SYNOPSIS

Name of Sponsor/Company: Astellas Pharma US, Inc.		
Name of Finished Product: YM672		
Name of Active Ingredient: YM672		
Title of Study: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of YM672 in the Treatment of Painful Bladder Syndrome/Interstitial Cystitis		
Responsible Medical Officer/Investigators: [redacted]		
Study Center(s): 28 in United States; 2 in Belgium; 1 in Denmark; 3 in Germany; 2 in Sweden.		
Publication (reference): None		
Study Period: 21 DEC 2005 to 23 APR 2007 **Date of first enrollment:** 30 DEC 2005 **Date of last evaluation:** 23 APR 2007	**Phase of Development:** Phase 2	
Objectives: The objective of this study was to evaluate the efficacy and safety of YM672 administered orally in the treatment of painful bladder syndrome (PBS)/interstitial cystitis (IC).		
Methodology: This was a randomized double-blind, placebo-controlled parallel group, multi-center Phase 2 study in subjects with painful bladder syndrome (PBS)/interstitial cystitis (IC). During a 1 to 6 week screening period, each subject was to complete a voiding diary including the date and time of all voids per day (24 hour period) for 7 consecutive days and volume per void for 3 consecutive days preceding the Baseline/Day 1 visit. Following the successful completion of the Screening period, subjects were randomized to a 12 week fixed-dose treatment phase followed by a 1 week post-treatment follow-up phase. Subjects were randomized to either receive 2400 mg /day YM672 administered orally (800 mg/dose TID) or placebo administered orally (0 mg/dose TID) in a 1:1 allocation. Scheduled visits occurred at Screening, Baseline/Day 1, Weeks 2, 4, 6, 8, 10, 12/End of Treatment (ET) and 13/End of Study. Subjects completed the IC Symptom Index Score, IC Problem Index Score, Severity of Pain (visual analog scale) and Severity of Urinary Urgency (visual analog scale) at Baseline/Day1, Weeks 4, 8 and 12/ET. Subjects completed the Global Response Assessment and Subject's Response to Treatment Questionnaire at Weeks 4, 8 and 12/ET. Subjects were to complete a voiding diary including the date and time of all voids per day (24 hour period) for 7 consecutive days and volume per void for 3 consecutive days preceding the scheduled visits of Weeks 4, 8 and 12/ET.		

Number of Patients (enrolled and analyzed): One hundred fifty (150) subjects were planned to be enrolled into the study. A total of 165 subjects were randomized; of these, 161 subjects were included in the full analysis set.

Diagnosis and Main Criteria for Inclusion: Subjects were between 18 and 80 years of age and were diagnosed with PBS/IC, defined as suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology, with symptoms for at least 12 consecutive weeks prior to the screening visit. Each subject was to have a score of at least 1 on the IC Problem Index Question 4 and an IC Symptom Index total score of at least 7 at the Baseline visit.

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

Strength	Bulk Lot Number
200 mg	[redacted]

Duration of Treatment (or Duration of Study, if applicable): Following a screening period of 1 to 6 weeks, subjects were to be treated for 12 weeks with an additional 1 week follow-up visit.

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

Strength	Bulk Lot Number
Placebo	[redacted]

Criteria for Evaluation: The primary efficacy endpoint was success defined as "Moderately Improved" or "Markedly Improved" PBS/IC on the subject-rated 7-point Global Response Assessment (GRA) (Appendix A of the protocol) at the Week 12/ET visit. The last observation during the treatment period was used as the value at ET.

Safety was assessed through evaluation of adverse events, vital signs, physical examination, ECGs, hematology, serum chemistry, and coagulation parameters and urinalysis.

Statistical Methods: Analysis for the primary efficacy variable (success defined as "Moderately Improved" or "Markedly Improved" on the subject-rated 7-point Global Response Assessment (GRA) at the Week 12/ET) was assessed by the Cochran-Mantel-Haenszel (CMH) test using modified ridit scores and stratified by pooled investigative sites. The Breslow-Day test was used to assess the consistency of treatment effect across investigative sites. The study was powered to detect a statistically significant treatment difference between YM672 and placebo with greater than 80% power if the YM672 success rate was 50% and the placebo success rate was 25%.

Summary

Demographics: A total of 161 subjects comprised the full analysis set (79 to placebo and 82 to YM672 800 mg TID).

Drug Administration: The percentage of subjects by duration of each study drug exposure category was similar between treatment groups. At week 12 (Days 79-92) there were 67.1% (53/79) placebo subjects and 65.9% (54/82) YM672 800 mg TID subjects on study medication (Table 7).

Efficacy Results: Using the full analysis set, the success rate was 25.3% for the placebo group compared to 20.7% for YM672 800 mg TID (p=0.5301). The site adjusted difference (YM672 800 mg TID – placebo) of the mean success rate was -4.3% with a 95% weighted confidence interval of -17.3% to 8.7%. The lack of effect of YM672 800 mg TID in the primary efficacy endpoint was confirmed by the same analysis using the per protocol set.

Safety Results: All 161 subjects who entered the treatment phase of the study and took at least one tablet of study drug were included in the safety analysis. Overall, 82.3% and 86.6% of subjects in the placebo and YM672 800 mg TID groups, respectively, experienced adverse events. Compared to the placebo group, more subjects in the YM672 800 mg TID group experienced adverse events in the primary system organ classes of gastrointestinal disorders, investigations, and skin and subcutaneous tissue disorders. A greater percentage of YM672 800 mg TID subjects experienced diarrhoea, headache, nausea, breath odour, skin odour abnormal, flatulence, alanine aminotransferase increased, bladder pain and constipation.

Three subjects (all placebo) had a total of five treatment emergent serious adverse events. All five serious adverse events were considered to have no relationship to study drug by investigators.

Thirty-four (34) subjects had adverse events that led to discontinuation of study drug (Table 13 presents any event occurring in >1 subject in active treatment group). The greatest number of adverse events leading to discontinuation was adverse events in the primary system organ class of gastrointestinal disorders [6/79 (7.6%) placebo, 6/82 (7.3%) YM672 800 mg TID].

CONCLUSIONS: The success rates were similar between YM672 800 mg TID and placebo for the primary endpoint of "Moderately Improved" or "Markedly Improved" PBS/IC on the subject-rated 7-point Global Response Assessment (GRA) at Week12/End of Treatment. The success rate was 25.3% for placebo subjects and 20.7% for YM672 800 mg TID treated subjects. The results of all secondary endpoints were similar to the primary endpoint results.

Overall, adverse events were comparable between treatment groups. A greater percentage of YM672 800 mg TID subjects experienced diarrhoea, headache, nausea, breath odour, skin odour abnormal, flatulence, alanine aminotransferase increased, bladder pain and constipation. A total of three subjects (all placebo) experienced five serious adverse events; all five events were considered to have no relationship to study drug by investigators.

Date of Report: 9 AUGUST 2007

Synopsis Table 1: Analysis Sets (All Randomized Subjects)

Analysis Set	Placebo (n=81)	YM672 800 mg TID (n=84)	Total (n=165)
Safety Set (1)	79 (97.5%)	82 (97.6%)	161 (97.6%)
Full Analysis Set (2)	79 (97.5%)	82 (97.6%)	161 (97.6%)
Per Protocol Set (3)	42 (51.9%)	48 (57.1%)	90 (54.5%)

(1) All subjects who entered treatment phase of study and took at least one tablet of study drug.

(2) All enrolled subjects who took at least one tablet of study drug.

(3) All enrolled subjects who did not have major protocol deviations.

Source: Table 12.1.1

Synopsis Table 2: Subject Disposition (All Randomized Subjects)

		Placebo (n=81)	YM672 800 mg TID (n=84)	Total (n=165)
Completed Treatment	Yes	52 (64.2%)	54 (64.3%)	106 (64.2%)
	No	29 (35.8%)	30 (35.7%)	59 (35.8%)
Reason for Discontinuation of Study	Randomized but never received drug	2 (2.5%)	2 (2.4%)	4 (2.4%)
	Adverse event	13 (16.0%)	21 (25.0%)	34 (20.6%)
	Withdrew consent (not related to adverse event)	4 (4.9%)	4 (4.8%)	8 (4.8%)
	Protocol violation	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Lost to follow-up	1 (1.2%)	2 (2.4%)	3 (1.8%)
	Sponsor elected to discontinue the subject or to end the study	1 (1.2%)	0 (0.0%)	1 (0.6%)
	Lack of Efficacy	6 (7.4%)	1 (1.2%)	7 (4.2%)
	Other	2 (2.5%)	0 (0.0%)	2 (1.2%)
Completed Post-Treatment	Yes	63 (77.8%)	64 (76.2%)	127 (77.0%)
	No	18 (22.2%)	20 (23.8%)	38 (23.0%)

Source: Table 12.1.2.1

Synopsis Table 3: Demographics and Other Baseline Characteristics (Full Analysis Set)

		Placebo (n=79)	YM672 800 mg TID (n=82)	Total (n=161)
Sex	Male	10 (12.7%)	12 (14.6%)	22 (13.7%)
	Female	69 (87.3%)	70 (85.4%)	139 (86.3%)
Race	White	70 (88.6%)	80 (97.6%)	150 (93.2%)
	Black or African-American	8 (10.1%)	2 (2.4%)	10 (6.2%)
	American Indian or Alaska Native	1 (1.3%)	0 (0.0%)	1 (0.6%)
Region	Europe	28 (35.4%)	31 (37.8%)	59 (36.6%)
	United States (US)	51 (64.6%)	51 (62.2%)	102 (63.4%)
Ethnicity (1)	Non Hispanic or Latino	48 (94.1%)	50 (98.0%)	98 (96.1%)
	Hispanic or Latino	3 (5.9%)	1 (2.0%)	4 (3.9%)
Age (Years)	N	79	82	161
	Mean	47.8	46.5	47.2
	STD	14.27	15.29	14.77
Weight (kg)	N	78	82	160
	Mean	71.4	72.7	72.0
	STD	17.11	16.60	16.81
Height (cm)	N	78	82	160
	Mean	165.5	165.8	165.6
	STD	7.65	8.66	8.16

(1) Only US sites were required to collect this information. The denominator is the total number of subjects enrolled by US sites.

Source: Table 12.2.1.1

Synopsis Table 4: Baseline PBS/IC Characteristics (Full Analysis Set)

		Placebo (n=79)	YM672 800 mg TID (n=82)	Total (n=161)
IC Symptom Index Score Sum (1)	N	79	81	160
	Mean	13.05	14.04	13.55
	STD	3.630	3.227	3.456
IC Problem Index Score Sum (2)	N	79	81	160
	Mean	11.47	12.15	11.81
	STD	3.297	2.838	3.082
Severity of Urinary Urgency (3)	N	79	81	160
	Mean	5.60	6.29	5.95
	STD	2.785	2.542	2.679
Severity of Bladder Pain, Pelvic Pain or Pain Accompanied by Urgency (4)	N	77	81	158
	Mean	6.15	6.99	6.58
	STD	2.367	2.177	2.303

(1) IC Symptom Index Score is the sum of four questions with a total possible score of 20. A higher score indicates more severe symptoms.

(2) IC Problem Index Score is the sum of four questions with a total possible score of 16. A higher score indicates more severe problems.

(3) Severity of Urinary Urgency: The subject averaged severity for the week prior to the specified visit and places a mark on a visual analog scale (10 cm line) ranging from none to extreme difficulty.

(4) Severity of Bladder Pain, Pelvic Pain or Pain Accompanied by Urinary Urgency: The subject averaged severity for the week prior to the specified visit and places a mark on a visual analog scale (10 cm line) ranging from none to extreme severe.

Source: Table 12.2.2.1

Synopsis Table 5: Baseline Bladder Diary Assessments (Full Analysis Set)

		Placebo (n=79)	YM672 800 mg TID (n=82)	Total (n=161)
Mean Number of Micturitions per Calendar Day	N	79	82	161
	Mean	12.87	13.46	13.17
	STD	5.159	5.850	5.512
Mean Number of Micturitions per Night	N	78	81	159
	Mean	2.65	2.92	2.79
	STD	1.759	1.963	1.864
Mean Voided Volume per Micturition	N	79	82	161
	Mean	155.96	159.51	157.77
	STD	80.397	66.101	73.255
Maximum Voided Volume per Micturition	N	79	82	161
	Mean	318.99	327.83	323.49
	STD	157.418	146.005	151.301

Source: Table 12.2.3.1

Synopsis Table 6: PBS/IC Therapeutic Interventions/Diagnostic Test History (Full Analysis Set)

	Placebo	YM672 800 mg TID	Total
All Regions	79	82	161
Cystoscopy	27 (34.2%)	21 (25.6%)	48 (29.8%)
Bladder Biopsy	8 (10.1%)	12 (14.6%)	20 (12.4%)
United States	51	51	102
Cystoscopy	12 (23.5%)	8 (15.7%)	20 (19.6%)
Bladder Biopsy	0 (0.0%)	2 (3.9%)	2 (2.0%)
Europe	28	31	59
Cystoscopy	15 (53.6%)	13 (41.9%)	28 (47.5%)
Bladder Biopsy	8 (28.6%)	10 (32.3%)	18 (30.5%)

Source: Table 12.2.4.1

Synopsis Table 7: Study Drug Exposure (Safety Set)

Visit	Placebo (n=79)	YM672 800 mg TID (n=82)
Day 1	79 (100.0%)	82 (100.0%)
Week 2 (Days 2 – 22)	79 (100.0%)	82 (100.0%)
Week 4 (Days 23 – 36)	69 (87.4%)	70 (85.4%)
Week 6 (Days 37 – 50)	64 (81.0%)	67 (81.7%)
Week 8 (Days 51 – 64)	57 (72.2%)	59 (72.0%)
Week 10 (Days 65 – 78)	54 (68.4%)	56 (68.3%)
Week 12 (Days 79 – 92)	53 (67.1%)	54 (65.9%)

Source: Table 12.3.1

Synopsis Table 8: Success Rate (1) by Visit Stratified by Site Using Observed Data (Full Analysis Set)

Visit	Placebo	YM672 800 mg TID	Difference [95 % CI] (2)	CMH P-value (3)	Breslow-Day P-value (4)
Week 4	11/64 (17.2%)	9/67 (13.4%)	-1.6% [-13.9%, 10.8%]	0.8071	0.5724
Week 8	19/54 (35.2%)	11/58 (19.0%)	-15.4% [-31.9%, 1.0%]	0.0673	0.5457
Week 12	10/37 (27.0%)	13/40 (32.5%)	6.4% [-14.8%, 27.5%]	0.5593	0.5153

(1) Success was defined as "Moderately Improved" or "Markedly Improved" PBS/IC on the subject-rated 7-point Global Response Assessment (GRA).

(2) The mean and 95% confidence interval were calculated using weighted averages where the weights adjust for the number of subjects enrolled in each treatment group at each site. These weights reflected their relative contribution to the Mantel-Haenszel statistic.

(3) P-value is from Cochran-Mantel-Haenszel (CMH) test stratified by investigative site. Sites with less than 8 subjects or no successes were pooled according to geographic location.

(4) P-value for test of treatment*site interaction is from the Breslow-Day test.

Source: Table 12.4.2.1, 12.4.2.2, 12.4.2.3

Synopsis Table 9: Mean Change in Secondary Efficacy Parameters from Baseline to End of Treatment (Full Analysis Set)

Parameter	YM672 800 mg TID – Placebo Treatment Difference	
	LS Mean [95% Confidence Interval]	P-value
IC Symptom Index Total Score	0.41 [-0.75, 1.58]	0.4827
IC Problem Index Total Score	0.37 [-0.74, 1.48]	0.5118
Mean Number of Micturitions per Calendar Day	0.49 [-0.67, 1.66]	0.4022
Mean Number of Micturitions per Night	-0.29 [-0.90, 0.33]	0.3577
Mean Voided Volume per Micturition (mL)	-7.73 [-23.6, 8.12]	0.3368
Maximum Voided Volume per Micturition (mL)	8.79 [-25.0, 42.63]	0.6084
Severity of Urinary Urgency	-0.05 [-0.94, 0.83]	0.9028
Severity of Bladder Pain	-0.13 [-1.08, 0.81]	0.7840

Source: Tables 12.4.3.1, 12.4.4.1, 12.4.5.1

Synopsis Table 10: Response to Subject Treatment Questionnaire (1) - Mean at End of Treatment (Full Analysis Set)

Question (2)	Placebo	YM672 800 mg TID	P-value (3)
1. Did your daytime frequency change?	-0.5	-0.4	0.7316
2. Did your nocturia change?	-0.4	-0.4	0.6930
3. Did your urgency change?	-0.4	-0.3	0.6750
4. Did the amount of time you have pain or discomfort change?	-0.5	-0.4	0.6274
5. Did the intensity of your pain or discomfort change?	-0.6	-0.5	0.8643
6. Did your ability to perform everyday activities change?	-0.3	-0.5	0.4214
7. Overall, has there been a change in your PBS/IC symptoms?	-0.6	-0.6	0.8979
8. Has there been a change in your most troubling symptom?	-0.4	-0.5	0.6466

(1) For each question each subject rated their response to treatment by comparing each condition during the past month with how they felt before starting this clinical study.
(2) Responses were based on a 7-point scale where +3=Significantly Aggravated, +2=Moderately Aggravated, +1=Mildly Aggravated, 0=Not Changed, -1=Mildly Improved, -2=Moderately Improved and -3=Significantly Improved.
(3) P-value is from a one-way ANOVA model.
Source: Tables 12.4.6.1.1, 12.4.6.2.1, 12.4.6.3.1, 12.4.6.4.1, 12.4.6.5.1, 12.4.6.6.1, 12.4.6.7.1, 12.4.6.8.1

Synopsis Table 11: Response to Subject Treatment Questionnaire (1) – Frequency of Question 9 at End of Treatment (Full Analysis Set)

Treatment Group	During the past month, what has been your most troubling symptom?					P-value (3)
	Frequency	Nocturia	Urgency	Pain or Discomfort	Others	
Placebo	18/67 (26.9%)	12/67 (17.9%)	12/67 (17.9%)	23/67 (34.3%)	2/67 (3.0%)	0.8369
YM672 800 MG TID	16/69 (23.2%)	12/69 (17.4%)	9/69 (13.0%)	30/69 (43.5%)	2/69 (2.9%)	

(1) For each question each subject rated their response to treatment by comparing each condition during the past month with how they felt before starting this clinical study.
(2) P-value is from a chi-square test.
Source: Table 12.4.6.9.1

Synopsis Table 12: Adverse Events Occurring in ≥ 5% of Subjects and Having a Higher Incidence in Active Treatment Group (Safety Set)

Adverse Event	Placebo (n=79)	YM672 800 mg TID (n=82)
Any Adverse Event	65 (82.3%)	71 (86.6%)
Diarrhoea	9 (11.4%)	20 (24.4%)
Headache	10 (12.7%)	20 (24.4%)
Nausea	6 (7.6%)	20 (24.4%)
Breath Odour	0 (0.0%)	14 (17.1%)
Skin Odour Abnormal	0 (0.0%)	9 (11.0%)
Flatulence	4 (5.1%)	8 (9.8%)
Alanine Aminotransferase Increased	1 (1.3%)	5 (6.1%)
Bladder Pain	3 (3.8%)	5 (6.1%)
Constipation	4 (5.1%)	5 (6.1%)

Source: Table 12.5.1

Synopsis Table 13: Adverse Events Leading to Permanent Discontinuation of Study Drug, Occurring in >1 Subject in Active Treatment Group (Safety Set)

Adverse Event	Placebo (n=79)	YM672 800 mg TID (n=82)
Any Adverse Event	13 (16.5%)	21 (25.6%)
Headache	3 (3.8%)	4 (4.9%)
Alanine Aminotransferase Increased	0 (0.0%)	4 (4.9%)
Aspartate Aminotransferase Increased	0 (0.0%)	3 (3.7%)
Diarrhoea	2 (2.5%)	2 (2.4%)
Urticaria	0 (0.0%)	2 (2.4%)

Source: Table 12.5.4