



Clinical trial results:

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 Leuporelin Acetate Treatment Group for Bone Mineral Density Assessment

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-002791-14 |
| Trial protocol | HU BE GB PL BG |
| Global end of trial date | 30 July 2015 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 10 August 2016 |
| First version publication date | 10 August 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | 1707-CL-0011 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01767090 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Acronym: TERRA |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Astellas Pharma BV |
| Sponsor organisation address | Sylviusweg 62, Leiden, Netherlands, 2333 BE |
| Public contact | Clinical Trial Disclosure, Astellas Pharma BV, Astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma BV, Astellas.resultsdisclosure@astellas.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 July 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 July 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

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 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

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 04 December 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Belgium: 9 |
| Country: Number of subjects enrolled | Bulgaria: 15 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Hungary: 29 |
| Country: Number of subjects enrolled | Japan: 149 |
| Country: Number of subjects enrolled | Poland: 136 |
| Country: Number of subjects enrolled | Romania: 111 |
| Country: Number of subjects enrolled | Ukraine: 84 |
| Country: Number of subjects enrolled | United Kingdom: 3 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 540 |
| EEA total number of subjects | 307 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 540 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This multinational, multicenter study was conducted at 97 contracted sites; 86 sites screened participants & 71 sites randomized participants 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) & Japan (31 sites).

Pre-assignment

Screening details:

After initial screening, eligible subjects enrolled into a non-medicated observational period, which included at least one complete menstrual cycle. After the observational period patients who met selection criteria were randomized into Part 1 of the study. Overall, 912 subjects were screened, 372 failed screening and 540 subjects were randomized.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Overall Period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

The study drug, except for open-label active control (leuporelin acetate), was packed using a double-blind method. All participants took 3 tablets once daily in the morning of which none, one, two or all tablets were placebo (15 mg group: 3x5 mg, 10 mg group: 2x5 mg and 1 placebo, 5 mg group 1x5 mg and 2 placebo, 3 mg group: 3x1 mg, placebo group: 3 placebo). All tablets were identical. Participants randomized to open-label leuporelin acetate received open-label injections only.

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo - Part 1 |

Arm description:

Participants received 3 matching placebo tablets once a day for 12 weeks in Part 1.

| | |
|--|--------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo to match ASP1707 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo to ASP1707 taken orally once a day.

| | |
|------------------|--------------|
| Arm title | ASP1707 3 mg |
|------------------|--------------|

Arm description:

Participants received ASP1707 3 mg treatment for both part 1 and 2 of the study (weeks 1-24).

Participants took 3 tablets once daily in the morning of which no tablets were placebo (3 mg group: 3x1 mg).

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ASP1707 3 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received ASP1707 3 mg (3x1 mg tablets) orally once a day. The tablets contained ASP1707

as the active compound in 1 mg dosage strengths.

| | |
|------------------|--------------|
| Arm title | ASP1707 5 mg |
|------------------|--------------|

Arm description:

Participants received ASP1707 5 mg treatment for both part 1 and 2 of the study (weeks 1-24).
Participants took 3 tablets once daily in the morning of which two tablets were placebo (5 mg group 1x5 mg and 2 placebo).

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo to match ASP1707 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo to ASP1707 taken orally once a day.

| | |
|--|--------------|
| Investigational medicinal product name | ASP1707 5 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received ASP1707 5 mg (1x5 mg tablet) orally once a day. The tablets contained ASP1707 as the active compound in 5 mg dosage strengths.

| | |
|------------------|---------------|
| Arm title | ASP1707 10 mg |
|------------------|---------------|

Arm description:

Participants received ASP1707 10 mg treatment for both part 1 and 2 of the study (weeks 1-24).
Participants took 3 tablets once daily in the morning of which one tablet was placebo (10 mg group: 2x5 mg and 1 placebo).

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | ASP1707 10 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received ASP1707 10 mg (2x5 mg tablets) orally once a day. The tablets contained ASP1707 as the active compound in 5 mg dosage strengths.

| | |
|--|--------------------------|
| Investigational medicinal product name | Placebo to match ASP1707 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo to ASP1707 taken orally once a day.

| | |
|------------------|---------------|
| Arm title | ASP1707 15 mg |
|------------------|---------------|

Arm description:

Participants received ASP1707 15 mg treatment for both part 1 and 2 of the study (weeks 1-24).
Participants took 3 tablets once daily in the morning of which no tablets were placebo (15 mg group: 3x5 mg).

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------|
| Investigational medicinal product name | ASP1707 15 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received ASP1707 15 mg (3x5 mg tablets) orally once a day. The tablets contained ASP1707 as the active compound in 5 mg dosage strengths.

| | |
|------------------|---------------------|
| Arm title | Leuprorelin acetate |
|------------------|---------------------|

Arm description:

Participants received open-label gonadotropin-releasing hormone (GnRH) agonist 3.75 mg leuprorelin acetate (administered by subcutaneous injection once a month) for both part 1 and 2 of the study (for up to 24 weeks).

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Leuprorelin Acetate |
| Investigational medicinal product code | |
| Other name | Prostap® SR |
| Pharmaceutical forms | Powder and solvent for solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Leuprorelin acetate 3.75 mg monthly subcutaneous injection.

| Number of subjects in period 1 | Placebo - Part 1 | ASP1707 3 mg | ASP1707 5 mg |
|--|------------------|--------------|--------------|
| Started | 89 | 87 | 92 |
| Treated | 88 | 86 | 91 |
| Completed | 75 | 68 | 79 |
| Not completed | 14 | 19 | 13 |
| Randomized but never received study drug | 1 | 1 | 1 |
| Protocol violation | 9 | 11 | 3 |
| Other | 1 | - | 1 |
| Pregnancy | 1 | 1 | 1 |
| Adverse event | - | 4 | 3 |
| Withdrawal by subject | 2 | 2 | 4 |

| Number of subjects in period 1 | ASP1707 10 mg | ASP1707 15 mg | Leuprorelin acetate |
|--|---------------|---------------|---------------------|
| Started | 90 | 90 | 92 |
| Treated | 90 | 88 | 89 |
| Completed | 72 | 68 | 69 |
| Not completed | 18 | 22 | 23 |
| Randomized but never received study drug | - | 2 | 3 |
| Protocol violation | 9 | 5 | 5 |
| Other | - | - | 1 |
| Pregnancy | - | 1 | - |

| | | | |
|-----------------------|---|---|----|
| Adverse event | 2 | 7 | 2 |
| Withdrawal by subject | 7 | 7 | 12 |

Period 2

| | |
|------------------------------|--|
| Period 2 title | Part 2 (Placebo arm switched to ASP1707) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

The study drug, except for open- label active control, was packed using a double-blind method. All participants took 3 tablets once daily in the morning of which none, one, two or all tablets were placebo (15 mg group: 3x5 mg, 10 mg group: 2x5 mg and 1 placebo, 5 mg group 1x5 mg and 2 placebo). All tablets were identical.

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ASP1707 3 mg - Part 2 |

Arm description:

Participants who received placebo in part 1 were switched to ASP1707 3 mg treatment for part 2 of the study. Participants took 3 tablets once daily in the morning of which no tablets were placebo (3 mg group: 3x1 mg).

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ASP1707 3 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received ASP1707 3 mg (3x1 mg tablets) orally once a day. The tablets contained ASP1707 as the active compound in 1 mg dosage strengths.

| | |
|------------------|-----------------------|
| Arm title | ASP1707 5 mg - Part 2 |
|------------------|-----------------------|

Arm description:

Participants who received placebo in part 1 were switched to ASP1707 5 mg treatment for part 2 of the study. Participants took 3 tablets once daily in the morning of which two tablets were placebo (5 mg group 1x5 mg and 2 placebo).

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ASP1707 5 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received ASP1707 5 mg (1x5 mg tablet) orally once a day. The tablets contained ASP1707 as the active compound in 5 mg dosage strengths.

| | |
|--|--------------------------|
| Investigational medicinal product name | Placebo to match ASP1707 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo to ASP1707 taken orally once a day.

| | |
|------------------|------------------------|
| Arm title | ASP1707 10 mg - Part 2 |
|------------------|------------------------|

Arm description:

Participants who received placebo in part 1 were switched to ASP1707 10 mg treatment for part 2 of the study. Participants took 3 tablets once daily in the morning of which one tablet was placebo (10 mg group: 2x5 mg and 1 placebo).

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | ASP1707 10 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received ASP1707 10 mg (2x5 mg tablets) orally once a day. The tablets contained ASP1707 as the active compound in 5 mg dosage strengths.

| | |
|--|--------------------------|
| Investigational medicinal product name | Placebo to match ASP1707 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo to ASP1707 taken orally once a day.

| | |
|------------------|------------------------|
| Arm title | ASP1707 15 mg - Part 2 |
|------------------|------------------------|

Arm description:

Participants who received placebo in part 1 were switched to ASP1707 15 mg treatment for part 2 of the study. Participants took 3 tablets once daily in the morning of which no tablets were placebo (15 mg group: 3x5 mg).

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | ASP1707 15 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received ASP1707 15 mg (3x5 mg tablets) orally once a day. The tablets contained ASP1707 as the active compound in 5 mg dosage strengths.

| Number of subjects in period 2^[1] | ASP1707 3 mg - Part 2 | ASP1707 5 mg - Part 2 | ASP1707 10 mg - Part 2 |
|---|-----------------------|-----------------------|------------------------|
| Started | 19 | 18 | 18 |
| Completed | 19 | 17 | 18 |
| Not completed | 0 | 1 | 0 |
| Withdrawal by subject | - | 1 | - |

| Number of subjects in period 2^[1] | ASP1707 15 mg - Part 2 |
|---|------------------------|
| Started | 20 |
| Completed | 19 |
| Not completed | 1 |
| Withdrawal by subject | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Data for period 2 are provided for participants initially randomized to placebo and randomly switched to 1 of the 4 ASP1707 groups for Part 2.

Baseline characteristics

Reporting groups

| | |
|--|---------------------|
| Reporting group title | Placebo - Part 1 |
| Reporting group description: Participants received 3 matching placebo tablets once a day for 12 weeks in Part 1. | |
| Reporting group title | ASP1707 3 mg |
| Reporting group description: Participants received ASP1707 3 mg treatment for both part 1 and 2 of the study (weeks 1-24). Participants took 3 tablets once daily in the morning of which no tablets were placebo (3 mg group: 3x1 mg). | |
| Reporting group title | ASP1707 5 mg |
| Reporting group description: Participants received ASP1707 5 mg treatment for both part 1 and 2 of the study (weeks 1-24). Participants took 3 tablets once daily in the morning of which two tablets were placebo (5 mg group 1x5 mg and 2 placebo). | |
| Reporting group title | ASP1707 10 mg |
| Reporting group description: Participants received ASP1707 10 mg treatment for both part 1 and 2 of the study (weeks 1-24). Participants took 3 tablets once daily in the morning of which one tablet was placebo (10 mg group: 2x5 mg and 1 placebo). | |
| Reporting group title | ASP1707 15 mg |
| Reporting group description: Participants received ASP1707 15 mg treatment for both part 1 and 2 of the study (weeks 1-24). Participants took 3 tablets once daily in the morning of which no tablets were placebo (15 mg group: 3x5 mg). | |
| Reporting group title | Leuprorelin acetate |
| Reporting group description: Participants received open-label gonadotropin-releasing hormone (GnRH) agonist 3.75 mg leuprorelin acetate (administered by subcutaneous injection once a month) for both part 1 and 2 of the study (for up to 24 weeks). | |

| Reporting group values | Placebo - Part 1 | ASP1707 3 mg | ASP1707 5 mg |
|------------------------------------|------------------|--------------|--------------|
| Number of subjects | 89 | 87 | 92 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|---------------|
| Age continuous Units: years arithmetic mean standard deviation | 33.3 ± 5.9 | 34.7 ± 5.4 | 33.2 ± 5.4 |
| Gender categorical Units: | | | |
| Male | 0 | 0 | 0 |
| Female | 89 | 87 | 92 |

| Reporting group values | ASP1707 10 mg | ASP1707 15 mg | Leuprorelin acetate |
|------------------------------------|---------------|---------------|---------------------|
| Number of subjects | 90 | 90 | 92 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|-------------|
| Age continuous Units: years arithmetic mean standard deviation | 34.2 ± 6.2 | 33.5 ± 6.2 | 33 ± 6.5 |
| Gender categorical Units: | | | |
| Male | 0 | 0 | 0 |
| Female | 90 | 90 | 92 |

| | | | |
|------------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 540 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----|--|--|
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: | | | |
| Male | 0 | | |
| Female | 540 | | |

End points

End points reporting groups

| | |
|--|------------------------|
| Reporting group title | Placebo - Part 1 |
| Reporting group description: Participants received 3 matching placebo tablets once a day for 12 weeks in Part 1. | |
| Reporting group title | ASP1707 3 mg |
| Reporting group description: Participants received ASP1707 3 mg treatment for both part 1 and 2 of the study (weeks 1-24). Participants took 3 tablets once daily in the morning of which no tablets were placebo (3 mg group: 3x1 mg). | |
| Reporting group title | ASP1707 5 mg |
| Reporting group description: Participants received ASP1707 5 mg treatment for both part 1 and 2 of the study (weeks 1-24). Participants took 3 tablets once daily in the morning of which two tablets were placebo (5 mg group 1x5 mg and 2 placebo). | |
| Reporting group title | ASP1707 10 mg |
| Reporting group description: Participants received ASP1707 10 mg treatment for both part 1 and 2 of the study (weeks 1-24). Participants took 3 tablets once daily in the morning of which one tablet was placebo (10 mg group: 2x5 mg and 1 placebo). | |
| Reporting group title | ASP1707 15 mg |
| Reporting group description: Participants received ASP1707 15 mg treatment for both part 1 and 2 of the study (weeks 1-24). Participants took 3 tablets once daily in the morning of which no tablets were placebo (15 mg group: 3x5 mg). | |
| Reporting group title | Leuprorelin acetate |
| Reporting group description: Participants received open-label gonadotropin-releasing hormone (GnRH) agonist 3.75 mg leuprorelin acetate (administered by subcutaneous injection once a month) for both part 1 and 2 of the study (for up to 24 weeks). | |
| Reporting group title | ASP1707 3 mg - Part 2 |
| Reporting group description: Participants who received placebo in part 1 were switched to ASP1707 3 mg treatment for part 2 of the study. Participants took 3 tablets once daily in the morning of which no tablets were placebo (3 mg group: 3x1 mg). | |
| Reporting group title | ASP1707 5 mg - Part 2 |
| Reporting group description: Participants who received placebo in part 1 were switched to ASP1707 5 mg treatment for part 2 of the study. Participants took 3 tablets once daily in the morning of which two tablets were placebo (5 mg group 1x5 mg and 2 placebo). | |
| Reporting group title | ASP1707 10 mg - Part 2 |
| Reporting group description: Participants who received placebo in part 1 were switched to ASP1707 10 mg treatment for part 2 of the study. Participants took 3 tablets once daily in the morning of which one tablet was placebo (10 mg group: 2x5 mg and 1 placebo). | |
| Reporting group title | ASP1707 15 mg - Part 2 |
| Reporting group description: Participants who received placebo in part 1 were switched to ASP1707 15 mg treatment for part 2 of the study. Participants took 3 tablets once daily in the morning of which no tablets were placebo (15 mg group: 3x5 mg). | |

Primary: Change from Baseline to the End of Treatment (EoT) (12 Weeks) of the Mean Numeric Rating Scale (NRS) Pain Score for Overall Pelvic Pain (Dysmenorrhea and Non-Menstrual Pelvic Pain)

| | |
|-----------------|---|
| End point title | Change from Baseline to the End of Treatment (EoT) (12 Weeks) of the Mean Numeric Rating Scale (NRS) Pain Score for Overall Pelvic Pain (Dysmenorrhea and Non-Menstrual Pelvic Pain) ^[1] |
|-----------------|---|

End point description:

Pelvic pain measured daily by participants in an e-diary using NRS (scale 0 – 10, where 0 anchors 'no pain' & 10 'worst pain you can imagine'). Score of 1-3 represented 'mild pain' (nagging, annoying, interfering little with Activities of Daily Living [ADL]), 4-6 'moderate pain' (interferes significantly with ADL), & 7-10 'severe pain' (disabling, unable to perform ADL). Overall pelvic pain calculated as the mean of the NRS scale scores from the last 28-day period (whole menstrual cycle, including menstrual & nonmenstrual bleeding days) before each visit. Analysis population consisted of Full Analysis Set 1 (FAS1), which consisted of all randomized participants who received at least 1 dose of double-blind study medication (placebo or ASP1707) or at least 1 dose of leuporelin acetate & who had a primary NRS pain score for overall pelvic pain at baseline & at least 1 evaluable post-baseline NRS pain score for overall pelvic pain, defined as having at least 14 days of pain score.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and EoT (last 28 days)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Not applicable, the leuporelin arm was excluded from the primary analysis.

| End point values | Placebo - Part 1 | ASP1707 3 mg | ASP1707 5 mg | ASP1707 10 mg |
|--|------------------------|------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 77 | 87 | 82 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.56 (-1.91 to -1.21) | -1.63 (-1.99 to -1.27) | -1.93 (-2.27 to -1.6) | -2.29 (-2.64 to -1.94) |

| End point values | ASP1707 15 mg | | | |
|--|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 84 | | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -2.13 (-2.47 to -1.79) | | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Linear Trend Analysis (Primary) |
|----------------------------|---------------------------------|

Statistical analysis description:

ANCOVA model that includes treatment group (excluding leuporelin group) and region as fixed factors and baseline value as a covariate. Includes linear contract based on all treatment groups (excluding leuporelin) and information until Visit 6 (included). Last non-missing observation before first intake of study drug is used as baseline. EoT (Part 1) corresponds to the last non-missing observation during Part 1 of the study.

| | |
|-------------------|--|
| Comparison groups | Placebo - Part 1 v ASP1707 3 mg v ASP1707 5 mg v ASP1707 10 mg v ASP1707 15 mg |
|-------------------|--|

| | |
|---|----------------------|
| Number of subjects included in analysis | 411 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.001 |
| Method | ANCOVA |

Notes:

[2] - 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).

Primary: Change from Baseline to the EoT of the Mean NRS Pain Score for Dysmenorrhea

| | |
|-----------------|--|
| End point title | Change from Baseline to the EoT of the Mean NRS Pain Score for Dysmenorrhea ^[3] |
|-----------------|--|

End point description:

Pelvic pain measured daily by participants in an e-diary using NRS (scale 0 – 10, where 0 anchors 'no pain' & 10 'worst pain you can imagine'). Score of 1-3 represented 'mild pain' (nagging, annoying, interfering little with Activities of Daily Living [ADL]), 4-6 'moderate pain' (interferes significantly with ADL), & 7-10 'severe pain' (disabling, unable to perform ADL). Dysmenorrhea pelvic pain was calculated as the mean of the NRS scale scores from the menstrual bleeding days within the 28-day period. A score of 0 was applied if there was no menstrual bleeding during the 28-day period. Analysis population consisted of the FAS1.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and EoT (last 28 days)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Not applicable, the leuprorelin arm was excluded from the primary analysis.

| End point values | Placebo - Part 1 | ASP1707 3 mg | ASP1707 5 mg | ASP1707 10 mg |
|--|------------------|------------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 77 | 87 | 82 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.5 (-2 to -1) | -2.72 (-3.22 to -2.21) | -2.85 (-3.33 to -2.38) | -3.97 (-4.46 to -3.48) |

| End point values | ASP1707 15 mg | | | |
|--|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 84 | | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -4.18 (-4.66 to -3.7) | | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Linear Trend Analysis (Primary) |
|----------------------------|---------------------------------|

Statistical analysis description:

ANCOVA model that includes treatment group (excluding leuprorelin group) and region as fixed factors and baseline value as a covariate. Includes linear contract based on all treatment groups (excluding

leuporelin) and information until Visit 6 (included). Last non-missing observation before first intake of study drug is used as baseline. EoT (Part 1) corresponds to the last non-missing observation during Part 1 of the study.

| | |
|---|--|
| Comparison groups | Placebo - Part 1 v ASP1707 3 mg v ASP1707 5 mg v ASP1707 10 mg v ASP1707 15 mg |
| Number of subjects included in analysis | 411 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | < 0.001 |
| Method | ANCOVA |

Notes:

[4] - 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).

Primary: Change from Baseline to the EoT of the Mean NRS Pain Score for Non-Menstrual Pelvic Pain (NMPP)

| | |
|-----------------|--|
| End point title | Change from Baseline to the EoT of the Mean NRS Pain Score for Non-Menstrual Pelvic Pain (NMPP) ^[5] |
|-----------------|--|

End point description:

Pelvic pain measured daily by participants in an e-diary using NRS (scale 0 – 10, where 0 anchors 'no pain' & 10 'worst pain you can imagine'). Score of 1-3 represented 'mild pain' (nagging, annoying, interfering little with Activities of Daily Living [ADL]), 4-6 'moderate pain' (interferes significantly with ADL), & 7-10 'severe pain' (disabling, unable to perform ADL). NMPP was calculated as the mean of the NRS scale scores from all days except menstrual bleeding days within the 28-day period. The analysis population consisted of the FAS1.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and EoT (last 28 days)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Not applicable, the leuporelin arm was excluded from the primary analysis.

| End point values | Placebo - Part 1 | ASP1707 3 mg | ASP1707 5 mg | ASP1707 10 mg |
|--|------------------------|------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 77 | 87 | 82 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.53 (-1.88 to -1.19) | -1.51 (-1.87 to -1.16) | -1.8 (-2.14 to -1.47) | -2.03 (-2.37 to -1.68) |

| End point values | ASP1707 15 mg | | | |
|--|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 84 | | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.86 (-2.2 to -1.52) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Linear Trend Analysis (Primary) |
| Statistical analysis description: | |
| ANCOVA model that includes treatment group (excluding leuprorelin group) and region as fixed factors and baseline value as a covariate. Includes linear contrast based on all treatment groups (excluding leuprorelin) and information until Visit 6 (included). Last non-missing observation before first intake of study drug is used as baseline. EoT (Part 1) corresponds to the last non-missing observation during Part 1 of the study. | |
| Comparison groups | Placebo - Part 1 v ASP1707 3 mg v ASP1707 5 mg v ASP1707 10 mg v ASP1707 15 mg |
| Number of subjects included in analysis | 411 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0.029 |
| Method | ANCOVA |

Notes:

[6] - 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).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first study drug administration to End of Study (EoS) visit (42 days after intake of last dose of study drug)

Adverse event reporting additional description:

Analysis population consisted of the Safety Analysis Set 1 (SAF1), which consisted of all randomized participants who took at least 1 dose of study medication (ASP1707 or leuprorelin acetate or placebo).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Part 1 Placebo |
|-----------------------|----------------|

Reporting group description:

Participants received 3 matching placebo tablets once a day for 12 weeks in Part 1.

| | |
|-----------------------|---------------------|
| Reporting group title | Part 1 ASP1707 3 mg |
|-----------------------|---------------------|

Reporting group description:

Participants received ASP1707 3 mg treatment during part 1 of the study. Participants took 3 tablets once daily in the morning of which no tablets were placebo (3 mg group: 3x1 mg).

| | |
|-----------------------|----------------------|
| Reporting group title | Part 1 ASP1707 15 mg |
|-----------------------|----------------------|

Reporting group description:

Participants received ASP1707 15 mg treatment during part 1 of the study. Participants took 3 tablets once daily in the morning of which no tablets were placebo (15 mg group: 3x5 mg).

| | |
|-----------------------|----------------------|
| Reporting group title | Part 1 ASP1707 10 mg |
|-----------------------|----------------------|

Reporting group description:

Participants received ASP1707 10 mg treatment during part 1 of the study. Participants took 3 tablets once daily in the morning of which one tablet was placebo (10 mg group: 2x5 mg and 1 placebo).

| | |
|-----------------------|---------------------|
| Reporting group title | Part 1 ASP1707 5 mg |
|-----------------------|---------------------|

Reporting group description:

Participants received ASP1707 5 mg treatment during part 1 of the study. Participants took 3 tablets once daily in the morning of which two tablets were placebo (5 mg group 1x5 mg and 2 placebo).

| | |
|-----------------------|----------------------------|
| Reporting group title | Part 1 Leuprorelin acetate |
|-----------------------|----------------------------|

Reporting group description:

Participants received open-label GnRH agonist 3.75 mg leuprorelin acetate (administered by subcutaneous injection once a month) for part 1 of the study (for weeks 1-12).

| | |
|-----------------------|---------------------|
| Reporting group title | Part 2 ASP1707 3 mg |
|-----------------------|---------------------|

Reporting group description:

Participants who received 3 mg ASP1707 or who were switched from placebo in Part 1 received 3 mg ASP1707 from weeks 13-24 (Part 2), once daily. Participants took 3 tablets once daily in the morning of which no tablets were placebo (3 mg group: 3x1 mg).

| | |
|-----------------------|---------------------|
| Reporting group title | Part 2 ASP1707 5 mg |
|-----------------------|---------------------|

Reporting group description:

Participants who received 5 mg ASP1707 or who were switched from placebo in Part 1 received 5 mg ASP1707 from weeks 13-24 (Part 2). Participants took 3 tablets once daily in the morning of which two tablets were placebo (5 mg group 1x5 mg and 2 placebo).

| | |
|-----------------------|----------------------|
| Reporting group title | Part 2 ASP1707 10 mg |
|-----------------------|----------------------|

Reporting group description:

Participants who received 10 mg ASP1707 or who were switched from placebo in Part 1 received 10 mg ASP1707 from weeks 13-24 (Part 2). Participants took 3 tablets once daily in the morning of which one tablet was placebo (10 mg group: 2x5 mg and 1 placebo).

| | |
|-----------------------|----------------------|
| Reporting group title | Part 2 ASP1707 15 mg |
|-----------------------|----------------------|

Reporting group description:

Participants who received 15 mg ASP1707 or who were switched from placebo in Part 1 received 15 mg ASP1707 from weeks 13-24 (Part 2). Participants took 3 tablets once daily in the morning of which no tablets were placebo (15 mg group: 3x5 mg).

| | |
|-----------------------|---------------------------|
| Reporting group title | Part 2 Leuporelin acetate |
|-----------------------|---------------------------|

Reporting group description:

Participants received open-label GnRH agonist 3.75 mg leuporelin acetate (administered by subcutaneous injection once a month) for both in part 2 of the study (for weeks 13-24).

| Serious adverse events | Part 1 Placebo | Part 1 ASP1707 3 mg | Part 1 ASP1707 15 mg |
|---|----------------|---------------------|----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 3 / 86 (3.49%) | 0 / 88 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dural fistula | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 86 (1.16%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 86 (1.16%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mallory-Weiss syndrome | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 86 (1.16%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 86 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Part 1 ASP1707 10 mg | Part 1 ASP1707 5 mg | Part 1 Leuprorelin acetate |
|---|----------------------|---------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dural fistula | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mallory-Weiss syndrome | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 91 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serious adverse events | Part 2 ASP1707 3 mg | Part 2 ASP1707 5 mg | Part 2 ASP1707 10 mg |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 7 / 102 (6.86%) | 2 / 94 (2.13%) |

| | | | |
|---|----------------------------------|-----------------------------------|----------------------------------|
| number of deaths (all causes) number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations Liver function test abnormal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 102 (0.98%) 1 / 1 0 / 0 | 1 / 94 (1.06%) 0 / 1 0 / 0 |
| Injury, poisoning and procedural complications Head injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 102 (0.98%) 0 / 1 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 102 (0.98%) 0 / 1 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Nervous system disorders Dural fistula subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 90 (0.00%) 0 / 0 0 / 0 | 0 / 102 (0.00%) 0 / 0 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Loss of consciousness subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 102 (0.98%) 0 / 1 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Syncope subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 102 (0.98%) 0 / 1 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Pregnancy, puerperium and perinatal conditions Abortion spontaneous subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 90 (0.00%) 0 / 0 0 / 0 | 0 / 102 (0.00%) 0 / 0 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 102 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 102 (0.98%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mallory-Weiss syndrome | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 102 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 102 (0.98%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 102 (0.00%) | 1 / 94 (1.06%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 102 (0.98%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 102 (0.98%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Ureteric obstruction | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 102 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 102 (0.98%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------------|----------------------------|--|
| Serious adverse events | Part 2 ASP1707 15 mg | Part 2 Leuprorelin acetate | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 76 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dural fistula | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mallory-Weiss syndrome | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Part 1 Placebo | Part 1 ASP1707 3 mg | Part 1 ASP1707 15 mg |
|---|------------------|---------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 88 (27.27%) | 20 / 86 (23.26%) | 35 / 88 (39.77%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | 4 / 86 (4.65%) | 17 / 88 (19.32%) |
| occurrences (all) | 6 | 4 | 18 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 10 / 88 (11.36%) | 9 / 86 (10.47%) | 12 / 88 (13.64%) |
| occurrences (all) | 11 | 10 | 12 |
| Gastrointestinal disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Nausea subjects affected / exposed occurrences (all) | 4 / 88 (4.55%) 4 | 2 / 86 (2.33%) 2 | 2 / 88 (2.27%) 2 |
| Reproductive system and breast disorders Menstruation delayed subjects affected / exposed occurrences (all) | 0 / 88 (0.00%) 0 | 1 / 86 (1.16%) 1 | 2 / 88 (2.27%) 2 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 3 / 88 (3.41%) 3 | 2 / 86 (2.33%) 2 | 3 / 88 (3.41%) 3 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 88 (9.09%) 9 | 5 / 86 (5.81%) 6 | 8 / 88 (9.09%) 9 |

| Non-serious adverse events | Part 1 ASP1707 10 mg | Part 1 ASP1707 5 mg | Part 1 Leuprorelin acetate |
|--|------------------------|------------------------|----------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 31 / 90 (34.44%) | 24 / 91 (26.37%) | 39 / 89 (43.82%) |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) | 10 / 90 (11.11%) 11 | 12 / 91 (13.19%) 13 | 25 / 89 (28.09%) 26 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 12 / 90 (13.33%) 14 | 6 / 91 (6.59%) 6 | 15 / 89 (16.85%) 15 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 7 / 90 (7.78%) 7 | 2 / 91 (2.20%) 2 | 4 / 89 (4.49%) 5 |
| Reproductive system and breast disorders Menstruation delayed subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 4 | 4 / 91 (4.40%) 5 | 5 / 89 (5.62%) 5 |
| Psychiatric disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Insomnia subjects affected / exposed occurrences (all) | 2 / 90 (2.22%) 2 | 1 / 91 (1.10%) 1 | 5 / 89 (5.62%) 5 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 6 | 4 / 91 (4.40%) 4 | 5 / 89 (5.62%) 5 |

| Non-serious adverse events | Part 2 ASP1707 3 mg | Part 2 ASP1707 5 mg | Part 2 ASP1707 10 mg |
|--|---------------------|-----------------------|----------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 14 / 90 (15.56%) | 23 / 102 (22.55%) | 16 / 94 (17.02%) |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 4 | 8 / 102 (7.84%) 9 | 2 / 94 (2.13%) 2 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 2 / 90 (2.22%) 2 | 4 / 102 (3.92%) 4 | 2 / 94 (2.13%) 2 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 2 / 90 (2.22%) 2 | 1 / 102 (0.98%) 1 | 3 / 94 (3.19%) 3 |
| Reproductive system and breast disorders Menstruation delayed subjects affected / exposed occurrences (all) | 2 / 90 (2.22%) 2 | 2 / 102 (1.96%) 3 | 2 / 94 (2.13%) 3 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 1 / 90 (1.11%) 1 | 0 / 102 (0.00%) 0 | 0 / 94 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 6 / 90 (6.67%) 8 | 9 / 102 (8.82%) 11 | 9 / 94 (9.57%) 9 |

| Non-serious adverse events | Part 2 ASP1707 15 mg | Part 2 Leuprorelin acetate | |
|---|----------------------|----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 23 / 95 (24.21%) | 14 / 76 (18.42%) | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 5 / 95 (5.26%) | 2 / 76 (2.63%) | |
| occurrences (all) | 5 | 3 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 95 (5.26%) | 5 / 76 (6.58%) | |
| occurrences (all) | 6 | 5 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 95 (2.11%) | 2 / 76 (2.63%) | |
| occurrences (all) | 2 | 2 | |
| Reproductive system and breast disorders | | | |
| Menstruation delayed | | | |
| subjects affected / exposed | 3 / 95 (3.16%) | 1 / 76 (1.32%) | |
| occurrences (all) | 3 | 1 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 3 / 95 (3.16%) | 2 / 76 (2.63%) | |
| occurrences (all) | 3 | 2 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 8 / 95 (8.42%) | 3 / 76 (3.95%) | |
| occurrences (all) | 8 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 05 December 2012 | <ul style="list-style-type: none">-Spermicidal foam/gel/film/cream/suppository and occlusive cap were removed from inclusion criterion 6 because they are no longer acceptable nonhormonal contraceptive methods. According to the World Health Organization (WHO), spermicidal foam/gel/film/cream/suppository can increase the risk for certain sexually transmitted infections (including human immunodeficiency virus) and can cause local irritation of mucosal surfaces. In addition, spermicidally lubricated condoms do not have increased contraceptive efficacy compared to condoms without spermicide. Because of this, spermicidal foam/gel/film/cream/suppository is difficult to obtain or not available in many countries. Occlusive cap alone is not considered to be an effective contraceptive.-Total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides were added to the planned biochemistry tests because lipid changes had been added to the ASP1707 developmental risk management plan as a potential risk requiring monitoring in clinical studies. This did not change the amount of blood taken from the patients at any visit.-Administrative changes and typographical corrections were made. |
| 02 December 2014 | <ul style="list-style-type: none">-The duration for use of non-hormonal contraceptive methods after the last dose was updated from 12 weeks to 42 days to align with the period during which pregnancies had to be reported. This update did not change the benefit/risk ratio for patients.-Dunnett's test was added to appropriately adjust the comparisons of the active dose groups against placebo.-The database cutoff, which was planned after the last follow-up visit, was to be implemented after the EoS visit instead. These outputs were final and were used for the main analyses, including primary and all secondary efficacy analyses. The only data to be collected after this release would be in a limited number of patients that had completed the EoS visit but not yet the follow-up visit. This amendment only affected the timing of the analyses, and was not a formal interim analysis.-The planned study period was extended due to delayed recruitment.-The period for collection and follow-up of serious adverse events (SAEs) was made consistent throughout the protocol.-The updated Summary of Product Characteristics (SmPC) of leuprorelin acetate was added. The changes had no significant impact on the safety or physical or mental integrity of the patients, on the scientific value of the trial, on the conduct or management of the trial or on the quality or safety of any investigational medicinal products (IMP) used in the study.-Administrative changes and typographical corrections were made. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported