Name of Sponsor/Company: Astellas Pharma Global Development - Europe		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP3652		

SYNOPSIS

Title of Study:

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 patients with Bladder Pain Syndrome/Interstitial Cystitis.

Coordinating Investigator:

[redacted] Denmark.

Study Center(s):

The study was conducted in 60 sites in 12 European countries (Belgium, Czech Republic, Denmark, Germany, Latvia, Lithuania, the Netherlands, Poland, Portugal, Romania, Russia, and Spain).

Publication Based on the Study:

Not applicable.

Study Period:

Study Initiation Date (Date of First Enrollment):

31 May 2012

Study Completion Date (Date of Last Evaluation):

18 March 2014

Phase of Development:

Phase 2

Objectives:

The objectives of this study were:

- To investigate efficacy of ASP3652 in female patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC)
- To assess the optimal dose of ASP3652 for the treatment of female patients with BPS/IC
- To investigate safety and tolerability of ASP3652 in female patients with BPS/IC
- To investigate the pharmacokinetics and pharmacodynamics of ASP3652 in female patients with BPS/IC

Methodology:

This was a randomized, double-blind, placebo-controlled, parallel group, adaptive clinical study to evaluate efficacy, safety, pharmacodynamics and pharmacokinetics of ASP3652 in the treatment of female patients with

BPS/IC. The study consisted of 3 phases: an initial 3 week run-in period, a 12 week treatment period and a 2 week follow-up (FU) period, with a total study duration of approximately 17 weeks per patient.

During the initial "burn-in" period, 40 patients were randomized equally to 4 treatment groups (ASP3652: 50 mg bid, 150 mg bid, 300 mg bid or placebo bid). A Bayesian adaptive study design used accumulating efficacy data to adjust the probability of allocating new patients to individual treatment groups with the aim of stopping the study due to futility, or if clear signals of efficacy were observed. During the following 4 weeks, new patients were allocated according to this randomization vector. If more than 150 patients were randomized into the study, a decision was to be made after each interim analysis on whether to stop enrolment in the study due to futility or success, or to continue, based on the pre-defined decision rules. The unblinded interim evaluations were the responsibility of an independent Data Monitoring Committee (DMC).

During the run-in period, patients were treated with placebo (3 tablets, bid, single-blind). To be eligible for randomization, the mean daily pain (MDP) Score, calculated as the mean of consecutive scores of item 4 within the Female GenitoUrinary Pain Index (24 hours recall) (F-GUPI-24h) over the 7 days preceding the visit 2/Baseline visit (BV), had to be at least 4.0 on an 11 point Numerical Rating Scale (NRS) from 0 to 10. Patients were screened for eligibility which included safety laboratory analyses, physical and urine examination. Patients also completed a series of questionnaires to assess their baseline BPS/IC condition and level of pain on the Female Genitourinary Pain Index [F-GUPI]). In addition, patients underwent a cystoscopy (CS) without hydrodistension to assess visible Hunner's lesions and/or glomerulations and to exclude concomitant pathology.

During the 12 week double-blind, placebo-controlled treatment period, efficacy and safety were assessed after 2, 4, 8 and 12 weeks of treatment. Throughout the treatment period, patients recorded into an electronic diary the level of average pain over the previous 24 hours (item 4 of F-GUPI-24h) and the number of tablets actually taken once daily in the evening. During week 4, 8 and 12, the weeks prior to study visits 4, 5, and 6/End of Treatment (EoT), patients provided a daily report of the entire F-GUPI-24h. A micturition diary was kept on 3 consecutive days within the final week before visits 4, 5 and 6/EoT. The last study dose was taken in the evening before visit 6/EoT. The following safety variables were monitored throughout the study: adverse events (AEs), physical examination and vital signs, safety laboratory assessments, serum steatosis markers, 12-lead electrocardiograms (ECGs), post void residual volume (PVR), abuse liability and psychotropic effects using the Profile of Mood States (POMS) and Physician Withdrawal Checklist (PWC), depressive symptoms on the Center for Epidemiologic Studies Depression Scale (CES-D).

In a pre-defined proportion of the sites, approximately 40 patients were to participate in additional blood sampling for extended analysis of pharmacokinetic and pharmacodynamic parameters. At visit 4 (or visit 5) sampling was performed pre-dose and approximately at 30 minutes, 1, 2, 4, 6 and 8 hours after dosing.

Two weeks following visit 6/EoT, efficacy and safety endpoints were evaluated at visit 7/FU when patients were off treatment. Throughout the FU period of the study, patients recorded the level of pain over the previous 24 hours with one question (item 4 of F-GUPI-24h) once daily in the evening into an electronic diary. During the final week, prior to study visit 7/FU, patients provided a daily report of the entire F-GUPI-24h. A micturition diary was kept on 3 consecutive days during the final week before visit 7/FU.

Number of Patients (Planned, Enrolled and Analyzed):

A total of 385 patients were screened (10 patients were re-screened) of which 287 were randomized before enrolment was stopped due to futility at the recommendation of the DMC Table 2. A total of 286 (99.7%)

patients received at least 1 dose of study drug (1 patient was randomized in error to the 300 mg bid dose group and never received the double-blind study drug). A total of 40 (14.0%) patients discontinued; the proportion was similar across treatment groups. At selected sites, 21 patients participated in extended pharmacokinetic sampling and 32 patients in extended pharmacodynamic sampling.

Diagnosis and Main Criteria for Inclusion:

Healthy, Caucasian, female patients aged 18 years or older with a body mass index (BMI) of < 40 kg/m^2, diagnosed with BPS/IC for at least 3 months prior to screening (in the absence of urinary infection or other obvious pathology or identifiable causes), who had an NRS Score of ≥ 4 on item 4 of the F-GUPI and a confirmed MDP of ≥ 4 on item 4 of F GUPI-24h and who provided written informed consent, were eligible for inclusion. Patients were excluded with a significant PVR > 150 mL or < 150 mL in combination with associated clinically significant pathology (as judged by the investigator). Patients had to be practicing a highly reliable method of birth control.

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

ASP3652 was supplied as 25 mg or 100 mg tablets (Batch Numbers: 50 mg bid: [redacted], [redacted]; 150 mg bid: [redacted], [redacted] 300 mg bid: [redacted]. Matching placebo was supplied as 25 mg or 100 mg tablets (Batch Numbers: [redacted], [redacted]).

Patients received placebo (3 tablets, bid, single-blind) during run-in. This study had an adaptive design in which accumulating efficacy data was used to adjust the probability of allocating new subjects to treatment groups. ASP3652 was dosed at: 50 mg, 150 mg or 300 mg, bid. The number of placebo tablets was matched to each dose with a total of 3 tablets on each dosing occasion.

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

The study consisted of 3 phases: an initial 3 week run-in period, a 12 week treatment period and a 2 week FU period, with a total study duration of approximately 17 weeks per patient.

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

Not applicable.

Criteria for Evaluation:

Primary efficacy variable

- The primary efficacy variable was the change from baseline to week 12 in mean daily pain (MDP) (Item 4 of the F-GUPI-24h).

Key secondary efficacy variables

- Change from baseline in F-GUPI Total Score at week 12
- Change from baseline in F-GUPI Pain subscale Score (total of items 1 to 4) at week 12
- Change from baseline (last week of run-in) in urinary frequency (mean number of micturitions per 24 hours over 3 consecutive days) at week 12 (during the week prior to visit 6/EoT)

Other secondary efficacy variables

Variables based on the F-GUPI

- Change from baseline in F-GUPI Total score at week 4, week 8, week 12 and at 2 weeks FU after EoT
- Change from baseline in F-GUPI Pain subscale score at week 4, week 8, week 12 and at 2 weeks FU after EoT
- Change from baseline in F-GUPI Urinary subscale score at week 4, week 8, week 12/EoT and at 2 weeks FU after EoT
- Change from baseline in F-GUPI QoL Impact subscale score at week 4, week 8, week 12/EoT and at 2 weeks FU after EoT
- Change from baseline in severity of pain as assessed by item 4 of the F-GUPI at week 4, week 8, week 12/EoT and at 2 weeks FU after EoT
- Patients who report at least a 4-point decrease from baseline in F-GUPI Total Score at week 4, week 8, week 12 and EoT
- Patients who report at least a 7-point decrease from baseline in F-GUPI Total Score at week 4, week 8, week 12 and EoT

Variables based on the F-GUPI 24h

- Change from baseline in mean daily F-GUPI 24h Total score at week 4, week 8, week 12/EoT and at 2 weeks FU after EoT
- Change from baseline in MDP scores (using the 11-point NRS in item 4 of the F-GUPI 24h) at week 4, week 8, week 12 and at 2 weeks FU after EoT

Variables based on the GRA

- Global Response Assessment (GRA) score at Baseline, week 4, week 8, week 12/EoT and at 2 weeks FU after EoT
- Successful GRA response, defined as “moderately improved” or “markedly improved”, at week 4, week 8, week 12/EoT and at 2 weeks FU after EoT

Variables based on the Bladder Pain/Interstitial Cystitis Symptom Scale (BPIC-SS)

- Change from baseline in BPIC-SS Total Score at week 12/EoT
- Change from baseline in BPIC-SS Worst Bladder Pain Score (Item 8) at week 12/EoT

Efficacy variables based on the O’Leary-Sant questionnaires

- Change from baseline in Interstitial Cystitis Symptom Index (ICSI) Total score at week 12/EoT
- Change from baseline in Interstitial Cystitis Problems Index (ICPI) Total score at week 12/EoT

Efficacy variables based on the Short form of the McGill pain questionnaire (SF-MPQ)

- Change from baseline in SF-MPQ Sensory score, Affective score, and Total score at week 12/EoT
- Change from baseline in SF-MPQ VAS at week 12/EoT
- Present pain intensity at week 12/EoT

Efficacy variables based on the Female Sexual Function Index (FSFI)

- Change from baseline in FSFI domains of Desire, Arousal, Lubrication, Orgasm, Satisfaction, Pain and Total score at week 12/EoT

Efficacy Variables based on the Micturition Diary

- Change from baseline in mean number of micturitions per 24 hours at week 4, week 8, week 12 and at 2 weeks FU after EoT
- Change from baseline in mean number of nocturia episodes during the 3-day diary period prior to each visit at week 4, week 8, week 12/EoT and at 2 weeks FU after EoT
- Change from baseline in mean number of urgency episodes per 24 hours at week 4, week 8, week 12/EoT and at 2 weeks FU after EoT
- Change from baseline in mean level of urgency per micturition at week 4, week 8, week 12/EoT and at 2 weeks FU after EoT
- Change from baseline in Total Urgency Score (TUS) at week 4, week 8, week 12/EoT and at 2 weeks FU after EoT

Efficacy variables based on the European Quality of life questionnaire (EQ-5D)

- Change from baseline in EQ VAS at week 12 and at EoT

Safety variables

Safety assessments comprised the frequency, nature, relationship and severity of AEs, physical examination and vital signs, safety laboratory tests (urinalysis, troponin levels, hematology, biochemistry), serum steatosis markers (adiponectin blood levels and SteatoTest), 12 lead ECG, PVR assessed by transabdominal ultrasound, abuse liability and psychotropic effects using the POMS, the Physician Withdrawal Checklist (PWC) and depressive symptoms (CES-D).

Statistical Methods:

Analysis Sets

There were 8 analysis sets:

- Run-in Period Analysis Set (RPAS) comprising all patients who took at least 1 dose of single-blind run-in study drug
- Full Analysis Set (FAS) comprising all patients who took at least 1 dose of double-blind study medication after randomization and who had an MDP score at baseline and an MDP score post-baseline during the double-blind treatment period or had an MDP score at baseline and dropped out due to an AE
- Per Protocol Set (PPS) comprising all patients of the FAS who did not deviate from the terms of the protocol in ways which may have significantly affected the primary efficacy variable
- Safety Analysis Set (SAF) comprising all randomized patients who received at least 1 dose of double-blind medication
- Intent-to-Treat set (ITT) comprising all randomized patients who took at least 1 dose of double-blind study medication and who had an MDP score at baseline
- Randomized Analysis Set (RAS) comprising all randomized patients

- Pharmacokinetic Analysis Set (PKAS) comprising all patients 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
- Pharmacodynamic Analysis Set (PDAS) comprising patients 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

Table 1

The FAS was used for baseline summaries and all efficacy analyses. The RAS was used for the adaptive interim analyses and for a sensitivity analysis of the primary and key secondary efficacy variables at the end of the study after database hardlock and unblinding for the Bayesian analyses.

Efficacy

The primary efficacy variable was change from baseline to week 12 in MDP. The MDP scores at baseline and week 12 were the means of all the available values of Item 4 of the F-GUPI-24h questionnaire collected in the 7-day F-GUPI-24h periods prior to visit 2/BV and visit 6/EoT respectively. Values of Item 4 recorded on the day of the visit or for more than 7 days prior to the visit were not included. If a patient withdrew due to an AE after visit 2/BV the primary efficacy variable was set equal to 0. A Bayesian model was used to model changes from baseline to EoT in MDP score.

For the key secondary efficacy variable, change from baseline to week 12 in F-GUPI Total Score, if a patient withdrew due to an AE after visit 2/BV this variable was set equal to 0. Frequentist analyses were summarized for the other 2 key secondary efficacy variables: change from baseline in F-GUPI Pain Domain Score and change from baseline in urinary frequency (mean number of micturitions per 24 hours over 3 consecutive days) at week 12.

Other secondary efficacy variables were analyzed using frequentist and descriptive methods. Count data (nocturia episodes during 3 days prior to visit) were analyzed using a mixed effects Poisson regression model with treatment group and country as fixed factors and baseline value as a covariate. A logistic regression model was used to analyze responder analyses. Rate ratios of each ASP3652 treatment group over placebo and the corresponding 2-sided 95% CI were derived and where applicable, the P value for the rate ratio was presented.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic and pharmacodynamic concentrations were summarized descriptively**.**

Safety

AEs (MedDRA-coded version 11.1) were summarized by treatment group and AEs indicating withdrawal effects were summarized separately. The incidence and number of TEAEs were summarized by System Organ Class (SOC) and preferred term (PT) and also by intensity (i.e., mild, moderate, severe) and relationship to study drug (i.e., not related, possibly, probably related).

Laboratory variables (biochemistry, hematology and urinalysis and troponin levels) and changes from baseline for each post-baseline visit were summarized descriptively by treatment group for all visits, as well as change from baseline to each visit, EoT and FU visit. For the SteatoTest and assessment of adiponectin, changes from baseline for week 12, EoT and FU were summarized descriptively by treatment group. Hematology and biochemistry parameters were classified as low, normal or high and shift tables of changes relative to the reference range from baseline to each visit. Laboratory abnormalities were also evaluated for potential clinical

significance. The number and percentage of patients with a potentially clinically significant laboratory value occurring during the double-blind treatment period were summarized by treatment group.

Descriptive statistics were used to summarize vital signs (actual values and change from baseline) by treatment group. ECG variables were evaluated using the assessments provided by the Central Reader and summarized using descriptive statistics for actual values and change from baseline. Population based correction methods were used to estimate the QT interval. The PVR, CES-D total Score, POMS mood subscales and PWC were also summarized using descriptive statistics.

Summary of Results/Conclusions:

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Based on the primary efficacy endpoint, change from baseline to week 12 in MDP, no efficacy signal of ASP3652 on the disease activity in BPS/IC patients was observed in this proof of concept and dose-finding study Table 3. The placebo group and all ASP3652 dose groups showed similar decreases in the main endpoints that can be interpreted as a general placebo response. The study failed to demonstrate that any particular ASP3652 dose group was statistically better than placebo.

Bayesian statistical analysis indicated that the 300 mg bid group had the highest probability for being the maximum effective dose (0.586). However, the estimated difference from placebo was only -0.02 with a prediction interval ranging from -0.70 to 0.66. Thus the probability that the 300 mg dose was better than placebo by at least the futility difference of -0.4 points was 0.135. As this probability was lower than the pre-defined probability for futility (P value = 0.2), the study was stopped due to futility after 287 patients were randomized. Furthermore, no clear dose-response relationships were observed while the observed placebo response for MDP was in accordance with previously published clinical studies in BPS/IC.

Sensitivity analyses were performed on the primary efficacy endpoint to assess the robustness of the primary analysis, for which no differences were observed between active drug and placebo. A sensitivity analysis was also planned to exclude statistical outliers, however no statistical outliers were identified. Further subgroup analyses of the primary efficacy variable were also performed but no relevant changes from baseline to EoT were seen.

No relevant changes between active dose groups and placebo were observed for the key secondary endpoints of F-GUPI Total, F-GUPI pain domain, and mean number of micturitions/24 hours. Similarly, no consistent meaningful differences from placebo were observed for other secondary variables.

Safety Results:

Overall, the study did not reveal any significant safety signals in patients who received ASP3652 at doses up to 300 mg bid during the 12-week treatment period. ASP3652 was relatively safe and well tolerated in this BPS/IC patient population.

The rate of TEAEs was similar across all treatment groups (28.1% to 30.9%). Most TEAEs were of mild intensity. The incidence of the most common TEAEs (≥ 2% of patients in any treatment group) is presented in Table 4. No TEAEs were reported in any treatment group at an incidence of 6.0% or greater. The TEAEs with the highest incidence were Headache: 3.7% for placebo, 1.9% for 50 mg bid, 5.5% for 150 mg bid and 4.2% for 300 mg bid; and Fatigue: 1.2% for placebo, 5.7% for 50 mg bid, 1.8% for 150 mg bid and 3.1% for 300 mg bid.

Overall, treatment-related TEAEs were experienced by 8.5% of patients receiving placebo, 15.1% of patients receiving 50 mg bid, 16.4% of patients receiving 150 mg bid and 14.6% of patients receiving 300 mg bid. No dose response was observed and most treatment-related TEAEs were in the Gastrointestinal SOC. A total of 8 patients discontinued the study due to TEAEs.

No deaths occurred during the study. The incidence of treatment-emergent SAEs was low and similar between treatment groups (1.2% to 2.1%) Table 5. In total, 7 SAEs were reported in 6 patients (1 placebo patient had an SAE prior to their first double-blind dose). During the double-blind phase of the study, 6 treatment-emergent SAEs were reported in 5 patients. One patient in the 50 mg bid group experienced a serious TEAE of cardiac arrhythmia of moderate intensity that was assessed by the investigator as probably related to study drug. One patient in the 150 mg bid group experienced a serious TEAE of elevated liver enzyme that was assessed by the investigator as possibly related to study drug.

AEs of special interest included certain TEAEs in the categories of hepatotoxicity, cardiovascular events, urinary voiding frequency/pollakiuria, gastrointestinal and CNS/psychotropic events and did not show clear differences between placebo and ASP3652 treatment groups.

Clinical laboratory evaluations, vital signs and ECGs did not reveal any safety concerns and no patients in any treatment group exhibited withdrawal symptoms or psychotropic effects in this study.

CONCLUSIONS:

Based on the primary efficacy and the key secondary endpoints, the efficacy of ASP3652 on disease activity in BPS/IC patients could not be demonstrated in this proof of concept and dose-finding study of 12-weeks duration. The placebo group and all ASP3652 dose groups showed similar decreases in the main endpoints that can be interpreted as a general placebo response. The study demonstrated that no ASP3652 dose group was statistically better than placebo with regard to the primary and key secondary endpoints.

The study demonstrated no clinically relevant differences between ASP3652 dose groups and placebo with regard to subgroup analyses of efficacy endpoints.

No clinically relevant safety signals were evident in the patients that received ASP3652 up to a dose of 300 mg bid over a 12-week treatment period. ASP3652 was safe and well tolerated in this BPS/IC population and no dose response was seen. Specifically, there were no clinical laboratory evaluations, vital signs or ECGs that revealed any safety concerns and no patients in any treatment group exhibited withdrawal symptoms or psychotropic effects.

Date of Report: 27 November 2014

Table 1 Patient Disposition

	Placebo (n = 82)	ASP3652 50 mg bid (n = 53)	ASP3652 150 mg bid (n = 55)	ASP3652 300 mg bid (n = 97)	Total (n = 287)
Safety Analysis Set†	**82 (100.0%)**	**53 (100.0%)**	**55 (100.0%)**	**96 (99.0%)**	**286 (99.7%)**
Discontinued	13 (15.9%)	7 (13.2%)	7 (12.7%)	13 (13.5%)	40 (14.0%)
Reason for discontinuation:‡,§					
Withdrawal	6 (7.3%)	4 (7.5%)	1 (1.8%)	9 (9.4%)	20 (7.0%)
Protocol violation	4 (4.9%)	2 (3.8%)	1 (1.8%)	1 (1.0%)	8 (2.8%)
Adverse event	2 (2.4%)	1 (1.9%)	4 (7.3)	2 (2.1%)	9 (3.1%)
Other¶	1 (1.2%)	0	1 (1.8%)	1 (1.0%)	3 (1.0%)
Full Analysis Set††	**75 (91.5%)**	**49 (92.5%)**	**54 (98.2%)**	**90 (92.8%)**	**268 (93.4%)**
Discontinued	6 (8.0%)	3 (6.1%)	6 (11.1%)	8 (8.9%)	23 (8.6%)
Reason for discontinuation:‡,§					
Withdrawal	4 (5.3%)	2 (4.1%)	0	5 (5.6)	11 (4.1%)
Protocol violation	0	0	1 (1.9)	0	1 (1.4%)
Adverse event	2 (2.7)	1 (2.0%)	4 (7.4%)	2 (2.2%)	9 (3.4%)
Other	0	0	1 (1.9)	1 (1.1)	2 (0.7)
Per protocol Analysis Set‡‡	62 (75.6%)	43 (81.1%)	46 (83.6%)	73 (75.3%)	224 (78.0%)
PK Analysis Set§§	79 (96.3%)	49 (92.5%)	50 (90.9%)	90 (92.8%)	268 (93.4%)
PD Analysis Set¶¶	81 (98.8%)	50 (94.3%)	52 (94.5%)	93 (95.9%)	276 (96.2%)

PD: Pharmacodynamic; PK: Pharmacokinetic.

† All randomized patients who took at least 1 dose of double-blind study drug; 1 patient was randomized in error to the 300 mg bid dose group and never received the double-blind study drug.

‡ Based on the End of Treatment eCRF page; reasons are shown only those for which at least 1 patient discontinued.

§ Only the primary reason for discontinuation was collected.

¶ Discontinuation reason of 'Other' was related to family reasons for all 3 patients.

††All randomized patients who took at least one dose of double-blind study medication and who had an MDP score at baseline and an MDP score post-baseline during the double-blind treatment period or had an MDP score at baseline and dropped out due to an AE.

‡‡ All patients of the FAS who did not deviate from the terms of the protocol, in ways which could significantly affect the primary efficacy variable as specified in the major protocol violations (MPV).

§§ All patients who received active drug, for whom at least one 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 is known.

¶¶ All patients who received at least one dose of DB study drug and for whom at least one blood sample was collected for the anandamide concentrations.

Source: [Table 12.1.1.2, 12.1.1.3.2 and Table 12.1.1.3.3]

Table 2 Demographic and BPS/IC Related Baseline Characteristics (Safety Analysis Set)

	Placebo (n = 82)	**ASP3652 50 mg bid (n = 53)**	**ASP3652 150 mg bid (n = 55)**	**ASP3652 300 mg bid (n = 96)**	**Total (n = 286)**
Race					
White	82 (100%)	53 (100%)	55 (100%)	96 (100%)	286 (100%)
Age (years), mean/median	51.4/54.0	49.6/49.0	53.5/58.0	50.3/51.5	51.1/54.0
Age < 65 years, n (%)	62 (75.6%)	45 (84.9%)	42 (76.4%)	72 (75.0%)	221 (77.3%)
Age ≥ 65 years, n (%)	20 (24.4%)	8 (15.1%)	13 (23.6%)	24 (25.0%)	65 (22.7%)
Weight (kg)					
Mean	68.5	68.6	67.9	69.4	68.7
SD	12.35	13.91	10.86	11.42	12.03
Min	47	48	42	47	42
Median	67.0	67.0	67.0	68.3	67.5
Max	110	118	95	110	118
Height (cm)					
Mean	164.8	163.1	161.9	164.4	163.8
SD	5.88	6.34	5.85	7.43	6.57
Min	153	150	148	150	148
Median	164.0	162.0	164.0	163.0	164.0
Max	178	176	172	182	182
BMI (kg/m^2)					
Mean	25.21	25.87	25.89	25.75	25.64
SD	4.087	5.177	4.045	4.275	4.348
Min	18.4	17.7	15.8	17.3	15.8
Median	24.60	24.60	25.20	25.25	25.00
Max	36.3	37.9	35.3	35.1	37.9
BMI Category (kg/m^2)					
< 25	43 (52.4%)	27 (50.9%)	26 (47.3%)	46 (47.9%)	142 (49.7%)
25 to < 30	27 (32.9%)	14 (26.4%)	20 (36.4%)	31 (32.3%)	92 (32.2%)
≥ 30	12 (14.6%)	12 (22.6%)	9 (16.4%)	19 (19.8%)	52 (18.2%)
BPS/IC symptoms duration (months) mean/median	65.3/39.5	61.1/40.0	59.8/40.0	69.6/45.0	64.9/42.0
Prior BPS/IC medication, n (%)	40 (48.8%)	23 (43.4%)	25 (45.5%)	46 (47.9%)	134 (46.9%)
Hunner's Lesions present,					
Yes, n (%)	10 (12.2%)	9 (17.0%)	16 (29.1%)	28 (29.2%)	63 (22.0%)
No, n (%)	39 (47.6%)	25 (47.2%)	22 (40.0%)	36 (37.5%)	122 (42.7%)
Unknown, n (%)	33 (40.2%)	19 (35.8%)	17 (30.9%)	32 (33.3%)	101 (35.3%)

BMI: body mass index; BPS/IC: Bladder Pain Syndrome/Interstitial Cystitis

Source: [Table 12.1.2.1.1, Table 12.1.2.3.1 and Listing 13.2.4.1]

Table 3 Change from Baseline in MDP Score at End of Treatment: ANCOVA Model (FAS)

Statistic	Placebo (n = 75)	ASP3652 50 mg bid (n = 49)	ASP3652 150 mg bid (n = 54)	ASP3652 300 mg bid (n = 90)
n	74	49	52	89
Baseline Mean (SE)	6.72 (0.158)	6.47 (0.211)	6.64 (0.181)	6.46 (0.134)
EoT Mean (SE)	5.09 (0.288)	5.08 (0.263)	5.22 (0.299)	4.73 (0.231)
Change from Baseline Mean (SE)	-1.63 (0.272)	-1.39 (0.241)	-1.42 (0.368)	-1.73 (0.237)
Posterior θ_d (Std)	-1.72 (0.266)	-1.49 (0.292)	-1.56 (0.265)	-1.73 (0.225)
95% Credibility Interval	(-2.24,-1.19)	(-2.05,-0.92)	(-2.08,-1.04)	(-2.18,-1.29)
Posterior difference versus placebo (Std)	--	0.23 (0.395)	0.15 (0.379)	-0.02 (0.349)
95% Credibility Interval	--	(-0.54, 1.00)	(-0.59, 0.90)	(-0.70, 0.66)
Posterior probability (maximum effective dose)	0.000	0.183	0.231	0.586
Posterior probability (better than placebo)	--	0.285	0.341	0.523
Posterior probability (better by FD)	--	0.056	0.071	0.135
Posterior probability (better by CSD)	--	0.001	0.002	0.003

CSD: clinically significant difference (-1.0); EoT: end of treatment; FAS: Full Analysis Set; FD: futility difference from placebo (-0.4); SE: standard error; Std: standard deviation; θd: modeled change from baseline. For patients who withdrew due to an AE, change from baseline to EoT is set equal to 0.

Source: [Final DMC report] and [Table 12.3.1.1.1]

Table 4 TEAEs reported by ≥ 2% of Patients in Any Treatment group (SAF)

MedDRA (v11.1) System Organ Class Preferred Term	Placebo (n = 82)	ASP3652 50 mg bid (n = 53)	ASP3652 150 mg bid (n = 55)	ASP3652 300 mg bid (n = 96)	Total ASP3652 (n = 204)
Overall	24 (29.3%)	15 (28.3%)	17 (30.9%)	27 (28.1%)	59 (28.9%)
Gastrointestinal disorders					
Nausea	3 (3.7%)	0	3 (5.5%)	1 (1.0%)	4 (2.0%)
Vomiting	1 (1.2%)	1 (1.9%)	1 (1.8%)	2 (2.1%)	4 (2.0%)
Constipation	3 (3.7%)	1 (1.9%)	0	3 (3.1%)	4 (2.0%)
Dry mouth	0	1 (1.9%)	1 (1.8%)	2 (2.1%)	4 (2.0%)
Dyspepsia	0	1 (1.9%)	0	2 (2.1%)	3 (1.5%)
Abdominal distension	0	0	2 (3.6%)	0	2 (1.0%)
Diarrhoea	2 (2.4%)	0	0	0	0
Nervous system disorders					
Headache	3 (3.7%)	1 (1.9%)	3 (5.5%)	4 (4.2%)	8 (3.9%)
Infections and infestations					
Bronchitis	1 (1.2%)	2 (3.8%)	0	0	2 (1.0%)
Cystitis	2 (2.4%)	1 (1.9%)	0	0	1 (0.5%)
Upper respiratory tract infection	2 (2.4%)	0	0	0	0
General disorders and administration site conditions					
Fatigue	1 (1.2%)	3 (5.7%)	1 (1.8%)	3 (3.1%)	7 (3.4%)
Renal and urinary disorders					
Bladder Pain	1 (1.2%)	0	2 (3.6%)	2 (2.1%)	4 (2.0%)
Psychiatric disorders					
Insomnia	1 (1.2%)	1 (1.9%)	0	2 (2.1%)	3 (1.5%)
Musculoskeletal and connective tissue disorders					
Back pain	0	0	1 (1.8%)	2 (2.1%)	3 (1.5%)

SAF: Safety Analysis Set; TEAE: treatment-emergent adverse event.

Source: [Table 12.6.1.3]

Table 5 Summary of Serious Treatment-emergent Adverse Events (Preferred Term) (SAF)

MedDRA (v11.1) System Organ Class Preferred Term	Placebo (n = 82)	ASP3652 50 mg bid (n = 53)	ASP3652 150 mg bid (n = 55)	ASP3652 300 mg bid (n = 96)	Total ASP3652† (n = 204)
Overall	1 (1.2%)	1 (1.9%)	1 (1.8%)	2 (2.1%)	4 (2.0%)
Cardiac disorders					
Arrhythmia	0	1 (1.9%)	0	0	1 (0.5%)
Infections and infestations					
Pyelonephritis	0	0	0	1 (1.0%)	1 (0.5%)
Injury, poisoning and procedural complications					
Meniscus lesion	1 (1.2%)	0	0	1 (1.0%)	1 (0.5%)
Investigations					
Hepatic enzyme increased	0	0	1 (1.8%)	0	1 (0.5%)
Nervous system disorders					
Transient ischaemic attack	1 (1.2%)	0	0	0	0

SAF: Safety Analysis Set.

† Total for all active ASP3652 groups

Source: [Table 12.6.1.8]