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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 CP/CPPS

Coordinating Investigator:

[redacted] MD, PhD, [redacted], Germany.

Study Center(s):

The study was conducted at 35 centers in 6 European countries.

Publication Based on the Study:

None

Study Period:

1.6 years

Study Initiation Date (Date of First Enrollment):

30 June 2011

Study Completion Date (Date of Last Evaluation):

06 February 2013

Phase of Development:

Phase 2

Objectives:

The objectives of this study were:

- To investigate efficacy of ASP3652 in patients with chronic abacterial prostatitis (CP)/chronic pelvic pain syndrome (CPPS), i.e., obtain proof of concept.
- To assess the optimal dose of ASP3652 for treatment of patients with CP/CPPS.
- To investigate safety and tolerability of ASP3652 in patients with CP/CPPS.
- To investigate pharmacokinetics and pharmacodynamics of ASP3652 in patients with CP/CPPS.

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Methodology:

This was a randomized, double-blind, placebo-controlled, parallel group, multi-dose level, dose-finding, adaptive clinical trial with a treatment period of 12 weeks. The study consisted of 3 phases (screening, treatment and follow-up [FU]), with a total study duration of 16 weeks per patient, including 2 weeks for screening and the 2 weeks FU. The study investigated efficacy of 5 different dose levels of ASP3652: 25 mg bid, 75 mg bid, 150 mg bid and 300 mg qd and bid.

Adaptive Design

A Bayesian adaptive trial design was employed using accumulating efficacy and safety data to adjust the probability of allocating (new) patients to individual treatment groups:

1. An initial burn-in period of 60 patients was used in which these patients were randomized equally to the 6 treatment groups (10 patients per dose).
2. After the initial burn-in period a vector of probabilities, $q = (q_0, q_1, q_2, q_3, q_4, q_5)$, was created from an analysis of the current data. During the next 4 weeks, new patients were allocated according to this randomization vector.

At each 4-week interim analysis, the vector of allocation probabilities q was updated based on the observed interim clinical efficacy response based on the National Institutes of Health (NIH)-Chronic Prostatitis Symptom Index (CPSI) total score and pain domain score. Recruitment was not stopped to perform the interim analysis. After 175 patients had been randomized into the study, a decision was made after each interim analysis on whether to stop enrollment in the study.

Screening Phase (2 Weeks)

During the screening phase patients underwent eligibility screening, including safety laboratory analyses, physical examination and urine examination in order to assess all inclusion and exclusion criteria.

The physical examination determined prostate-related pain (i.e., pain on routine palpation of the [posterior] prostate) as well as generalized pelvic pain (i.e., pain on palpation of non prostate structures). This enabled sub-analysis of patients with prostate specific pain versus patients with generalized pelvic pain. On screening, a trans-abdominal ultrasound was performed to exclude prostate and bladder pathology (i.e., bladder/prostate calculi, prostate abscess, significant bladder diverticuli, bladder masses) as well as an ultrasound assessment of post-void residue of urine in the bladder.

If the patient could not be randomized within 2 weeks from the screening visit, because of evaluation of co-morbidity (e.g., urogenital malignancy) that could exclude the patient from participating in the study, the patient could be re-screened after this co-morbidity had been excluded. Patients diagnosed with a urinary tract infection (UTI) in the screening period could not be re-screened after treatment of the UTI. In case of positive hematuria and/or prostate-specific antigen (PSA) > 4 ng/mL, local procedures/guidelines were followed to

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exclude malignancy. If hematuria had been present and/or PSA had been ≥ 4 ng/mL (and did not show significant rise) for the last 6 months and malignancy had been adequately excluded by the investigator according to local diagnostic procedures, then the patient did not have to be excluded. Of note was that if the patient had a (negative) prostate biopsy, the patient could only be re-screened after 3 months following this biopsy.

To allow sub-analysis of efficacy endpoints in the inflammatory and non-inflammatory subcategory of type III prostatitis, in the screening period patients were categorized as having either category IIIa (inflammatory) or IIIb (non-inflammatory) CP/CPPS by measuring leukocyte counts in post-prostate-massage urine. A patient was considered category IIIa if ≥ 10 leukocytes per high power field (400X) were seen in the cell pellet of the centrifuged sample [Nickel et al, 2003]. For this study all samples were analyzed using flow cytometry. Additionally, some of the samples were analyzed by microscopy (as described above) for comparison.

The level of disease activity was also assessed (as part of the inclusion criteria) using the NIH-CPSI and scoring patients to the minimum of 15 points on the NIH-CPSI total score and 4 points on the 11 point numerical rating scale (NRS) for pain to include patients with moderate to severe disease activity [Wagenlehner et al, 2013].

Baseline Visit

During this visit inclusion criteria numbers 9, 10 and 11 were assessed (e.g., to verify patients' eligibility regarding the level of disease activity by recording the NIH-CPSI and to confirm that they were willing and able to comply with study requirements). The NIH-CPSI total score was confirmed to be 15 or higher and the average pain or discomfort over the last week, as assessed in question 4 of the NIH-CPSI (NRS for pain), was confirmed to be 4 or higher on a 0 to 10 scale. During this visit the safety and efficacy assessments were done to define the patient's baseline condition, except for the International Prostate Symptom Score (IPSS) and the Center for Epidemiologic Studies Depression Scale (CES-D), for which baselines were recorded at screening as a part of the exclusion criteria.

Treatment Phase

If the patients still complied with inclusion criteria 9, 10 and 11, they were randomized to the double-blind, placebo-controlled, parallel group treatment phase.

A Bayesian adaptive trial design was employed using accumulating efficacy and safety data to adjust the probability of allocating patients to individual treatment groups. The observed primary and key secondary efficacy data at week 12 (visit 6/end of treatment [EoT]) and the interim treatment results at week 4 (visit 4) and week 8 (visit 5) were used to update the dose-response curve and create the allocation probabilities for the next cohort of patients. During the interim analyses and for the final analysis a (longitudinal) model was used to predict the week 12 assessment from the available week 4 or week 8 data for subjects with a missing week 12 value. Withdrawals due to an AE were considered treatment failures (change from baseline in NIH-CPSI total

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score was set to 0). Allocation probabilities based on the 21-point pain domain (consisting of questions 1 to 4 of the NIH-CPSI) were also calculated and taken into account.

The allocation algorithm strived to achieve approximately the same sample size in the placebo group as in the maximum effective dose group.

Burn-in referred to the minimum number of patients needed until the first adaptation of the allocation probabilities was executed. An initial 'burn-in' period consisting of 60 randomized patients was used (10 patients/group) after which the allocation probabilities were adjusted for the first time based on the interim data observed in this period. Some patients used in the analyses had completed their week 12 (EoT) assessments, while others contributed to the analyses with only week 8 or week 4 data. During the next 4 weeks, patients were allocated to treatment groups according to this updated randomization scheme. For patients whose week 12 data were available, these data were used for the estimation of the new allocation probabilities. For patients with only week 4 or week 8 data, these data were used to estimate the week 12 data for these patients. Once their week 12 data was collected, these data were used for estimating the new allocation probabilities for the next cohort of patients. This procedure was repeated every 4 weeks. It should be noted that randomization was not stopped at any time during the study to analyze the data.

The unblinded interim evaluations were the responsibility of an independent Data Monitoring Committee (DMC).

Follow-up Phase (2 Weeks)

Two weeks following EoT, a FU visit was planned to evaluate study efficacy and safety endpoints. Between EoT and FU, the patients did not receive additional treatment for CP/CPPS. If the patient had withdrawn or discontinued prior to EoT, the patient was requested to complete visit 6/EoT as well as visit 7/FU to monitor safety and efficacy outcomes.

Study Visits

All study visits (from visit 1/screening to visit 7/FU) took place in the morning; preferably well before 11:00 (in order to stay in phase with the circadian rhythm of various pharmacodynamic and safety parameters). At visit 2/baseline visit (BV) and visit 6/EoT, patients were to appear at the clinic in a fasted condition (i.e., no food or beverages, except water, were allowed before blood samples had been obtained in order to have appropriate assessment of serum glucose and lipids which are used for the SteatoTest. Patients who had diabetes mellitus as a concomitant disease were excluded from this particular requirement: they did not have to change their normal eating habits before coming to the clinic.

Number of Patients (Planned, Enrolled and Analyzed):

Planned maximum: 350 patients

Actual: 239 patients enrolled (randomized)

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Full analysis set (FAS): 226 patients

Per protocol set (PPS): 193 patients

Safety analysis set (SAF): 238 patients

The disposition of patients in the FAS and SAF is presented in Table 1

Diagnosis and Main Criteria for Inclusion:

Patients enrolled were males with a diagnosis of CP/CPPS, aged ≥ 18 years, white and of Caucasian origin Table 2, with an NIH-CPSI total score of ≥ 15 at screening and randomization, a score of ≥ 4 on question number 4 of the NIH-CPSI at screening and randomization, who reported pain on palpitation of the prostate or surrounding tissues/non-prostate structures upon digital rectal examination or pain on palpitation of the perineum/genital area, and answered yes to at least 1 out of the 6 items from the combined questions 1 and 2 of the NIH-CPSI. Patients were excluded if they had isolated unilateral testicular, penile or scrotal pain as a solitary symptom, UTI or prostate infection at screening, any prior prostate and/or bladder intervention, intravesical therapy or pelvic/abdominal radiation or prostate biopsy within 3 months before screening, symptomatic urethral stricture, symptomatic bladder or ureteral calculi, lower urinary tract malignancy, severe bladder outlet obstruction, overactive bladder with incontinence, significant post-void residual (PVR) volume > 150 mL, clinically significant abnormalities on transabdominal ultrasound of the bladder and prostate, neurologic disease or defect affecting bladder function, currently active sexually transmitted disease, history of or known inflammatory bowel disease, severe fibromyalgia, severe irritable bowel syndrome and/or severe chronic fatigue syndrome, severe constipation and/or diarrhea, active diverticulitis and/or uninvestigated gastrointestinal bleeding, major depression, active hepatic and/or biliary disease, clinically significant abnormal urine or blood safety laboratory values, a body mass index of ≥ 40 kg/m^2, malignancy diagnosed within 5 years prior to the screening visit, except for curative treated localized non-melanoma skin cancer, clinically severe, unstable or uncontrolled medical illness that would have put the patient at safety risk or mask measures of efficacy in the investigator's opinion.

The use of prohibited medications during the 4 weeks prior to the screening visit excluded patients from entering the study. Restricted medications must have been on a stable dose for at least 4 weeks prior to the screening visit.

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

ASP3652 tablets 25 mg or 100 mg administered at doses of 25 mg bid, 75 mg bid, 150 mg bid and 300 mg qd and bid.

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

12 weeks

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

None.

Criteria for Evaluation:

The primary objective of this study was to determine the change from baseline in the NIH-CPSI total score at 12 weeks of treatment.

The secondary objectives of this study utilized the following assessments:

- NIH-CPSI
- Global response assessment
- Genitourinary pain index
- CPSI-24h (24-hour recall period)
- Short form McGill pain questionnaire
- 3-day urinary symptom diary
- IPSS
- Male Sexual Health Questionnaire
- European Quality of Life questionnaire in 5 Dimensions

The safety endpoints of this study utilized the following assessments:

- Adverse events (AEs) attributed to the cannabinoid system
- Profile of Mood States (POMS) and the Physician Withdrawal Checklist (PWC)
- CES-D
- 12-lead electrocardiogram (ECG), physical examination and vital signs
- Laboratory tests (urinalysis, urine sediment, hematology, biochemistry)
- PVR assessed by trans-abdominal ultrasound
- SteatoTest and adiponectin

Statistical Methods:

Efficacy Variables

Analysis of primary and key secondary variables

The methodology described below was utilized for the adaptive interim analyses as well as for the final Bayesian analysis at the end of the study after database hard-lock and unblinding.

The analysis set for the adaptive interim analyses was the randomized analysis set. The analysis set for the final analysis at the end of the study was the FAS.

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Analysis of Safety

AEs (MedDRA-coded) were summarized by treatment group; AEs indicating withdrawal effects were summarized separately. No formal statistical testing was performed on the individual or combined AE data. Frequency tables of treatment-emergent AEs (TEAEs) by System Organ Class and Preferred Term were produced. AEs were summarized by intensity (i.e., mild, moderate, severe) and relationship to study drug (not related, possibly, probably related).

Laboratory variables (biochemistry, hematology and urinalysis, SteatoTest, and adiponectin, testosterone and troponin levels) and changes from baseline for each post-BV were summarized descriptively by treatment group for all visits, as well as change from baseline to each visit, EoT and FU visit. For each hematology and biochemistry parameter, results were classified as low, normal or high according to the laboratory-supplied reference ranges. Shift tables of changes relative to the reference range from baseline to each visit, and to most extreme value during the double-blind treatment period by treatment group were provided. Laboratory abnormalities were also evaluated for potential clinical significance. The number and percent of patients with a laboratory value meeting the criteria for potential clinical significance 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. ECGs were evaluated using the assessments provided by the Central Reader. ECG variables by treatment group were 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 with descriptive statistics.

Summary of Results/Conclusions:

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Based on both the primary efficacy and the key secondary endpoints, no efficacy signal of ASP3652 on disease activity of CP/CPPS 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 size of the observed placebo response is in the range of placebo responses reported in literature for CP/CPPS studies [Cohen et al, 2012; Anothaisintawee et al, 2011; Wagenlehner et al, 2009; Nickel et al, 2008].

Although the 25 mg bid group was estimated to be the most likely maximum effective dose, this dose was not found to be superior to placebo in this study; the posterior probability that this dose was significantly better than placebo was less than 20%, thereby meeting the criteria for stopping the study for futility. The posterior mean change from baseline across doses for both endpoints did not indicate the presence of a dose relationship. The adaptive design of the study appeared to have worked out well, because based on the four-week independent

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interim analyses of the primary and key secondary endpoint, recruitment into the study was stopped for futility when 239 patients had been randomized.

Analyses of the primary efficacy variable NIH-CPSI in various subpopulations of the FAS population showed that for the subpopulations of patients: 1) with presence of the urinary domain of the Urinary, Psychological, Organ Specific, Infection, Neurological/Systemic, Tenderness of Skeletal Muscles, Sexual Dysfunction (UPOINTS) system at baseline, 2) with nocturnal voiding, 3) with ≥ 8 micturitions per 24 hours at baseline, 4) with less than 3 years' duration of disease, 5) without previous CP/CPPS medication, 6) being treated at sites that randomized more than 11 patients and 7) with a CES-D score under 16 at baseline, the ASP3652 dose groups had a larger decrease in NIH-CPSI at EoT than the placebo group.

Secondary efficacy endpoints generally did not show an advantage of any dose of ASP3652 over placebo, except for the urinary symptom endpoints that all showed larger improvements for all ASP3652 dose groups compared to the placebo group (i.e., the NIH-CPSI Urinary domain, number of micturitions per 24 hours, number of nocturnal voiding episodes, number of grade 3 or 4 urgency episodes, urgency level per micturition, total urgency score and the IPSS).

[redacted]

Safety Results:

Overall, this study did not reveal any safety signal in the patient groups that received ASP3652 with doses up to 300 mg bid over a 12-week treatment period. ASP3652 was safe and well-tolerated in this CP/CPPS patient population.

No TEAEs were reported in either the placebo group or the 150 mg bid group at an incidence of 5% or greater [Table 4]. In the 25 mg bid group, headache was reported by 3 patients (5.7%); in the 75 mg bid group abdominal pain upper was reported by 2 patients (7.1%); in the 300 mg qd group, headache was reported by 3 patients (8.6%) and nasopharyngitis was reported by 2 patients (5.7%) and in the 300 mg bid group insomnia was reported by 3 patients (7.9%). Drug-related TEAEs were experienced by 10 (17.9%) placebo patients and 30 (16.5%) ASP3652 patients [Table 5]. By preferred term, no drug-related TEAE occurred in more than 2 patients. Clinical laboratory evaluations, vital signs and ECGs did not reveal any safety concerns with ASP3652 dosing. No pregnancies in partners of patients were reported during the study. No patients in any treatment group exhibited withdrawal symptoms based on the PWC or psychotropic effects based on the POMS and CES-D.

No deaths occurred in the study. One patient each in the placebo, 25 mg bid and 150 mg bid ASP3652 groups experienced 1 serious TEAE each, and 2 patients in the 75 mg bid group each experienced 1 serious TEAE [Table 6]. No patients in either the 300 mg qd or the 300 mg bid group experienced a serious TEAE. Two of the serious TEAEs were severe (placebo and 150 mg bid), and none were considered related to study drug. No

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patients in the placebo group experienced a TEAE that led to permanent discontinuation of study drug; 1 patient in the 25 mg bid group and 2 patients in each of the remaining ASP3652 groups experienced a TEAE that led to permanent discontinuation of study drug.

AEs of special interest included certain TEAEs in the categories of hepatotoxicity, reproductive disorders, cardiovascular effects, urinary voiding frequency/pollakiuria, nephrotoxicity, hematopoietic disorders, gastrointestinal disorders, central nervous system/psychotropic effects, abuse liability/withdrawal, bladder hypotonia/urination and acute urinary retention. These AE categories had been selected to be of special interest based on nonclinical studies, the known mode of action of ASP3652 and results of the clinical pharmacology studies, and have been listed as such in the Investigator's Brochure and Development Risk Management Plan. Upon analysis of AEs in these categories, no safety signal (i.e., a noticeably higher incidence in patients dosed with ASP3652 compared to patients dosed with placebo) could be detected

CONCLUSIONS:

Based on both the primary efficacy and the key secondary endpoints, no efficacy signal of ASP3652 on disease activity of CP/CPPS patients was observed in this proof of concept and dose-finding study investigating 12 weeks of treatment. 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 posterior mean change from baseline across ASP3652 doses for both endpoints did not indicate the presence of a dose relationship.

Although the 25 mg bid group was estimated to be the most likely maximum effective dose, this dose was not found to be superior to placebo in this study; the posterior probability that this dose was significantly better than placebo was less than 20%, thereby meeting the criteria for stopping the study for futility. The adaptive design of the study appeared to have worked out well, because based on the four-week independent interim analyses of the primary and key secondary endpoint, recruitment into the study was stopped for futility when 239 (of the maximum 350) patients had been randomized.

Secondary efficacy endpoints generally did not show an advantage of any dose of ASP3652 over placebo, except for the urinary symptom endpoints that all showed larger improvements for all ASP3652 dose groups compared to the placebo group (i.e., the NIH-CPSI urinary domain, mean number of micturitions per 24 hours, number of nocturnal voiding episodes, mean number of grade 3 or 4 urgency episodes per 24 hours, mean level of urgency per micturition, total urgency score and the IPSS).

Overall, this study did not reveal any safety signal in the patients groups 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 CP/CPPS population, and no dose response was seen. Clinical laboratory evaluations, vital signs and ECGs did not reveal any safety concerns with ASP3652 dosing, and no patients in any treatment group exhibited withdrawal symptoms or psychotropic effects based on the questionnaires used in the study.

Date of Report: 18 Oct 2013

Table 1 Number of Patients in Each Analysis Set and Disposition of Patients in the Safety and Full Analysis Sets

	Placebo (n = 57)	ASP3652 25 mg bid (n = 53)	ASP3652 75 mg bid (n = 28)	ASP3652 300 mg qd (n = 35†)	ASP3652 150 mg bid (n = 28)	ASP3652 300 mg bid (n = 38)	Total (n = 239)
Safety Analysis Set†	**57 (100.0%)**	**53 (100.0%)**	**28 (100.0%)**	**34 (97.1%)**	**28 (100.0%)**	**38 (100.0%)**	**238 (99.6%)**
Discontinued	10 (17.9%)	7 (13.2%)	4 (14.3%)	7 (20.0%)	4 (14.3%)	7 (18.4%)	39 (16.4%)
Reason for discontinuation:‡,§							
Withdrawal	6 (10.7%)	3 (5.7%)	2 (7.1%)	2 (5.7%)	2 (7.1%)	3 (7.9%)	18 (7.6%)
Lost to follow-up	0	1 (1.9%)	0	0	0	0	1 (0.4%)
Protocol violation	4 (7.1%)	2 (3.8%)	0	1 (2.9%)	0	2 (5.3%)	9 (3.8%)
Adverse event	0	1 (1.9%)	2 (7.1%)	4 (11.4%)	2 (7.1%)	2 (5.3%)	11 (4.6%)
Full Analysis Set¶	**53 (93.0%)**	**52 (98.1%)**	**26 (92.9%)**	**34 (97.1%)**	**27 (96.4%)**	**34 (89.5%)**	**226 (94.6%)**
Discontinued	6 (11.3%)	6 (11.5%)	2 (7.7%)	7 (20.6%)	3 (11.1%)	3 (8.8%)	27 (11.9%)
Reason for discontinuation:‡,§							
Withdrawal	2 (3.8%)	2 (3.8%)	0	2 (5.9%)	1 (3.7%)	0	7 (3.1%)
Lost to follow-up	0	1 (1.9%)	0	0	0	0	1 (0.4%)
Protocol violation	4 (7.5%)	2 (3.8%)	0	1 (2.9%)	0	1 (2.9%)	8 (3.5%)
Adverse event	0	1 (1.9%)	2 (7.7%)	4 (11.8%)	2 (7.4%)	2 (5.9%)	11 (4.9%)
Per Protocol Analysis Set	**43 (75.4%)**	**46 (86.8%)**	**24 (85.7%)**	**26 (74.3%)**	**24 (85.7%)**	**30 (78.9%)**	**193 (80.8%)**

† All randomized patients who took at least 1 dose of double-blind study drug; 1 patient in the 300 mg qd dose group was randomized but was not dosed.

‡ 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.

¶ All randomized subjects who took a dose of double-blind study drug and who have an NIH-CPSI total score at baseline and at least 1 NIH-CPSI total score post-baseline during the double blind treatment period or have an NIH-CPSI total score at baseline and drop out due to AE.

Source: Table 12.1.1.2, Table 12.1.1.3.1, Table 12.1.1.3.2

Table 2 Demographic and Baseline Characteristics (SAF)

	Placebo (n = 56)	ASP3652 25 mg bid (n = 53)	ASP3652 75 mg bid (n = 28)	ASP3652 300 mg qd (n = 35)	ASP3652 150 mg bid (n = 28)	ASP3652 300 mg bid (n = 38)	Total (n = 238)
Race White	56 (100%)	53 (100%)	28 (100%)	35 (100%)	28 (100%)	38 (100%)	238 (100%)
Age (years), mean/median	45.9/47.0	46.0/44.0	45.4/45.0	43.7/44.0	43.0/41.5	46.9/43.5	45.4/44.0
Age ≥ 65 years, n (%)	4 (7.1%)	7 (13.2%)	2 (7.1%)	3 (8.6%)	3 (10.7%)	4 (10.5%)	23 (9.7%)
Weight (kg)							
Mean	89.2	84.3	85.0	80.4	85.0	87.1	85.5
SD	14.74	13.07	10.06	9.62	13.06	14.89	13.22
Min	63	55	68	54	63	58	54
Median	87.3	85.0	83.5	80.0	82.4	88.3	84.2
Max	136	115	106	97	115	133	136
Height (cm)							
Mean	179.7	178.6	178.7	176.7	179.0	178.4	178.6
SD	6.76	6.81	8.34	5.90	7.66	7.56	7.08
Min	166	160	160	165	164	160	160
Median	179.0	178.0	178.0	176.0	177.0	180.0	178.0
Max	197	196	196	191	205	191	205
BMI (kg/m^2)							
Mean	27.61	26.39	26.64	25.75	26.51	27.26	26.76
SD	4.257	3.537	2.799	2.972	3.643	3.486	3.595
Min	19.0	18.0	23.1	19.8	20.8	19.8	18.0
Median	27.20	26.00	26.40	25.90	26.55	27.50	26.60
Max	39.7	34.0	33.9	32.6	36.3	36.5	39.7
BMI Category (kg/m^2)							
< 25	15 (26.8%)	17 (32.1%)	10 (35.7%)	13 (37.1%)	11 (39.3%)	9 (23.7%)	75 (31.5%)
25 to < 30	29 (51.8%)	27 (50.9%)	15 (53.6%)	20 (57.1%)	11 (39.3%)	22 (57.9%)	124 (52.1%)
≥ 30	12 (21.4%)	9 (17.0%)	3 (10.7%)	2 (5.7%)	6 (21.4%)	7 (18.4%)	39 (16.4%)
CP/CPPS duration (months) mean/median	57.4/31.5	41.2/28.0	71.3/41.5	51.9/29.0	36.7/24.0	52.5/28.0	51.4/30.5
Prior CP/CPPS medication, n (%)	38 (67.9%)	38 (71.7%)	20 (71.4%)	23 (65.7%)	14 (50.0%)	28 (73.7%)	161 (67.6%)
CES-D Total Score, mean/median	8.3/7.0	9.2/10.0	8.9/8.0	7.7/6.0	8.2/8.5	9.1/9.0	8.7/8.0

BMI: body mass index; CES-D: Center for Epidemiologic Studies Depression Scale; CP/CPPS: chronic abacterial prostatitis/chronic pelvic pain syndrome

Source: Table 12.1.2.1.1, Table 12.1.2.3.1 and Table 12.6.5.4.1.

Table 3 Change from Baseline in NIH-CPSI Total Score (FAS)

Statistic	Placebo (n = 53)	ASP3652 25 mg bid (n = 52)	ASP3652 75 mg bid (n = 26)	ASP3652 300 mg qd (n = 34)	ASP3652 150 mg bid (n = 27)	ASP3652 300 mg bid (n = 34)
n	53	51	26	31	25	32
Baseline Mean (SE)	24.2 (0.71)	23.4 (0.73)	22.3 (0.98)	23.5 (0.78)	21.2 (0.71)	22.4 (0.90)
EoT Mean (SE)	17.0 (1.05)	16.1 (1.07)	14.9 (1.46)	16.6 (1.12)	13.8 (1.37)	15.6 (1.30)
Change from Baseline Mean (SE)	-7.2 (0.94)	-7.3 (0.95)	-6.7 (1.22)	-6.7 (1.19)	-7.4 (1.38)	-6.8 (1.18)
Posterior θ_d (Std) 95% Credibility Interval	-7.3 (0.97) (-9.2,-5.4)	-7.0 (0.68) (-8.3,-5.7)	-6.9 (0.69) (-8.2,-5.5)	-6.5 (0.78) (-8.1,-5.0)	-6.8 (0.60) (-8.0,-5.6)	-6.7 (0.70) (-8.1,-5.3)
Posterior difference versus placebo (Std) 95% Credibility Interval	--	0.3 (1.18) (-1.9,2.6)	0.4 (1.20) (-1.9,2.8)	0.7 (1.26) (-1.7,3.1)	0.5 (1.16) (-1.7,2.7)	0.6 (1.23) (-1.8,2.9)
Posterior probability (maximum effective dose)	--	0.328	0.189	0.157	0.129	0.196
Posterior probability (better than placebo)	--	0.399	0.363	0.280	0.335	0.316
Posterior probability (better by FD)	--	0.019	0.020	0.015	0.014	0.017
Posterior probability (better by CSD)	--	< 0.001	< 0.001	0.002	0.001	0.001

CSD: clinically significant difference (-4); EoT: end of treatment: FD: futility difference from placebo (-2); SE: standard error; Std: standard deviation; θ_d: modeled change from baseline

Source: Table 12.3.1.1.1.

Table 4 Summary of Treatment-Emergent Adverse Events Occurring in at Least 2% of Patients Taking Either Placebo or ASP3652 (All Doses) (Preferred Term)

MedDRA (v11.1) System Organ Class Preferred Term	Placebo (n = 56)	ASP3652 25 mg bid (n = 53)	ASP3652 75 mg bid (n = 28)	ASP3652 300 mg qd (n = 35)	ASP3652 150 mg bid (n = 28)	ASP3652 300 mg bid (n = 38)	Total ASP3652 (n = 182)
Nervous system disorders							
Headache	1 (1.8%)	3 (5.7%)	1 (3.6%)	3 (8.6%)	1 (3.6%)	1 (2.6%)	9 (4.9%)
Gastrointestinal disorders							
Abdominal pain upper	1 (1.8%)	2 (3.8%)	2 (7.1%)	1 (2.9%)	0	0	5 (2.7%)
GERD	2 (3.6%)	0	0	0	0	0	0
Infections and infestations							
Nasopharyngitis	1 (1.8%)	1 (1.9%)	1 (3.6%)	2 (5.7%)	1 (3.6%)	0	5 (2.7%)
Psychiatric disorders							
Insomnia	1 (1.8%)	2 (3.8%)	0	1 (2.9%)	1 (3.6%)	3 (7.9%)	7 (3.8%)
Renal and urinary disorders							
Urinary hesitation	1 (1.8%)	1 (1.9%)	0	0	1 (3.6%)	2 (5.3%)	4 (2.2%)
General disorders and administration site conditions							
Asthenia	2 (3.6%)	0	0	0	1 (3.6%)	0	1 (0.5%)
Respiratory, thoracic and mediastinal disorders							
Oropharyngeal pain	2 (3.6%)	0	0	0	0	0	0

GERD: Gastroesophageal reflux disease; MedDRA: Medical Dictionary for Regulatory Activities

Source: Table 12.6.1.4

Table 5 Overview of Treatment Emergent Adverse Events

Parameter	Placebo (n = 56)	ASP3652 25 mg bid (n = 53)	ASP3652 75 mg bid (n = 28)	ASP3652 300 mg qd (n = 35)	ASP3652 150 mg bid (n = 28)	ASP3652 300 mg bid (n = 38)
Incidence of TEAEs	23 (41.1%)	17 (32.1%)	12 (42.9%)	14 (40.0%)	15 (53.6%)	15 (39.5%)
Incidence of Drug-Related TEAEs†	10 (17.9%)	9 (17.0%)	3 (10.7%)	6 (17.1%)	5 (17.9%)	7 (18.4%)
Incidence of Deaths	0	0	0	0	0	0
Incidence of Serious TEAEs	1 (1.8%)	1 (1.9%)	2 (7.1%)	0	1 (3.6%)	0
Incidence of Serious Drug-Related TEAEs	0	0	0	0	0	0
Incidence of TEAEs Leading to Permanent Discontinuation of Study Drug	0	1 (1.9%)	2 (7.1%)	2 (5.7%)	2 (7.1%)	2 (5.3%)
Incidence of Drug-Related TEAEs Leading to Permanent Discontinuation of Study Drug	0	1 (1.9%)	1 (3.6%)	2 (5.7%)	1 (3.6%)	2 (5.3%)

TEAEs: treatment-emergent adverse events

† Possible or probable, as assessed by the investigator, or records where the relationship was missing

Source: Table 12.6.1.1

Table 6 Summary of Serious Treatment-Emergent Adverse Events (Preferred Term)

MedDRA (v11.1) System Organ Class Preferred Term	Placebo (n = 56)	ASP3652 25 mg bid (n = 53)	ASP3652 75 mg bid (n = 28)	ASP3652 300 mg qd (n = 35)	ASP3652 150 mg bid (n = 28)	ASP3652 300 mg bid (n = 38)	Total ASP3652 (n = 182)
Ear and labyrinth disorders							
Deafness neurosensory	0	1 (1.9%)	0	0	0	0	1 (0.5%)
Infections and infestations							
Pneumonia	0	0	1 (3.6%)	0	0	0	1 (0.5%)
Musculoskeletal and connective tissue disorders							
Arthralgia	0	0	1 (3.6%)	0	0	0	1 (0.5%)
Renal and urinary disorders							
Renal colic	0	0	0	0	1 (3.6%)	0	1 (0.5%)
Nervous system disorders							
Radiculopathy	1 (1.8%)	0	0	0	0	0	0

MedDRA: Medical Dictionary for Regulatory Activities

Source: Table 12.6.1.8