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 Leuprorelin 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 partcipants & 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	Investigator, Subject

Blinding implementation details:

The study drug, except for open-label active control (leuprorelin 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 leuprorelin 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	33.3	34.7	33.2
standard deviation	± 5.9	± 5.4	± 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	34.2	33.5	33
standard deviation	± 6.2	± 6.2	± 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 leuprorelin 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 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%)	-1.56 (-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 leuprorelin group) and region as fixed factors and baseline value as a covariate. Includes linear contract 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[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

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[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 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%)	-1.53 (-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 contract 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 Leuprorelin acetate

Reporting group description:

Participants received open-label GnRH agonist 3.75 mg leuprorelin 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)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 90 (0.00%)	1 / 102 (0.98%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
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%)	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
Surgical and medical procedures			
Tooth extraction			
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
Nervous system disorders			
Dural fistula			
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
Loss of consciousness			
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
Syncope			
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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
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

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	4 / 88 (4.55%)	2 / 86 (2.33%)	2 / 88 (2.27%)
occurrences (all)	4	2	2
Reproductive system and breast disorders			
Menstruation delayed			
subjects affected / exposed	0 / 88 (0.00%)	1 / 86 (1.16%)	2 / 88 (2.27%)
occurrences (all)	0	1	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 88 (3.41%)	2 / 86 (2.33%)	3 / 88 (3.41%)
occurrences (all)	3	2	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 88 (9.09%)	5 / 86 (5.81%)	8 / 88 (9.09%)
occurrences (all)	9	6	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	10 / 90 (11.11%)	12 / 91 (13.19%)	25 / 89 (28.09%)
occurrences (all)	11	13	26
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 90 (13.33%)	6 / 91 (6.59%)	15 / 89 (16.85%)
occurrences (all)	14	6	15
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 90 (7.78%)	2 / 91 (2.20%)	4 / 89 (4.49%)
occurrences (all)	7	2	5
Reproductive system and breast disorders			
Menstruation delayed			
subjects affected / exposed	4 / 90 (4.44%)	4 / 91 (4.40%)	5 / 89 (5.62%)
occurrences (all)	4	5	5
Psychiatric disorders			

Insomnia			
subjects affected / exposed	2 / 90 (2.22%)	1 / 91 (1.10%)	5 / 89 (5.62%)
occurrences (all)	2	1	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 90 (4.44%)	4 / 91 (4.40%)	5 / 89 (5.62%)
occurrences (all)	6	4	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	4 / 90 (4.44%)	8 / 102 (7.84%)	2 / 94 (2.13%)
occurrences (all)	4	9	2
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 90 (2.22%)	4 / 102 (3.92%)	2 / 94 (2.13%)
occurrences (all)	2	4	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 90 (2.22%)	1 / 102 (0.98%)	3 / 94 (3.19%)
occurrences (all)	2	1	3
Reproductive system and breast disorders			
Menstruation delayed			
subjects affected / exposed	2 / 90 (2.22%)	2 / 102 (1.96%)	2 / 94 (2.13%)
occurrences (all)	2	3	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 102 (0.00%)	0 / 94 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 90 (6.67%)	9 / 102 (8.82%)	9 / 94 (9.57%)
occurrences (all)	8	11	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	-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	-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