SYNOPSIS

Title of Study: A Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Assess the Efficacy, Safety, and Dose-Response Relationship of ASP1707 in Subjects with Endometriosis Associated Pelvic Pain for 12 Weeks, Followed by a 12-Week Double-blind Extension without Placebo Control, Including a 24-Week Open-label Leuprorelin Acetate Treatment Group for Bone Mineral Density Assessment

Investigators/Coordinating Investigator: [redacted] MD, PhD; [redacted] MD, PhD; and [redacted] MD, PhD

Study Center(s): This multinational, multicenter study was conducted at 97 contracted sites; 86 sites screened patients and 71 sites randomized patients in a total of 9 countries: Belgium (5 sites), Bulgaria (4 sites), Germany (2 sites), Hungary (7 sites), Poland (8 sites), Romania (6 sites), Ukraine (6 sites), the United Kingdom (2 sites) and Japan (31 sites).

Publication Based on the Study: None.

Study Period: Dec 2012 – Jul 2015

Study Initiation Date (Date of First Enrollment): 04 Dec 2012

Study Completion Date (Date of Last Evaluation): 30 Jul 2015

Phase of Development: Phase 2

Objectives:

Part 1 (Weeks 1-12, Double-blind Phase; Placebo, ASP1707 and Open-label Active-control)

Primary Objectives

- To assess the efficacy of ASP1707 in reduction of endometriosis associated pelvic pain
- To assess the dose-response relationship of ASP1707 in reduction of endometriosis associated pelvic pain

Secondary Objectives

- To assess the safety and tolerability of ASP1707 in patients with endometriosis associated pelvic pain
- To assess the dose- response relationship of ASP1707 in reduction of serum estradiol (E2) levels
- To assess the pharmacokinetics of ASP1707 in patients with endometriosis associated pelvic pain

Part 2 (Weeks 13-24, Double-blind Extension Phase; ASP1707 and Open-label Active-control)

Objectives

- To assess 24-week safety and tolerability of ASP1707, including bone mineral density (BMD), E2 levels and menstrual bleeding control
- To assess 24-week efficacy of ASP1707 in reduction of endometriosis associated pelvic pain
- To assess the pharmacokinetics of ASP1707 in patients with endometriosis associated pelvic pain

Methodology: This was a multinational, multi-center, double-blind, randomized, parallel-group, placebo-controlled phase 2 study for the first 12 weeks (part 1) followed by a double-blind extension up to 24 weeks without placebo control (part 2). In addition, 1 group was treated with the gonadotropin releasing hormone (GnRH) agonist leuprorelin acetate as open-label active-control throughout parts 1 and 2 as a positive control for BMD assessment.

At visit 1, patients were screened for suitability to be enrolled in this study.

After screening, eligible patients were enrolled into a nonmedicated observational period, which was to include at least 1 complete menstrual cycle.

After the observational period, patients returned to the clinic on days 1 to 4 of the menstrual cycle (day 1 was the first day of menstrual bleeding, day 4 the fourth day of menstrual bleeding), which was visit 2. At visit 2, the diary pain scores from the electronic diary (e-diary) and duration of the menstrual cycle were checked against the selection criteria.

Patients who met the selection criteria were randomized to part 1 and part 2 at visit 2. After part 1, patients randomized to 1 of the ASP1707 groups or open-label active-control continued on the assigned treatment in part 2. Patients randomized to placebo in part 1 were randomly switched to 1 of the 4 ASP1707 groups for the remaining 12-week treatment period (part 2).

Patients completed an e-diary during the observational period and during the 24-week treatment period on a daily basis preferably at the same time every day. The e-diary data included daily pelvic pain scores, days and amount of bleeding, occurrence of sexual intercourse and dyspareunia, use of rescue medication and questionnaires needing daily completion. Other symptoms and health outcome questionnaires were completed at clinic visits using the e-diary.

Number of Patients (Planned, Enrolled and Analyzed): It was planned that a total of 504 patients (84 patients per treatment group) would be enrolled into the study, including approximately 144 patients (including 24 active-control [leuprorelin acetate]) in the Japanese subpopulation and approximately 360 patients (including 60 active-control [leuprorelin acetate]) in the European subpopulation. A total of 540 patients were randomized to receive treatment (359 ASP1707, 89 placebo, 92 leuprorelin acetate). Of the randomized patients, 532 (98.5%) patients received at least 1 dose of study drug (ASP1707, placebo or leuprorelin acetate) and were included in the safety analysis set 1 (SAF1). Of the SAF1 patients, 75 (84.3%) patients received at least 1 dose of placebo in part 1, switched to ASP1707 in part 2 and received at least 1 dose of ASP1707 in part 2 and were included in the safety analysis set 2 (SAF2). Of the randomized patients, 494 (91.5%) patients received at least 1 dose of double-blind study drug (placebo or ASP1707) or at least 1 dose of open-label leuprorelin acetate and had a primary numeric rating scale (NRS) pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain and were included in the full analysis set 1 (FAS1). Of the FAS1 patients, 74 (83.1%) patients received at least 1 dose of placebo in part 1, switched to ASP1707 in part 2, received at least 1 dose of ASP1707 in part 2 and had at least 1 evaluable NRS pain score for overall pelvic pain after dispensing of study drug at visit 6 and were included in the full analysis set 2 (FAS2) (patients who were randomized to leuprorelin acetate or ASP1707 in part 1 were not included in FAS2). Of the FAS1 patients, 459 (85.0%) patients did not meet criteria for exclusion from the PPS and were included in the per protocol set 1 (PPS1). Of the FAS2 patients, 70 (78.7%) patients did not meet criteria for exclusion from the PPS and were included in the per protocol set 2 (PPS2). A total of 408 patients met the criteria for inclusion in the pharmacokinetic analysis set (PKAS). A total of 517 patients met the criteria for inclusion in the pharmacodynamic analysis set (PDAS). The FAS1 was used for all efficacy analyses that are presented in part 1 and parts 1 + 2 tables, listings and figures (TLFs). The FAS2 was used for efficacy analyses that are presented in part 2 TLFs. Primary and secondary efficacy analyses were repeated on the PPS1 and PPS2. The SAF1 was used for demographic and baseline characteristics and safety analyses that are presented in part 1 and parts 1 + 2 TLFs. The SAF2 was used for safety analyses that are presented in part 2 TLFs. The

pharmacokinetic analyses were performed on the PKAS. The pharmacodynamic analyses were performed on the PDAS.

Diagnosis and Main Criteria for Inclusion: Patients were female, aged 18 (20 in Japan) up to and including 45 years with endometriosis diagnosed surgically (laparoscopy, laparotomy) within 5 years before signing informed consent; had a confirmed menstrual cycle length (24 to 35 days inclusive); and based on the diary input during the last full menstrual cycle prior to visit 2, were suffering from endometriosis associated dysmenorrhea and nonmenstrual pelvic pain (NMPP) (NRS > 0 in both domains), with at least 1 of the following: Moderate to severe dysmenorrhea (mean NRS pain score ≥ 4 [over all menstrual days]), moderate NMPP (NRS pain score ≥ 4 on at least 7 nonmenstrual days [not necessarily consecutively]) or severe NMPP (NRS pain score ≥ 7 on at least 3 nonmenstrual days [not necessarily consecutively]). Patients who were breastfeeding or had a pregnancy within 24 weeks prior to signing informed consent or had the intention to become pregnant during the study or had surgery for endometriosis within the 4 weeks before signing informed consent were excluded, as were patients with a known concurrent uterine myoma > 3 cm, abnormal vaginal bleeding, history of hysterectomy or bilateral oophorectomy, concurrent or previous pelvic infection within 8 weeks before signing informed consent, clinically relevant abnormalities at gynecological exam at screening, including abnormal cervical cytology, concurrent disease with chronic abdominal pain of nonendometriosis origin or pituitary adenoma. Also excluded were patients with contraindication or hypersensitivity for GnRH analogs or ibuprofen, with use of hormonal contraceptives or other drugs with effects on gynecological endocrinology (within 4 weeks prior to the start of screening), depot-medroxyprogesterone acetate (MPA) or danazol (within 12 weeks prior to the start of screening), GnRH agonist (within 24 weeks prior to the start of screening), drugs metabolized solely by cytochrome P450 3A4 (CYP3A4) (within 2 weeks prior to visit 2) or anticoagulants or drugs with effects on BMD (within 12 weeks prior to the start of screening).

Test Product, Dose and Mode of Administration, Batch Numbers:

ASP1707, oral, tablets 1 or 5 mg administered at doses of 3, 5, 10 or 15 mg once daily.

Duration of Treatment (or Duration of Study, if applicable):

The duration of treatment was 24 weeks total: 12 weeks during part 1 and 12 weeks during part 2.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Placebo tablets, oral, to match ASP1707.

Leuprorelin acetate, subcutaneous injection, administered at a dose of 3.75 mg per month.

Criteria for Evaluation:

Efficacy

Part 1 (Weeks 1-12, Double-blind Phase; Placebo, ASP1707 and Open-label Active-control)

The primary efficacy variables of part 1 of the study were change from baseline to the end-of-treatment (EoT) of the mean NRS pain score for overall pelvic pain (defined as mean NRS pain score on all days, on menstrual and nonmenstrual), change from baseline to the EoT of the mean NRS pain score for dysmenorrhea (defined as mean NRS pain score on menstrual bleeding days) and change from baseline to the EoT of the mean NRS pain score for NMPP (defined as mean NRS pain score on nonmenstrual bleeding days).

The secondary efficacy variables of part 1 of the study included change from baseline to EoT of the mean NRS pain interference with daily activities (this endpoint was inadvertently omitted from the protocol and overlooked in the SAP analyses but was listed as the first secondary endpoint in the ordering of secondary endpoints in SAP Appendix 3), change from baseline to the EoT of the mean NRS dyspareunia score, occurrence of response (≥ 30% improvement from baseline of the mean NRS score) at the EoT for overall pelvic pain, dysmenorrhea, NMPP and dyspareunia, change from baseline to the EoT of the mean scores of the modified Biberoglu and Behrman (B&B) symptom and sign domains, change from baseline to the EoT of the use of protocol defined rescue medication, change from baseline to the EoT of the mean pain interference score (mean of 7 interference items) of the Brief Pain Inventory (BPI), Patient Global Impression of Change (PGIC) at the EoT, change from baseline to the EoT in the Endometriosis Health Profile-5 (EHP-5) score, change from baseline to the EoT of the Female Sexual Function Index (FSFI) score (sexual well-being), change from baseline to the EoT of the Beck Depression Inventory-II (BDI-II) score and change from baseline to the EoT in the European quality of life 5-dimension 5-level scale (EQ-5D-5L) score.

Part 2 (Weeks 13-24, Double-blind Extension Phase; ASP1707 and Open-label Active-control)

The secondary efficacy variables of part 2 of the study included change from baseline to EoT of the mean NRS pain interference with daily activities, change from baseline to the EoT of the mean NRS pain score for overall pelvic pain (dysmenorrhea and NMPP), change from baseline to the EoT of the mean NRS pain score for dysmenorrhea (defined as mean NRS pain score on menstrual bleeding days), change from baseline to the EoT of the mean NRS pain score for NMPP (defined as mean NRS pain score on nonmenstrual bleeding days), change from baseline to the EoT of the mean NRS dyspareunia score, occurrence of response (≥ 30% improvement on NRS) at the EoT for overall pelvic pain, dysmenorrhea, NMPP and dyspareunia, change from baseline to the EoT of the mean scores of the modified B&B symptom and sign domains, change from baseline to the EoT of the use of protocol defined rescue medication, change from baseline to the EoT of the mean pain interference score (mean of 7 interference items) of the BPI, PGIC at the EoT, change from baseline to the EoT in EHP-5 score, change from baseline to the EoT of the FSFI score (sexual well-being), change from baseline to the EoT of the BDI-II score and change from baseline to the EoT in the EQ-5D-5L score.

Pharmacokinetics

Pharmacokinetics was assessed by measuring concentrations of $ASP1707_{total}$ (i.e., total concentration of the R- and S-enantiomers without distinguishing the individual enantiomers) in plasma specimens taken from patients not randomized to leuprorelin acetate. Plasma samples from patients receiving ASP1707 10 mg and ASP1707 15 mg (parts 1 + 2) were also used for the analysis of the 2 separate ASP1707 enantiomers (i.e., ASP1707 and AS1948006).

Pharmacodynamics

Pharmacodynamics were assessed by measuring serum concentrations of E2, luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone and bone alkaline phosphatase (bALP) and by measuring urine concentration of collagen type 1 cross-linked N-telopeptide (NTx).

Safety

Safety was assessed for each study part by evaluation of adverse events (AEs), serious adverse events (SAEs), safety laboratory tests, vital signs, weight, safety 12-lead electrocardiograms (ECGs), BMD assessed by Dual

Energy X-Ray Absorptiometry (DXA) scan, physical and gynecological examination, bleeding patterns, hot flashes and return of menstruation.

Statistical Methods:

Efficacy:

The primary endpoints were mean NRS pain score for overall pelvic pain, dysmenorrhea and NMPP, over each 28-day cycle. The change from baseline (visit 2) to EoT (part 1) of the mean NRS pain score for overall pelvic pain was analyzed by using an analysis of covariance (ANCOVA) model that included treatment group (excluding leuprorelin acetate group) and region (Europe and Japan) as fixed factors and baseline NRS pain score of overall pelvic pain as a covariate. A test for a linear trend was applied by using the linear contrast based on the ordinal dose (contrast coefficients: -2, -1, 0, 1, 2). Results were described by 2-sided P value, least squares (LS) means estimate of the contrast with 95% CI.

In addition, pairwise comparisons of each ASP1707 group vs placebo were done using Dunnett's test.

Similar analyses were performed separately for the primary endpoints of dysmenorrhea and NMPP.

The primary analysis was conducted on the entire study population, followed by separate analyses for the Japanese and European subpopulations.

The primary analysis of primary variables was performed on the FAS.

The secondary analysis of the primary endpoints was performed on the PPS.

The primary efficacy endpoints were summarized by serum E2 group (0 pg/mL ≤ Serum E2 < 20 pg/mL, 20 pg/mL ≤ Serum E2 ≤ 50 pg/mL, Serum E2 > 50 pg/mL) at EoT (EoT part 1 for part 1 outputs, EoT part 2 for part 2 outputs and EoT parts 1 + 2 for parts 1 + 2 outputs), and were analyzed by using an ANCOVA model that included treatment group (excluding leuprorelin acetate group), region (Europe and Japan), serum E2 group and serum E2 group-by-treatment group interaction as fixed factors and baseline NRS pain score as a covariate for the FAS. Posthoc subgroup analyses included analyses of the primary efficacy variables by categorized mean NRS pain score at baseline, country or categorized modified B&B NMPP symptom at baseline by using an ANCOVA with treatment group (excluding leuprorelin acetate group), region (Europe and Japan), the subgroup variable and the subgroup variable by treatment group interaction as fixed factors and baseline NRS pain score as a covariate.

The analysis used for the primary efficacy variables was repeated on the secondary efficacy variables of pain interference with daily activities; NRS pain scores for overall pelvic pain, dysmenorrhea and NMPP; and NRS dyspareunia. Posthoc analyses included subgroup analyses of the NRS pain scores for overall pelvic pain, dysmenorrhea and NMPP by categorized mean NRS pain score at baseline or categorized modified B&B NMPP symptom at baseline by using a similar ANCOVA that was used for the posthoc subgroup analyses of the primary efficacy variables; analysis of the NRS dyspareunia in patients with a score > 0 at baseline; and subgroup analysis of the NRS dyspareunia by country by using a similar ANCOVA that was used for the posthoc subgroup analyses of the primary efficacy variables.

Responders for overall pelvic pain, dysmenorrhea and NMPP, with response defined as a reduction of the mean NRS score between baseline and EoT (part 1 and part 2) of at least 30%, 50%, 60% and 70% (both not adjusted and adjusted for increase of rescue medication use at EoT), were analyzed by a logistic regression model including treatment group (excluding leuprorelin acetate group), region and baseline score; of these responder

analyses, the 30% unadjusted responder analysis was prespecified and the remaining responder analyses were posthoc analyses. As described in the Report on the Measurement Properties of the Endometriosis Pain Daily Diary [clinical study report (CSR) Attachment 2], meaningful changes for overall pelvic pain, dysmenorrhea and NMPP can be represented by reductions over the course of a trial of 60%, 70% and 60% in NRS pain scores, respectively. The dose groups were included once as the ordinal dose to assess a dose-related trend and once as a categorical variable to assess the comparison of each dose with placebo. Responders for dyspareunia, with response defined as a reduction of the mean NRS score between baseline and EoT (part 1 and part 2) of at least 30% (prespecified) and 50% (posthoc), not adjusted for increase of rescue medication use at EoT, were analyzed in the same way as the unadjusted responder analyses for overall pelvic pain, dysmenorrhea and NMPP.

For the modified B&B scale, scores for the 2 signs and for the 3 symptoms were summarized as categorical variables by treatment group and visit. EoT (part 1 and part 2) was analyzed by a Cochran Mantel Haenszel (CMH) row mean score test including treatment group (excluding leuprorelin acetate group), region and each sign and symptom separately. Number of patients with increase, no change and decrease of severity within each sign and symptom by visit with respect to baseline were displayed. All scores were also summarized as continuous variables by treatment group and visit. Change from baseline to each postbaseline assessment was also included for each variable. For the scores as continuous variables, change from baseline (screening for signs and visit 2 for symptoms) to EoT (part 1 and part 2) were analyzed separately for each score in the same way as the primary efficacy variables. For posthoc analyses, the modified B&B total score was summarized as a categorical variable and was analyzed by a CMH row mean score test including treatment group (excluding leuprorelin acetate group), region and the total score. Change from baseline to EoT (part 1 and parts 1 + 2) of modified B&B total score as a continuous variable was analyzed for the overall population by using an ANCOVA model with treatment group (excluding leuprorelin acetate group), region (Europe and Japan), the subgroup variable (categorized baseline modified B&B NMPP symptom) and the subgroup variable by treatment group interaction as fixed factors and baseline value as a covariate.

The number of patients using any protocol defined rescue medication was described by treatment group and visit and was analyzed by a CMH test including treatment group (excluding leuprorelin acetate group), region and variable use of rescue medication (yes, no) at EoT (part 1 and part 2). Number of days using rescue medication, percentage of days using rescue medication, including patients not taking any rescue medication (treated as 0%), and mean daily dosage were summarized by treatment group and visit, including change from baseline to EoT and were analyzed in the same way as the primary efficacy variables.

For BPI, each of the 4 scores for pain severity and each of the 7 scores for pain interference were summarized by treatment group and visit, including change from baseline to each post baseline assessment. Total score for BPI pain severity and BPI pain interference were also summarized by treatment group and visit, including change from baseline to each post baseline assessment. Change from baseline to EoT (part 1 and part 2) for BPI pain interference was analyzed in the same way as the primary efficacy variables (excluding leuprorelin acetate group).

The scores for PGIC at EoT (part 1 and part 2) were summarized by treatment group and visit and were analyzed by ordinal logistic regression (proportional odds model) including treatment group (excluding leuprorelin acetate group) and region. A score test for the proportional odds assumption was done. The derived PGIC variable (“No change or worse” [includes PGIC categories “very much worse,” “much worse, “minimally

worse" and "no change"] or "Improved" [includes PGIC categories "minimally improved," "much improved" and "very much improved"]) was also summarized by treatment group and visit and was analyzed by a CMH test including treatment group (excluding leuprorelin acetate group), region and the derived variable at EoT (part 1 and part 2).

Transformed scores of each of the 11 items for EHP-5 were summarized by treatment group and visit, including change from baseline to each postbaseline assessment. Change from baseline to EoT (part 1 and part 2) were analyzed in the same way as the primary efficacy variables for the FAS and PPS.

The 6 domains of the FSFI scale and total score were summarized by treatment group and visit, including change from baseline to each postbaseline assessment. Change from baseline to EoT (part 1 and part 2) were analyzed in the same way as the primary efficacy variables for the FAS and PPS.

BDI-II total scores were summarized by treatment group and visit, including change from baseline to each postbaseline assessment. Number and percentage of patients in categories of minimal depression (total score between 0 and 13), mild depression (total score between 14 and 19), moderate depression (total score between 20 and 28) and severe depression (total score between 29 and 63) were summarized by treatment group and visit.

Each of the 5 dimensions for EQ-5D-5L was summarized by treatment group and visit as categorical variables. The EQ-5D-5L VAS score was summarized by treatment group and visit, including change from baseline to each postbaseline assessment and was analyzed in the same way as the primary efficacy variables.

Descriptive statistics for the secondary efficacy variables were presented by treatment group and visit.

The other analyses that were conducted were as follows. Percentage change from baseline to each postbaseline assessment of the mean NRS pain score for overall pelvic pain, dysmenorrhea and NMPP was summarized by treatment group and visit. Percentage change from baseline to EoT (part 1 and part 2) was analyzed separately for overall pelvic pain, dysmenorrhea and NMPP in the same way as the primary efficacy variables.

As exploratory analysis, the possible impact of the use of rescue medication on the primary endpoint of the study in part 1 was analyzed as per the primary analyses for overall pelvic pain, dysmenorrhea and NMPP, adding the mean change in daily dosage of rescue medication as a covariate.

The number of patients with a decrease no greater than 1.1% (i.e., percentage change from baseline $\geq$ -1.1%) and the number of patients with a decrease greater than 1.1% (i.e., percentage change from baseline < -1.1%) in BMD (Hip – Total Hip and Spine) at visit 10 in responders and nonresponders for each of the overall pelvic pain, dysmenorrhea and NMPP at EoT (parts 1 + 2) were summarized by treatment group. Response was defined as a reduction from baseline of at least 30% in the mean NRS pain score over the last 28 days at EoT (part 1 and part 2). Results of this analysis are described in the safety results section, immediately following the results section on the safety variable of BMD.

Pharmacokinetics:

Individual and summary tables of plasma concentration of $ASP1707_{total}$ and a listing of blood collection times and concentrations were provided. For the ASP1707 10 mg and 15 mg groups, individual and summary tables of plasma concentration for all time points were provided for the following:

- ASP1707 (= R-enantiomer)

- AS1948006 (= S-enantiomer of ASP1707)
- Sum of the 2 enantiomers ASP1707 and AS1948006 (sum of R+S or $ASP1707_{sum}$): since the molecular weight of both metabolites is equal, the sum of both enantiomers is the arithmetic sum of both concentration results. It was anticipated that $ASP1707_{sum}$ would be equal to $ASP1707_{total}$.
- Ratio of enantiomers: (ASP1707 / AS1948006)
- Ratio of $ASP1707_{total}$ and $ASP1707_{sum}$. This compared the original concentrations, measured without separating the enantiomers, to the (newer) concentrations measuring R- and S-enantiomers separately.

Summary statistics were provided including n, mean, SD, geometric mean, minimum, median, maximum and coefficient of variation (CV). Values below the lower limit of quantification (BLOQ) (50 pg/mL for $ASP1707_{total}$ and 100 pg/mL for the 2 enantiomers) were set to 0 for calculation of descriptive statistics. Box plots and scatter plots (both normal and semi-log) of predose $ASP1707_{total}$ plasma concentrations by dose were produced.

Pharmacodynamics:

Individual and summary tables for serum levels of E2, LH, FSH, progesterone and bALP, and individual and summary tables for urine levels of NTx, by visit and treatment group were produced. Summary statistics included n, mean, SD, geometric mean, minimum, median, maximum and CV. BLOQ values were set to 0 for calculation of descriptive statistics. For serum E2, mean values of part 1 and part 2 were included as representative data by period. For serum E2, a summary table with the number and percentage of patients that were within, above or below the target range (20-50 pg/mL [73.4-183.5 pmol/L]) was provided by visit, where serum E2 was measured. Graphics of mean serum/urine concentrations for each parameter were produced per treatment group and visit. Spaghetti plots of individual serum concentrations of serum E2, overall and by treatment group, were produced for responders and nonresponders for mean NRS pain score for overall pelvic pain, dysmenorrhea and NMPP. Response was defined as a reduction from baseline of at least 30% in the mean NRS pain score over the last 28 days at EoT (part 1 and part 2). Scatter plots of individuals, overall and by treatment group, were produced for the relationship between percentage change from baseline for BMD, by location (hip–total hip and spine), and mean serum concentrations of E2 at EoT (parts 1 + 2) in responders (30% responder analysis) and nonresponders for overall pelvic pain at EoT (parts 1 + 2). The BMD threshold was defined before soft lock, corresponding to a drop of 1.1%. Spaghetti plots of individual serum concentrations of serum E2, overall and by treatment group, were produced for responders (30% responder analysis) for overall pelvic pain in patients below the BMD threshold for hip–total hip and spine-adjusted total spine.

Posthoc analyses included analysis of the change from baseline to EoT (part 1 and parts 1 + 2) in serum concentrations of bALP (µg/L) and urine concentrations of NTx/creatinine (nmol/mmol creatinine) and NTx (nmol), overall and by region, by using an ANCOVA model with treatment group and region (Europe and Japan) as fixed factors and baseline value as a covariate. A test for a linear trend was applied by using the linear contrast based on the ordinal dose (contrast coefficients for part 1: -2, -1, 0, 1, 2; contrast coefficients for parts 1 + 2: -5.25, -3.25, 1.75, 6.75). Results were described by 2-sided P value, LS means estimate of the contrast with 95% CI. In addition, pairwise comparisons between all treatment groups were done.

Safety:

Summaries of patients with TEAEs, by system organ class (SOC) and preferred term (PT), were produced and presented for each treatment group for TEAEs, TEAEs by severity, TEAEs (excluding serious TEAEs) ≥ 5% in

any treatment group, treatment-related TEAEs, treatment-related TEAEs by severity, all and treatment-related serious TEAEs and all and treatment-related TEAEs leading to permanent discontinuation of study drug. For each summary, patients were counted only once within a PT or an SOC.

Clinical laboratory test results (hematology, biochemistry, continuous urinalysis parameters) were summarized by treatment group at each assessment and were presented in SI units. Additionally, within-patient change from baseline for each postbaseline measurement was presented. For the qualitative urinalysis parameters, the number and percentage of patients with positive/negative results was displayed by treatment group. Each hematology and biochemistry result was classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges. Number and percentage of patients with values below or above the reference range were shown. Shift tables of reference range changes from baseline to each postbaseline assessment were displayed as well. Clinically significant abnormal values were reported as AEs. The number and percent of patients who met the liver function test (LFT) criteria at any time during the treatment period were summarized by treatment group for the following groups:

- Alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN), > 5 x ULN, > 10 x ULN and > 20 x ULN
- Aspartate aminotransferase (AST) > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- AST or ALT > 3 x ULN
- Total bilirubin > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN (the patient's ALT and/or AST and total bilirubin values were to be measured within the same sample to be counted)

The maximum on-treatment value, defined as the maximum value of all postbaseline assessments, was derived for LFTs. Evaluation of drug-induced serious hepatotoxicity (eDISH) plots were produced.

Vital signs and weight were summarized by treatment group and visit. Additionally, a within-patient change from baseline for each postbaseline measurement was presented.

ECG interpretation was summarized by treatment group and visit for both central and local laboratory. ECG variables (PR interval, RR interval, heart rate [HR], QRS interval, QT interval, QT interval corrected for heart rate by Fridericia's formula [QTcF] and QT interval corrected for heart rate by Bazett's formula [QTcB]) were summarized for each treatment group at each visit and including changes from baseline to each visit. The QT interval, QT corrected for heart rate (QTc) interval and HR were also summarized by the number and percent of patients within predefined categories. These summaries were based on the mean maximum value for QT and QTc and on the mean minimum value for HR during the treatment period by treatment group.

Patients that were taking ASP1707 or leuprorelin acetate for 24 weeks and for whom baseline and part 2 (week 16+) valid DXA scans were available (to guarantee sufficient duration for an evaluation of the treatment effect on BMD) were included in the BMD analyses. The percentage change from baseline to visit 6 (week 12) and visit 10 (week 24) of BMD by location (hip – total hip, spine – adjusted total spine and hip – femoral neck) were summarized by treatment group. The 2-sided 90% CI of the mean was calculated. If the lower limit of the 90% CI in a treatment group was above -2.2% at 24 weeks, then the change in BMD compared to baseline was considered a success for that treatment group. Percentage change from baseline of the BMD by location was analyzed using an ANCOVA model that included actual treatment and region (Europe and Japan) as fixed

factors and baseline BMD as a covariate. Pairwise comparisons of each ASP1707 group vs leuprorelin acetate group were done using Dunnett's test. Line plots of percentage change from baseline of BMD by location, treatment group and visit, overall and by region were included. Posthoc analyses included separate analyses for each region (Europe and Japan) of the percentage change from baseline to visits 6 and 10 of the BMD by location (hip – total hip, spine – adjusted total spine and hip - femoral neck), using an ANCOVA model with actual treatment (ASP1707 3 mg, ASP1707 5 mg, ASP1707 10 mg, ASP1707 15 mg and leuprorelin acetate 3.75 mg) as a fixed factor and baseline BMD as a covariate. Pairwise comparisons of each ASP1707 group vs leuprorelin group was done using Dunnett's test.

Results for the gynecological examination were presented by treatment group and visit. Bleeding pattern variables (i.e., number of bleeding days, number of nonbleeding days, number of menstrual bleeding days, number of nonmenstrual bleeding days due to sexual activity, number of nonmenstrual bleeding days due to other reasons, number of patients without bleeding) were summarized by treatment group and visit. Posthoc analyses included analyses, overall and by region, of the change from baseline to EoT (part 1, part 2 and parts 1 + 2) in mean number of menstrual bleeding days over the last 28 days and mean number of menstrual bleeding days over the last 28 days in patients with at least 1 menstrual bleeding day, using the same method that was used for the primary efficacy endpoints. The number of patients with any hot flashes was summarized by treatment group and visit. The number of hot flashes within the time period and the number of hot flashes per day were summarized by treatment group and visit, including change from baseline at each postbaseline assessment. Change from baseline to EoT (part 1 and part 2) was analyzed in the same way as the primary efficacy variables. The time from last dose to return of menstruation was summarized by treatment group. Additionally, summaries stratified by serum E2 group (0 pg/mL ≤ serum E2 < 20 pg/mL, 20 pg/mL ≤ serum E2 ≤ 50 pg/mL, serum E2 > 50 pg/mL) at EoT (part 1 and part 2) were provided. Posthoc analyses included analyses, overall and by region, of the change from baseline to EoT (part 1 and parts 1 + 2) in the mean number of sanitary products used over the last 28 days, using the same method that was used for the primary efficacy endpoints.

Summary of Results/Conclusions:

The number of patients randomized in each analysis set and the primary reasons for discontinuation during part 1 of the study are presented for the overall population in Table 1 and for the Japanese population in Table 2. The majority of patients in the overall population were European (FAS1, 358/494 [72.5%]; SAF1, 384/532 [72.2%]), which was true across all treatment groups in each analysis set Table 3 and Table 1. Thus results for the European patients drove those for the overall patients. This CSR discusses the primary endpoints, pain interference with daily activities, the responder analyses for overall pelvic pain, dysmenorrhea and NMPP and the analyses of BMD for the overall, Japanese and European populations and limits the discussion of all other results to the overall and Japanese populations.

In general, all treatment groups were similar with respect to demographics and baseline characteristics in the overall population [Table 4] and the Japanese population [Table 5].

In the overall population, the median duration of exposure for all ASP1707 dose groups was 12.14 weeks in part 1 of the study and 24.14 weeks in parts 1 and 2 of the study. In the Japanese population, median duration of exposure to ASP1707 was comparable to that in the overall population. In the European population, median duration of exposure to ASP1707 closely resembled that in the overall population.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy Results: In the overall population (FAS1), ASP1707 reduced overall pelvic pain, dysmenorrhea and NMPP in part 1 (baseline to week 12): statistically significant linear trends were found among the ASP1707 dose groups for change from baseline to EoT of part 1 (week 12) in the mean NRS pain score for overall pelvic pain ($P = 0.001$), dysmenorrhea ($P < 0.001$) and NMPP ($P = 0.029$) Table 6. Compared to placebo, statistically significant differences in the absolute change from baseline in mean NRS pain scores were observed in the ASP1707 10 mg group for overall pelvic pain ($P = 0.011$) and in all ASP1707 dose groups for dysmenorrhea ($P \leq 0.003$).

In general, response rates for the efficacy endpoints at week 24 were similar to or slightly better than response rates at week 12, indicating that most of the treatment effect was observed by 3 months and that this effect was maintained until 6 months of treatment.

Mean NRS pain scores for overall pelvic pain, dysmenorrhea and NMPP at EoT of part 2 (week 24) were similar to or slightly reduced compared to those at week 12. Thus, most of the treatment response was reached within the first 3 months of treatment and the response was maintained until 6 months of treatment.

Between the Japanese population Table 7 and overall population Table 6, consistent differences in NRS pain scores of the active treatment groups vs placebo group were found for overall pelvic pain and dysmenorrhea. Baseline levels for NMPP were considerably lower in Japanese patients compared to overall patients and no effect of ASP1707 on absolute change in NMPP was observed in the Japanese population. However, in the placebo vs ASP1707 10 mg groups, 65.0% vs 73.9% of Japanese population patients achieved ≥ 30% treatment response for NMPP, compared to 63.0% vs 80.5% of the overall population Table 14.

In the European population Table 8, results for overall pelvic pain, dysmenorrhea and NMPP were consistent with those in the overall population. Baseline levels for NMPP were comparable in the European and overall populations. Statistically significant linear trends were found among the ASP1707 dose groups for change from baseline to EoT of part 1 (week 12) in the mean NRS pain score for overall pelvic pain ($P = 0.003$), dysmenorrhea ($P < 0.001$) and NMPP ($P = 0.014$). Compared to placebo, statistically significant differences in the absolute change from baseline in mean NRS pain scores were observed in the ASP1707 10 mg group for overall pelvic pain ($P = 0.032$) and in the ASP1707 5 mg, 10 mg and 15 mg groups for dysmenorrhea ($P \leq 0.017$).

Overall pelvic pain, dysmenorrhea and NMPP were evaluated by postbaseline serum E2 subgroups (i.e., 0 pg/mL ≤ serum E2 < 20 pg/mL, 20 pg/mL ≤ serum E2 ≤ 50 pg/mL and serum E2 > 50 pg/mL). Due to the variability in serum E2 levels both between and within individuals, and due to the small sample sizes in some subgroups, it was difficult to draw meaningful conclusions from this analysis.

For NRS score for pain interference with daily activities in the overall population, a statistically significant linear trend was found from baseline to week 12 among the ASP1707 dose groups ($P = 0.004$) Table 9. Compared to placebo, the change from baseline to week 12 in NRS score for pain interference with daily activities was statistically significant for ASP1707 10 mg ($P = 0.002$), ASP1707 15 mg ($P = 0.029$) and leuprorelin ($P = 0.002$). From baseline to week 24 compared to week 12, additional reductions observed in the ASP1707 dose groups were greatest in the ASP1707 10 mg and 15 mg groups.

Baseline levels for NRS score for pain interference with daily activities were considerably lower in Japanese patients compared to overall patients and no effect of ASP1707 on change in NRS score for pain interference

with daily activities was observed in the Japanese population Table 10. NRS scores for pain interference with daily activities in the European population Table 11 were comparable to those in the overall population Table 9.

In the overall population, a large placebo effect on dyspareunia reduction was observed, which was similar to or better than that of ASP1707 for deep dyspareunia and which was similar to or slightly worse than that of ASP1707 for superficial dyspareunia. There were no statistically significant differences in the change from baseline to week 12 in mean NRS pain scores between the placebo group and the ASP1707 groups (P = 0.704 and P = 0.853 for deep and superficial dyspareunia, respectively). At week 24 compared to week 12, there was a slight additional reduction in all ASP1707 dose groups except for the ASP1707 3 mg group. The numbers of patients with superficial or deep dyspareunia in the Japanese population were too small to draw meaningful conclusions.

In this study, a response was defined as a reduction of at least 30%, 50%, 60% or 70% in the mean NRS pain score from baseline to EoT over the last 28 days. Responder analyses were conducted without and with adjustment for increase of rescue medication at EoT (the 30% unadjusted responder analysis was prespecified and the remaining responder analyses were posthoc analyses). In the overall population (FAS1), for overall pelvic pain, dysmenorrhea and NMPP, respectively, the linear trend among the ASP1707 dose groups in part 1 was statistically significant for responder patients with a reduction from baseline to EoT of part 1 (week 12) in mean NRS pain score of at least 60%, 70% and 60% (which were identified as meaningful changes), irrespective of adjustment for increase of rescue medication use at EoT.

30% responder analyses (not adjusted for increase of rescue medication use at EoT):

- In the overall population, the linear trend among the ASP1707 dose groups in part 1 was statistically significant for overall pelvic pain (P = 0.003) Table 12 and dysmenorrhea (P < 0.001) Table 13, but not for NMPP (P = 0.058) Table 14.
- In the overall population in part 2, the percentage of responder patients at EoT (week 24) compared to week 12 had increased in most ASP1707 dose groups, with responder rates remaining unchanged in the ASP1707 10 mg (overall pelvic pain Table 12, NMPP Table 14) and 15 mg (dysmenorrhea Table 13) groups.
- Comparable results were obtained in the Japanese population and European population; the highest response rates for all 3 pain endpoints were observed in the ASP1707 10 mg group Table 12, Table 13 and Table 14.

50%, 60% and 70% responder analyses (not adjusted for increase of rescue medication use at EoT):

- In the overall population, the linear trend among the ASP1707 dose groups in part 1 was statistically significant for overall pelvic pain (P < 0.001 in all 3 analyses) Table 12, dysmenorrhea (P < 0.001 in all 3 analyses) Table 13 and NMPP (50% responder analysis, P = 0.039; 60% responder analysis, P = 0.026; and 70% responder analysis, P = 0.011) Table 14.
- In the overall population in part 2, the percentage of responder patients at EoT (week 24) compared to week 12 had increased in all ASP1707 dose groups for overall pelvic pain Table 12 and NMPP Table 14 and in the ASP1707 3 mg and 5 mg groups for dysmenorrhea Table 13.
- In general, comparable results were obtained in the Japanese population and European population Table 12, Table 13 and Table 14.

30%, 50%, 60% and 70% responder analyses (adjusted for increase of rescue medication use at EoT, i.e., patients who increased their rescue medication use at EoT are considered nonresponders):

- In the overall population, the linear trend among the ASP1707 dose groups in part 1 was statistically significant for overall pelvic pain (P < 0.001 in all 4 analyses) Table 15, dysmenorrhea (P < 0.001 in all 4 analyses) Table 16 and NMPP (30% responder analysis, P = 0.004; 50% responder analysis, P = 0.005; 60% responder analysis, P = 0.006; and 70% responder analysis, P = 0.002) Table 17.
- In the overall population in part 2, the percentage of responder patients at EoT (week 24) compared to week 12 had increased in all ASP1707 dose groups for overall pelvic pain Table 15 and NMPP Table 17 and in the ASP1707 3 mg and 5 mg groups for dysmenorrhea Table 16.
- In general, comparable results were obtained in the Japanese population and European population Table 15 Table 16 and Table 17.

Dyspareunia responders: The placebo response rates were high for superficial dyspareunia (30% responder analysis: placebo, 52.3% vs ASP1707 dose groups, 56.8% to 66.7%) and deep dyspareunia (30% responder analysis: placebo, 63.3% vs ASP1707 dose groups, 58.0% to 70.8%). In the 30% and 50% responder analyses in the overall population (not adjusted for increase of rescue medication use at EoT), the linear trend among the ASP1707 dose groups in part 1 was not statistically significant for superficial dyspareunia (30% responder analysis, P = 0.211; 50% responder analysis, P = 0.386) or deep dyspareunia (30% responder analysis, P = 0.434; 50% responder analysis, P = 0.960). In part 2 for both responder analyses, the percentage of responder patients at EoT (week 24) compared to week 12 had increased in the ASP1707 15 mg group and remained relatively unchanged in all other ASP1707 groups for deep dyspareunia and had increased in all ASP1707 dose groups for superficial dyspareunia. ASP1707 treatment for up to 24 weeks appears not to worsen superficial dyspareunia (i.e., vaginal dryness). The small number of responders in the Japanese population does not allow comparisons between the Japanese and overall populations in the responder rates for superficial or deep dyspareunia.

The outcomes of the monthly assessed modified B&B scale in the overall population showed a statistically significant treatment effect of ASP1707 from baseline to week 12 for the sign of pelvic tenderness (P < 0.001) and the symptoms of dysmenorrhea (P < 0.001) and NMPP (P = 0.012). A treatment effect of ASP1707 was also observed from baseline to week 24 for the sign of pelvic tenderness and the symptoms of dysmenorrhea and NMPP. In the Japanese population, a smaller proportion of patients generally showed a decrease in severity compared to the corresponding treatment groups in the overall population. For dysmenorrhea and NMPP in the overall population, the outcomes of the monthly assessed modified B&B scale from baseline to week 12 were in line with those of the daily assessed NRS.

At week 12 and week 24 in the overall population, the percentage of patients who used protocol-defined rescue medication decreased with increasing ASP1707 dose. The change from baseline to week 12 compared to placebo in the number of days with rescue medication use was statistically significant in the ASP1707 10 mg group (P = 0.002) and ASP1707 15 mg group (P = 0.047). In the ASP1707 10 mg group, the change from baseline to week 12 compared to placebo was statistically significant for the percentage of days with rescue medication use (P = 0.004) and the mean daily dosage of rescue medication (P = 0.008). Comparable results were obtained in the Japanese population, although Japanese patients compared to overall patients had lower baseline values for mean percentage of days with rescue medication use and mean daily dosage of rescue medication use.

The total score for BPI pain interference was analyzed for the overall population (FAS1) only. Compared to placebo, the change (decrease) from baseline to week 12 in mean total score for BPI pain interference was statistically significant only in the ASP1707 10 mg group (P = 0.007).

With regards to the proportion of patients in the PGIC categories at week 12, a statistically significant effect of ASP1707 compared to placebo was observed in the overall population (P < 0.001). The majority of patients in all treatment groups evaluated their clinical condition at week 12 relative to baseline as "Much improved" or "Minimally improved." At week 12, the effect of ASP1707 compared to placebo was also statistically significant with regards to the proportion of patients in the derived PGIC categories of "Improved" vs "No change or worse" (P < 0.001). At week 24 compared to week 12, proportions of patients had increased in the "Much improved" and "Very much improved" categories. Comparable results at weeks 12 and 24 were obtained in the Japanese population, which had a notably lower placebo effect than the overall population (40.0% vs 60.0% of placebo patients evaluated their clinical condition at week 12 relative to baseline as "Improved").

For the EHP-5, the linear trend among the ASP1707 dose groups from baseline to week 12 was statistically significant for 9 of the 11 EHP-5 items, with higher decreases in mean scores for the EHP-5 items in higher dose groups of ASP1707; the linear trend was not statistically significant for lack of social support (P = 0.105) or infertility (P = 0.282). The mean change from baseline to week 12 in the scores for most EHP-5 items was greater in the ASP1707 dose groups than in the placebo group (scores for self-image and infertility in the ASP1707 3 mg group were smaller than those in the placebo group). In general, the change from baseline to week 24 in mean scores for the EHP-5 items was comparable to the change from baseline to week 12.

Pharmacokinetic Results: The predose plasma concentration of $ASP1707_{total}$ increased with increasing ASP1707 dose.

At steady state in patients receiving ASP1707 10 mg or 15 mg, the sum of the plasma concentrations of ASP1707 and AS1948006 (i.e., $ASP1707_{sum}$) is similar to the plasma concentration of $ASP1707_{total}$.

The pharmacokinetic findings were comparable between the overall and Japanese populations.

Pharmacodynamic Results: $ASP1707_{total}$ showed a clear dose-dependent decrease in serum E2 levels. However, E2 results were highly variable both between and within patients. Due to this variability and the skewness of the data, medians were used in addition to means. Median serum concentrations of E2 were within the target range (20-50 pg/mL) for all time points during treatment with ASP1707 10 mg and 15 mg. Decreases in mean serum E2 levels from baseline to EoT of part 1 were greater in all ASP1707 dose groups than in the placebo group. In the leuprorelin group, decreases from baseline in mean serum concentrations of E2 were greater than in all ASP1707 dose groups. Mean and median serum E2 concentrations in the leuprorelin group were below the lower limit of the target range (20 pg/mL) from week 4 to EoT (parts 1 and 2).

Dose-dependent decreases in serum LH levels were observed after ASP1707 treatment for 12 weeks (ASP1707 5 mg and 15 mg groups [decreases were greater than in the placebo group]) and 24 weeks (ASP1707 5 mg, 10 mg and 15 mg groups). Decreases in mean serum levels of LH were greater with leuprorelin than with ASP1707.

Across the ASP1707 dose groups, no clear dose-response in the serum levels of FSH was noted. Compared to the ASP1707 dose groups, mean serum FSH levels were similar in the placebo group and were lower in the leuprorelin group.

$ASP1707_{total}$ showed a dose-dependent decrease in serum progesterone levels in all ASP1707 dose groups after 12 and 24 weeks of treatment. Decreases in mean serum progesterone levels from baseline to EoT of part 1 were greater in all ASP1707 dose groups than in the placebo group. Decreases in mean serum levels of progresterone with leuprorelin were comparable to those with ASP1707 10 mg and ASP1707 15 mg.

Regarding the change from baseline in serum bALP, the linear trend among the ASP1707 dose groups was not statistically significant at EoT of part 1 (P = 0.078), but was statistically significant at EoT of part 2 (P = 0.001). At EoT of part 1, serum levels of bALP were similar between the placebo group and the ASP1707 dose groups. At EoT of part 2 compared to EoT of part 1, the mean change from baseline in serum bALP had increased across the ASP1707 dose groups. The changes were relatively small, with the largest change seen in the ASP1707 15 mg group. The change observed in the leuprorelin group was similar to that in the ASP1707 15 mg group.

The linear trend among the ASP1707 dose groups was statistically significant for the change from baseline in urine NTx/creatinine at EoT of part 1 (P < 0.001) and at EoT of part 2 (P = 0.005). At EoT of part 1, the change from baseline in urine NTx/creatinine compared to placebo was statistically significantly greater in the ASP1707 15 mg group (P < 0.001). At EoT of part 2 compared to EoT of part 1, the mean change from baseline in urine NTx/creatinine was relatively unchanged in the ASP1707 5 mg group, had decreased in the ASP1707 3 mg and 10 mg groups and had increased in the ASP1707 15 mg group. In the leuprorelin group, the change from baseline in urine NTx/creatinine at EoT of part 1 and at EoT of part 2 was more than 2-fold greater than that in the ASP1707 15 mg group.

Safety Results: In the overall population, the incidence of TEAEs was generally comparable across all doses of ASP1707 and leuprorelin. At least 1 TEAE was experienced during part 1 of the study by 50.0% of placebo-treated patients, 57.2% of ASP1707-treated patients and 58.4% of leuprorelin-treated patients and, in parts 1 and 2 combined among patients who remained within the same treatment group for the entire duration of the study, by 67.3% of ASP1707-treated patients and 65.2% of leuprorelin-treated patients.

The 2 most commonly reported TEAEs were hot flash and headache Table 18 and Table 19. The incidence of hot flash was lower in the ASP1707 dose groups than in the leuprorelin group (part 1: ASP1707 3 mg to 15 mg vs leuprorelin, 4.7% to 19.3% vs 28.1%; entire study: ASP1707 3 mg to 15 mg vs leuprorelin, 7.0% to 21.6% vs 28.1%) Table 18. The incidence of headache was lower in the ASP1707 dose groups than in the leuprorelin group (part 1: ASP1707 3 mg to 15 mg vs leuprorelin, 6.6% to 13.6% vs 16.9%; entire study: ASP1707 3 mg to 15 mg vs leuprorelin, 11.0% to 17.0% vs 20.2%).

In part 1 of the study, severe TEAEs were most frequently reported in the leuprorelin group (12.4%), followed by the ASP1707 15 mg (10.2%), ASP1707 10 mg (10.0%) and ASP1707 3 mg (9.3%). In parts 1 and 2 combined among patients who remained on the same treatment throughout the study, the incidence of severe TEAEs during the entire study was comparable between the leuprorelin group (14.6%) and the ASP1707 dose groups (ASP1707 10 mg: 14.4%; ASP1707 15 mg: 13.6%; ASP1707 5 mg: 11.0%; ASP1707 3 mg: 10.5%).

No deaths were reported during the study. During part 1, 5 serious TEAEs were reported (1 placebo vs 4 ASP1707 [3 ASP1707 3 mg, 1 ASP1707 10 mg]) Table 20. Of the patients in parts 1 and 2 combined who remained within the same treatment group for the entire study duration (24 weeks), 8 patients experienced serious TEAEs with onset in part 2 (all ASP1707 [6 ASP1707 5 mg and 1 each ASP1707 10 mg and 15 mg]) Table 21. In addition, serious TEAEs with onset in part 2 were experienced by 2 patients who received

placebo in part 1 and ASP1707 in part 2 (1 patient received placebo followed by ASP1707 5 mg and 1 patient received placebo followed by ASP1707 10 mg) Table 22. Of the serious TEAEs, a dural fistula in part 1 and an LFT abnormal in part 2 were assessed by the investigator as probably related to study drug.

In general, no clinically significant effects on hematology and biochemistry laboratory abnormalities were observed. Clinically significant elevations in LFTs were observed in few ASP1707-treated patients and were generally transient.

Among ASP1707-treated patients, no clinically significant treatment-emergent trend was noted in the vital sign parameters and no clear pattern or dose-related trend was observed in vital signs. No clinically significant abnormal ECG findings were reported.

Leuprorelin and all ASP1707 dose groups showed statistically significant losses in BMD at week 24 compared to baseline. However, treatment with ASP1707 compared to leuprorelin resulted in statistically significantly less BMD loss at 24 weeks. The effect of ASP1707 on BMD of spine was lower for the 10-mg dose compared to the 15-mg dose. In the ASP1707 10 mg group, mean BMD loss was -1.19% for total hip and -1.32% for spine; in the ASP1707 15 mg group, mean BMD loss was -1.34% for total hip and -2.25% for spine; and in the leuprorelin group, mean BMD loss was -2.30% for total hip and -3.91% for spine. The percentage decrease in mean BMD with leuprorelin observed in this study is in line with that observed in previous clinical studies with leuprorelin.

A dose-dependent trend for ASP1707 was observed from baseline to 12 weeks of treatment in the reduction of mean number of bleeding days (ASP1707 10 mg vs ASP1707 15 mg: reduction from 6 to 3 vs 2 bleeding days) and increase in the percentage of patients with amenorrhea (ASP1707 10 mg vs ASP1707 15 mg: 35.6% vs 56.8% of patients achieved amenorrhea).

At the end of 12 weeks of treatment for hot flashes as recorded in the e-diary, the linear trend among the ASP1707 dose groups was statistically significant (P = 0.001) for the number of hot flashes over the last 28 days, and the number of hot flashes was statistically significantly higher (P = 0.002) in the ASP1707 15 mg group compared to the placebo group.

In terms of the safety results, the Japanese and European populations were generally comparable to the overall population.

CONCLUSIONS:

Overall, ASP1707 showed dose-dependent efficacy in reducing endometriosis-associated pelvic pain. A statistically significant linear trend was found among the ASP1707 treatment groups for overall pelvic pain, dysmenorrhea and NMPP, with higher decreases in mean NRS pain scores in higher dose groups of ASP1707. In addition, a statistically significant improvement compared to placebo was found for overall pelvic pain with ASP1707 10 mg and for dysmenorrhea with all ASP1707 doses.

For overall pelvic pain, dysmenorrhea and NMPP, respectively, the linear trend among the ASP1707 dose groups in part 1 was statistically significant for responder patients with a reduction from baseline to EoT of part 1 (week 12) in mean NRS pain score of at least 60%, 70% and 60% (which were identified as meaningful changes), irrespective of adjustment for increase of rescue medication use at EoT.

When adjusted for increase of rescue medication use at EoT (i.e., patients who increased their rescue medication use at EoT are considered nonresponders), the percentage of responder patients (30%, 50%, 60% and 70%

responder analyses) at week 12 compared to placebo was statistically significantly greater for overall pelvic pain, dysmenorrhea and NMPP in the ASP1707 10 mg and 15 mg groups.

The primary analyses were supported by the analyses of the secondary efficacy endpoints of NRS score for pain interference with daily activities and EHP-5, a questionnaire for measuring health status in women with endometriosis. ASP1707 10 mg and ASP1707 15 mg were statistically significantly better than placebo and were comparable to leuprorelin in reducing NRS score for pain interference with daily activities. In the EHP-5, mean scores for 9 of the 11 EHP-5 items decreased with increasing ASP1707 doses. Changes from baseline in most EHP-5 items were broadly similar between the ASP1707 10 mg and 15 mg groups.

In this phase 2 combined proof-of-concept and dose finding study, ASP1707 appeared to be well tolerated and effective in the treatment of endometriosis-associated pelvic pain.

At all doses tested, ASP1707 showed dose-dependent decreases in BMD. The effect of ASP1707 on BMD was considerably smaller than that of leuprorelin.

Although ASP1707 10 mg and 15 mg have similar effects on endometriosis pain reduction, 10 mg has less effect on BMD (spine) and therefore a slightly better benefit:risk profile.

Date of Report: 09 Mar 2016

Table 1 Patient Disposition and Analysis Sets – Part 1, Overall Population (Randomized Patients)

Parameter	Placebo (n = 89)	ASP1707 3 mg (n = 87)	ASP1707 5 mg (n = 92)	ASP1707 10 mg (n = 90)	ASP1707 15 mg (n = 90)	Leuprorelin (n = 92)	Total (n = 540)
Randomized, n (%)							
SAF1†	88 (98.9)	86 (98.9)	91 (98.9)	90 (100.0)	88 (97.8)	89 (96.7)	532 (98.5)
FAS1‡	81 (91.0)	77 (88.5)	87 (94.6)	82 (91.1)	84 (93.3)	83 (90.2)	494 (91.5)
PPS1§	77 (86.5)	71 (81.6)	81 (88.0)	76 (84.4)	76 (84.4)	78 (84.8)	459 (85.0)
PKAS¶	80 (89.9)	76 (87.4)	86 (93.5)	82 (91.1)	84 (93.3)	0	408 (75.6)
PDAS††	87 (97.8)	81 (93.1)	89 (96.7)	88 (97.8)	85 (94.4)	87 (94.6)	517 (95.7)
Discontinued, n (%)							
Yes	14 (15.7)	16 (18.4)	8 (8.7)	14 (15.6)	15 (16.7)	16 (17.4)	83 (15.4)
Protocol violation	9 (10.1)	11 (12.6)	3 (3.3)	9 (10.0)	5 (5.6)	5 (5.4)	42 (7.8)
Withdrawal by patient	2 (2.2)	1 (1.1)	2 (2.2)	4 (4.4)	3 (3.3)	6 (6.5)	18 (3.3)
Adverse event	0	3 (3.4)	0	1 (1.1)	5 (5.6)	1 (1.1)	10 (1.9)
Randomized/registered but never received/dispensed study drug	1 (1.1)	1 (1.1)	1 (1.1)	0	2 (2.2)	3 (3.3)	8 (1.5)
Pregnancy	1 (1.1)	0	1 (1.1)	0	0	0	2 (0.4)
Other	1 (1.1)	0	1 (1.1)	0	0	1 (1.1)	3 (0.6)

FAS1: full analysis set 1; NRS: numeric rating scale; PDAS: pharmacodynamic analysis set; PKAS: pharmacokinetic analysis set; PPS1: per protocol set 1; SAF1: safety analysis set 1.

† All randomized patients who took at least 1 dose of study medication (ASP1707 or leuprorelin or placebo).

‡ All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

§ All patients from the FAS1 who did not meet criteria for exclusion from the PPS1.

¶ All patients from the SAF1 population for whom at least 1 plasma sample was collected to determine the ASP1707 plasma concentration.

†† All patients from the SAF1 for whom at least 1 sample was collected.

Source: Tables 12.1.1.2.1.1, 12.1.1.4.1.1

Table 2 Patient Disposition and Analysis Sets – Part 1, Japanese Population (Randomized Patients)

Parameter	Placebo (n = 24)	ASP1707 3 mg (n = 25)	ASP1707 5 mg (n = 25)	ASP1707 10 mg (n = 25)	ASP1707 15 mg (n = 25)	Leuprorelin (n = 25)	Total (n = 149)
Randomized, n (%)							
SAF1†	24 (100.0)	25 (100.0)	25 (100.0)	25 (100.0)	25 (100.0)	24 (96.0)	148 (99.3)
FAS1‡	20 (83.3)	22 (88.0)	24 (96.0)	23 (92.0)	25 (100.0)	22 (88.0)	136 (91.3)
PPS1§	20 (83.3)	21 (84.0)	23 (92.0)	20 (80.0)	22 (88.0)	20 (80.0)	126 (84.6)
PKAS¶	20 (83.3)	21 (84.0)	24 (96.0)	22 (88.0)	25 (100.0)	0	112 (75.2)
PDAS††	24 (100.0)	23 (92.0)	25 (100.0)	24 (96.0)	25 (100.0)	24 (96.0)	145 (97.3)
Discontinued, n (%)							
Yes	5 (20.8)	4 (16.0)	1 (4.0)	5 (20.0)	3 (12.0)	8 (32.0)	26 (17.4)
Protocol violation	4 (16.7)	2 (8.0)	1 (4.0)	3 (12.0)	0	2 (8.0)	12 (8.1)
Withdrawal by patient	0	0	0	1 (4.0)	1 (4.0)	4 (16.0)	6 (4.0)
Adverse event	0	2 (8.0)	0	1 (4.0)	2 (8.0)	0	5 (3.4)
Randomized/registered but never received/dispensed study drug	0	0	0	0	0	1 (4.0)	1 (0.7)
Other	1 (4.2)	0	0	0	0	1 (4.0)	2 (1.3)

FAS1: full analysis set 1; NRS: numeric rating scale; PDAS: pharmacodynamic analysis set; PKAS: pharmacokinetic analysis set; PPS1: per protocol set 1; SAF1: safety analysis set 1.

† All randomized patients who took at least 1 dose of study medication (ASP1707 or leuprorelin or placebo).

‡ All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

§ All patients from the FAS1 who did not meet criteria for exclusion from the PPS1.

¶ All patients from the SAF1 population for whom at least 1 plasma sample was collected to determine the ASP1707 plasma concentration.

†† All patients from the SAF1 for whom at least 1 sample was collected.

Source: Tables 12.1.1.2.2.1 and 12.1.1.4.2.1

Table 3 Patient Disposition and Analysis Sets – Part 1, European Population (Randomized Patients)

Parameter	Placebo (n = 65)	ASP1707 3 mg (n = 62)	ASP1707 5 mg (n = 67)	ASP1707 10 mg (n = 65)	ASP1707 15 mg (n = 65)	Leuprorelin (n = 67)	Total (n = 391)
Randomized, n (%)							
SAF1†	64 (98.5)	61 (98.4)	66 (98.5)	65 (100.0)	63 (96.9)	65 (97.0)	384 (98.2)
FAS1‡	61 (93.8)	55 (88.7)	63 (94.0)	59 (90.8)	59 (90.8)	61 (91.0)	358 (91.6)
PPS1§	57 (87.7)	50 (80.6)	58 (86.6)	56 (86.2)	54 (83.1)	58 (86.6)	333 (85.2)
PKAS¶	60 (92.3)	55 (88.7)	62 (92.5)	60 (92.3)	59 (90.8)	0	296 (75.7)
PDAS††	63 (96.9)	58 (93.5)	64 (95.5)	64 (98.5)	60 (92.3)	63 (94.0)	372 (95.1)
Discontinued, n (%)							
Yes	9 (13.8)	12 (19.4)	7 (10.4)	9 (13.8)	12 (18.5)	8 (11.9)	57 (14.6)
Protocol violation	5 (7.7)	9 (14.5)	2 (3.0)	6 (9.2)	5 (7.7)	3 (4.5)	30 (7.7)
Withdrawal by patient	2 (3.1)	1 (1.6)	2 (3.0)	3 (4.6)	2 (3.1)	2 (3.0)	12 (3.1)
Adverse event	0	1 (1.6)	0	0	3 (4.6)	1 (1.5)	5 (1.3)
Randomized/registered but never received/dispensed study drug	1 (1.5)	1 (1.6)	1 (1.5)	0	2 (3.1)	2 (3.0)	7 (1.8)
Pregnancy	1 (1.5)	0	1 (1.5)	0	0	0	2 (0.5)
Other	0	0	1 (1.5)	0	0	0	1 (0.3)

FAS1: full analysis set 1; NRS: numeric rating scale; PDAS: pharmacodynamic analysis set; PKAS: pharmacokinetic analysis set; PPS1: per protocol set 1; SAF1: safety analysis set 1.

† All randomized patients who took at least 1 dose of study medication (ASP1707 or leuprorelin or placebo).

‡ All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

§ All patients from the FAS1 who did not meet criteria for exclusion from the PPS1.

¶ All patients from the SAF1 population for whom at least 1 plasma sample was collected to determine the ASP1707 plasma concentration.

†† All patients from the SAF1 for whom at least 1 sample was collected.

Source: Tables 12.1.1.2.3.1 and 12.1.1.4.3.1

Table 4 Summary of Demographics and Baseline Characteristics – Overall Population (SAF1)

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 (72.7)	61 (70.9)	65 (71.4)	65 (72.2)	63 (71.6)	254 (71.5)	65 (73.0)	383 (72.0)
Asian	24 (27.3)	25 (29.1)	25 (27.5)	25 (27.8)	25 (28.4)	100 (28.2)	24 (27.0)	148 (27.8)
Other†	0	0	1 (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 (52.3)	49 (57.0)	52 (57.1)	44 (48.9)	43 (48.9)	188 (53.0%)	51 (57.3)	285 (53.6%)
Prior surgical treatment	85 (96.6)	81 (94.2)	84 (92.3)	87 (96.7)	88 (100.0)	340 (95.8%)	86 (96.6)	511 (96.1%)
Ever pregnant (yes), n (%)	45 (51.1)	44 (51.2)	38 (41.8)	43 (47.8)	42 (47.7)	167 (47.0)	36 (40.4)	248 (46.6)
Previous adenomyosis history, n (%)	13 (14.8)	15 (17.4)	13 (14.3)	20 (22.2)	13 (14.8)	61 (17.2)	11 (12.4)	85 (16.0)

BMI: body mass index; Max: maximum; Min: minimum; SAF1: safety analysis set 1.

SAF1: All randomized patients who took at least 1 dose of study medication (ASP1707 or leuprorelin acetate or placebo).

† Black or African American and other race categories combined.

Source: Tables 12.1.2.1.1.1, 12.1.2.2.1.1, 12.1.2.3.1.1 and 12.1.2.4.1.1

Table 5 Demographic and Baseline Characteristics – Japanese Population (SAF1)

Parameter	Placebo (n = 24)	ASP1707 3 mg (n = 25)	ASP1707 5 mg (n = 25)	ASP1707 10 mg (n = 25)	ASP1707 15 mg (n = 25)	ASP1707 Total (n = 100)	Leuprorelin (n = 24)	Total (n = 148)
Race, n (%)								
White	0	0	0	0	0	0	0	0
Asian	24 (100.0)	25 (100.0)	25 (100.0)	25 (100.0)	25 (100.0)	100 (100.0)	24 (100.0)	148 (100.0)
Other†	0	0	0	0	0	0	0	0
Mean (Min-Max)								
Age (years)	34.3 (21-45)	36.8 (22-45)	36.3 (30-43)	34.9 (21-45)	35.6 (23-45)	35.9 (21-45)	34.5 (22-45)	35.4 (21-45)
Weight (kg)	56.8 (44-75)	56.4 (42-77)	58.2 (46-86)	56.2 (36-80)	56.0 (44-81)	56.7 (36-86)	54.3 (37-74)	56.3 (36-86)
Height (cm)	160.3 (149-169)	160.5 (151-169)	162.0 (151-168)	161.4 (153-170)	160.9 (149-176)	161.2 (149-176)	161.2 (147-170)	161.1 (147-176)
BMI (kg/m^2)	22.1 (18-32)	21.9 (17-27)	22.2 (17-32)	21.6 (15-33)	21.6 (18-33)	21.8 (15-33)	20.8 (17-28)	21.7 (15-33)
Mean (Min-Max)								
Menstruation								
Cycle length (days)	28.3 (24-31)	27.4 (24-34)	27.8 (25-31)	28.5 (25-32)	27.4 (25-30)	27.8 (24-34)	27.8 (25-30)	27.9 (24-34)
Age (years) at menarche	11.0 (9-14)	11.4 (8-14)	11.6 (8-15)	11.1 (8-13)	11.3 (10-13)	11.3 (8-15)	11.2 (8-14)	11.3 (8-15)
Mean (Min-Max)								
Endometriosis onset								
Age (years) at onset	29.2 (16-43)	30.6 (17-41)	32 (17-41)	30.1 (19-44)	32.0 (19-42)	31.2 (17-44)	31.0 (22-43)	30.8 (16-44)
Months since onset	60.6 (2-278)	72.8 (2-213)	50.7 (1-189)	58.0 (1-266)	42.3 (1-124)	55.9 (1-266)	42.0 (5-128)	54.4 (1-278)
Previous endometriosis history, n (%)								
Prior medication treatment	22 (91.7)	24 (96.0)	24 (96.0)	22 (88.0)	24 (96.0)	94 (94.0)	22 (91.7)	138 (93.2)
Prior surgical treatment	22 (91.7)	24 (96.0)	23 (92.0)	24 (96.0)	25 (100.0)	96 (96.0)	23 (95.8)	141 (95.3)
Ever pregnant (yes), n (%)	12 (50.0)	13 (52.0)	13 (52.0)	6 (24.0)	11 (44.0)	43 (43.0)	7 (29.2)	62 (41.9)
Previous adenomyosis history, n (%)	4 (16.7)	8 (32.0)	6 (24.0)	12 (48.0)	9 (36.0)	35 (35.0)	5 (20.8)	44 (29.7)

BMI: body mass index; Max: maximum; Min: minimum; SAF1: safety analysis set 1.

SAF1: All randomized patients who took at least 1 dose of study medication (ASP1707 or leuprorelin acetate or placebo).

† Black or African American and other race categories combined.

Source: Tables 12.1.2.1.2.1; 12.1.2.2.2.1; 12.1.2.3.2.1; 12.1.2.4.2.1

Table 6 Change From Baseline to Week 12 (EoT for Part 1) in Mean NRS Pain Score for Overall Pelvic Pain, Dysmenorrhea and NMPP – Overall Population (FAS1)

Parameter	Placebo (n = 81)	ASP1707 3 mg (n = 77)	ASP1707 5 mg (n = 87)	ASP1707 10 mg (n = 82)	ASP1707 15 mg (n = 84)	P value†	Estimate†	Leuprorelin (n = 83)
Overall pelvic pain								
Raw mean (SD)								
Baseline	4.12 (1.84)	3.94 (1.73)	4.17 (1.56)	4.05 (1.71)	4.10 (1.84)	—	—	4.20 (1.80)
Week 12 (EoT)	2.41 (1.81)	2.25 (1.86)	2.08 (1.78)	1.65 (1.50)	1.85 (2.09)	—	—	1.62 (2.06)
CFB to week 12	-1.71 (1.80)	-1.69 (1.52)	-2.09 (1.81)	-2.39 (1.62)	-2.25 (1.99)	—	—	-2.58 (2.11)
Mean Percentage CFB to week 12	-38.7 (36.7)	-43.8 (37.7)	-49.0 (39.1)	-60.1 (31.2)	-55.8 (44.4)	—	—	-64.2 (41.1)
Adjusted Mean CFB to week 12	-1.56	-1.63	-1.93	-2.29	-2.13	—	-1.8015	—
95% CI	(-1.91, -1.21)	(-1.99, -1.27)	(-2.27, -1.60)	(-2.64, -1.94)	(-2.47, -1.79)	0.001	—	—
Difference vs Placebo								
Mean		-0.07	-0.37	-0.73	-0.57	—	—	—
95% CI		(-0.68, 0.54)	(-0.96, 0.22)	(-1.32, -0.13)	(-1.17, 0.02)	—	—	—
P value‡		0.996	0.338	0.011	0.063	—	—	—
Dysmenorrhea								
Raw mean (SD)								
Baseline	5.93 (1.56)	5.21 (1.72)	5.30 (1.75)	5.46 (1.52)	5.48 (1.84)	—	—	5.74 (1.59)
Week 12 (EoT)	4.05 (2.26)	2.66 (2.21)	2.54 (2.47)	1.46 (2.09)	1.26 (2.17)	—	—	0.34 (1.23)
CFB to week 12	-1.89 (2.53)	-2.55 (2.41)	-2.76 (2.51)	-4.00 (2.33)	-4.22 (2.88)	—	—	-5.40 (1.81)
Mean Percentage CFB to week 12	-26.2 (52.2)	-24.1 (212.1)	-51.8 (49.3)	-72.8 (41.1)	-71.3 (55.2)	—	—	-94.5 (18.9)
Adjusted Mean CFB to week 12	-1.50	-2.72	-2.85	-3.97	-4.18	—	-6.6156	—
95% CI	(-2.00, -1.00)	(-3.22, -2.21)	(-3.33, -2.38)	(-4.46, -3.48)	(-4.66, -3.70)	< 0.001	—	—
Difference vs Placebo								
Mean		-1.22	-1.35	-2.47	-2.68	—	—	—
95% CI		(-2.09, -0.35)	(-2.19, -0.51)	(-3.32, -1.62)	(-3.53, -1.83)	—	—	—
P value‡		0.003	< 0.001	< 0.001	< 0.001	—	—	—

Table continued on next page

Parameter	Placebo (n = 81)	ASP1707 3 mg (n = 77)	ASP1707 5 mg (n = 87)	ASP1707 10 mg (n = 82)	ASP1707 15 mg (n = 84)	P value†	Estimate†	Leuprorelin (n = 83)
NMPP								
Raw mean (SD)								
Baseline	3.70 (2.13)	3.62 (1.94)	3.88 (1.81)	3.68 (1.94)	3.77 (2.07)	—	—	3.78 (2.09)
Week 12 (EoT)	2.02 (1.90)	2.02 (1.87)	1.87 (1.79)	1.54 (1.50)	1.77 (2.08)	—	—	1.60 (2.07)
CFB to week 12	-1.68 (1.83)	-1.60 (1.61)	-2.00 (1.91)	-2.14 (1.75)	-2.01 (2.03)	—	—	-2.18 (2.26)
Mean Percentage CFB to week 12	-39.7 (84.5)	-42.0 (55.7)	-46.5 (53.2)	-56.1 (45.8)	-43.1 (116.0)	—	—	-59.8 (44.4)
Adjusted Mean CFB to week 12	-1.53	-1.51	-1.80	-2.03	-1.86	—	-1.1723	—
95% CI	(-1.88, -1.19)	(-1.87, -1.16)	(-2.14, -1.47)	(-2.37, -1.68)	(-2.20, -1.52)	0.029	—	—
Difference vs Placebo								
Mean		0.02	-0.27	-0.49	-0.33	—	—	—
95% CI		(-0.58, 0.62)	(-0.85, 0.31)	(-1.08, 0.09)	(-0.91, 0.26)	—	—	—
P value‡		1.000	0.616	0.127	0.448	—	—	—

CFB: change from baseline; EoT: end-of-treatment; FAS1: full analysis set 1; NMPP: nonmenstrual pelvic pain; NRS: numeric rating scale

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Adjusted means, CIs, differences versus placebo and P values are adjusted for region and overall pelvic pain to baseline. Leuprorelin is included for comparison, and is not part of the primary analysis. Values for raw means, SDs and changes from baseline are unadjusted.

† Overall treatment effect from linear trend. (Primary)

‡ Pairwise comparisons of each active group vs placebo based on Dunnett's test. (Tested after primary)

Source: Tables 12.3.1.1.1.1, 12.3.1.2.1.1, 12.3.1.8.1.1, 12.3.2.1.1.1, 12.3.2.2.1.1, 12.3.2.8.1.1, 12.3.3.1.1.1, 12.3.3.2.1.1 and 12.3.3.8.1.1

Table 7 Change From Baseline to Week 12 (EoT for Part 1) in Mean NRS Pain Score for Overall Pelvic Pain, Dysmenorrhea and NMPP – Japanese Population (FAS1)

Parameter	Placebo (n = 20)	ASP1707 3 mg (n = 22)	ASP1707 5 mg (n = 24)	ASP1707 10 mg (n = 23)	ASP1707 15 mg (n = 25)	P value†	Estimate†	Leuprorelin (n = 22)
Overall pelvic pain								
Raw mean (SD)								
Baseline	2.06 (1.34)	2.50 (1.08)	3.16 (1.28)	2.88 (1.76)	2.88 (1.81)	—	—	2.83 (1.34)
Week 12 (EoT)	1.47 (1.06)	1.38 (1.11)	2.13 (1.45)	1.44 (1.41)	1.56 (2.19)	—	—	1.48 (1.65)
CFB to week 12	-0.59 (0.69)	-1.11 (1.20)	-1.03 (1.06)	-1.44 (0.93)	-1.33 (1.24)	—	—	-1.36 (1.36)
Mean Percentage CFB to week 12	-26.7 (34.2)	-43.6 (46.2)	-35.0 (41.7)	-55.8 (31.5)	-55.4 (43.2)	—	—	-57.0 (45.6)
Adjusted Mean CFB to week 12	-0.74	-1.16	-0.93	-1.40	-1.29	—	-1.3373	—
95% CI	(-1.19, -0.29)	(-1.59, -0.74)	(-1.34, -0.52)	(-1.82, -0.99)	(-1.69, -0.89)	0.053	—	—
Difference vs Placebo								
Mean		-0.42	-0.19	-0.66	-0.55	—	—	—
95% CI		(-1.19, 0.35)	(-0.96, 0.58)	(-1.43, 0.10)	(-1.30, 0.20)	—	—	—
P value‡		0.449	0.922	0.109	0.215	—	—	—
Dysmenorrhea								
Raw mean (SD)								
Baseline	5.69 (1.34)	5.02 (1.45)	5.30 (1.66)	5.48 (1.34)	5.67 (1.80)	—	—	5.44 (1.59)
Week 12 (EoT)	4.75 (1.72)	2.48 (1.69)	2.74 (2.39)	1.48 (2.10)	1.17 (2.04)	—	—	0.41 (1.10)
CFB to week 12	-0.94 (1.68)	-2.54 (2.07)	-2.56 (2.14)	-4.00 (2.10)	-4.50 (2.73)	—	—	-5.03 (2.12)
Mean Percentage CFB to week 12	-15.1 (29.9)	-50.2 (32.9)	-50.3 (40.4)	-73.8 (37.0)	-74.2 (43.9)	—	—	-91.0 (24.7)
Adjusted Mean CFB to week 12	-0.77	-2.81	-2.65	-3.97	-4.35	—	-8.3172	—
95% CI	(-1.64, 0.10)	(-3.64, -1.98)	(-3.44, -1.85)	(-4.78, -3.16)	(-5.13, -3.57)	< 0.001	—	—
Difference vs Placebo								
Mean		-2.04	-1.88	-3.20	-3.58	—	—	—
95% CI		(-3.55, -0.54)	(-3.35, -0.41)	(-4.68, -1.72)	(-5.03, -2.13)	—	—	—
P value‡		0.004	0.007	<0.001	< 0.001	—	—	—

Table continued on next page

Parameter	Placebo (n = 20)	ASP1707 3 mg (n = 22)	ASP1707 5 mg (n = 24)	ASP1707 10 mg (n = 23)	ASP1707 15 mg (n = 25)	P value†	Estimate†	Leuprorelin (n = 22)
NMPP								
Raw mean (SD)								
Baseline	1.31 (1.47)	1.87 (1.17)	2.68 (1.53)	2.20 (1.96)	2.24 (2.09)	—	—	2.33 (1.57)
Week 12 (EoT)	0.82 (0.99)	1.09 (1.10)	1.89 (1.46)	1.33 (1.41)	1.46 (2.19)	—	—	1.47 (1.65)
CFB to week 12	-0.49 (0.64)	-0.78 (1.23)	-0.78 (1.19)	-0.87 (0.97)	-0.77 (1.32)	—	—	-0.86 (1.49)
Mean Percentage CFB to week 12	-18.1 (157.1)	-38.8 (80.9)	-28.0 (65.6)	-39.3 (68.3)	-12.0 (199.2)	—	—	-48.7 (53.7)
Adjusted Mean CFB to week 12	-0.73	-0.85	-0.60	-0.84	-0.73	—	0.0157	—
95% CI	(-1.17, -0.29)	(-1.26, -0.43)	(-1.00, -0.20)	(-1.24, -0.43)	(-1.12, -0.34)	0.981	—	—
Difference vs Placebo								
Mean		-0.12	0.13	-0.11	0	—	—	—
95% CI		(-0.87, 0.64)	(-0.63, 0.89)	(-0.86, 0.65)	(-0.74, 0.74)	—	—	—
P value‡		0.985	0.978	0.989	1.000	—	—	—

CFB: change from baseline; EoT: end-of-treatment; FAS1: full analysis set 1; NMPP: nonmenstrual pelvic pain; NRS: numeric rating scale

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Adjusted means, CIs, differences versus placebo and P values are adjusted for region and overall pelvic pain to baseline. Leuprorelin is included for comparison, and is not part of the primary analysis. Values for raw means, SDs and changes from baseline are unadjusted.

† Overall treatment effect from linear trend. (Primary)

‡ Pairwise comparisons of each active group vs placebo based on Dunnett's test. (Tested after primary)

Source: Tables 12.3.1.1.2.1, 12.3.1.2.2.1, 12.3.1.8.2.1, 12.3.2.1.2.1, 12.3.2.2.2.1, 12.3.2.8.2.1, 12.3.3.1.2.1, 12.3.3.2.2.1 and 12.3.3.8.2.1

Table 8 Change From Baseline to Week 12 (EoT for Part 1) in Mean NRS Pain Score for Overall Pelvic Pain, Dysmenorrhea and NMPP – European Population (FAS1)

Parameter	Placebo (n = 61)	ASP1707 3 mg (n = 55)	ASP1707 5 mg (n = 63)	ASP1707 10 mg (n = 59)	ASP1707 15 mg (n = 59)	P value†	Estimate†	Leuprorelin (n = 61)
Overall pelvic pain								
Raw mean (SD)								
Baseline	4.80 (1.43)	4.51 (1.60)	4.55 (1.49)	4.50 (1.47)	4.62 (1.60)	—	—	4.69 (1.70)
Week 12 (EoT)	2.71 (1.91)	2.59 (1.99)	2.06 (1.90)	1.74 (1.54)	1.98 (2.05)	—	—	1.67 (2.20)
CFB to week 12	-2.08 (1.90)	-1.92 (1.58)	-2.49 (1.88)	-2.77 (1.68)	-2.64 (2.13)	—	—	-3.02 (2.17)
Mean Percentage CFB to week 12	-42.6 (36.9)	-43.8 (34.1)	-54.3 (37.0)	-61.7 (31.2)	-56.0 (45.2)	—	—	-66.8 (39.4)
Adjusted Mean CFB to week 12	-1.99	-1.96	-2.51	-2.81	-2.63	—	-2.1384	—
95% CI	(-2.42, -1.56)	(-2.41, -1.51)	(-2.94, -2.09)	(-3.25, -2.37)	(-3.07, -2.20)	0.003	—	—
Difference vs Placebo								
Mean		0.03	-0.52	-0.82	-0.64	—	—	—
95% CI		(-0.75, 0.81)	(-1.28, 0.23)	(-1.59, -0.05)	(-1.41, 0.12)	—	—	—
P value‡		1.000	0.260	0.032	0.127	—	—	—
Dysmenorrhea								
Raw mean (SD)								
Baseline	6.01 (1.62)	5.29 (1.83)	5.30 (1.79)	5.46 (1.59)	5.41 (1.86)	—	—	5.85 (1.59)
Week 12 (EoT)	3.82 (2.38)	2.73 (2.39)	2.47 (2.51)	1.46 (2.10)	1.31 (2.24)	—	—	0.31 (1.28)
CFB to week 12	-2.20 (2.69)	-2.56 (2.55)	-2.83 (2.64)	-4.00 (2.43)	-4.10 (2.96)	—	—	-5.54 (1.68)
Mean Percentage CFB to week 12	-29.9 (57.5)	-13.6 (250.0)	-52.4 (52.6)	-72.4 (42.9)	-70.0 (59.7)	—	—	-95.8 (16.4)
Adjusted Mean CFB to week 12	-1.80	-2.72	-2.99	-4.03	-4.17	—	-6.0559	—
95% CI	(-2.38, -1.21)	(-3.33, -2.11)	(-3.56, -2.41)	(-4.62, -3.44)	(-4.76, -3.58)	< 0.001	—	—
Difference vs Placebo								
Mean		-0.92	-1.19	-2.23	-2.37	—	—	—
95% CI		(-1.98, 0.14)	(-2.21, -0.16)	(-3.27, -1.20)	(-3.41, -1.33)	—	—	—
P value‡		0.108	0.017	< 0.001	< 0.001	—	—	—

Table continued on next page

Parameter	Placebo (n = 61)	ASP1707 3 mg (n = 55)	ASP1707 5 mg (n = 63)	ASP1707 10 mg (n = 59)	ASP1707 15 mg (n = 59)	P value†	Estimate†	Leuprorelin (n = 61)
NMPP								
Raw mean (SD)								
Baseline	4.48 (1.68)	4.32 (1.73)	4.33 (1.70)	4.26 (1.60)	4.42 (1.70)	—	—	4.30 (2.01)
Week 12 (EoT)	2.41 (1.97)	2.39 (1.99)	1.86 (1.91)	1.62 (1.54)	1.90 (2.04)	—	—	1.65 (2.21)
CFB to week 12	-2.07 (1.93)	-1.93 (1.63)	-2.47 (1.93)	-2.64 (1.74)	-2.53 (2.06)	—	—	-2.65 (2.30)
Mean Percentage CFB to week 12	-46.7 (38.7)	-43.2 (42.6)	-53.6 (46.3)	-62.6 (31.8)	-56.2 (47.3)	—	—	-63.8 (40.3)
Adjusted Mean CFB to week 12	-2.01	-1.95	-2.48	-2.69	-2.50	—	-1.7180	—
95% CI	(-2.44, -1.59)	(-2.40, -1.50)	(-2.90, -2.07)	(-3.12, -2.26)	(-2.93, -2.07)	0.014	—	—
Difference vs Placebo								
Mean		0.06	-0.47	-0.68	-0.49	—	—	—
95% CI		(-0.71, 0.84)	(-1.22, 0.27)	(-1.44, 0.08)	(-1.24, 0.27)	—	—	—
P value‡		0.999	0.340	0.093	0.324	—	—	—

CFB: change from baseline; EoT: end-of-treatment; FAS1: full analysis set 1; NMPP: nonmenstrual pelvic pain; NRS: numeric rating scale

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Adjusted means, CIs, differences versus placebo and P values are adjusted for region and overall pelvic pain to baseline. Leuprorelin is included for comparison, and is not part of the primary analysis. Values for raw means, SDs and changes from baseline are unadjusted.

† Overall treatment effect from linear trend. (Primary)

‡ Pairwise comparisons of each active group vs placebo based on Dunnett's test. (Tested after primary)

Source: Tables 12.3.1.1.3.1, 12.3.1.2.3.1, 12.3.1.8.3.1, 12.3.2.1.3.1, 12.3.2.2.3.1, 12.3.2.8.3.1, 12.3.3.1.3.1, 12.3.3.2.3.1 and 12.3.3.8.3.1

Table 9 Mean NRS Score for Pain Interference with Daily Activities Over the Last 28 Days - Overall Population (FAS1)

Parameter	Placebo (n = 81)	ASP1707 3 mg (n = 77)	ASP1707 5 mg (n = 87)	ASP1707 10 mg (n = 82)	ASP1707 15 mg (n = 84)	P value	Estimate	Leuprorelin (n = 83)
Raw mean (SD)								
Baseline	3.32 (2.01)	3.28 (1.83)	3.31 (1.89)	3.24 (1.88)	3.26 (2.19)	—	—	3.18 (2.07)
CFB to week 12	-1.35 (1.57)	-1.58 (1.48)	-1.66 (1.71)	-2.01 (1.72)	-1.80 (1.95)	—	—	-1.98 (2.00)
Adjusted Mean CFB to week 12	-1.25	-1.50	-1.57	-1.96	-1.74	—	-1.4376†	-1.95
95% CI	(-1.57, -0.92)	(-1.83, -1.17)	(-1.88, -1.26)	(-2.27, -1.64)	(-2.05, -1.42)	0.004†	—	(-2.27, -1.63)
Difference vs placebo‡								
Mean		-0.26	-0.32	-0.71	-0.49	—	—	-0.71
95% CI		(-0.71, 0.19)	(-0.76, 0.11)	(-1.15, -0.27)	(-0.93, -0.05)	—	—	(-1.15, -0.26)
P value		0.264	0.146	0.002	0.029	—	—	0.002
Difference vs leuprorelin‡								
Mean	0.71	0.45	0.38	-0.01	0.21	—	—	—
95% CI	(0.26, 1.15)	(0.00, 0.90)	(-0.05, 0.82)	(-0.44, 0.43)	(-0.22, 0.65)	—	—	—
P value	0.002	0.048	0.083	0.981	0.336	—	—	—
Raw mean (SD)								
CFB to week 24		-1.81 (1.72)	-1.93 (1.93)	-2.20 (2.03)	-2.10 (2.16)	—	—	-2.36 (2.14)
Adjusted Mean CFB to week 24		-1.71	-1.81	-2.12	-2.01	—	-2.4240§	-2.32
95% CI		(-2.04, -1.38)	(-2.13, -1.49)	(-2.45, -1.80)	(-2.33, -1.69)	0.107§	—	(-2.65, -2.00)
Difference vs leuprorelin‡								
Mean		0.61	0.51	0.20	0.31	—	—	—
95% CI		(0.16, 1.07)	(0.07, 0.95)	(-0.25, 0.65)	(-0.13, 0.76)	—	—	—
P value		0.008	0.023	0.379	0.169	—	—	—

ANCOVA: analysis of covariance; CFB: change from baseline; EoT: end-of-treatment; FAS1: full analysis set 1; NRS: numeric rating scale

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Last nonmissing observation before first intake of study drug is used as baseline.

Week 12 (EoT for part 1) corresponds to the last nonmissing observation during part 1 of the study.

Week 24 (EoT for part 2) corresponds to the last nonmissing observation during treatment.

† Overall treatment effect from linear trend of placebo and ASP1707 doses.

‡ From the pairwise comparisons in the ANCOVA model that includes treatment group and region as fixed factors and baseline value as a covariate.

§ Overall treatment effect from linear trend ASP1707 doses.

Source: Tables 12.3.17.1.1, 12.3.17.2.1.1 and 12.3.17.2.1.3

Table 10 Mean NRS Score for Pain Interference with Daily Activities Over the Last 28 Days - Japanese Population (FAS1)

Parameter	Placebo (n = 20)	ASP1707 3 mg (n = 22)	ASP1707 5 mg (n = 24)	ASP1707 10 mg (n = 23)	ASP1707 15 mg (n = 25)	P value	Estimate	Leuprorelin (n = 22)
Raw mean (SD)								
Baseline	1.77 (1.19)	2.26 (1.17)	2.87 (1.48)	2.59 (1.66)	2.57 (1.77)	—	—	2.22 (1.36)
CFB to week 12	-0.62 (0.54)	-1.26 (1.13)	-0.85 (1.04)	-1.38 (1.27)	-1.20 (1.29)	—	—	-1.20 (1.16)
Adjusted Mean CFB to week 12	-0.80	-1.30	-0.71	-1.33	-1.15	—	-0.7264†	-1.25
95% CI	(-1.27, -0.34)	(-1.74, -0.87)	(-1.13, -0.29)	(-1.75, -0.90)	(-1.56, -0.75)	0.302†	—	(-1.68, -0.81)
Difference vs placebo‡								
Mean		-0.50	0.09	-0.53	-0.35	—	—	-0.45
95% CI		(-1.14, 0.13)	(-0.54, 0.72)	(-1.16, 0.11)	(-0.97, 0.27)	—	—	(-1.08, 0.19)
P value		0.119	0.780	0.102	0.264	—	—	0.165
Difference vs leuprorelin‡								
Mean	0.45	-0.06	0.54	-0.08	0.09	—	—	—
95% CI	(-0.19, 1.08)	(-0.67, 0.56)	(-0.07, 1.14)	(-0.69, 0.53)	(-0.50, 0.69)	—	—	—
P value	0.165	0.858	0.083	0.799	0.755	—	—	—
Raw mean (SD)								
CFB to week 24		-1.39 (1.15)	-1.05 (1.41)	-1.19 (1.75)	-1.48 (1.17)	—	—	-1.37 (1.30)
Adjusted Mean CFB to week 24		-1.50	-0.89	-1.16	-1.45	—	-1.0735§	-1.50
95% CI		(-2.01, -0.98)	(-1.39, -0.40)	(-1.66, -0.66)	(-1.94, -0.97)	0.645§	—	(-2.01, -0.98)
Difference vs leuprorelin‡								
Mean		-0.00	0.60	0.33	0.04	—	—	—
95% CI		(-0.73, 0.72)	(-0.12, 1.32)	(-0.39, 1.06)	(-0.67, 0.75)	—	—	—
P value		0.991	0.099	0.359	0.909	—	—	—

ANCOVA: analysis of covariance; CFB: change from baseline; EoT: end-of-treatment; FAS1: full analysis set 1; NRS: numeric rating scale

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Last nonmissing observation before first intake of study drug is used as baseline.

Week 12 (EoT for part 1) corresponds to the last nonmissing observation during part 1 of the study.

Week 24 (EoT for part 2) corresponds to the last nonmissing observation during treatment.

† Overall treatment effect from linear trend of placebo and ASP1707 doses.

‡ From the pairwise comparisons in the ANCOVA model that includes treatment group and region as fixed factors and baseline value as a covariate.

§ Overall treatment effect from linear trend ASP1707 doses.

Source: Tables 12.3.17.1.2, 12.3.17.2.2.1 and 12.3.17.2.2.3

Table 11 Mean NRS Score for Pain Interference with Daily Activities Over the Last 28 Days - European Population (FAS1)

Parameter	Placebo (n = 61)	ASP1707 3 mg (n = 55)	ASP1707 5 mg (n = 63)	ASP1707 10 mg (n = 59)	ASP1707 15 mg (n = 59)	P value	Estimate	Leuprorelin (n = 61)
Raw mean (SD)								
Baseline	3.83 (1.97)	3.69 (1.89)	3.47 (2.01)	3.50 (1.91)	3.55 (2.30)	—	—	3.52 (2.18)
CFB to week 12	-1.59 (1.72)	-1.70 (1.59)	-1.97 (1.82)	-2.26 (1.82)	-2.05 (2.13)	—	—	-2.27 (2.17)
Adjusted Mean CFB to week 12	-1.47	-1.65	-2.03	-2.31	-2.07	—	-1.8723†	-2.30
95% CI	(-1.86, -1.08)	(-2.06, -1.24)	(-2.42, -1.65)	(-2.71, -1.92)	(-2.47, -1.68)	0.003†	—	(-2.69, -1.91)
Difference vs placebo‡								
Mean		-0.18	-0.57	-0.84	-0.61	—	—	-0.84
95% CI		(-0.75, 0.38)	(-1.11, -0.02)	(-1.40, -0.29)	(-1.16, -0.05)	—	—	(-1.39, -0.29)
P value		0.523	0.043	0.003	0.033	—	—	0.003
Difference vs leuprorelin‡								
Mean	0.84	0.65	0.27	-0.01	0.23	—	—	—
95% CI	(0.29, 1.39)	(0.09, 1.22)	(-0.28, 0.82)	(-0.56, 0.55)	(-0.32, 0.79)	—	—	—
P value	0.003	0.024	0.330	0.977	0.414	—	—	—
Raw mean (SD)								
CFB to week 24		-1.98 (1.89)	-2.27 (2.01)	-2.59 (2.01)	-2.36 (2.42)	—	—	-2.72 (2.28)
Adjusted Mean CFB to week 24		-1.87	-2.33	-2.63	-2.35	—	-3.0565§	-2.74
95% CI		(-2.28, -1.47)	(-2.70, -1.95)	(-3.01, -2.24)	(-2.74, -1.96)	0.099§	—	(-3.12, -2.36)
Difference vs leuprorelin‡								
Mean		0.86	0.41	0.11	0.39	—	—	—
95% CI		(0.31, 1.42)	(-0.12, 0.95)	(-0.43, 0.65)	(-0.16, 0.93)	—	—	—
P value		0.002	0.132	0.693	0.162	—	—	—

ANCOVA: analysis of covariance; CFB: change from baseline; EoT: end-of-treatment; FAS1: full analysis set 1; NRS: numeric rating scale

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Last nonmissing observation before first intake of study drug is used as baseline.

Week 12 (EoT for part 1) corresponds to the last nonmissing observation during part 1 of the study.

Week 24 (EoT for part 2) corresponds to the last nonmissing observation during treatment.

† Overall treatment effect from linear trend of placebo and ASP1707 doses.

‡ From the pairwise comparisons in the ANCOVA model that includes treatment group and region as fixed factors and baseline value as a covariate.

§ Overall treatment effect from linear trend ASP1707 doses.

Source: Tables 12.3.17.1.3, 12.3.17.2.3.1 and 12.3.17.2.3.3

Table 12 Responders for Overall Pelvic Pain (≥ 30%, ≥ 50%, ≥ 60% and ≥ 70% Reduction in Mean NRS Score from Baseline to EoT Over the Last 28 Days, No Adjustment for Increase of Rescue Medication Use at EoT) – Overall, Japanese and European Populations (FAS1)

Region	Overall Pelvic Pain Responders (according to reduction in mean NRS score from baseline to EoT)		Placebo†	ASP1707 3 mg		ASP1707 5 mg		ASP1707 10 mg		ASP1707 15 mg		P value§	Leuprorelin
				%	P value‡	%	P value‡	%	P value‡	%	P value‡		
Overall Population	**Overall Pelvic Pain**	**Week**	**(n = 81)**	**(n = 77)**		**(n = 87)**		**(n = 82)**		**(n = 84)**			**(n = 83)**
	Responders	12¶	56.8%	70.1%	0.078	65.5%	0.235	80.5%	0.001	75.0%	0.013	0.003	78.3%
	(≥ 30% reduction)	24††	—	75.3%		74.7%		80.5%		79.8%		0.326	85.5%
	Responders	12¶	35.8%	48.1%	0.117	50.6%	0.045	63.4%	< 0.001	59.5%	0.002	< 0.001	65.1%
	(≥ 50% reduction)	24††	—	63.6%		62.1%		69.5%		70.2%		0.202	77.1%
	Responders	12¶	29.6%	37.7%	0.279	44.8%	0.037	56.1%	< 0.001	53.6%	0.002	< 0.001	61.4%
	(≥ 60% reduction)	24††	—	57.1%		51.7%		62.2%		63.1%		0.208	73.5%
	Responders	12¶	24.7%	28.6%	0.583	40.2%	0.027	42.7%	0.014	47.6%	0.002	< 0.001	54.2%
	(≥ 70% reduction)	24††	—	49.4%		48.3%		52.4%		53.6%		0.450	68.7%
Japanese Population	**Overall Pelvic Pain**	**Week**	**(n = 20)**	**(n = 22)**		**(n = 24)**		**(n = 23)**		**(n = 25)**			**(n = 22)**
	Responders	12¶	50.0%	72.7%	0.109	54.2%	0.576	78.3%	0.039	72.0%	0.092	0.086	72.7%
	(≥ 30% reduction)	24††	—	77.3%		66.7%		65.2%		76.0%		0.907	72.7%
	Responders	12¶	20.0%	50.0%	0.020	37.5%	0.051	56.5%	0.004	56.0%	0.004	0.005	54.5%
	(≥ 50% reduction)	24††	—	63.6%		50.0%		43.5%		68.0%		0.678	63.6%
	Responders	12¶	10.0%	36.4%	0.026	29.2%	0.032	52.2%	0.002	56.0%	< 0.001	< 0.001	50.0%
	(≥ 60% reduction)	24††	—	59.1%		41.7%		39.1%		60.0%		0.820	59.1%
	Responders	12¶	10.0%	31.8%	0.045	20.8%	0.103	34.8%	0.022	48.0%	0.003	0.002	50.0%
	(≥ 70% reduction)	24††	—	50.0%		37.5%		34.8%		40.0%		0.541	59.1%
European Population	**Overall Pelvic Pain**	**Week**	**(n = 61)**	**(n = 55)**		**(n = 63)**		**(n = 59)**		**(n = 59)**			**(n = 61)**
	Responders	12¶	59.0%	69.1%	0.243	69.8%	0.196	81.4%	0.008	76.3%	0.043	0.011	80.3%
	(≥ 30% reduction)	24††	—	74.5%		77.8%		86.4%		81.4%		0.225	90.2%
	Responders	12¶	41.0%	47.3%	0.509	55.6%	0.110	66.1%	0.007	61.0%	0.030	0.004	68.9%
	(≥ 50% reduction)	24††	—	63.6%		66.7%		79.7%		71.2%		0.189	82.0%
	Responders	12¶	36.1%	38.2%	0.807	50.8%	0.098	57.6%	0.019	52.5%	0.070	0.011	65.6%
	(≥ 60% reduction)	24††	—	56.4%		55.6%		71.2%		64.4%		0.165	78.7%
	Responders	12¶	29.5%	27.3%	0.768	47.6%	0.043	45.8%	0.073	47.5%	0.047	0.008	55.7%
	(≥ 70% reduction)	24††	—	49.1%		52.4%		59.3%		59.3%		0.202	72.1%

EoT: end-of-treatment; FAS1: full analysis set 1; NRS: numeric rating scale

Footnotes continued on next page

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Last nonmissing observation before first intake of study drug is used as baseline.

Percentages are calculated with respect to n, missing data are not counted for the percentages.

From a logistic regression model including treatment group (excluding leuprorelin group), region and baseline score at EoT.

† Patients taking placebo in part 1 switched to ASP1707 at the end of part 1 (visit 6). Patients are not included in summary for week 24 (EoT of part 2).

‡ Treatment effect with dose groups defined as a categorical variable to assess the comparison of each dose with placebo.

§ Overall treatment effect with dose groups defined as an ordinal dose to assess a dose-related trend.

¶ EoT (part 1) corresponds to the last nonmissing observation during part 1 of the study.

†† EoT (part 2) corresponds to the last nonmissing observation during part 2 of the study.

Source: Tables 12.3.5.1.1.1, 12.3.5.1.1.3, 12.3.5.1.2.1, 12.3.5.1.2.3, 12.3.5.1.3.1, 12.3.5.1.3.3, 12.3.5.1.4.1, 12.3.5.1.4.3, 12.3.5.1.5.1, 12.3.5.1.5.3, 12.3.5.1.6.1, 12.3.5.1.6.3, 12.3.5.1.25.1, 12.3.5.1.25.3, 12.3.5.1.26.1, 12.3.5.1.26.3, 12.3.5.1.27.1, 12.3.5.1.27.3, 12.3.5.1.28.1, 12.3.5.1.28.3, 12.3.5.1.29.1, 12.3.5.1.29.3, 12.3.5.1.30.1 and 12.3.5.1.30.3

Table 13 Responders for Dysmenorrhea (≥ 30%, ≥ 50%, ≥ 60% and ≥ 70% Reduction in Mean NRS Score from Baseline to EoT Over the Last 28 Days, No Adjustment for Increase of Rescue Medication Use at EoT) – Overall, Japanese and European Populations (FAS1)

Region	Dysmenorrhea Responders (according to reduction in mean NRS score from baseline to EoT)		Placebo†	ASP1707 3 mg		ASP1707 5 mg		ASP1707 10 mg		ASP1707 15 mg		P value§	Leuprorelin
				%	P value‡	%	P value‡	%	P value‡	%	P value‡		
Overall Population	**Dysmenorrhea**	**Week**	**(n = 81)**	**(n = 77)**		**(n = 87)**		**(n = 82)**		**(n = 84)**			**(n = 83)**
	Responders	12¶	49.4%	66.2%	0.014	66.7%	0.011	85.4%	< 0.001	81.0%	< 0.001	< 0.001	97.6%
	(≥ 30% reduction)	24††	—	66.2%		80.5%		81.7%		81.0%		0.045	98.8%
	Responders	12¶	30.9%	46.8%	0.028	56.3%	< 0.001	80.5%	< 0.001	76.2%	< 0.001	< 0.001	95.2%
	(≥ 50% reduction)	24††	—	61.0%		67.8%		72.0%		76.2%		0.038	97.6%
	Responders	12¶	24.7%	40.3%	0.030	50.6%	< 0.001	72.0%	< 0.001	73.8%	< 0.001	< 0.001	92.8%
	(≥ 60% reduction)	24††	—	51.9%		58.6%		68.3%		71.4%		0.006	96.4%
	Responders	12¶	19.8%	32.5%	0.080	41.4%	0.004	69.5%	< 0.001	72.6%	< 0.001	< 0.001	92.8%
	(≥ 70% reduction)	24††	—	44.2%		55.2%		61.0%		67.9%		0.002	96.4%
Japanese Population	**Dysmenorrhea**	**Week**	**(n = 20)**	**(n = 22)**		**(n = 24)**		**(n = 23)**		**(n = 25)**			**(n = 22)**
	Responders	12¶	30.0%	63.6%	0.033	62.5%	0.035	87.0%	< 0.001	84.0%	< 0.001	< 0.001	95.5%
	(≥ 30% reduction)	24††	—	72.7%		70.8%		69.6%		84.0%		0.382	95.5%
	Responders	12¶	10.0%	50.0%	0.010	54.2%	0.005	78.3%	< 0.001	80.0%	< 0.001	< 0.001	90.9%
	(≥ 50% reduction)	24††	—	63.6%		58.3%		52.2%		80.0%		0.225	90.9%
	Responders	12¶	10.0%	36.4%	0.067	41.7%	0.031	69.6%	< 0.001	72.0%	< 0.001	< 0.001	86.4%
	(≥ 60% reduction)	24††	—	54.5%		50.0%		47.8%		68.0%		0.267	86.4%
	Responders	12¶	5.0%	27.3%	0.092	37.5%	0.030	69.6%	< 0.001	72.0%	< 0.001	< 0.001	86.4%
	(≥ 70% reduction)	24††	—	40.9%		50.0%		39.1%		60.0%		0.203	86.4%
European Population	**Dysmenorrhea**	**Week**	**(n = 61)**	**(n = 55)**		**(n = 63)**		**(n = 59)**		**(n = 59)**			**(n = 61)**
	Responders	12¶	55.7%	67.3%	0.116	68.3%	0.082	84.7%	< 0.001	79.7%	0.003	< 0.001	98.4%
	(≥ 30% reduction)	24††	—	63.6%		84.1%		86.4%		79.7%		0.053	100.0%
	Responders	12¶	37.7%	45.5%	0.323	57.1%	0.022	81.4%	< 0.001	74.6%	< 0.001	< 0.001	96.7%
	(≥ 50% reduction)	24††	—	60.0%		71.4%		79.7%		74.6%		0.064	100.0%
	Responders	12¶	29.5%	41.8%	0.144	54.0%	0.005	72.9%	< 0.001	74.6%	< 0.001	< 0.001	95.1%
	(≥ 60% reduction)	24††	—	50.9%		61.9%		76.3%		72.9%		0.006	100.0%
	Responders	12¶	24.6%	34.5%	0.270	42.9%	0.040	69.5%	< 0.001	72.9%	< 0.001	< 0.001	95.1%
	(≥ 70% reduction)	24††	—	45.5%		57.1%		69.5%		71.2%		0.002	100.0%

EoT: end-of-treatment; FAS1: full analysis set 1; NRS: numeric rating scale

Footnotes continued on next page

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Last nonmissing observation before first intake of study drug is used as baseline.

Percentages are calculated with respect to n, missing data are not counted for the percentages.

From a logistic regression model including treatment group (excluding leuprorelin group), region and baseline score at EoT.

† Patients taking placebo in part 1 switched to ASP1707 at the end of part 1 (visit 6). Patients are not included in summary for week 24 (EoT of part 2).

‡ Treatment effect with dose groups defined as a categorical variable to assess the comparison of each dose with placebo.

§ Overall treatment effect with dose groups defined as an ordinal dose to assess a dose-related trend.

¶ EoT (part 1) corresponds to the last nonmissing observation during part 1 of the study.

†† EoT (part 2) corresponds to the last nonmissing observation during part 2 of the study.

Source: Tables 12.3.6.1.1.1, 12.3.6.1.1.3, 12.3.6.1.2.1, 12.3.6.1.2.3, 12.3.6.1.3.1, 12.3.6.1.3.3, 12.3.6.1.4.1, 12.3.6.1.4.3, 12.3.6.1.5.1, 12.3.6.1.5.3, 12.3.6.1.6.1, 12.3.6.1.6.3, 12.3.6.1.25.1, 12.3.6.1.25.3, 12.3.6.1.26.1, 12.3.6.1.26.3, 12.3.6.1.27.1, 12.3.6.1.27.3, 12.3.6.1.28.1, 12.3.6.1.28.3, 12.3.6.1.29.1, 12.3.6.1.29.3, 12.3.6.1.30.1 and 12.3.6.1.30.3

Table 14 Responders for NMPP (≥ 30%, ≥ 50%, ≥ 60% and ≥ 70% Reduction in Mean NRS Score from Baseline to EoT Over the Last 28 Days, No Adjustment for Increase of Rescue Medication Use at EoT) – Overall, Japanese and European Populations (FAS1)

Region	NMPP Responders (according to reduction in mean NRS score from baseline to EoT)		Placebo†	ASP1707 3 mg		ASP1707 5 mg		ASP1707 10 mg		ASP1707 15 mg		P value§	Leuprorelin
				%	P value‡	%	P value‡	%	P value‡	%	P value‡		
Overall Population	**NMPP**	**Week**	**(n = 81)**	**(n = 77)**		**(n = 87)**		**(n = 82)**		**(n = 84)**			**(n = 83)**
	Responders (≥ 30% reduction)	12¶	63.0%	67.5%	0.527	67.8%	0.481	80.5%	0.013	71.4%	0.226	0.058	73.5%
		24††	—	70.1%		72.4%		80.5%		77.4%		0.162	79.5%
	Responders (≥ 50% reduction)	12¶	46.9%	53.2%	0.394	52.9%	0.340	61.0%	0.060	59.5%	0.073	0.039	60.2%
		24††	—	62.3%		62.1%		72.0%		67.9%		0.235	73.5%
	Responders (≥ 60% reduction)	12¶	40.7%	46.8%	0.411	48.3%	0.249	52.4%	0.115	56.0%	0.034	0.026	56.6%
		24††	—	57.1%		50.6%		64.6%		63.1%		0.163	69.9%
	Responders (≥ 70% reduction)	12¶	34.6%	35.1%	0.910	40.2%	0.340	45.1%	0.145	50.0%	0.028	0.011	50.6%
		24††	—	48.1%		47.1%		59.8%		57.1%		0.091	67.5%
Japanese Population	**NMPP**	**Week**	**(n = 20)**	**(n = 22)**		**(n = 24)**		**(n = 23)**		**(n = 25)**			**(n = 22)**
	Responders (≥ 30% reduction)	12¶	65.0%	68.2%	0.743	62.5%	0.912	73.9%	0.421	64.0%	0.898	0.771	54.5%
		24††	—	68.2%		66.7%		65.2%		72.0%		0.721	63.6%
	Responders (≥ 50% reduction)	12¶	45.0%	59.1%	0.161	41.7%	0.407	47.8%	0.412	52.0%	0.249	0.481	50.0%
		24††	—	63.6%		45.8%		52.2%		64.0%		0.738	59.1%
	Responders (≥ 60% reduction)	12¶	30.0%	59.1%	0.020	29.2%	0.390	39.1%	0.237	52.0%	0.037	0.196	50.0%
		24††	—	63.6%		37.5%		52.2%		56.0%		0.965	59.1%
	Responders (≥ 70% reduction)	12¶	30.0%	45.5%	0.111	20.8%	0.748	30.4%	0.535	48.0%	0.054	0.188	50.0%
		24††	—	45.5%		33.3%		47.8%		48.0%		0.577	59.1%
European Population	**NMPP**	**Week**	**(n = 61)**	**(n = 55)**		**(n = 63)**		**(n = 59)**		**(n = 59)**			**(n = 61)**
	Responders (≥ 30% reduction)	12¶	62.3%	67.3%	0.569	69.8%	0.370	83.1%	0.012	74.6%	0.149	0.030	80.3%
		24††	—	70.9%		74.6%		86.4%		79.7%		0.127	85.2%
	Responders (≥ 50% reduction)	12¶	47.5%	50.9%	0.742	57.1%	0.299	66.1%	0.046	62.7%	0.098	0.027	63.9%
		24††	—	61.8%		68.3%		79.7%		69.5%		0.215	78.7%
	Responders (≥ 60% reduction)	12¶	44.3%	41.8%	0.762	55.6%	0.222	57.6%	0.158	57.6%	0.147	0.042	59.0%
		24††	—	54.5%		55.6%		69.5%		66.1%		0.091	73.8%
	Responders (≥ 70% reduction)	12¶	36.1%	30.9%	0.517	47.6%	0.211	50.8%	0.120	50.8%	0.107	0.018	50.8%
		24††	—	49.1%		52.4%		64.4%		61.0%		0.102	70.5%

EoT: end-of-treatment; FAS1: full analysis set 1; NMPP: nonmenstrual pelvic pain; NRS: numeric rating scale

Footnotes continued on next page

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Last nonmissing observation before first intake of study drug is used as baseline.

Percentages are calculated with respect to n, missing data are not counted for the percentages.

From a logistic regression model including treatment group (excluding leuprorelin group), region and baseline score at EoT.

† Patients taking placebo in part 1 switched to ASP1707 at the end of part 1 (visit 6). Patients are not included in summary for week 24 (EoT of part 2).

‡ Treatment effect with dose groups defined as a categorical variable to assess the comparison of each dose with placebo.

§ Overall treatment effect with dose groups defined as an ordinal dose to assess a dose-related trend.

¶ EoT (part 1) corresponds to the last nonmissing observation during part 1 of the study.

†† EoT (part 2) corresponds to the last nonmissing observation during part 2 of the study.

Source: Tables 12.3.7.1.1.1, 12.3.7.1.1.3, 12.3.7.1.2.1, 12.3.7.1.2.3, 12.3.7.1.3.1, 12.3.7.1.3.3, 12.3.7.1.4.1, 12.3.7.1.4.3, 12.3.7.1.5.1, 12.3.7.1.5.3, 12.3.7.1.6.1, 12.3.7.1.6.3, 12.3.7.1.25.1, 12.3.7.1.25.3, 12.3.7.1.26.1, 12.3.7.1.26.3, 12.3.7.1.27.1, 12.3.7.1.27.3, 12.3.7.1.28.1, 12.3.7.1.28.3, 12.3.7.1.29.1, 12.3.7.1.29.3, 12.3.7.1.30.1 and 12.3.7.1.30.3

Table 15 Responders for Overall Pelvic Pain (≥ 30%, ≥ 50%, ≥ 60% and ≥ 70% Reduction in Mean NRS Score from Baseline to EoT Over the Last 28 Days, Considering Those Who Increase Rescue Medication as Nonresponders) – Overall, Japanese and European Populations (FAS1)

Region	Overall Pelvic Pain Responders (according to reduction in mean NRS score from baseline to EoT)		Placebo†	ASP1707 3 mg		ASP1707 5 mg		ASP1707 10 mg		ASP1707 15 mg		P value§	Leuprorelin
				%	P value‡	%	P value‡	%	P value‡	%	P value‡		
Overall Population	**Overall Pelvic Pain**	**Week**	**(n = 81)**	**(n = 77)**		**(n = 87)**		**(n = 82)**		**(n = 84)**			**(n = 83)**
	Responders	12¶	46.9%	64.9%	0.022	56.3%	0.221	79.3%	< 0.001	70.2%	0.002	< 0.001	75.9%
	(≥ 30% reduction)	24††	—	72.7%		70.1%		78.0%		72.6%		0.681	81.9%
	Responders	12¶	30.9%	44.2%	0.084	43.7%	0.075	63.4%	< 0.001	54.8%	0.002	< 0.001	62.7%
	(≥ 50% reduction)	24††	—	61.0%		58.6%		68.3%		64.3%		0.354	74.7%
	Responders	12¶	28.4%	35.1%	0.362	39.1%	0.129	56.1%	< 0.001	48.8%	0.006	< 0.001	60.2%
	(≥ 60% reduction)	24††	—	54.5%		48.3%		61.0%		57.1%		0.350	72.3%
	Responders	12¶	23.5%	27.3%	0.589	36.8%	0.053	42.7%	0.009	44.0%	0.004	< 0.001	54.2%
	(≥ 70% reduction)	24††	—	46.8%		44.8%		51.2%		50.0%		0.460	67.5%
Japanese Population	**Overall Pelvic Pain**	**Week**	**(n = 20)**	**(n = 22)**		**(n = 24)**		**(n = 23)**		**(n = 25)**			**(n = 22)**
	Responders	12¶	40.0%	72.7%	0.028	41.7%	0.692	78.3%	0.009	72.0%	0.022	0.023	68.2%
	(≥ 30% reduction)	24††	—	77.3%		58.3%		65.2%		68.0%		0.778	68.2%
	Responders	12¶	15.0%	50.0%	0.009	25.0%	0.143	56.5%	0.002	56.0%	0.002	0.002	50.0%
	(≥ 50% reduction)	24††	—	63.6%		41.7%		43.5%		64.0%		0.744	59.1%
	Responders	12¶	10.0%	36.4%	0.025	16.7%	0.202	52.2%	0.001	56.0%	< 0.001	< 0.001	50.0%
	(≥ 60% reduction)	24††	—	40.9%		66.7%		60.9%		44.0%		0.888	59.1%
	Responders	12¶	10.0%	31.8%	0.045	16.7%	0.193	34.8%	0.022	48.0%	0.003	0.002	50.0%
	(≥ 70% reduction)	24††	—	50.0%		29.2%		34.8%		40.0%		0.673	59.1%
European Population	**Overall Pelvic Pain**	**Week**	**(n = 61)**	**(n = 55)**		**(n = 63)**		**(n = 59)**		**(n = 59)**			**(n = 61)**
	Responders	12¶	49.2%	61.8%	0.150	61.9%	0.137	79.7%	< 0.001	69.5%	0.022	0.003	78.7%
	(≥ 30% reduction)	24††	—	70.9%		74.6%		83.1%		74.6%		0.452	86.9%
	Responders	12¶	36.1%	41.8%	0.537	50.8%	0.103	66.1%	0.001	54.2%	0.048	0.004	67.2%
	(≥ 50% reduction)	24††	—	60.0%		65.1%		78.0%		64.4%		0.353	80.3%
	Responders	12¶	34.4%	34.5%	0.982	47.6%	0.135	57.6%	0.011	45.8%	0.205	0.026	63.9%
	(≥ 60% reduction)	24††	—	52.7%		54.0%		69.5%		57.6%		0.300	77.0%
	Responders	12¶	27.9%	25.5%	0.745	44.4%	0.061	45.8%	0.048	42.4%	0.102	0.015	55.7%
	(≥ 70% reduction)	24††	—	45.5%		50.8%		57.6%		54.2%		0.264	70.5%

EoT: end-of-treatment; FAS1: full analysis set 1; NRS: numeric rating scale

Footnotes continued on next page

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Last nonmissing observation before first intake of study drug is used as baseline.

Percentages are calculated with respect to n, missing data are not counted for the percentages.

From a logistic regression model including treatment group (excluding leuprorelin group), region and baseline score at EoT.

† Patients taking placebo in part 1 switched to ASP1707 at the end of part 1 (visit 6). Patients are not included in summary for week 24 (EoT of part 2).

‡ Treatment effect with dose groups defined as a categorical variable to assess the comparison of each dose with placebo.

§ Overall treatment effect with dose groups defined as an ordinal dose to assess a dose-related trend.

¶ EoT (part 1) corresponds to the last nonmissing observation during part 1 of the study.

†† EoT (part 2) corresponds to the last nonmissing observation during part 2 of the study.

Source: Tables 12.3.5.1.13.1, 12.3.5.1.13.3, 12.3.5.1.14.1, 12.3.5.1.14.3, 12.3.5.1.15.1, 12.3.5.1.15.3, 12.3.5.1.16.1, 12.3.5.1.16.3, 12.3.5.1.17.1, 12.3.5.1.17.3, 12.3.5.1.18.1, 12.3.5.1.18.3, 12.3.5.1.19.1, 12.3.5.1.19.3, 12.3.5.1.20.1, 12.3.5.1.20.3, 12.3.5.1.21.1, 12.3.5.1.21.3, 12.3.5.1.22.1, 12.3.5.1.22.3, 12.3.5.1.23.1, 12.3.5.1.23.3, 12.3.5.1.24.1, 12.3.5.1.24.3

Table 16 Responders for Dysmenorrhea (≥ 30%, ≥ 50%, ≥ 60% and ≥ 70% Reduction in Mean NRS Score from Baseline to EoT Over the Last 28 Days, Considering Those Who Increase Rescue Medication as Nonresponders) – Overall, Japanese and European Populations (FAS1)

Region	Dysmenorrhea Responders (according to reduction in mean NRS score from baseline to EoT)		Placebo†	ASP1707 3 mg		ASP1707 5 mg		ASP1707 10 mg		ASP1707 15 mg		P value§	Leuprorelin
				%	P value‡	%	P value‡	%	P value‡	%	P value‡		
Overall Population	**Dysmenorrhea**	**Week**	**(n = 81)**	**(n = 77)**		**(n = 87)**		**(n = 82)**		**(n = 84)**			**(n = 83)**
	Responders	12¶	45.7%	59.7%	0.032	55.2%	0.114	84.1%	< 0.001	76.2%	< 0.001	< 0.001	89.2%
	(≥ 30% reduction)	24††	—	61.0%		73.6%		80.5%		73.8%		0.065	90.4%
	Responders	12¶	28.4%	42.9%	0.036	46.0%	0.012	79.3%	< 0.001	71.4%	< 0.001	< 0.001	86.7%
	(≥ 50% reduction)	24††	—	55.8%		62.1%		70.7%		69.0%		0.056	89.2%
	Responders	12¶	23.5%	37.7%	0.040	42.5%	0.007	70.7%	< 0.001	69.0%	< 0.001	< 0.001	85.5%
	(≥ 60% reduction)	24††	—	50.6%		54.0%		67.1%		65.5%		0.022	89.2%
	Responders	12¶	18.5%	29.9%	0.100	34.5%	0.022	68.3%	< 0.001	67.9%	< 0.001	< 0.001	85.5%
	(≥ 70% reduction)	24††	—	42.9%		50.6%		59.8%		63.1%		0.005	89.2%
Japanese Population	**Dysmenorrhea**	**Week**	**(n = 20)**	**(n = 22)**		**(n = 24)**		**(n = 23)**		**(n = 25)**			**(n = 22)**
	Responders	12¶	25.0%	63.6%	0.012	45.8%	0.139	87.0%	< 0.001	80.0%	< 0.001	< 0.001	86.4%
	(≥ 30% reduction)	24††	—	68.2%		58.3%		69.6%		76.0%		0.475	81.8%
	Responders	12¶	10.0%	50.0%	0.009	41.7%	0.026	78.3%	< 0.001	76.0%	< 0.001	< 0.001	81.8%
	(≥ 50% reduction)	24††	—	59.1%		50.0%		52.2%		72.0%		0.331	77.3%
	Responders	12¶	10.0%	36.4%	0.062	33.3%	0.083	69.6%	< 0.001	68.0%	< 0.001	< 0.001	81.8%
	(≥ 60% reduction)	24††	—	54.5%		41.7%		47.8%		64.0%		0.356	77.3%
	Responders	12¶	5.0%	27.3%	0.086	29.2%	0.067	69.6%	< 0.001	68.0%	< 0.001	< 0.001	81.8%
	(≥ 70% reduction)	24††	—	40.9%		41.7%		39.1%		60.0%		0.170	77.3%
European Population	**Dysmenorrhea**	**Week**	**(n = 61)**	**(n = 55)**		**(n = 63)**		**(n = 59)**		**(n = 59)**			**(n = 61)**
	Responders	12¶	52.5%	58.2%	0.342	58.7%	0.297	83.1%	< 0.001	74.6%	0.006	< 0.001	90.2%
	(≥ 30% reduction)	24††	—	58.2%		79.4%		84.7%		72.9%		0.078	93.4%
	Responders	12¶	34.4%	40.0%	0.429	47.6%	0.098	79.7%	< 0.001	69.5%	< 0.001	< 0.001	88.5%
	(≥ 50% reduction)	24††	—	54.5%		66.7%		78.0%		67.8%		0.082	93.4%
	Responders	12¶	27.9%	38.2%	0.197	46.0%	0.029	71.2%	< 0.001	69.5%	< 0.001	< 0.001	86.9%
	(≥ 60% reduction)	24††	—	49.1%		58.7%		74.6%		66.1%		0.024	93.4%
	Responders	12¶	23.0%	30.9%	0.354	36.5%	0.111	67.8%	< 0.001	67.8%	< 0.001	< 0.001	86.9%
	(≥ 70% reduction)	24††		43.6%		54.0%		67.8%		64.4%		0.011	93.4%

Footnotes appear on next page

EoT: end-of-treatment; FAS1: full analysis set 1; NRS: numeric rating scale

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Last nonmissing observation before first intake of study drug is used as baseline.

Percentages are calculated with respect to n, missing data are not counted for the percentages.

From a logistic regression model including treatment group (excluding leuprorelin group), region and baseline score at EoT.

† Patients taking placebo in part 1 switched to ASP1707 at the end of part 1 (visit 6). Patients are not included in summary for week 24 (EoT of part 2).

‡ Treatment effect with dose groups defined as a categorical variable to assess the comparison of each dose with placebo.

§ Overall treatment effect with dose groups defined as an ordinal dose to assess a dose-related trend.

¶ EoT (part 1) corresponds to the last nonmissing observation during part 1 of the study.

†† EoT (part 2) corresponds to the last nonmissing observation during part 2 of the study.

Source: Tables 12.3.6.1.13.1, 12.3.6.1.13.3, 12.3.6.1.14.1, 12.3.6.1.14.3, 12.3.6.1.15.1, 12.3.6.1.15.3, 12.3.6.1.16.1, 12.3.6.1.16.3, 12.3.6.1.17.1, 12.3.6.1.17.3, 12.3.6.1.18.1, 12.3.6.1.18.3, 12.3.6.1.19.1, 12.3.6.1.19.3, 12.3.6.1.20.1, 12.3.6.1.20.3, 12.3.6.1.21.1, 12.3.6.1.21.3, 12.3.6.1.22.1, 12.3.6.1.22.3, 12.3.6.1.23.1, 12.3.6.1.23.3, 12.3.6.1.24.1, 12.3.6.1.24.3.

Table 17 Responders for NMPP (≥ 30%, ≥ 50%, ≥ 60% and ≥ 70% Reduction in Mean NRS Score from Baseline to EoT Over the Last 28 Days, Considering Those Who Increase Rescue Medication as Nonresponders) – Overall, Japanese and European Populations (FAS1)

Region	NMPP Responders (according to reduction in mean NRS score from baseline to EoT)		Placebo†	ASP1707 3 mg		ASP1707 5 mg		ASP1707 10 mg		ASP1707 15 mg		P value§	Leuprorelin
				%	P value‡	%	P value‡	%	P value‡	%	P value‡		
Overall Population	**NMPP**	**Week**	**(n = 81)**	**(n = 77)**		**(n = 87)**		**(n = 82)**		**(n = 84)**			**(n = 83)**
	Responders (≥ 30% reduction)	12¶	50.6%	62.3%	0.132	58.6%	0.292	79.3%	< 0.001	66.7%	0.035	0.004	72.3%
		24††	—	67.5%		67.8%		78.0%		71.4%		0.320	78.3%
	Responders (≥ 50% reduction)	12¶	37.0%	48.1%	0.146	46.0%	0.189	59.8%	0.003	54.8%	0.016	0.005	59.0%
		24††	—	59.7%		58.6%		69.5%		61.9%		0.432	72.3%
	Responders (≥ 60% reduction)	12¶	33.3%	42.9%	0.197	42.5%	0.172	52.4%	0.012	51.2%	0.014	0.006	55.4%
		24††	—	54.5%		47.1%		63.4%		57.1%		0.286	68.7%
	Responders (≥ 70% reduction)	12¶	27.2%	32.5%	0.437	35.6%	0.182	45.1%	0.014	46.4%	0.007	0.002	50.6%
		24††	—	45.5%		43.7%		58.5%		52.4%		0.129	66.3%
Japanese Population	**NMPP**	**Week**	**(n = 20)**	**(n = 22)**		**(n = 24)**		**(n = 23)**		**(n = 25)**			**(n = 22)**
	Responders (≥ 30% reduction)	12¶	45.0%	68.2%	0.110	50.0%	0.565	73.9%	0.042	64.0%	0.155	0.151	45.4%
		24††	—	68.2%		58.3%		65.2%		68.0%		0.778	63.6%
	Responders (≥ 50% reduction)	12¶	25.0%	59.1%	0.007	29.2%	0.196	47.8%	0.031	52.0%	0.014	0.061	50.0%
		24††	—	63.6%		37.5%		52.2%		60.0%		0.806	59.1%
	Responders (≥ 60% reduction)	12¶	15.0%	59.1%	0.001	20.8%	0.178	39.1%	0.024	52.0%	0.002	0.028	50.0%
		24††	—	63.6%		29.2%		52.2%		52.0%		0.885	59.1%
	Responders (≥ 70% reduction)	12¶	15.0%	45.5%	0.010	16.7%	0.312	30.4%	0.088	48.0%	0.004	0.029	50.0%
		24††	—	45.5%		25.0%		47.8%		44.0%		0.641	59.1%
European Population	**NMPP**	**Week**	**(n = 61)**	**(n = 55)**		**(n = 63)**		**(n = 59)**		**(n = 59)**			**(n = 61)**
	Responders (≥ 30% reduction)	12¶	52.5%	60.0%	0.399	61.9%	0.277	81.4%	< 0.001	67.8%	0.086	0.008	78.7%
		24††	—	67.3%		71.4%		83.1%		72.9%		0.287	83.6%
	Responders (≥ 50% reduction)	12¶	41.0%	43.6%	0.782	52.4%	0.209	64.4%	0.012	55.9%	0.104	0.015	62.3%
		24††	—	58.2%		66.7%		76.3%		62.7%		0.429	77.0%
	Responders (≥ 60% reduction)	12¶	39.3%	36.4%	0.726	50.8%	0.208	57.6%	0.050	50.8%	0.209	0.034	57.4 %
		24††	—	50.9%		54.0%		67.8%		59.3%		0.182	72.1%
	Responders (≥ 70% reduction)	12¶	31.1%	27.3%	0.619	42.9%	0.190	50.8%	0.033	45.8%	0.104	0.010	50.8%
		24††	—	45.5%		50.8%		62.7%		55.9%		0.142	68.9%

EoT: end-of-treatment; FAS1: full analysis set 1; NMPP: nonmenstrual pelvic pain; NRS: numeric rating scale

Footnotes continued on next page

FAS1: All randomized patients who received at least 1 dose of double-blind study medication and who have a primary NRS pain score for overall pelvic pain at baseline and at least 1 evaluable postbaseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

Last nonmissing observation before first intake of study drug is used as baseline.

Percentages are calculated with respect to n, missing data are not counted for the percentages.

From a logistic regression model including treatment group (excluding leuprorelin group), region and baseline score at EoT.

† Patients taking placebo in part 1 switched to ASP1707 at the end of part 1 (visit 6). Patients are not included in summary for week 24 (EoT of part 2).

‡ Treatment effect with dose groups defined as a categorical variable to assess the comparison of each dose with placebo.

§ Overall treatment effect with dose groups defined as an ordinal dose to assess a dose-related trend.

¶ EoT (part 1) corresponds to the last nonmissing observation during part 1 of the study.

†† EoT (part 2) corresponds to the last nonmissing observation during part 2 of the study.

Source: Tables 12.3.7.1.13.1, 12.3.7.1.13.3, 12.3.7.1.14.1, 12.3.7.1.14.3, 12.3.7.1.15.1, 12.3.7.1.15.3, 12.3.7.1.16.1, 12.3.7.1.16.3, 12.3.7.1.17.1, 12.3.7.1.17.3, 12.3.7.1.18.1, 12.3.7.1.18.3, 12.3.7.1.19.1, 12.3.7.1.19.3, 12.3.7.1.20.1, 12.3.7.1.20.3, 12.3.7.1.21.1, 12.3.7.1.21.3, 12.3.7.1.22.1, 12.3.7.1.22.3, 12.3.7.1.23.1, 12.3.7.1.23.3., 12.3.7.1.24.1, 12.3.7.1.24.3.

Table 18 Most Common TEAEs (At Least 5% of Patients in Any Treatment Group) in Part 1 – Overall Population (SAF1)

MedDRA v13.0 Preferred Term, n (%)	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)
Hot flush	4 (4.5)	4 (4.7)	12 (13.2)	10 (11.1)	17 (19.3)	43 (12.1)	25 (28.1)
Headache	10 (11.4)	9 (10.5)	6 (6.6)	12 (13.3)	12 (13.6)	39 (11.0)	15 (16.9)
Nasopharyngitis	8 (9.1)	5 (5.8)	4 (4.4)	4 (4.4)	8 (9.1)	21 (5.9)	5 (5.6)
Nausea	4 (4.5)	2 (2.3)	2 (2.2)	7 (7.8)	2 (2.3)	13 (3.7)	4 (4.5)
Menstruation delayed	0	1 (1.2)	4 (4.4)	4 (4.4)	2 (2.3)	11 (3.1)	5 (5.6)
Insomnia	3 (3.4)	2 (2.3)	1 (1.1)	2 (2.2)	3 (3.4)	8 (2.3)	5 (5.6)

SAF1: safety analysis set 1; TEAE: treatment-emergent adverse event.

SAF1: All randomized patients who took at least 1 dose of study medication (ASP1707 or leuprorelin acetate or placebo).

Source: Table 12.6.1.10.1.1

Table 19 Most Common TEAEs (At Least 5% of Patients in Any Treatment Group) in Patients with Same Treatment in Both Parts 1 and 2 – Overall Population (SAF1)

MedDRA v13.0 Preferred Term, n (%)	Placebo (Part 1 Only) for Comparison (n = 88)	Patients With Same Treatment in Both Parts 1 and 2					
		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 (4.5)	6 (7.0)	16 (17.6)	11 (12.2)	19 (21.6)	52 (14.6)	25 (28.1)
Headache	10 (11.4)	10 (11.6)	10 (11.0)	13 (14.4)	15 (17.0)	48 (13.5)	18 (20.2)
Nasopharyngitis	8 (9.1)	9 (10.5)	12 (13.2)	11 (12.2)	13 (14.8)	45 (12.7)	7 (7.9)
Nausea	4 (4.5)	3 (3.5)	3 (3.3)	8 (8.9)	3 (3.4)	17 (4.8)	5 (5.6)
Menstruation delayed	0	2 (2.3)	4 (4.4)	4 (4.4)	3 (3.4)	13 (3.7)	5 (5.6)
Abdominal pain lower	2 (2.3)	2 (2.3)	2 (2.2)	5 (5.6)	2 (2.3)	11 (3.1)	2 (2.2)
Insomnia	3 (3.4)	3 (3.5)	1 (1.1)	2 (2.2)	5 (5.7)	11 (3.1)	7 (7.9)
Dizziness	1 (1.1)	1 (1.2)	1 (1.1)	4 (4.4)	5 (5.7)	11 (3.1)	3 (3.4)
Influenza	4 (4.5)	5 (5.8)	0	1 (1.1)	4 (4.5)	10 (2.8)	1 (1.1)
Cystitis	0	0	3 (3.3)	1 (1.1)	5 (5.7)	9 (2.5)	2 (2.2)
Arthralgia	1 (1.1)	2 (2.3)	1 (1.1)	2 (2.2)	1 (1.1)	6 (1.7)	6 (6.7)

SAF1: safety analysis set 1; TEAE: treatment-emergent adverse event.

SAF1: All randomized patients who took at least 1 dose of study medication (ASP1707 or leuprorelin acetate or placebo).

Source: Tables 12.6.1.2.1.1 and 12.6.1.10.1.3

Table 20 By-patient Summary of Serious TEAEs in Part 1 – Overall Population (SAF1)

Treatment Group Patient No./Age/Race	MedDRA v13.0 Preferred Term	Onset/Stop Day (Last Dose Day)	Severity	Outcome	Investigator Assessment of Relationship to Study Drug
Placebo					
[redacted]	Abortion spontaneous	102/102 (88)	Mild	Recovered	Not Related
ASP1707 3 mg					
[redacted]	Ureteric obstruction	42/45 (167)	Severe	Recovered	Not Related
[redacted]	Dural fistula	15/ongoing (83)	Mild	Not Recovered	Probable
[redacted]	Vertigo positional	58/210 (172)	Moderate	Recovered	Not Related
ASP1707 10 mg					
[redacted]	Mallory-Weiss syndrome	42/46 (37)	Moderate	Recovered	Not Related

SAF1: safety analysis set 1; TEAE: treatment-emergent adverse event.

[redacted]

Source: Appendix 13.2.7.4

Table 21 By-patient Summary of Serious TEAEs (Onset in Part 2) in Patients With Same Treatment in Both Parts 1 and 2 – Overall Population (SAF1)

Treatment Group Patient No./Age/Race	MedDRA v13.0 Preferred Term	Onset/Stop Day (Last Dose Day)	Severity	Outcome	Investigator Assessment of Relationship to Study Drug
ASP1707 5 mg					
[redacted]	Abdominal pain lower	211/217 (173)	Moderate	Recovered	Not Related
	Dysmenorrhoea	211/217 (173)	Moderate	Recovered	Not Related
[redacted]	Endometriosis	207/209 (168)	Mild	Recovered	Not Related
[redacted]	Pneumonia	204/218 (169)	Moderate	Recovered	Not Related
[redacted]	Small intestinal obstruction	98/111 (98)	Severe	Recovered	Not Related
[redacted]	Liver function test abnormal	141/246 (155)	Moderate	Recovered	Probable
[redacted]	Tooth extraction	163/164 (171)	Mild	Recovered	Not Related
ASP1707 10 mg					
[redacted]	Subileus	140/144 (139)	Severe	Recovered	Not Related
ASP1707 15 mg					
[redacted]	Endometriosis	91/98 (134)	Severe	Recovered	Not Related
	Endometriosis	133/ongoing (134)	Severe	Not Recovered	Not Related

SAF1: safety analysis set 1; TEAE: treatment-emergent adverse event.

SAF1: All randomized patients who took at least 1 dose of study medication (ASP1707 or leuprorelin acetate or placebo).

[redacted].

Source: Appendix 13.2.7.4

Table 22 By-patient Summary of Serious TEAEs (Onset in Part 2) in Patients Who Received Placebo in Part 1 and ASP1707 in Part 2 – Overall Population (SAF1)

Treatment Groups in Part 1 and Part 2 Patient No./Age/Race	MedDRA v13.0 Preferred Term	Onset/Stop Day (Last Dose Day)	Severity	Outcome	Investigator Assessment of Relationship to Study Drug
Placebo - ASP1707 5 mg					
[redacted]	Loss of consciousness	139/139 (171)	Moderate	Recovered	Not Related
	Syncope	139/139 (171)	Mild	Recovered	Not Related
	Head injury	139/142 (171)	Moderate	Recovered	Not Related
Placebo - ASP1707 10 mg					
[redacted]	Liver function test abnormal	169/211 (169)	Mild	Recovered	Not Related

SAF1: safety analysis set 1; TEAE: treatment-emergent adverse event.

SAF1: All randomized patients who took at least 1 dose of study medication (ASP1707 or leuprorelin acetate or placebo).

[redacted]

Source: Appendix 13.2.7.4