement of lumbar spine or femur BMD *T*-scores ($n = 29$) and violation of inclusion/exclusion criteria ($n = 13$). Adverse events leading to withdrawal included insomnia ($n = 2$), dural fistula ($n = 1$), headache ($n = 4$), tinnitus ($n = 1$), hot flush ($n = 2$), dyspnea ($n = 1$) gastroesophageal reflux disease ($n = 1$), decreased appetite ($n = 1$), eczema ($n = 1$), dizziness ($n = 1$), fatigue ($n = 1$), paresthesia ($n = 1$), visual impairment ($n = 1$) and intervertebral disc disorder ($n = 1$) (Fig. 2). Demographics and baseline characteristics were similar among treatment groups (Table I). In the overall population, treatment compliance among subjects treated with ASP1707 was 99.6% during Part 1 and 99.5% during Parts 1 and 2. The proportion of patients with no bleeding days at EoT Part 1 increased in a dose-dependent manner (placebo, 5%; 3 mg, 12%; 5 mg, 21%; 10 mg, 36%; 15 mg, 57%; leuprorelin, 80%).

Primary efficacy results

After 12 weeks of treatment with ASP1707, the mean (95% CI) changes in NRS for OPP were −1.56 (−1.91, −1.21), −1.63 (−1.99, −1.27), −1.93

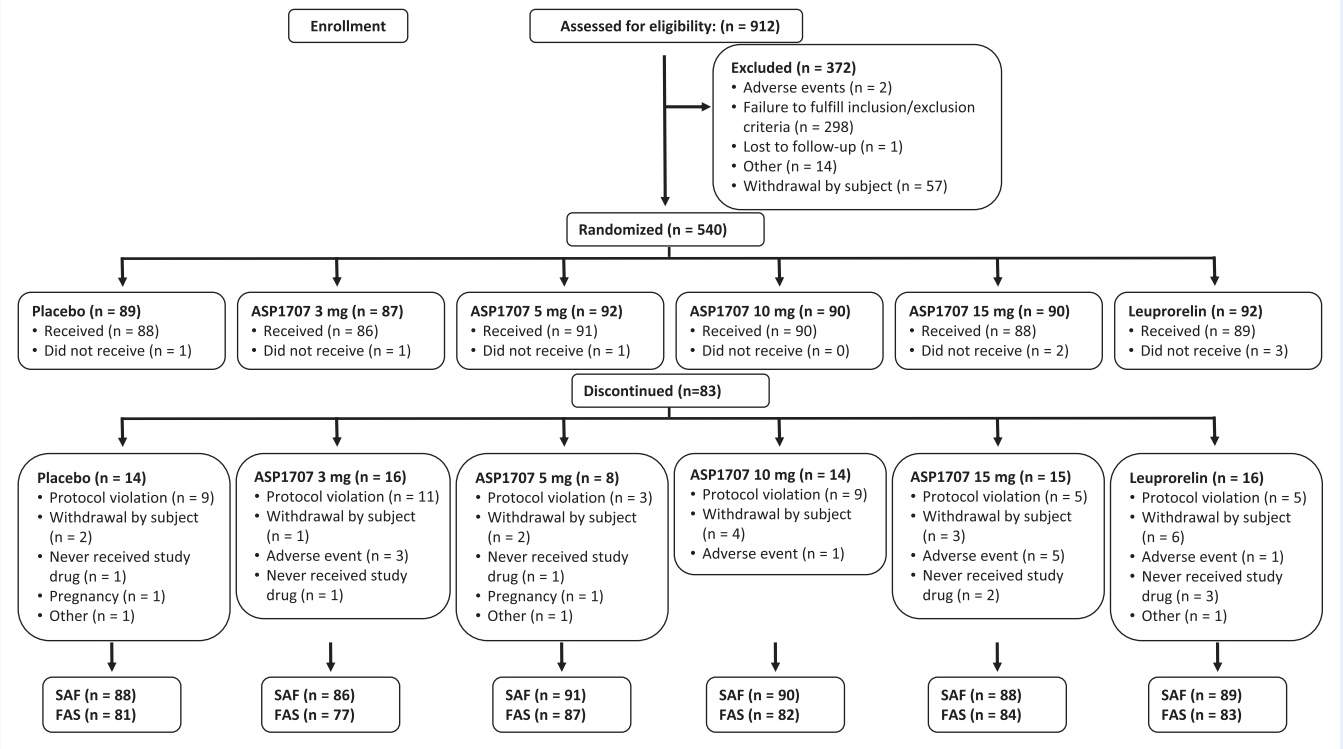

Figure 2 Subject disposition (CONSORT flow diagram). FAS, full analysis set; SAF, safety analysis set.

(−2.27, −1.60), −2.29 (−2.64, −1.94), and −2.13 (−2.47, −1.79) for placebo, ASP1707 3 mg, ASP1707 5 mg, ASP1707 10 mg, and ASP1707 15 mg, respectively. Mean (95% CI) changes in NRS for dysmenorrhea were −1.50 (−2.00, −1.00), −2.72 (−3.22, −2.21), −2.85 (−3.33, −2.38), −3.97 (−4.46, −3.48), and −4.18 (−4.66, −3.70), respectively. Mean (95% CI) changes in NRS for NMPP were −1.53 (−1.88, −1.19), −1.51 (−1.87, −1.16), −1.80 (−2.14, −1.47), −2.03 (−2.37, −1.68), and −1.86 (−2.20, −1.52), respectively. A statistically significant dose-related treatment effect was observed among ASP1707 dose groups for OPP ($P = 0.001$), dysmenorrhea ($P < 0.001$), and NMPP ($P = 0.029$) from baseline to EoT Part 1 (Fig. 3). Compared with placebo, statistically significant differences in the absolute change from baseline in mean NRS were observed for OPP (10 mg, $P = 0.011$) and dysmenorrhea (3 mg, $P = 0.003$; 5 mg, $P < 0.001$; 10 mg, $P < 0.001$; 15 mg, $P < 0.001$) (Fig. 3). In terms of the 10-mg dose of ASP1707, the number of patients needed to treat in order to observe an improvement of ≥1 point in the NRS from baseline to EoT (Part 1) over placebo are 4, 4, and 10 for OPP, dysmenorrhea, and NMPP, respectively. This compares to 5, 3, and 17 for leuprorelin for OPP, dysmenorrhea, and NMPP, respectively.

Secondary efficacy results

Mean numeric rating score for pain at end of treatment Part 2

For the subjects with the same treatment in both parts of the study, from baseline to EoT Part 2 (Week 24), there was a minor additional reduction in mean NRS for OPP and dysmenorrhea compared with the change observed in Part 1; the change in mean NRS for NMPP was comparable to the change from baseline to EoT Part 1 (Week 12) (Fig. 3).

Mean numeric rating score for pain interference with daily activities and dyspareunia

From baseline to EoT Part 1, a statistically significant dose-related treatment effect was found among ASP1707 dose groups ($P = 0.004$) in NRS for pain interference with daily activities (Supplementary Fig. S1). Compared with placebo, the change from baseline to EoT Part 1 in NRS for pain interference with daily activities was statistically significant for ASP1707 10 mg ($P = 0.002$), 15 mg ($P = 0.029$), and leuprorelin ($P = 0.002$), but not for ASP1707 3 mg ($P = 0.264$) or 5 mg ($P = 0.146$) (Supplementary Table SI). Additional reductions were observed at EoT Part 2 with ASP1707 10 and 15 mg and with leuprorelin. The change from baseline to EoT (Parts 1 and 2) of mean NRS for dyspareunia was neither dose dependent nor statistically significant (compared with placebo) at any dose of ASP1707.

Modified Biberoglu and Behrman scale signs and symptoms

From baseline to EoT Part 1 (Week 12), a statistically significant dose-related treatment effect was observed among ASP1707 dose groups for pelvic tenderness ($P < 0.001$), dysmenorrhea ($P < 0.001$), NMPP ($P < 0.001$), induration ($P < 0.001$) and dyspareunia ($P = 0.002$) (Table II). A statistically significant treatment effect of ASP1707 was also observed from baseline to EoT Part 2 for pelvic tenderness ($P = 0.003$), dysmenorrhea ($P < 0.001$) and NMPP ($P = 0.024$).

Percentage of days using rescue medication

The proportion of subjects who used rescue medication at EoT Part 1 was higher in the placebo group (79%) than in any of the ASP1707 groups, and decreased with increasing ASP1707 dose from 73% in the

Table I Demographics and baseline characteristics—overall population (safety analysis set).

Parameter	Placebo ($n = 88$)	ASP1707 3 mg ($n = 86$)	ASP1707 5 mg ($n = 91$)	ASP1707 10 mg ($n = 90$)	ASP1707 15 mg ($n = 88$)	ASP1707 total ($n = 355$)	Leuprorelin ($n = 89$)	Total ($N = 532$)
Race, *n* (%)								
White	64 (73)	61 (71)	65 (71)	65 (72)	63 (72)	254 (71.5)	65 (73)	383 (72.0)
Asian	24 (27)	25 (29)	25 (28)	25 (28)	25 (28)	100 (28.2)	24 (27)	148 (27.8)
Other[a]	0	0	1 (1)	0	0	0	0	1 (0.2)
Mean (min–max)								
Age (years)	33.5 (18–45)	34.7 (22–45)	33.3 (19–45)	34.2 (20–45)	33.7 (18–45)	34.0 (18–45)	33.1 (19–45)	33.7 (18–45)
Weight (kg)	62.5 (44–113)	62.7 (42–97)	61.8 (40–90)	63.5 (36–110)	61.0 (44–90)	62.3 (36–110)	62.2 (37–95)	62.3 (36–113)
Height (cm)	164.2 (149–180)	164.7 (151–186)	164.6 (150–180)	164.2 (153–180)	164.5 (149–183)	164.5 (149–186)	165.6 (147–180)	164.6 (147–186)
BMI (kg/m^2)	23.2 (18–37)	23.1 (17–38)	22.8 (16–32)	23.5 (15–42)	22.6 (17–33)	23.0 (15–42)	22.6 (17–35)	23.0 (15–42)
Mean (min–max)								
Menstruation								
Cycle length (days)	28.4 (24–34)	27.8 (24–34)	28.2 (24–33)	28.5 (24–32)	28.4 (25–33)	28.2 (24–34)	28.3 (25–32)	28.3 (24–34)
Age (years) at menarche	11.8 (9–17)	11.9 (8–16)	11.9 (8–18)	11.7 (7–16)	11.7 (9–15)	11.8 (7–18)	11.9 (8–16)	11.8 (7–18)
Mean (min–max)								
Endometriosis onset								
Age (years) at onset	30.2 (14–43)	30.5 (17–44)	30.4 (17–44)	30.7 (19–44)	31.0 (14–42)	30.6 (14–44)	29.9 (15–43)	30.4 (14–44)
Months since onset	39.6 (1–278)	50.9 (1–213)	34.9 (1–189)	41.7 (1–266)	32.0 (1–140)	39.8 (1–266)	38.5 (1–182)	39.5 (1–278)
Previous endometriosis history, *n* (%)								
Prior medication treatment	46 (52)	49 (57)	52 (57)	44 (49)	43 (49)	188 (53.0)	51 (57)	285 (53.6)
Prior surgical treatment	85 (97)	81 (94)	84 (92)	87 (97)	88 (100)	340 (95.8)	86 (97)	511 (96.1)
Ever pregnant (yes)	45 (51)	44 (51)	38 (42)	43 (48)	42 (48)	167 (47.0)	36 (40)	248 (46.6)
Previous adenomyosis history, *n* (%)	13 (15)	15 (17)	13 (14)	20 (22)	13 (15)	61 (17)	11 (12)	85 (16)

[a]Black or African American and other race categories combined.

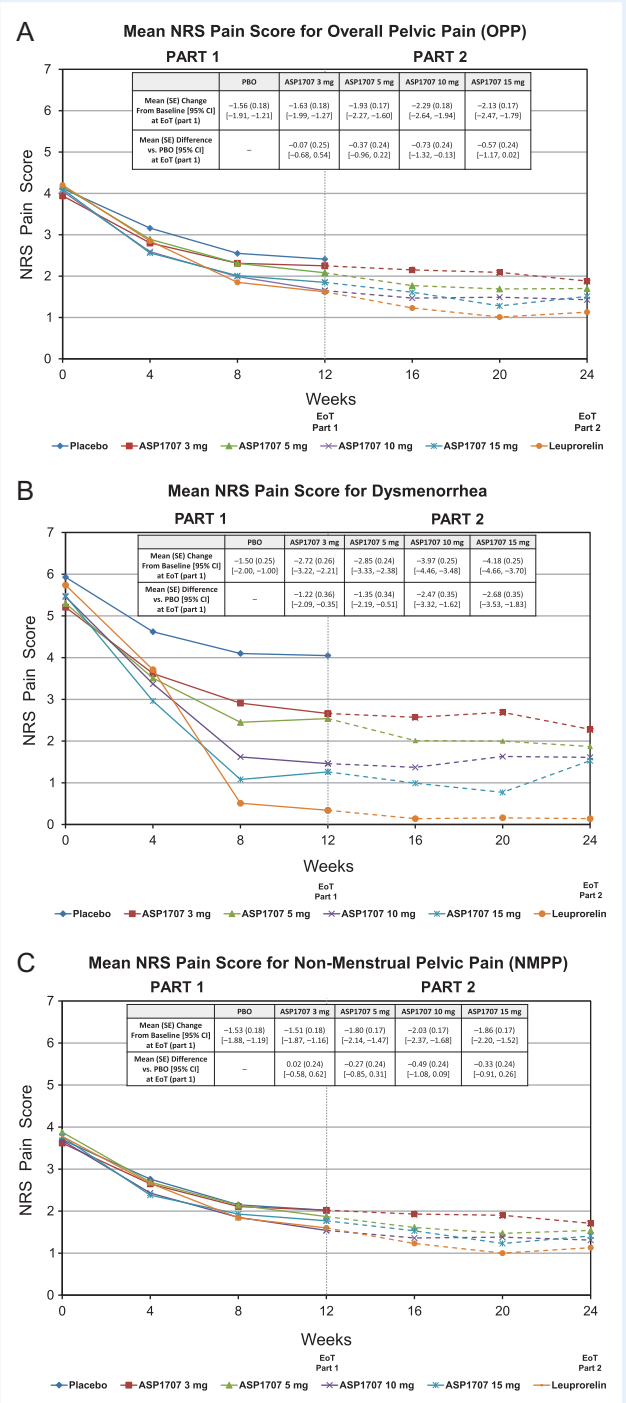

Figure 3 Change from baseline to end of treatment Part 1 (Week 12) and end of treatment Part 2 (Week 24) in mean numeric rating score for overall pelvic pain (A), dysmenorrhea (B) and non-menstrual pelvic pain (C) (full analysis set). EoT, end of treatment; NMPP, non-menstrual pelvic pain; NRS, numeric rating score; OPP, overall pelvic pain; PBO, placebo.

3-mg group to 37% in the 15-mg group; a statistically significant dose-related treatment effect was observed ($P < 0.001$). The proportion of subjects using rescue medication in each ASP1707 dose group was smaller at EoT Part 2 than at EoT Part 1.

Serum estradiol levels

A dose–response relationship in serum E2 levels was observed with ASP1707 (Fig. 4). Decreases in mean serum E2 levels from baseline to EoT Part 1 were greater in all ASP1707 dose groups than in the placebo group. A large variability in serum E2 concentrations was observed; however, median serum concentrations of E2 were within the target range (20–50 pg/mL) for the ASP1707 10- and 15-mg groups for all time points during treatment. In the leuprorelin group, decreases from baseline in mean serum E2 were greater than in all ASP1707 dose groups; median serum concentrations were below the lower limit of the target range, and median values were below the limit of quantification after Week 2.

Plasma ASP1707 concentrations

In the overall population, the mean predose plasma concentration of ASP1707 at Visit 3 (Week 2) increased with dose of ASP1707 (Supplementary Table SII).

Results from additional analyses

Results of patient reported outcomes, including the Endometriosis Health Profile-5, FSFI (Supplementary Table SIII), BDI-II (Supplementary Table SIV), EQ-5D-5L (Supplementary Table SV), Patient Global Impression of Change, as well as results from additional PD (Supplementary Tables SVI and SVII) and PK analyses can be found in the Supplementary materials.

Safety

Treatment-emergent adverse events

The frequency of treatment-emergent AEs (TEAEs) varied slightly (50–65%) across doses of ASP1707, placebo, and leuprorelin. During Part 1, at least one TEAE was experienced by 203 out of 355 subjects (57%) receiving ASP1707 (any dose), 52 out of 89 subjects (58%) receiving leuprorelin, and 44 out of 88 subjects (50%) receiving placebo. The most common TEAEs (≥5% of subjects) reported for all treatment groups over the entire study were hot flush, headache, and nasopharyngitis (Table III). The incidence of hot flush and headache was 15 and 14%, respectively, with ASP1707 at 24 weeks. Following leuprorelin treatment, these incidences were 28 and 20%, respectively. Nasopharyngitis was more commonly reported among ASP1707 groups (13%) compared with leuprorelin (8%).

No deaths were reported in the study. Serious TEAEs were experienced in Part 1 by one subject (1%) in the placebo group (spontaneous abortion), three subjects (4%) in the ASP1707 3-mg group (ureteric obstruction, dural fistula, and vertigo positional), and one subject (1%) in the ASP1707 10-mg group (Mallory–Weiss syndrome).

During Part 2, serious TEAEs were experienced by six subjects (7%) in the ASP1707 5-mg group (abdominal pain lower, small intestinal obstruction, pneumonia, liver function test abnormal, dysmenorrhea, and endometriosis), one subject (1%) in the ASP1707 10-mg group (subileus), and one subject (1%) in the ASP1707 15-mg group (worsening of endometriosis). One subject in the ASP1707 5-mg group had elevated (within 3 × upper limit of normal) aspartate aminotransferase and alanine aminotransferase at the end of part 1. During Part 2, alanine aminotransferase was elevated to >3 × upper limit of normal, and the study drug was permanently discontinued. This serious AE was considered probably related to the study drug and the event was

Table II Modified Biberoglu and Behrman scale signs and symptoms (Biberoglu and Behrman, 1981; Vincent, Kennedy and Stratton, 2010): change from baseline to end of treatment Part 1 (full analysis set).

Parameter	Placebo	ASP1707 3 mg	ASP1707 5 mg	ASP1707 10 mg	ASP1707 15 mg	Treatment effect[a]	Leuprorelin
Symptoms							
Dysmenorrhea	−0.66	−1.12	−1.20	−1.53	−1.70	<.001	−2.08
	(−0.85, −0.47)	(−1.32, −0.92)	(−1.38, −1.01)	(−1.73, −1.34)	(−1.89, −1.51)		(−2.26, −1.91)
		$P = 0.004$	$P < 0.001$	$P < 0.001$	$P < 0.001$		
NMPP	−0.72	−0.81	−0.98	−1.01	−1.09	<.001	−1.26
	(−0.88, −0.56)	(−0.98, −0.65)	(−1.14, −0.83)	(−1.17, −0.85)	(−1.25, −0.94)		(−1.42, −1.10)
		$P = 0.831$	$P = 0.055$	$P = 0.033$	$P = 0.003$		
Dyspareunia	−0.54	−0.68	−0.89	−0.79	−0.98	.002	−0.92
	(−0.76, −0.32)	(−0.90, −0.46)	(−1.10, −0.68)	(−1.00, −0.58)	(−1.20, −0.77)		(−1.14, −0.70)
		$P = 0.732$	$P = 0.048$	$P = 0.229$	$P = 0.007$		
Signs							
Pelvic tenderness	−0.44	−0.61	−0.80	−0.77	−1.03	<.001	−1.03
	(−0.60, −0.29)	(−0.76, −0.45)	(−0.95, −0.66)	(−0.92, −0.62)	(−1.18, −0.88)		(−1.18, −0.88)
		$P = 0.345$	$P = 0.002$	$P = 0.009$	$P < 0.001$		
Induration	−0.42	−0.58	−0.70	−0.69	−0.79	<.001	−0.85
	(−0.58, −0.26)	(−0.75, −0.42)	(−0.86, −0.54)	(−0.85, −0.53)	(−0.95, −0.63)		(−1.01, −0.69)
		$P = 0.427$	$P = 0.043$	$P = 0.063$	$P = 0.005$		

Data are presented as mean (95% two-sided CI) and *P*-values of difference versus placebo were calculated from an analysis of covariance model that includes treatment group (excluding leuprorelin group) and region as fixed factors and baseline value as a covariate.
[a]Overall treatment effect from linear trend across placebo and ASP1707 groups.
NMPP, non-menstrual pelvic pain.

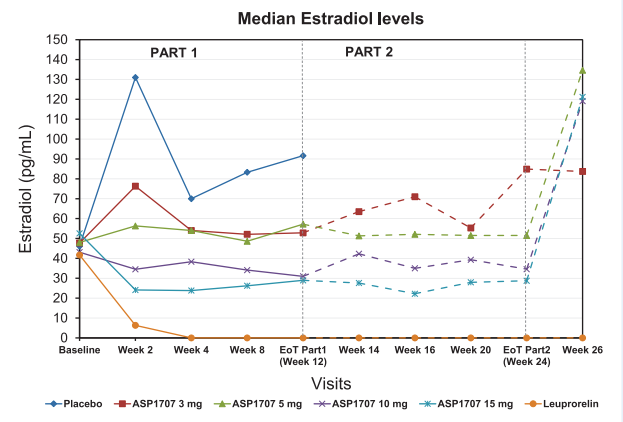

Figure 4 Median serum estradiol concentrations at end of treatment Parts 1 and 2.

resolved 91 days after discontinuation. No serious TEAEs were reported in the leuprorelin group.

Bone health

Leuprorelin and all ASP1707 dose groups showed statistically significant reductions in BMD from baseline at EoT Part 2 (24 weeks) compared with baseline (Table IV). The percentage reduction across all ASP1707 dose groups was significantly lower than leuprorelin for total hip ($P \leq 0.017$) and spine ($P \leq 0.001$). The effect of ASP1707 on the BMD of the spine was lower for the 10-mg dose group compared with the 15-mg dose group. At EoT Part 2 (24 weeks), a dose-dependent effect on TBS was observed, although the percentage changes from baseline were smaller for TBS than for BMD. Only the effects of ASP1707 15 mg and leuprorelin reached statistical significance compared with baseline TBS.

Discussion

ASP1707 showed dose-dependent efficacy in reducing endometriosis-associated pelvic pain. A statistically significant dose-related treatment effect was found among the ASP1707 treatment groups for OPP, dysmenorrhea, and NMPP, with higher decreases in mean NRS in higher dose groups of ASP1707. Although the study was not powered for pairwise comparison of each ASP1707 group versus placebo, statistically significant differences were observed between placebo and ASP1707 10 mg for OPP ($P = 0.011$) and between placebo and all ASP1707 groups for dysmenorrhea after 12 weeks of treatment ($P \leq 0.003$). Additionally, ASP1707 produced a statistically significant dose-related treatment effect ($P = 0.004$) in decreasing NRS for pain interference with daily activities, compared with placebo. No dose-related treatment effect was observed in the mean NRS for dyspareunia at any dose at EoT Part 1 (Week 12) or 2 (Week 24).

A placebo response was observed in all pain endpoints. Subjects receiving placebo experienced a 39% decrease from baseline in OPP,

Table III Treatment-emergent adverse events (≥5% of subjects in any treatment group) in subjects with the same treatment in both Parts 1 and 2 (safety analysis set).

Adverse event	Placebo[a] (*n* = 88)	Subjects with same treatment in both Parts 1 and 2[b]					
		ASP1707 3 mg (*n* = 86)	ASP1707 5 mg (*n* = 91)	ASP1707 10 mg (*n* = 90)	ASP1707 15 mg (*n* = 88)	ASP1707 total (*n* = 355)	Leuprorelin (*n* = 89)
Hot flush	4 (5)	6 (7)	16 (18)	11 (12)	19 (22)	52 (15)	25 (28)
Headache	10 (11)	10 (12)	10 (11)	13 (14)	15 (17)	48 (14)	18 (20)
Nasopharyngitis	8 (9)	9 (11)	12 (13)	11 (12)	13 (15)	45 (13)	7 (8)
Nausea	4 (5)	3 (4)	3 (3)	8 (9)	3 (3)	17 (5)	5 (6)
Menstruation delayed	0	2 (2)	4 (4)	4 (4)	3 (3)	13 (4)	5 (6)
Abdominal pain lower	2 (2)	2 (2)	2 (2)	5 (6)	2 (2)	11 (3)	2 (2)
Insomnia	3 (3)	3 (4)	1 (1)	2 (2)	5 (6)	11 (3)	7 (8)
Dizziness	1 (1)	1 (1)	1 (1)	4 (4)	5 (6)	11 (3)	3 (3)
Influenza	4 (5)	5 (6)	0	1 (1)	4 (5)	10 (3)	1 (1)
Cystitis	0	0	3 (3)	1 (1)	5 (6)	9 (3)	2 (2)
Arthralgia	1 (1)	2 (2)	1 (1)	2 (2)	1 (1)	6 (2)	6 (7)

[a]Subjects who received placebo in Part 1 (12 weeks) for comparison purposes.
[b]Data from subjects who received ASP1707 or leuprorelin during the 24 weeks of treatment.
Data are *n* (%).

a 26% decrease in dysmenorrhea, and a 40% decrease in NMPP at EoT Part 1. This is consistent with the effects observed in other 12-week, randomized, double-blind, placebo-controlled clinical studies of endometriosis-associated pelvic pain with infliximab and dienogest (Koninckx *et al.*, 2008; Strowitzki *et al.*, 2010)

Gonadotropin-releasing hormone analogs, such as leuprorelin, are associated with complete suppression of E2 levels and hypoestrogenic side-effects (Whitehouse *et al.*, 1990; Dawood *et al.*, 1995; Olive, 2008; Bowles, 2010). In this study, the decrease in serum E2 observed in the leuprorelin group was greater than in all ASP1707 dose groups, and median serum E2 concentrations in the leuprorelin group were below the lower limit of the target range. This is consistent with other studies in which leuprorelin was associated with castrate level decreases in E2 (Whitehouse *et al.*, 1990; Dawood *et al.*, 1995; Olive, 2008). ASP1707 produced dose-dependent decreases in serum E2 levels and the medians remained within the target range of 20–50 pg/mL. This difference in effect on E2 levels between the leuprorelin and the ASP1707 group could explain the observed differences in certain AEs (e.g. hot flushes) and the effects on bone health. Leuprorelin and all ASP1707 dose groups showed statistically significant losses in BMD compared with baseline; however, compared with leuprorelin, ASP1707 resulted in significantly less BMD loss at EoT Part 2 (24 weeks). Furthermore, ASP1707 3, 5, and 10 mg had a smaller impact on TBS compared with ASP1707 15 mg and leuprorelin, implying a lower impact on bone microarchitecture. Collectively, these findings are consistent with the Barbieri hypothesis and indicate that a GnRH antagonist may allow for sufficient pain relief while minimizing adverse effects associated with a GnRH agonist. Furthermore, this partial suppression of E2 associated with a GnRH antagonist may simplify management of endometriosis and no longer require the treating physician to mechanistically balance pain relief and AEs when treating with a GnRH agonist. As the current study demonstrates the potential for reduced adverse hypoestrogenic effects for up to 6 months of treatment with ASP1707, longer-term trials will be required to confirm whether this benefit can persist with treatment of longer duration. In addition, patient-specific factors such as age and baseline bone health can be considered along with the degree of bone loss observed over a treatment period to determine the long-term impact on bone health (Binkley *et al.*, 2017). Based on the results reported herein, it would be reasonable to propose that the 10-mg dose offers the greatest efficacy while also appearing safe in regard to BMD.

These findings are consistent with those observed in two Phase III studies of another GnRH antagonist, Elagolix (Taylor *et al.*, 2017). In a similar patient population, this mechanism of action was shown to significantly improve dysmenorrhea and NMPP scores versus placebo after 6 months of treatment. Hypoestrogenic adverse effects (e.g. hot flush, reduced BMD) were observed, and the impact on BMD appeared to be lower with a lower dose of Elagolix. Together with results of the TERRA study, these findings support the potential benefit of GnRH antagonist.

This study does have limitations to be considered. While Part 1 of the study included a placebo group, the study was not powered to make pairwise comparisons of each ASP1707 group versus placebo. In addition, the placebo-controlled portion of this study was 12 weeks in duration which precludes long-term comparison with ASP1707. Part 2 of this study was designed to provide a longer duration of exposure of ASP1707 to gain a better understanding of any potential impact on BMD; longer-term impact (i.e. 1 year) and a more comprehensive safety profile will require further investigation. Lastly, this study enrolled patients from Europe and Japan. Any potential variation in treatment response among patients from

Table IV Change from baseline to end of treatment (24 weeks) of bone mineral density and trabecular bone score in subjects receiving the same treatment for Parts 1 and 2 (safety analysis set).

Parameter	ASP1707 3 mg (*n* = 86)	ASP1707 5 mg (*n* = 91)	ASP1707 10 mg (*n* = 90)	ASP1707 15 mg (*n* = 88)	Leuprorelin (*n* = 89)	*P*-value[a]
Bone mineral density						
Total hip						
Percent change from baseline						<0.001
n	67	75	63	64	65	
Adjusted mean	−0.5	−1.3	−1.2	−1.3	−2.3	
95% CI	(−0.98, −0.04)	(−1.8, −0.88)	(−1.7, −0.71)	(−1.8, −0.86)	(−2.8, −1.8)	
Difference versus leuprorelin						
Adjusted mean	1.8	1.0	1.1	1.0		
95% CI	(0.98, 2.6)	(0.19, 1.8)	(0.28, 1.9)	(0.13, 1.8)		
P-value[b]	<0.001	0.010	0.004	0.017		
Spine						
Percent change from baseline						<0.001
n	67	76	65	65	65	
Adjusted mean	−1.2	−1.2	−1.3	−2.3	−3.9	
95% CI	(−1.8, −0.63)	(−1.8, −0.64)	(−1.9, −0.72)	(−2.9, −1.7)	(−4.5, −3.3)	
Difference versus leuprorelin						
Adjusted mean	2.7	2.7	2.6	1.7		
95% CI	(1.7, 3.7)	(1.7, 3.7)	(1.6, 3.6)	(0.62, 2.7)		
P-value[b]	<0.001	<0.001	<0.001	<0.001		
Trabecular bone score						
Spine						
Percent change from baseline						
n	50	50	48	47	54	
Mean ± SEM	0.23 ± 0.36	−0.39 ± 0.42	−0.87 ± 0.4	−1.5 ± 0.47	−1.2 ± 0.46	
P-value[c]	–	–	–	<0.01	<0.05	

[a]For overall treatment effect (*F*-test).
[b]Pairwise comparisons of each ASP1707 group versus leuprorelin based on Dunnett's test in the ANCOVA model that includes treatment group and region as fixed factors and baseline BMD as a covariate.
[c]Comparisons between groups using Student's *t*-test.

different regions as well as differences in clinical practice will need to be considered when translating these results to clinical practice. Clinically, these data may have a considerable impact on future treatment options for endometriosis-associated pain. Treatment with GnRH antagonists may provide an alternative to GnRH agonists, which are associated with bone loss (Lupron Depot® Package Insert). Even with add-back therapy, the potential for incomplete attenuation of bone loss remains a factor to consider (Lee *et al.*, 2016). Additionally, add-back therapy is not without contraindications (i.e. deep vein thrombosis, pulmonary embolism) and label warnings (i.e. visual abnormalities) (AYGESTIN® Package Insert). It has been reported that only ~30% of women with endometriosis who receive leuprolide acetate also receive add-back therapy (Fuldeore *et al.*, 2010). In the current study, with all doses of ASP1707, serum E2 levels remained within a target range, and the effects on bone health were low.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

T.D'.H., T.F. and G.H. contributed to the design of the work; T.D'.H., Y.O., R.B., B.L., G.M.H., K.M. and L.S. contributed to the acquisition, analysis, or interpretation of data for the work. All authors had full access to study data, contributed to drafting and revising the work, approved the final version to be published, and agree to take responsibility for all aspects of the work. The study sponsor was involved in development of the study protocol, in collaboration with the authors, and contributed to the study design, data collection and analysis, decision to publish, and preparation of the article.

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Conflict of interest

T.D'.H. is Vice President and Head of Global Medical Affairs Fertility at Merck, Darmstadt, Germany since 1 October 2015. At the time that the TERRA study was conducted, he served as Principal Investigator in his role as Coordinator of the Leuven University Fertility Center. Since October 2015, T.D'.H. has left Leuven University Hospital Gasthuisberg, but continues to serve as Professor in Reproductive Medicine and Biology at KU Leuven (University of Leuven) Belgium and at the Dept. of Obstetrics, Gynecology, and Reproduction at Yale University, New Haven, USA. T.F. and Y.O. report personal consulting fees from Astellas Pharma Inc. during the conduct of the study and outside the submitted work. G.M.H. and L.S. are employed by Astellas Pharma Europe B.V.; K. M. is employed by Astellas Pharma Inc.; B.L. was a biostatistician for Astellas Pharma Europe B.V. during conduct of the study; R.B. was a contract Associate Director of Medical Science for Astellas during conduct of the study.

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