Clinical trial results:
A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel group, Adaptive, Combined Proof of Concept and Dose-Finding Study to Investigate Efficacy, Safety, Pharmacodynamics and Pharmacokinetics of ASP3652 in the Treatment of Female Subjects with Bladder Pain Syndrome / Interstitial Cystitis

Summary

EudraCT number	2011-004555-39
Trial protocol	BE NL CZ DE LV PT ES PL DK LT
Global end of trial date	18 March 2014

Results information

Result version number	v1
This version publication date	23 May 2016
First version publication date	25 June 2015

Trial information

Trial identification

Sponsor protocol code	3652-CL-0018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01613586
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development
Sponsor organisation address	Sylviusweg 62, Leiden, Netherlands, 2333 BE
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, 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	18 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate efficacy of ASP3652 in female subjects with Bladder Pain Syndrome / Interstitial Cystitis (BPS/IC).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH 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 and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 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	Romania: 47
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Czech Republic: 45
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Latvia: 24
Country: Number of subjects enrolled	Lithuania: 12
Worldwide total number of subjects	287
EEA total number of subjects	239

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)	222
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the 3-week run-in period, patients were treated with single-blind placebo (3 tablets twice a day). To be eligible for randomization, the mean daily pain (MDP) score had to be at least 4.0 on an 11-point numerical rating scale from 0-10.

Period 1

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

Blinding implementation details:

Allocation: Randomised 1:1:1:1 for burn-in period of 40 subjects; thereafter Bayesian adaptive allocation based on monthly interim analyses.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects took three matching placebo tablets twice a day for 12 weeks, followed by a 2-week follow-up period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally twice a day.

Arm title	ASP3652 50 mg BID

Arm description:

Subjects took two 25 mg ASP3652 tablets and one placebo tablet twice a day (BID) for 12 weeks, followed by a 2-week follow-up period.

Arm type	Experimental
Investigational medicinal product name	ASP3652
Investigational medicinal product code	ASP3652
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally twice a day.

Arm title	ASP3652 150 mg BID

Arm description:

Subjects took two 25 mg and one 100 mg ASP3652 tablet twice a day for 12 weeks, followed by a 2-week follow-up period.

Arm type	Experimental

Investigational medicinal product name	ASP3652
Investigational medicinal product code	ASP3652
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally twice a day.

Arm title	ASP3652 300 mg BID

Arm description:

Subjects took three 100 mg ASP3652 tablets twice a day for 12 weeks, followed by a 2-week follow-up period.

Arm type	Experimental
Investigational medicinal product name	ASP3652
Investigational medicinal product code	ASP3652
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally twice a day.

Number of subjects in period 1	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID
Started	82	53	55
Completed	69	46	48
Not completed	13	7	7
Randomized but never received study drug	-	-	-
Consent withdrawn by subject	6	4	1
Protocol violation	4	2	1
Other	1	-	1
Adverse event	2	1	4

Number of subjects in period 1	ASP3652 300 mg BID
Started	97
Completed	83
Not completed	14
Randomized but never received study drug	1
Consent withdrawn by subject	9
Protocol violation	1
Other	1
Adverse event	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects took three matching placebo tablets twice a day for 12 weeks, followed by a 2-week follow-up period.	
Reporting group title	ASP3652 50 mg BID
Reporting group description:	
Subjects took two 25 mg ASP3652 tablets and one placebo tablet twice a day (BID) for 12 weeks, followed by a 2-week follow-up period.	
Reporting group title	ASP3652 150 mg BID
Reporting group description:	
Subjects took two 25 mg and one 100 mg ASP3652 tablet twice a day for 12 weeks, followed by a 2-week follow-up period.	
Reporting group title	ASP3652 300 mg BID
Reporting group description:	
Subjects took three 100 mg ASP3652 tablets twice a day for 12 weeks, followed by a 2-week follow-up period.	

Reporting group values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID
Number of subjects	82	53	55
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	51.4	49.6	53.5
standard deviation	± 15.84	± 14.78	± 16.56
Gender categorical Units: Subjects			
Female	82	53	55
Male	0	0	0
Race Units: Subjects			
White	82	53	55
Other	0	0	0
Hunner's lesions present? Units: Subjects			
Yes	10	9	16
No	39	25	22
Unknown	33	19	17
Missing	0	0	0
Previous or current medication treatment for bladder pain syndrome/Interstitial cystitis (BPS/IC) Units: Subjects			
No	42	30	30
Yes	40	23	25

Time since BPS/IC Diagnosis Units: months			
arithmetic mean	34.4	34.6	30.6
standard deviation	± 35.87	± 38.43	± 33.15
Duration of BPS/IC Symptoms Units: months			
arithmetic mean	65.3	61.1	59.8
standard deviation	± 76.6	± 58.82	± 61.05

Reporting group values	ASP3652 300 mg BID	Total	
Number of subjects	97	287	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	50.5		
standard deviation	± 16.74	-	
Gender categorical Units: Subjects			
Female	97	287	
Male	0	0	
Race Units: Subjects			
White	97	287	
Other	0	0	
Hunner's lesions present? Units: Subjects			
Yes	28	63	
No	36	122	
Unknown	32	101	
Missing	1	1	
Previous or current medication treatment for bladder pain syndrome/Interstitial cystitis (BPS/IC) Units: Subjects			
No	50	152	
Yes	47	135	
Time since BPS/IC Diagnosis Units: months			
arithmetic mean	34.7		
standard deviation	± 43.93	-	
Duration of BPS/IC Symptoms Units: months			
arithmetic mean	70.1		
standard deviation	± 66.6	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects took three matching placebo tablets twice a day for 12 weeks, followed by a 2-week follow-up period.	
Reporting group title	ASP3652 50 mg BID
Reporting group description:	
Subjects took two 25 mg ASP3652 tablets and one placebo tablet twice a day (BID) for 12 weeks, followed by a 2-week follow-up period.	
Reporting group title	ASP3652 150 mg BID
Reporting group description:	
Subjects took two 25 mg and one 100 mg ASP3652 tablet twice a day for 12 weeks, followed by a 2-week follow-up period.	
Reporting group title	ASP3652 300 mg BID
Reporting group description:	
Subjects took three 100 mg ASP3652 tablets twice a day for 12 weeks, followed by a 2-week follow-up period.	

Primary: Change from Baseline to End of Treatment in Mean Daily Pain (MDP)

End point title	Change from Baseline to End of Treatment in Mean Daily Pain (MDP)
End point description:	
The MDP is the mean of the 7 daily consecutive pain measurements, i.e. the mean of the 7 daily consecutive scores of item 4 of the Female GenitoUrinary Pain Index (F-GUPI)-24h, recorded in the last week prior to Baseline and Week 12. The F-GUPI-24h is a validated instrument for evaluating symptoms of BPS/IC. Item 4 in the F-GUPI-24h rates the average pain over the past 24 hours on an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (pain as bad as you can imagine). This endpoint was analyzed using a Bayesian longitudinal dose-response model. In the table below, the row for "arithmetic mean (standard deviation)" is actually summarizing the posterior mean change from Baseline to end of treatment (EoT) and corresponding standard deviation. For subjects who withdrew due to an adverse event, the change from baseline to EoT in MDP score was set to 0.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[1]	49[2]	52[3]	89[4]
Units: units on a scale				
arithmetic mean (standard deviation)	-1.72 (± 0.266)	-1.49 (± 0.292)	-1.56 (± 0.265)	-1.73 (± 0.225)

Notes:

[1] - Full analysis set with available baseline data

[2] - Full analysis set with available baseline data

[3] - Full analysis set with available baseline data

[4] - Full analysis set with available baseline data

Statistical analyses

Statistical analysis title	Bayesian Analysis

Statistical analysis description:

A Bayesian longitudinal dose-response model was used to model changes from baseline to end of treatment in MDP score. The posterior difference versus placebo and 95% credibility interval are presented, along with the posterior probability of the dose group being the maximum effective dose.

Comparison groups	Placebo v ASP3652 50 mg BID
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.183 [5]
Method	Bayesian longitudinal dose-response mode
Parameter estimate	Posterior difference versus placebo
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	1
Variability estimate	Standard deviation
Dispersion value	0.395

Notes:

[5] - Posterior probability of maximum effective dose

Statistical analysis title	Bayesian Analysis

Statistical analysis description:

A Bayesian longitudinal dose-response model was used to model changes from baseline to end of treatment in MDP score. The posterior difference versus placebo and 95% credibility interval are presented, along with the posterior probability of the dose group being the maximum effective dose.

Comparison groups	Placebo v ASP3652 150 mg BID
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.231 [6]
Method	Bayesian longitudinal dose-response mode
Parameter estimate	Posterior difference versus placebo
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.9
Variability estimate	Standard deviation
Dispersion value	0.379

Notes:

[6] - Posterior probability of maximum effective dose

Statistical analysis title	Bayesian Analysis

Statistical analysis description:

A Bayesian longitudinal dose-response model was used to model changes from baseline to end of treatment in MDP score. The posterior difference versus placebo and 95% credibility interval are presented, along with the posterior probability of the dose group being the maximum effective dose.

Comparison groups	Placebo v ASP3652 300 mg BID
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.586 [7]
Method	Bayesian longitudinal dose-response mode
Parameter estimate	Posterior difference versus placebo
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.66
Variability estimate	Standard deviation
Dispersion value	0.349

Notes:

[7] - Posterior probability of maximum effective dose

Secondary: Change from Baseline to End of Treatment in F-GUPI Total Score

End point title	Change from Baseline to End of Treatment in F-GUPI Total Score

End point description:

The Female GenitoUrinary Pain Index (F-GUPI) is a validated instrument used to assess symptoms in women with genitourinary pain complaints. The F-GUPI combines aspects of the 3 most important symptom domains of BPS/IC with a recall period of one week:
- Pain subscale: comprises 4 questions (Items 1 to 4) on location, symptomatology, frequency and severity;
- Voiding problems/Urinary subscale: comprises 2 questions (Items 5 and 6) on irritative and obstructive symptoms;
- Effects on the quality of life (QoL): comprises 3 questions (Items 7 to 9) on impact.

The F-GUPI Total score ranges from 0 to 45 with higher scores indicating increasing disease activity. This endpoint was analyzed using a Bayesian longitudinal dose-response model. In the table below, the data are summarizing the posterior mean change from Baseline to EoT and corresponding standard deviation.
For subjects who withdrew due to an adverse event, the change from baseline to EoT was set to 0.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[8]	49[9]	50[10]	89[11]
Units: units on a scale				
arithmetic mean (standard deviation)	-7.5 (± 1.07)	-6.6 (± 0.94)	-6.5 (± 0.84)	-7.1 (± 0.79)

Notes:

[8] - Full analysis set with available baseline data

[9] - Full analysis set with available baseline data

[10] - Full analysis set with available baseline data

[11] - Full analysis set with available baseline data

Statistical analyses

Statistical analysis title	Bayesian Analysis

Statistical analysis description:

A Bayesian longitudinal dose-response model was used to model changes from baseline to end of treatment in F-GUPI total score. The posterior difference versus placebo and 95% credibility interval are presented, along with the posterior probability of the dose group being the maximum effective dose.

Comparison groups	Placebo v ASP3652 50 mg BID
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.28
Method	Bayesian longitudinal dose-response mode
Parameter estimate	Posterior difference versus placebo
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	3.8
Variability estimate	Standard deviation
Dispersion value	1.43

Statistical analysis title	Bayesian Analysis

Statistical analysis description:

A Bayesian longitudinal dose-response model was used to model changes from baseline to end of treatment in F-GUPI total score. The posterior difference versus placebo and 95% credibility interval are presented, along with the posterior probability of the dose group being the maximum effective dose.

Comparison groups	Placebo v ASP3652 150 mg BID
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.143
Method	Bayesian longitudinal dose-response mode
Parameter estimate	Posterior difference versus placebo
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	3.8
Variability estimate	Standard deviation
Dispersion value	1.38

Statistical analysis title	Bayesian Analysis

Statistical analysis description:

A Bayesian longitudinal dose-response model was used to model changes from baseline to end of treatment in F-GUPI total score. The posterior difference versus placebo and 95% credibility interval are presented, along with the posterior probability of the dose group being the maximum effective dose.

Comparison groups	Placebo v ASP3652 300 mg BID
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.577
Method	Bayesian longitudinal dose-response mode
Parameter estimate	Posterior difference versus placebo
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	3
Variability estimate	Standard deviation
Dispersion value	1.29

Secondary: Change from Baseline to End of Treatment in F-GUPI Pain Domain Score

End point title	Change from Baseline to End of Treatment in F-GUPI Pain Domain Score

End point description:

The Female GenitoUrinary Pain Index (F-GUPI) is a validated instrument used to assess the degree of symptoms in women with genitourinary pain complaints. The pain subscale comprises 4 questions (Items 1 to 4) on location, symptomatology, frequency and severity, with a recall period of one week. The pain subscale score ranges from 0 to 23 where higher scores indicate increasing pain.
Least squares (LS) means were generated from an analysis of covariance (ANCOVA) model with treatment group and country as factors and the Baseline value as a covariate.
Last observation carried forward (LOCF) imputation was used; for subjects who withdrew due to an adverse event, change from baseline to EoT was set to 0.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[12]	49[13]	50[14]	89[15]
Units: units on a scale				
least squares mean (standard error)	-3.8 (± 0.49)	-3.8 (± 0.61)	-3.1 (± 0.6)	-4.1 (± 0.45)

Notes:

[12] - Full analysis set with available baseline data

[13] - Full analysis set with available baseline data

[14] - Full analysis set with available baseline data

[15] - Full analysis set with available baseline data

Statistical analyses

Statistical analysis title	Frequentist Analysis

Statistical analysis description:

The F-GUPI pain domain score was analyzed in an analysis of covariance (ANCOVA) model with treatment group and country as factors and baseline value as covariate.

Comparison groups	Placebo v ASP3652 50 mg BID
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference vs placebo
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.79

Statistical analysis title	Frequentist Analysis

Statistical analysis description:

The F-GUPI pain domain score was analyzed in an analysis of covariance (ANCOVA) model with treatment group and country as factors and baseline value as covariate.

Comparison groups	Placebo v ASP3652 150 mg BID
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference vs placebo
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	0.78

Statistical analysis title	Frequentist Analysis

Statistical analysis description:

The F-GUPI pain domain score was analyzed in an analysis of covariance (ANCOVA) model with treatment group and country as factors and baseline value as covariate.

Comparison groups	Placebo v ASP3652 300 mg BID
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference vs placebo
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.67

Secondary: Change from Baseline to End of Treatment in Mean Number of Micturitions per 24 Hours

End point title	Change from Baseline to End of Treatment in Mean Number of Micturitions per 24 Hours

End point description:

The average number of micturitions (urinations) per 24 hours was derived from the number of times a subject urinated (excluding incontinence only episodes) per day as recorded by the subject in a micturition diary for 3 days prior to the Baseline and Week 12 clinic visits. LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate. Last observation carried forward imputation was used.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71[16]	44[17]	49[18]	87[19]
Units: micturitions				
least squares mean (standard error)	-1.92 (± 0.642)	0.16 (± 0.818)	-1.56 (± 0.775)	-1.09 (± 0.583)

Notes:

[16] - Full analysis set with available Baseline data

[17] - Full analysis set with available Baseline data

[18] - Full analysis set with available Baseline data

[19] - Full analysis set with available Baseline data

Statistical analyses

Statistical analysis title	Frequentist Analysis

Statistical analysis description:

The change from baseline in the number of micturitions per 24 hours was analyzed in an analysis of covariance (ANCOVA) model with treatment group and country as factors and baseline value as covariate.

Comparison groups	Placebo v ASP3652 50 mg BID
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean difference vs placebo
Point estimate	2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	4.15
Variability estimate	Standard error of the mean
Dispersion value	1.046

Statistical analysis title	Frequentist Analysis

Statistical analysis description:

The change from baseline in the number of micturitions per 24 hours was analyzed in an analysis of covariance (ANCOVA) model with treatment group and country as factors and baseline value as covariate.

Comparison groups	Placebo v ASP3652 150 mg BID
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean difference vs placebo
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	2.35
Variability estimate	Standard error of the mean
Dispersion value	1.007

Statistical analysis title	Frequentist Analysis

Statistical analysis description:

The change from baseline in the number of micturitions per 24 hours was analyzed in an analysis of covariance (ANCOVA) model with treatment group and country as factors and baseline value as covariate.

Comparison groups	Placebo v ASP3652 300 mg BID

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean difference vs placebo
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	2.55
Variability estimate	Standard error of the mean
Dispersion value	0.873

Secondary: Change from Baseline in MDP Scores at Weeks 4, 8, 12 and at Follow-up

End point title	Change from Baseline in MDP Scores at Weeks 4, 8, 12 and at Follow-up

End point description:

The MDP is the mean of the 7 daily consecutive pain measurements, i.e. the mean of the 7 daily consecutive scores of item 4 of the Female GenitoUrinary Pain Index (F-GUPI)-24h, recorded in the last week prior to Baseline and Week 12. The F-GUPI-24h is a validated instrument for evaluating symptoms of BPS/IC. Item 4 in the F-GUPI-24h rates the average pain over the past 24 hours on an 11-point numerical rating scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine).
This endpoint was analysed using the full analysis set with no imputation for missing data.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: units on a scale				
least squares mean (standard error)				
Week 4 (n=67, 44, 49, 82)	-0.7 (± 0.184)	-0.82 (± 0.227)	-0.76 (± 0.214)	-0.97 (± 0.166)
Week 8 (n=68, 46, 51, 84)	-1.25 (± 0.223)	-1.13 (± 0.271)	-1.43 (± 0.257)	-1.28 (± 0.2)
Week 12 (n=65, 45, 46, 82)	-1.81 (± 0.262)	-1.61 (± 0.316)	-1.45 (± 0.312)	-1.79 (± 0.234)
Follow-Up (n=55, 40, 42, 66)	-1.76 (± 0.277)	-1.48 (± 0.328)	-1.45 (± 0.317)	-1.84 (± 0.255)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in F-GUPI Total Score at Weeks 4, 8, 12 and Follow-up

End point title	Change from Baseline in F-GUPI Total Score at Weeks 4, 8, 12 and Follow-up

End point description:

The Female GenitoUrinary Pain Index (F-GUPI) is a validated instrument used to assess symptoms in women with genitourinary pain complaints. The F-GUPI combines aspects of the 3 most important symptom domains of BPS/IC with a recall period of one week:
- Pain subscale: comprises 4 questions (Items 1 to 4) on location, symptomatology, frequency and severity;
- Voiding problems/Urinary subscale: comprises 2 questions (Items 5 and 6) on irritative and obstructive symptoms;
- Effects on the quality of life (QoL): comprises 3 questions (Items 7 to 9) on impact.

The F-GUPI Total score ranges from 0 to 45 with higher scores indicating increasing disease activity.
This endpoint was analysed using the full analysis set with no imputation for missing data.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and Follow-up (2 weeks after end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: units on a scale				
least squares mean (standard error)				
Week 4 (n=73, 49, 48, 89)	-3.9 (± 0.76)	-3.3 (± 0.93)	-2.8 (± 0.94)	-4.7 (± 0.69)
Week 8 (n=67, 45, 48, 85)	-5.5 (± 0.93)	-4.2 (± 1.14)	-6 (± 1.1)	-5.9 (± 0.83)
Week 12 (n=66, 44, 45, 81)	-7.7 (± 1.08)	-8.3 (± 1.32)	-5.8 (± 1.31)	-7.6 (± 0.98)
Follow-Up (n=56, 41, 39, 62)	-7.7 (± 1.26)	-7.3 (± 1.49)	-8.1 (± 1.52)	-8.7 (± 1.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in F-GUPI Pain Domain Score at Weeks 4, 8, 12 and Follow-Up

End point title	Change from Baseline in F-GUPI Pain Domain Score at Weeks 4, 8, 12 and Follow-Up

End point description:

The Female GenitoUrinary Pain Index (F-GUPI) is a validated instrument used to assess the degree of symptoms in women with genitourinary pain complaints. The pain subscale comprises 4 questions (Items 1 to 4) on location, symptomatology, frequency and severity, with a recall period of one week. The pain subscale score ranges from 0 to 23 where higher scores indicate increasing pain.

This endpoint was analysed using the full analysis set with no imputation for missing data.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: units on a scale				
least squares mean (standard error)				
Week 4 (n=73, 49, 48, 89)	-2.1 (± 0.39)	-1.7 (± 0.48)	-1.6 (± 0.48)	-2.5 (± 0.35)
Week 8 (n=67, 45, 48, 85)	-3 (± 0.46)	-2.4 (± 0.56)	-3.2 (± 0.54)	-3.3 (± 0.41)
Week 12 (n=66, 44, 45, 81)	-4 (± 0.53)	-4.3 (± 0.64)	-3.1 (± 0.64)	-4.3 (± 0.48)
Follow-Up (n=56, 41, 39, 62)	-3.8 (± 0.62)	-4.1 (± 0.73)	-3.9 (± 0.75)	-4.9 (± 0.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Visit in F-GUPI Urinary Symptoms Score

End point title	Change from Baseline to Each Visit in F-GUPI Urinary Symptoms Score

End point description:

The Female GenitoUrinary Pain Index (F-GUPI) is a validated instrument used to assess the degree of symptoms in women with genitourinary pain complaints. The voiding problems/urinary subscale comprises 2 questions (Items 5 and 6) on irritative and obstructive symptoms with a recall period of one week. The urinary subscale score ranges from 0 to 10, where 10 indicates worse symptoms.
This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: units on a scale				
least squares mean (standard error)				
Week 4 (n=73, 49, 48, 89)	-0.68 (± 0.233)	-0.73 (± 0.285)	-0.44 (± 0.287)	-1.04 (± 0.212)
Week 8 (n=67, 45, 48, 85)	-1.12 (± 0.269)	-1.01 (± 0.329)	-1.16 (± 0.318)	-1.08 (± 0.239)
Week 12 (n=66, 44, 45, 81)	-1.74 (± 0.282)	-1.74 (± 0.346)	-1.02 (± 0.343)	-1.37 (± 0.257)
End of Treatment (n=74, 49, 50, 89)	-1.68 (± 0.275)	-1.57 (± 0.339)	-1.26 (± 0.335)	-1.37 (± 0.251)

Follow-Up (n=75, 49, 54, 90)	-1.66 (± 0.315)	-1.31 (± 0.372)	-1.93 (± 0.38)	-1.62 (± 0.303)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Visit in F-GUPI Quality of Life Impact Score

End point title	Change from Baseline to Each Visit in F-GUPI Quality of Life Impact Score

End point description:

The Female GenitoUrinary Pain Index (F-GUPI) is a validated instrument used to assess the degree of symptoms in women with genitourinary pain complaints. The effects on the quality of life (QoL) subscale comprises 3 questions (Items 7 to 9) on impact with a recall period of one week. The quality of life impact subscale score ranges from 0 to 12, where 12 indicates more impact on quality of life.
This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: units on a scale				
least squares mean (standard error)				
Week 4 (n=73, 49, 48, 89)	-1.04 (± 0.269)	-0.79 (± 0.329)	-0.72 (± 0.331)	-1.19 (± 0.244)
Week 8 (n=67, 45, 48, 85)	-1.38 (± 0.324)	-0.86 (± 0.396)	-1.69 (± 0.383)	-1.53 (± 0.288)
Week 12 (n=66, 44, 45, 81)	-1.94 (± 0.369)	-2.27 (± 0.453)	-1.73 (± 0.449)	-1.96 (± 0.335)
End of Treatment (n=74, 49, 50, 89)	-1.91 (± 0.35)	-2.09 (± 0.432)	-1.98 (± 0.426)	-1.94 (± 0.32)
Follow-Up (n=56, 41, 39, 62)	-2.21 (± 0.431)	-1.95 (± 0.508)	-2.3 (± 0.518)	-2.22 (± 0.412)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Visit in Severity of Pain

End point title	Change from Baseline to Each Visit in Severity of Pain

End point description:

Severity of pain was assessed by item 4 of the F-GUPI. The F-GUPI is a validated instrument for evaluating symptoms of BPS/IC. Item 4 in the F-GUPI rates the average pain over the past week on an 11-point numerical rating scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine).
This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: units on a scale				
least squares mean (standard error)				
Week 4 (n=73, 49, 48, 89)	-1.03 (± 0.185)	-0.77 (± 0.227)	-0.77 (± 0.228)	-1.04 (± 0.169)
Week 8 (n=67, 45, 48, 85)	-1.43 (± 0.23)	-1.2 (± 0.281)	-1.65 (± 0.271)	-1.46 (± 0.206)
Week 12 (n=66, 44, 45, 81)	-2.02 (± 0.259)	-1.99 (± 0.318)	-1.56 (± 0.315)	-2.02 (± 0.237)
End of Treatment (n=74, 49, 50, 89)	-1.89 (± 0.248)	-1.76 (± 0.305)	-1.66 (± 0.301)	-1.95 (± 0.227)
Follow-Up (n=56, 41, 39, 62)	-1.99 (± 0.301)	-1.9 (± 0.356)	-1.74 (± 0.364)	-2.19 (± 0.29)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least 4 Points Decrease in F-GUPI Total Score at Each Visit

End point title	Percentage of Subjects with at Least 4 Points Decrease in F-GUPI Total Score at Each Visit

End point description:

The Female GenitoUrinary Pain Index (F-GUPI) is a validated instrument used to assess symptoms in women with genitourinary pain complaints. The F-GUPI combines aspects of the 3 most important symptom domains of BPS/IC with a recall period of one week:
- Pain subscale: comprises 4 questions (Items 1 to 4) on location, symptomatology, frequency and severity;
- Voiding problems/Urinary subscale: comprises 2 questions (Items 5 and 6) on irritative and obstructive symptoms;
- Effects on the quality of life (QoL): comprises 3 questions (Items 7 to 9) on impact.

The F-GUPI Total score ranges from 0 to 45 with higher scores indicating increasing disease activity.
This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used. For subjects who withdrew due to an AE, change from Baseline to EoT value is set equal to 0.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: percentage of subjects				
number (not applicable)				
Week 4 (n=73, 49, 48, 89)	49.3	36.7	37.5	46.1
Week 8 (n=67, 45, 48, 85)	55.2	44.4	54.2	55.3
Week 12 (n=66, 44, 45, 81)	65.2	61.4	46.7	65.4
End of Treatment (n=74, 49, 50, 89)	60.8	55.1	48	62.9
Follow-Up (n=56, 41, 39, 62)	62.5	53.7	61.5	71

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least 7 Points Decrease in F-GUPI Total Score at Each Visit

End point title	Percentage of Subjects with at Least 7 Points Decrease in F-GUPI Total Score at Each Visit

End point description:

The Female GenitoUrinary Pain Index (F-GUPI) is a validated instrument used to assess symptoms in women with genitourinary pain complaints. The F-GUPI combines aspects of the 3 most important symptom domains of BPS/IC with a recall period of one week:
- Pain subscale: comprises 4 questions (Items 1 to 4) on location, symptomatology, frequency and severity;
- Voiding problems/Urinary subscale: comprises 2 questions (Items 5 and 6) on irritative and obstructive symptoms;
- Effects on the quality of life (QoL): comprises 3 questions (Items 7 to 9) on impact.

The F-GUPI Total score ranges from 0 to 45 with higher scores indicating increasing disease activity. This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used. For subjects who withdrew due to an AE, change from Baseline to EoT value is set equal to 0.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: percentage of subjects				
number (not applicable)				
Week 4 (n=73, 49, 48, 89)	30.1	22.4	25	33.7
Week 8 (n=67, 45, 48, 85)	40.3	33.3	41.7	41.2
Week 12 (n=66, 44, 45, 81)	47	43.2	35.6	50.6

End of Treatment (n=74, 49, 50, 89)	43.2	38.8	36	48.3
Follow-Up (n=56, 41, 39, 62)	48.2	41.5	43.6	58.1

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Visit in Mean Daily F-GUPI-24h Total Score

End point title	Change from Baseline to Each Visit in Mean Daily F-GUPI-24h Total Score

End point description:

The Female GenitoUrinary Pain Index-24 hour (F-GUPI-24h) is a validated instrument used to assess symptoms in women with genitourinary pain complaints over the past 24 hours. The F-GUPI combines aspects of the 3 most important symptom domains of BPS/IC with a recall period of 24 hours:
- Pain subscale: comprises 4 questions (Items 1 to 4) on location, symptomatology, frequency and severity;
- Voiding problems/Urinary subscale: comprises 2 questions (Items 5 and 6) on irritative and obstructive symptoms;
- Effects on the quality of life (QoL): comprises 3 questions (Items 7 to 9) on impact.

The F-GUPI-24h total score ranges from 0 to 45 with higher scores indicating increasing disease activity. This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: units on a scale				
least squares mean (standard error)				
Week 4 (n=67, 44, 49, 82)	-2.4 (± 0.74)	1.2 (± 0.92)	-2.1 (± 0.87)	-4.3 (± 0.67)
Week 8 (n=68, 46, 51, 84)	-4.8 (± 0.91)	-3.6 (± 1.1)	-4.9 (± 1.04)	-5.2 (± 0.81)
Week 12 (n=65, 45, 46, 82)	-6.8 (± 1.07)	-5.9 (± 1.29)	-5.5 (± 1.28)	-6.5 (± 0.96)
End of Treatment (n=74, 49, 52, 89)	-6.3 (± 1.01)	-5.6 (± 1.24)	-5.9 (± 1.2)	-6.6 (± 0.92)
Follow-Up (n=55, 40, 42, 66)	-7.5 (± 1.19)	-5.9 (± 1.41)	-5.6 (± 1.36)	-6.8 (± 1.09)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a Successful Global Response Assessment

Response at Each Visit

End point title	Percentage of Subjects with a Successful Global Response Assessment Response at Each Visit

End point description:

Patient-assessed treatment effect was measured using a global response assessment (GRA). A self-reported 7 grade GRA was used to evaluate a patient's clinical condition relative to Baseline (grades: markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved or markedly improved). Successful GRA response was defined as the scores moderately improved or markedly improved disease on the patient-rated 7-point scale.
This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: percentage of subjects				
number (not applicable)				
Week 4 (n=73, 49, 48, 89)	27.4	14.3	31.3	29.2
Week 8 (n=67, 45, 48, 85)	44.8	28.9	31.3	35.3
Week 12 (n=66, 44, 45, 81)	47	45.5	33.3	55.6
End of Treatment (n=74, 49, 50, 89)	45.9	40.8	36	52.8
Follow-Up (n=56, 41, 39, 62)	50	31.7	33.3	51.6

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in Bladder Pain/Interstitial Cystitis Symptom Scale (BPIC-SS) Total Score

End point title	Change from Baseline to End of Treatment in Bladder Pain/Interstitial Cystitis Symptom Scale (BPIC-SS) Total Score

End point description:

The BPIC-SS questionnaire consists of eight questions concerning bladder pain over the previous seven days. Items 1 to 5 address pain and are rated from 0 (never) to 4 (always), Items 6 and 7 address the impact of bladder pain, rated from 0 (not at all) to 4 (a great deal) and Item 8 is an 11-point NRS describing the worst bladder pain experienced in the previous seven days ranging from 0 (no bladder pain) to 10 (worst possible bladder pain).
The BPIC-SS Total score ranges from 0 up to 38, with higher scores indicative of worse pain. A total score of 19 or more is taken to indicate moderate/severe disease.
This endpoint was analysed using the full analysis set; LOCF imputation was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	44	45	81
Units: units on a scale				
least squares mean (standard error)	-8.7 (± 0.96)	-9.3 (± 1.2)	-7.9 (± 1.19)	-8.7 (± 0.89)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in BPIC-SS Worst Bladder Pain Score

End point title	Change from Baseline to End of Treatment in BPIC-SS Worst Bladder Pain Score

End point description:

Item 8 of the BPIC-SS is an 11-point NRS describing the worst bladder pain experienced in the previous seven days. The response for this question ranges from 0 (no bladder pain) to 10 (worst possible bladder pain).
This endpoint was analysed using the full analysis set; LOCF imputation was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	44	45	81
Units: units on a scale				
least squares mean (standard error)	-2.1 (± 0.28)	-2.3 (± 0.35)	-2.1 (± 0.35)	-2.4 (± 0.26)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in Interstitial Cystitis Symptom Index (ICSI) Total Score

End point title	Change from Baseline to End of Treatment in Interstitial Cystitis Symptom Index (ICSI) Total Score

End point description:

The Interstitial Cystitis Symptom Index (ICSI) consists of 4 questions which are all rated from 0 (not at

all/none) to 5 (almost always):
- Frequency of strong need to urinate with little or no warning
- Needing to urinate again within two hours of urinating
- Frequency of having to get up to urinate at night
- Experience of pain or burning in the bladder
The ICSI Total score ranges from 0 to 20 and can be categorized to indicate mild (0 to 6), moderate (7 to 14), or severe (15 to 20) symptoms.
This endpoint was analysed using the full analysis set; LOCF imputation was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	44	45	81
Units: units on a scale				
least squares mean (standard error)	-2.8 (± 0.5)	-3.6 (± 0.62)	-2.4 (± 0.62)	-3 (± 0.46)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in Interstitial Cystitis Problem Index (ICPI) Total Score

End point title	Change from Baseline to End of Treatment in Interstitial Cystitis Problem Index (ICPI) Total Score

End point description:

The Interstitial Cystitis Problem Index (ICPI) consists of 4 questions which ask if symptoms of IC have been a problem. Responses are rated from 0 (no problem) to 4 (big problem):
- Frequency of urination
- Getting up at night to urinate
- Needing to urinate with little warning
- Burning pain, discomfort or pressure in the bladder
The ICPI Total score ranges from 0 to 16, with higher scores indicating more severe symptoms.
This endpoint was analysed using the full analysis set; LOCF imputation was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	44	45	81
Units: Units on a scale				
least squares mean (standard error)	-2.7 (± 0.48)	-3.5 (± 0.6)	-2.1 (± 0.59)	-2.9 (± 0.44)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in Short Form of the McGill Pain Questionnaire (SF-MPQ) Total Score

End point title	Change from Baseline to End of Treatment in Short Form of the McGill Pain Questionnaire (SF-MPQ) Total Score

End point description:

The short form of the McGill pain questionnaire (SF-MPQ) asks about the sensory, affective and evaluative dimensions of pain experience. Higher scores on the SF-MPQ are indicative of more severe disease. The sensory and affective dimensions of the SF-MPQ ask the respondent how each of a set of different adjectives describe their pain over the previous week. Responses to each question range from 0 (None) to 3 (Severe).
The sum of the responses within each dimension give the SF-MPQ Sensory score (ranging from 0 to 33) and the SF-MPQ Affective score (ranging from 0 to 12). These sum of these two scores gives the SF-MPQ Total score.
This endpoint was analysed using the full analysis set; LOCF imputation was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	44	45	81
Units: units on a scale				
least squares mean (standard error)	-6.9 (± 1.12)	-8.8 (± 1.41)	-5 (± 1.39)	-8 (± 1.04)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in Female Sexual Function Index (FSFI) Total Score

End point title	Change from Baseline to End of Treatment in Female Sexual Function Index (FSFI) Total Score

End point description:

Sexual functioning was assessed using the FSFI, a validated 19-item, self-administered questionnaire

from which scores for assessing six key domains of sexual function and satisfaction can be derived. Each of the 19 items ranges from 0 or 1 (a score of 0 in some questions indicates that no sexual activity occurred in the previous month) up to a maximum of 5. The sum of the responses within each domain are added together and multiplied by a domain factor to give a domain score which can vary up to a maximum value of 6. The FSFI Total score is then calculated as the sum of the six separate domains and ranges from 2 to 36. A FSFI total score of less than or equal to 26.55 has been classified as "Female sexual Dysfunction".
This endpoint was analysed using the full analysis set; LOCF imputation was used.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	44	44	81
Units: units on a scale				
arithmetic mean (standard deviation)	2.69 (± 7.616)	3.06 (± 6.279)	-0.08 (± 8.73)	2.1 (± 7.794)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Number of Micturitions per 24 Hours at Weeks 4, 8, 12 and Follow-up

End point title	Change from Baseline in Mean Number of Micturitions per 24 Hours at Weeks 4, 8, 12 and Follow-up

End point description:

The average number of micturitions (urinations) per 24 hours was derived from the number of times a subject urinated (excluding incontinence only episodes) per day as recorded by the subject in a micturition diary for 3 days prior to each visit.
This endpoint was analysed using the full analysis set with no imputation for missing data.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: micturitions				
least squares mean (standard error)				
Week 4 (n=65, 41, 47, 78)	-1.29 (± 0.504)	0.83 (± 0.638)	-0.42 (± 0.594)	-1.29 (± 0.46)
Week 8 (n=64, 41, 48, 81)	-1.37 (± 0.756)	0.53 (± 0.951)	-0.01 (± 0.877)	-0.57 (± 0.676)

Week 12 (n=62, 41, 43, 78)	-1.98 (± 0.708)	0.17 (± 0.876)	-1.24 (± 0.858)	-1.17 (± 0.637)
Follow-Up (n=61, 39, 41, 74)	-3.13 (± 0.743)	0.94 (± 0.938)	-0.59 (± 0.919)	-0.86 (± 0.682)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Visit in Mean Number of Nocturia Episodes per 24 Hours

End point title	Change from Baseline to Each Visit in Mean Number of Nocturia Episodes per 24 Hours

End point description:

Nocturia is defined as waking at night one or more times to void (i.e. any voiding associated with sleep disturbance between the time the subject goes to bed with the intention to sleep until the time the subjects gets up in the morning with the intention to stay awake). A "night time" episode of incontinence only was not considered a nocturia episode. The number of nocturia episodes per 24 hours was derived from the average number of times a subject urinated during sleeping time in the 3 day prior to each visit as recorded in the micturition diary.
This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: nocturia episodes				
arithmetic mean (standard error)				
Week 4 (n=65, 41, 47, 78)	-1 (± 1)	-0.4 (± 1.35)	0.6 (± 0.55)	-0.5 (± 0.44)
Week 8 (n=64, 41, 48, 81)	-1.1 (± 0.86)	-0.3 (± 1.31)	-1 (± 0.66)	-1 (± 0.48)
Week 12 (n=62, 41, 43, 78)	-1.5 (± 0.89)	0.2 (± 1.12)	-0.6 (± 0.71)	-1.1 (± 0.46)
End of Treatment (n=71, 44, 49, 87)	-1.7 (± 0.81)	0.1 (± 1.05)	-1 (± 0.64)	-0.9 (± 0.42)
Follow-Up (n=61, 39, 41, 74)	-3 (± 0.94)	0.8 (± 1.36)	-1.1 (± 0.64)	-0.9 (± 0.53)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Visit in Mean Number of Urgency Episodes per 24 Hours

End point title	Change from Baseline to Each Visit in Mean Number of Urgency Episodes per 24 Hours

End point description:

Urgency is defined as the complaint of a sudden, compelling desire to pass urine, which is difficult to

defer. Each episode was graded using the following 5 point scale based on Patient Perception of Intensity of Urgency Scale (PPIUS):
0 = No urgency; 1 = Mild urgency, could postpone voiding as long as necessary; 2 = Moderate urgency, could postpone voiding for a short time; 3 = Severe urgency, could not postpone voiding, had to rush to the toilet; 4 = Urge incontinence, leaked before arriving to the toilet.
The mean number of urgency episodes per 24 hours was derived from the average number of times a subject recorded an urgency episode of severity of 3 or 4 per day during the 3-day micturition diary period.
This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used. LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: urgency episodes				
least squares mean (standard error)				
Week 4 (n=65, 41, 47, 78)	-2.36 (± 0.492)	-0.15 (± 0.622)	-0.71 (± 0.582)	-1.29 (± 0.45)
Week 8 (n=64, 41, 48, 81)	-2.95 (± 0.585)	-1.23 (± 0.734)	-1.51 (± 0.68)	-1.6 (± 0.523)
Week 12 (62, 41, 43, 78)	-2.8 (± 0.569)	-0.58 (± 0.701)	-2.26 (± 0.691)	-2.4 (± 0.511)
End of Treatment (n=71, 44, 49, 87)	-2.57 (± 0.516)	-0.57 (± 0.656)	-2.15 (± 0.624)	-2.42 (± 0.468)
Follow-Up (n=61, 39, 41, 74)	-3.68 (± 0.612)	0.28 (± 0.771)	-1.99 (± 0.758)	-2.31 (± 0.561)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Visit in Mean Level of Urgency per Micturition

End point title	Change from Baseline to Each Visit in Mean Level of Urgency per Micturition

End point description:

Each episode was graded using the following 5 point scale based on Patient Perception of Intensity of Urgency Scale (PPIUS):
0 = No urgency; 1 = Mild urgency, could postpone voiding as long as necessary; 2 = Moderate urgency, could postpone voiding for a short while; 3 = Severe urgency, could not postpone voiding, but had to rush to the toilet in order not to wet myself; 4 = Urge incontinence, leaked before arriving to the toilet.
The mean level of urgency was derived from the average severity grade recorded by the subject for each micturition, with or without incontinence, during the 3-day micturition diary period.
This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: units on a scale				
least squares mean (standard error)				
Week 4 (n=65, 41, 47, 78)	-0.2 (± 0.058)	-0.1 (± 0.074)	-0.03 (± 0.069)	-0.2 (± 0.053)
Week 8 (n=64, 41, 48, 81)	-0.33 (± 0.067)	-0.21 (± 0.084)	-1.19 (± 0.078)	-0.29 (± 0.06)
Week 12 (n=62, 41, 43, 78)	-0.35 (± 0.074)	-0.17 (± 0.091)	-0.2 (± 0.09)	-0.28 (± 0.066)
End of Treatment (n=71, 44, 49, 87)	-0.31 (± 0.071)	-0.14 (± 0.091)	-0.18 (± 0.086)	-0.35 (± 0.065)
Follow-Up (n=61, 39, 41, 74)	-0.4 (± 0.076)	-0.19 (± 0.096)	-0.25 (± 0.094)	-0.32 (± 0.07)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Visit in Total Urgency Score (TUS) per 24 Hours

End point title	Change from Baseline to Each Visit in Total Urgency Score (TUS) per 24 Hours

End point description:

The total urgency score (TUS) per 24 hours is the sum of the PPIUS urgency gradings from all valid diary days recorded by the subject in the 3 days prior to each visit in the micturition diary divided by the number of valid days. Each episode was graded using the following 5 point scale based on Patient Perception of Intensity of Urgency Scale (PPIUS):
0 = No urgency; 1 = Mild urgency, could postpone voiding as long as necessary; 2 = Moderate urgency, could postpone voiding for a short while; 3 = Severe urgency, could not postpone voiding, but had to rush to the toilet in order not to wet myself; 4 = Urge incontinence, leaked before arriving to the toilet.
This endpoint was analysed using the full analysis set with no imputation for missing data, except for End of Treatment where LOCF was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12 and follow-up (2 weeks after the end of treatment)

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	49	54	90
Units: units on a sclae				
least squares mean (standard error)				
Week 4 (n=65, 41, 47, 78)	-5.63 (± 1.391)	1.69 (± 1.762)	-1.76 (± 1.644)	-4.88 (± 1.272)
Week 8 (n=64, 41, 48, 81)	-6.85 (± 1.709)	-0.86 (± 2.146)	-2.22 (± 1.983)	-4.61 (± 1.527)
Week 12 (n=62, 41, 43, 78)	-8.18 (± 1.612)	-0.7 (± 1.99)	-5.61 (± 1.954)	-7.53 (± 1.45)
End of Treatment (n=71, 44, 49, 87)	-7.74 (± 1.493)	-0.68 (± 1.9)	-5.96 (± 1.806)	-7.57 (± 1.356)
Follow-Up (n=61, 39, 41, 74)	-11.51 (± 1.617)	1.59 (± 2.038)	-4.3 (± 2)	-7.31 (± 1.483)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in European Quality of Life Visual Analogue Scale (EQ VAS)

End point title	Change from Baseline to End of Treatment in European Quality of Life Visual Analogue Scale (EQ VAS)

End point description:

On the EQ visual analogue scale (EQ-VAS) the subject is asked to rate their health as a number between 0 (The worst health you can imagine) and 100 (the best health you can imagine).
This endpoint was analysed using the full analysis set; LOCF imputation was used.
LS means were generated from an ANCOVA model with treatment group and country as factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	44	45	81
Units: units on a scale				
least squares mean (standard error)	8.5 (± 2.16)	11.2 (± 2.69)	7.3 (± 2.68)	9 (± 2)

Statistical analyses

No statistical analyses for this end point

Secondary: ASP3652 Plasma Concentration

End point title	ASP3652 Plasma Concentration[20]

End point description:

The lower limit of quantification (LLOQ) of ASP3652 is 0.5 ng/ml in plasma.
Values that are below the LLOQ were set to 0. This endpoint was analysed using the Pharmacokinetics Analysis Set which comprised all subjects who received active treatment, for whom at least 1 blood sample was collected for measurement of the ASP3652 plasma concentrations, and for whom the time of sampling and the time of dosing on the day of sampling was known.

End point type	Secondary

End point timeframe:

Week 4 and Week 8, 1-4 hours post morning dose, Week 12 (or end of treatment), 12-16 hours post previous evening dose

Notes:

[20] - 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: Plasma concentration of ASP3652 not calculated for subjects in the placebo treatment group.

End point values	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	49	88	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 4 (n=41, 45, 74)	438.945 (± 733.0389)	1973.302 (± 2305.887)	5544.765 (± 5724.552)	
Week 8 (n=43, 47, 77)	450.359 (± 511.6218)	2088.381 (± 2485.641)	5082.27 (± 6004.383)	
Week 12 (n=47, 46, 84)	59.243 (± 195.945)	352.891 (± 1443.167)	411.458 (± 1366.536)	

Statistical analyses

No statistical analyses for this end point

Secondary: N-arachidonoyl-ethanolamide (Anandamide) Plasma Concentration

End point title	N-arachidonoyl-ethanolamide (Anandamide) Plasma Concentration

End point description:

The LLOQ of N-arachidonoyl-ethanolamide is 0.05 ng/mL in plasma.
This endpoint was analysed using the Pharmacodynamic Analysis Set (PDAS) which comprised subjects who received at least 1 dose of study drug and for whom at least 1 blood sample was collected for measurement of the anandamide concentrations.

End point type	Secondary

End point timeframe:

Baseline (pre-dose), Weeks 4 and 8, 1-4 hours post morning dose and Week 12 (or end of treatment), 12-16 hours post previous evening dose.

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	50	52	93
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=79, 48, 52, 90)	0.506 (± 0.2359)	0.549 (± 0.3)	0.557 (± 0.284)	0.515 (± 0.2268)
Week 4 (n=60, 41, 45, 74)	0.436 (± 0.2193)	1.52 (± 0.6961)	2.099 (± 0.8471)	2.217 (± 0.8053)
Week 8 (n=63, 43, 48, 78)	0.378 (± 0.1723)	1.532 (± 0.7422)	2.013 (± 0.8204)	2.085 (± 0.8143)
Week 12 (n=70, 46, 43, 82)	0.482 (± 0.2397)	1.01 (± 0.4713)	1.405 (± 0.7689)	1.76 (± 0.7981)

Statistical analyses

No statistical analyses for this end point

Secondary: Oleoylethanolamide Plasma Concentration

End point title	Oleoylethanolamide Plasma Concentration

End point description:

The LLOQ for oleoylethanolamide is 0.5 ng/mL in plasma.
This endpoint was analysed using the pharmacodynamics analysis set.

End point type	Secondary

End point timeframe:

Baseline (pre-dose), Weeks 4 and 8, 1-4 hours post morning dose and Week 12 (or end of treatment), 12-16 hours post previous evening dose.

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	50	52	93
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=79, 48, 52, 90)	2.578 (± 0.9946)	2.726 (± 1.2024)	2.812 (± 1.3616)	2.633 (± 0.9027)
Week 4 (n=60, 41, 45, 74)	2.157 (± 0.9664)	7.125 (± 2.7562)	8.86 (± 2.7888)	9.277 (± 2.9515)
Week 8 (n=63, 43, 48, 78)	1.903 (± 0.7191)	7.119 (± 2.6435)	8.607 (± 2.5604)	8.923 (± 3.0675)
Week 12 (n=70, 46, 43, 82)	2.313 (± 0.9464)	5.21 (± 1.9694)	6.967 (± 3.2457)	8.184 (± 3.1632)

Statistical analyses

No statistical analyses for this end point

Secondary: Palmitoylethanolamide Plasma Concentration

End point title	Palmitoylethanolamide Plasma Concentration

End point description:

The LLOQ for palmitoylethanolamide in plasma is 0.5 ng/mL.
This endpoint was analysed using the pharmacodynamics analysis set.

End point type	Secondary

End point timeframe:

Baseline (pre-dose), Weeks 4 and 8, 1-4 hours post morning dose and Week 12 (or end of treatment), 12-16 hours post previous evening dose.

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	50	52	93
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=79, 48, 52, 90)	2.544 (± 0.9556)	2.627 (± 1.0885)	2.846 (± 1.4928)	2.597 (± 0.9674)
Week 4 (n=60, 41, 45, 74)	2.243 (± 0.9792)	4.93 (± 1.6596)	5.736 (± 1.9207)	5.833 (± 1.696)
Week 8 (n=63, 43, 48, 78)	2.016 (± 0.7513)	4.852 (± 1.4955)	5.578 (± 1.6733)	5.502 (± 1.6368)
Week 12 (n=70, 46, 43, 82)	2.405 (± 0.8336)	3.941 (± 1.0663)	4.813 (± 1.8189)	4.154 (± 1.7693)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in Post-Void Residual (PVR) Volume

End point title	Change from Baseline to End of Treatment in Post-Void Residual (PVR) Volume

End point description:

PVR volume was assessed by a transabdominal ultrasound bladder scan.
This endpoint was analysed using the safety analysis set; LOCF imputation was used.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	51	53	93
Units: mL				
arithmetic mean (standard deviation)	0.8 (± 17.23)	3.5 (± 23.17)	3.6 (± 14.25)	-1.9 (± 33.15)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in Profile of Mood States (POMS) Total Mood Disturbance Score

End point title	Change from Baseline to End of Treatment in Profile of Mood States (POMS) Total Mood Disturbance Score

End point description:

Psychotropic effects emerging during the study were measured using the POMS questionnaire, which asks subjects to rate how they feel in relation to each of 65 adjectives commonly used to describe mood states. Responses are given on a 5-point scale (0=Not at all, 1=A little, 2=Moderate, 3=Quite a bit, and 4=Extremely). The responses to groups of questions can be summed to calculate six factors: Tension-Anxiety (range 0 to 36), Depression-Rejection (range 0 to 60), Anger-Hostility (range 0 to 48), Vigor-Activity (range 0 to 32), Fatigue-Inertia (range 0 to 28) and Confusion-Bewilderment (range 0 to 28). The Total Mood Disturbance (TMD) score is calculated by summing the six factors while weighting the Vigor-Activity score negatively. The range of this total score is from -32 to 200. A score below -30 or above 68 is considered abnormal.
This endpoint was analysed using the safety analysis set; LOCF imputation was used.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	51	50	91
Units: units on a scale				
arithmetic mean (standard deviation)	-10.1 (± 24.11)	-6.5 (± 23.29)	-14.6 (± 24.43)	-3.2 (± 24.73)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment in Center for Epidemiologic Studies Depression Scale (CES-D) score

End point title	Change from Baseline to End of Treatment in Center for Epidemiologic Studies Depression Scale (CES-D) score

End point description:

The 20-item CES-D scale questionnaire is a validated, short, self-report scale designed to measure depressive symptomatology. Responses to each item are from 0 (“rarely or not at all”) to 3 (“most or all of the time”). The total score is calculated as the sum of the scores for the 20 questions and has a range from 0 to 60. Negative changes from Baseline indicate improvements in depressive symptoms during the study.

This endpoint was analysed in the safety analysis set; LOCF imputation was used.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	47	46	83
Units: units on a scale				
arithmetic mean (standard deviation)	1 (± 8.81)	3.2 (± 8.19)	0.8 (± 10.02)	2 (± 10.12)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from End of Treatment to Follow-up in the Physician Withdrawal Checklist (PWC) Score

End point title	Change from End of Treatment to Follow-up in the Physician Withdrawal Checklist (PWC) Score

End point description:

Withdrawal effects from study drug were measured by the PWC. The PWC has twenty items, each rated on a 4-point scale (0=not present; 1=mild; 2=moderate; 3=severe). It is evaluated after permanent discontinuation of treatment, i.e., at the Follow-up visit. The total score was calculated as the sum of the scores provided in response to the 20 items. It has a range from 0 to 60. Missing value were not imputed.
This endpoint was analysed using the safety analysis set.

End point type	Secondary

End point timeframe:

Week 12 (or end of treatment if earlier) and 2 weeks after the end of treatment

End point values	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID	ASP3652 300 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	42	40	67
Units: units on a scale				
arithmetic mean (standard deviation)	-0.2 (± 2.19)	0 (± 1.55)	-0.1 (± 1.48)	-0.3 (± 1.58)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study medication until 2 days after the last dose. Overall mean duration of drug exposure was 78 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects took matching placebo tablets twice a day for 12 weeks, followed by a 2-week follow-up period.

Reporting group title	ASP3652 50 mg BID

Reporting group description:

Subjects took two 25 mg ASP3652 tablets and one placebo tablet twice a day (BID) for 12 weeks, followed by a 2-week follow-up period.

Reporting group title	ASP3652 150 mg BID

Reporting group description:

Subjects took two 25 mg and one 100 mg ASP3652 tablet twice a day for 12 weeks, followed by a 2-week follow-up period.

Reporting group title	ASP3652 300 mg BID

Reporting group description:

Subjects took three 100 mg ASP3652 tablets twice a day for 12 weeks, followed by a 2-week follow-up period.

Serious adverse events	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 82 (1.22%)	1 / 53 (1.89%)	1 / 55 (1.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 82 (0.00%)	0 / 53 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Meniscus lesion			
subjects affected / exposed	1 / 82 (1.22%)	0 / 53 (0.00%)	0 / 55 (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

Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 53 (1.89%)	0 / 55 (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
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 82 (1.22%)	0 / 53 (0.00%)	0 / 55 (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
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 53 (0.00%)	0 / 55 (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	ASP3652 300 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 96 (2.08%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Meniscus lesion			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	ASP3652 50 mg BID	ASP3652 150 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 82 (15.85%)	9 / 53 (16.98%)	7 / 55 (12.73%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 82 (3.66%)	1 / 53 (1.89%)	3 / 55 (5.45%)
occurrences (all)	3	1	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 82 (1.22%)	3 / 53 (5.66%)	1 / 55 (1.82%)
occurrences (all)	1	3	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 82 (0.00%)	0 / 53 (0.00%)	2 / 55 (3.64%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	3 / 82 (3.66%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences (all)	3	1	0
Diarrhoea			
subjects affected / exposed	2 / 82 (2.44%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences (all)	2	0	0
Dry mouth			

subjects affected / exposed	0 / 82 (0.00%)	1 / 53 (1.89%)	1 / 55 (1.82%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	3 / 82 (3.66%)	0 / 53 (0.00%)	3 / 55 (5.45%)
occurrences (all)	3	0	3
Vomiting			
subjects affected / exposed	1 / 82 (1.22%)	1 / 53 (1.89%)	1 / 55 (1.82%)
occurrences (all)	1	1	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	1 / 82 (1.22%)	0 / 53 (0.00%)	2 / 55 (3.64%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 82 (0.00%)	0 / 53 (0.00%)	1 / 55 (1.82%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 82 (1.22%)	2 / 53 (3.77%)	0 / 55 (0.00%)
occurrences (all)	1	2	0
Cystitis			
subjects affected / exposed	2 / 82 (2.44%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences (all)	2	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 82 (2.44%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	ASP3652 300 mg BID		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	16 / 96 (16.67%)		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 96 (4.17%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 96 (3.13%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	3 / 96 (3.13%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	2 / 96 (2.08%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 96 (2.08%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 96 (2.08%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 96 (2.08%)		
occurrences (all)	2		
Renal and urinary disorders			

Bladder pain subjects affected / exposed occurrences (all)	2 / 96 (2.08%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 96 (2.08%) 3		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Cystitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 96 (0.00%) 0 0 / 96 (0.00%) 0 0 / 96 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2013	1. Initially, patients were required to undergo a cystoscopy at Screening to ascertain BPS/IC disease characteristics (i.e., the presence/absence of Hunner's lesions and glomerulations). The cystoscopy at Screening could be omitted provided results of a previous cystoscopy with hydrodistension were available which could enable the classification of patients into subgroups with and without Hunner's lesions (glomerulations have been implied in previous diagnostic criteria, but are currently not regarded as specific for BPS/IC). However, the omission of the procedure had no consequences for selection criteria, as the cystoscopy was not meant for diagnosing confounding or confusable bladder conditions. 2. The original protocol stated that the use of antibiotics was not permitted between visit 1/screening and visit 7/FU. In the protocol amendment, these restrictions were reduced to allow antibiotic treatments of up to 2 weeks in duration for indications/infections not including the genitourinary tract. Short regimens of systemic antibiotics for treatment of infections other than UTI were not expected to influence BPS/IC efficacy and safety endpoints. A clinical study with long term antibiotics in BPS/IC did not show convincing efficacy (Warren et al, 2000) and AUA (Hanno et al, 2011) and EAU (2010) guidelines do not regard the use of antibiotics as an effective treatment of BPS/IC.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported