Name of Sponsor/Company: Astellas Pharma Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP8062		

SYNOPSIS

Title of Study: A Phase 2a, Randomized, Double-blind Placebo-controlled, Parallel-group Study to Assess the Analgesic Efficacy and Safety of ASP8062 in Subjects with Fibromyalgia

Investigators/Coordinating Investigator: [redacted], MD, [redacted], US

Study Centers: 24 sites in the US.

Publication Based on the Study: Not applicable

Study Period:

Study Initiation Date (Date of First Enrollment): 08 May 2017

Study Completion Date (Date of Last Evaluation): 06 Mar 2018

Phase of Development: Phase 2a

Objectives:

Primary:

- To assess analgesic efficacy of ASP8062 relative to placebo
- To assess the safety and tolerability of ASP8062 relative to placebo

Secondary:

- To assess treatment differences in physical function of ASP8062 relative to placebo
- To assess the improvements in overall patient status (e.g., fibromyalgia symptoms, global functioning) of ASP8062 relative to placebo

Methodology:

Patients were randomly assigned to receive ASP8062 30 mg once daily or placebo in a 1:1 ratio. The study consisted of a screening period (up to 42 days) including a 7-day baseline electronic diary (e-diary) run-in, a double-blind treatment period of 8 weeks, and a follow-up period of 4 weeks.

At the screening visit (visit 1) the diagnosis of fibromyalgia, severity and duration of disease were determined. Patients who met the eligibility criteria were instructed via phone call, if medically appropriate, to wash-out of any prohibited medications. At visit 2, patients were instructed how to complete the 7-day baseline e-diary run-in and recorded daily average pain scores on a 0 to 10 numerical rating scale (NRS) and sleep quality information with the Fibromyalgia Sleep Diary (FMSD).

Patients returned to the site for the randomization visit (visit 3) and those fulfilling entry criteria were randomized to double-blind treatment. During treatment and follow-up periods, patients recorded a daily

average pain NRS score and the FMSD in the e-diary. Patients returned to the site for efficacy and safety assessment and collection of blood samples for pharmacokinetic analyses at 2 and 4 weeks after randomization and at the end of treatment (EOT) visit (week 8).

Acetaminophen (paracetamol) could be used as rescue therapy for intolerable pain due to fibromyalgia during all study periods. Nonsteroidal anti-inflammatory drugs were allowed (with the exception of celecoxib), as needed, for nonfibromyalgia pain, such as headache.

An additional visit during the follow-up period was scheduled at 2 weeks after the EOT visit and a phone call at the end of study.

Number of Patients (Planned, Enrolled and Analyzed):

The planned sample size was 178 patients who were to be randomized in a 1:1 ratio to ASP8062 30 mg once daily (89 patients) or placebo once daily (89 patients).

Out of 409 patients who provided informed consent and 183 patients were randomized; 95 patients were assigned to receive ASP8062 30 mg and 88 patients were assigned to receive placebo.

All randomized patients received at least 1 dose of study drug and are part of the safety analysis set (SAF) and the full analysis set (FAS). The per protocol analysis set (PPS) included 180 patients while the pharmacokinetic data set (PKAS) included 95 patients [Figure 1; Table 1].

Diagnosis and Main Criteria for Inclusion:

Patients aged 18-80 years who met both the 1990 and 2010 American College of Rheumatology criteria for fibromyalgia (widespread pain for ≥ 3 months, pain in ≥ 11 of 18 tender point sites, Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 or WPI 3 to 6 and SS scale score ≥ 9, Symptoms present at a similar level for at least 3 months without other disorder which would explain it) and who had a pain score of ≥ 4 on the Fibromyalgia Impact Questionnaire Revised (FIQR) were included. A mean daily average pain score had to be ≥ 4 and ≤ 9 on an 11-point 0 to 10 NRS during the baseline diary run-in period.

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

ASP8062 was administered orally as a 30-mg daily dose as single tablets of 5 and 25 mg strength. Batch numbers for the ASP8062 blister strips were: 55966.2 (5 mg); 55966.6, 55966.7, 55966.8, 55966.9 (25 mg).

Doses were taken orally in the morning with or without food. In case a patient forgot a dose, the dose was to be taken as soon as they remembered but prior to bedtime that day. The next dose was to be taken as planned (no double dose).

Duration of Treatment:

Patients received assigned treatment for a period of 8 weeks.

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

Placebo tablets were administered orally as identical tablets to the ASP8062 tablets. Batch numbers for the placebo blister strips were: 55966.1 (5 mg placebo); 55966.3, 55966.4, 55966.5 (25 mg placebo).

Patients in the placebo group received 2 matching placebo tablets orally in the same way as the test product.

Criteria for Evaluation:

Primary Efficacy Endpoint

- Change from baseline to week 8 in the mean daily average pain score assessed by NRS (0 to 10 scale) in the patient's daily e-diary

Key Secondary Efficacy Endpoints

- Patient's response defined as achieving ≥ 30 % reduction from baseline to week 8 and EOT in mean daily average pain score assessed by NRS (0 to 10 scale) in the patient's daily e-diary
- Patient's response defined as achieving ≥ 50 % reduction from baseline to week 8 and EOT in mean daily average pain score assessed by NRS (0 to 10 scale) in the patient's daily e-diary
- Change from baseline to weeks 2, 4, 8, and EOT in the FIQR Function, Symptoms, and Overall Impact subscales
- Overall patient improvement assessed by the Patient Global Impression of Change (PGIC) at weeks 2, 4, 8, and EOT

Safety Variables

Safety was assessed based on treatment-emergent adverse events (TEAEs), clinical laboratory evaluation, vital signs, electrocardiograms, physical examination and Columbia-Suicide Severity Rating Scale.

Statistical Methods:

All data processing, descriptive summaries and analyses were performed using UNIX SAS version 9.3 or higher. Unless otherwise stated, all hypothesis testing was 1-sided at the 5% significance level and 2-sided 90% confidence interval (CI) is presented when applicable.

Analysis Sets

The analysis sets included the FAS comprising all randomized patients who took at least 1 dose of study drug presented by the randomized treatment group; the SAF comprising all randomized patients who received at least 1 dose of study drug presented by the treatment actually received; the PPS comprising a subset of patients from the FAS who met criteria based on adherence to the protocol which could affect the primary efficacy endpoint or select secondary efficacy endpoints and the PKAS comprising of the subset of SAF for which at least 1 postdose ASP8062 plasma concentration is available. The FAS was regarded as the main analysis set for efficacy variables; the PPS was used for used for sensitivity analyses. All safety analyses were performed on the SAF. The PKAS was used for pharmacokinetic analyses.

Efficacy Analysis for Primary Endpoint

The hypothesis for comparisons of the primary efficacy endpoint was as follows:

H0: The mean change from baseline to week 8 in mean daily average pain score assessed by NRS (0 to 10 scale) for ASP8062 30 mg once daily group is same as (or higher, i.e., worse than) the placebo group

H1: The change from baseline to week 8 in mean daily average pain score assessed by NRS (0 to 10 scale) for ASP8062 30 mg once daily group is less (i.e., better) than the placebo group

The change from baseline to week 8 in the mean daily average pain NRS used a mixed model repeated measures (MMRM) analysis, where the model included the effects for treatment group, center (pooled when necessary),

time (study week 1 to 8) and treatment-by-time interaction, as well as the covariates of baseline mean daily average pain NRS and baseline pain-by-time interaction. The unconstrained between-timepoint covariance structure was used. This analysis utilized observed data, and there was no imputation for missing data. Least squares (LS) estimates for the primary endpoint are shown for each treatment group, and for the treatment comparisons of ASP8062 vs placebo with 2-sided 90% CIs. A 1-sided 5% significance level was used for the comparison involving ASP8062 vs placebo.

As a sensitivity analysis, the same analysis of the primary efficacy endpoint as described above was repeated using the PPS. Subgroup analyses for the primary endpoint were carried out as well.

Efficacy Analysis for Secondary Endpoints

The primary analysis for the secondary endpoints of mean daily average pain score (≥ 30% and 50% reduction from baseline to week 8 and to EOT) were carried out with the Fisher's Exact Test. For the week 8 analysis, patients with missing data were classified as nonresponders (baseline observation carried forward; BOCF) and an additional analysis used modified BOCF. For the EOT analysis, last observation carried forward (LOCF) was used.

The primary analysis for the change from baseline to weeks 2, 4 and 8 for the FIQR subscales of Function, Symptoms and Overall Impact used the same MMRM analysis as used for the primary endpoint. The primary analysis for the change from baseline to EOT for the FIQR subscales used an ANCOVA model, with covariates of baseline FIQR subscale score and center (pooled when necessary). An additional ANCOVA analysis was conducted at week 8 with modified BOCF for patients with missing data.

The primary analysis for the PGIC used the proportional odds model for ordinal data, with model term for treatment group. The analysis was used to assess PGIC at weeks 2, 4, 8 and EOT. For patients with missing data, the analysis at weeks 2, 4 and 8 was conducted using imputation of "No Change" for patients who discontinued due to lack of efficacy or AEs, and imputation by LOCF for patients with missing data for other reasons. An additional analysis at weeks 2, 4 and EOT used LOCF.

Safety Analysis

Adverse events were coded using MedDRA v20.0. A TEAE is defined as any AE which started, or worsened, after the first dose of study drug through 30 days after the last dose of study drug. The number and percentage of patients with TEAEs, TEAEs leading to discontinuation, serious TEAEs and TEAEs related to study drug as assessed by the investigator are summarized by SOC, PT and treatment group. TEAEs were summarized by severity and by relationship to study drug. Clinical laboratory tests, vital signs, electrocardiogram results and the C-SSRS were summarized.

Summary of Results/Conclusions:

Demographics:

Disposition of patients and analysis sets can be found in [Figure 1] and [Table 1].

Patients in the SAF were primarily female (96.2%), not Hispanic or Latino (80.9%), white (76.0%), and in the EudraCT age category of 18 to 64 years (84.2%) [Table 2]. The mean weight, height and BMI were similar between the 2 treatment groups.

Concomitant Medications:

Approximately 13% of patients were administered concomitant medications to treat any pain during the double-blind treatment period (14.7% of patients in the ASP8062 group and 11.4% of patients in the placebo group) and during the follow-up period. The 2 most common concomitant medications for any pain in the ASP8062 and placebo groups were naproxen (5.3% and 3.4%, respectively) and ibuprofen (4.2% and 4.5%, respectively).

Efficacy/Pharmacokinetic Results:

Efficacy Results:

Patients in both groups did have an improvement during the double-blind treatment period compared to baseline, but there were no statistically significant differences in the response between treatment groups for any efficacy endpoint, including the FMSD.

- For the primary endpoint of the change from baseline in the mean daily average pain score at week 8 the difference in LS mean was 0.06 and not statistically significant (P = 0.590) [Table 3].
- The results of the secondary endpoints are as follows.
    - The percentage of patients who had a ≥ 30% and ≥ 50% reduction in the mean daily average pain score at week 8 was 25.3% and 14.7%, respectively, for the ASP8062 group and 31.8%, and 12.5%, respectively, for the placebo group; the differences between groups were not statistically significant (P = 0.874 and P = 0.412, respectively).
    - There were no statistically significant differences in the change from baseline for the FIQR Function, Symptoms or Overall Impact subscale scores between the 2 treatment groups at any time during the study.
    - The difference in the improvement of fibromyalgia symptoms from baseline as assessed by PGIC between the 2 treatment groups was not statistically significant at any of the timepoints (weeks 2, 4, 8 and EOT).

Pharmacokinetic Results

In general, the majority of patients had ASP8062 concentrations on weeks 2, 4 and 8/EOT 1 to 4 hours postdose that were higher than the other sampling timepoints. Mean concentrations at weeks 2, 4 and 8/EOT 1 to 4 hours postdose were 162.8 ng/mL compared to 75.5 ng/mL, 85.5 ng/mL and 131.7 ng/mL on day 1 1 to 4 hours postdose, weeks 2, 4, 8/EOT predose and weeks 2, 4, 8/EOT > 4 hours postdose, respectively.

Safety Results:

- There were no deaths or serious TEAEs during the conduct of this study.
- Overall, more patients administered ASP8062 (67 [70.5%]) reported at least 1 TEAE in comparison with patients administered placebo (43 [48.9%]); drug-related TEAEs were similarly distributed (45 [47.4%] vs 19 [21.6%], respectively). TEAEs leading to discontinuation of study drug were observed for 10 (10.5%) patients in the ASP8062 group and for 3 (3.4%) patients in the placebo group.
- Dizziness was the most commonly reported TEAE in patients administered ASP8062 (28 [29.5%] patients); it was experienced by patients treated with ASP8062 almost 13 times the incidence of patients administered placebo (2 [2.3%] patients). In the ASP8062 group, TEAEs of dizziness resulted in discontinuation of treatment in 8 patients; the severity was mild in 3 patients, moderate in 4 patients and

severe in 1 patient. Of the other 20 patients with TEAEs of dizziness, 2 patients experienced moderate events of dizziness; the other 18 were mild. The TEAE of dizziness was resolved in 3 days or less in 11 of 28 patients administered ASP8062 and occurred shortly after taking medication (onset day was day 1 in 17 patients). Most of these TEAEs of dizziness were considered possibly related to study drug (30 events out of 33). The most commonly other TEAEs experienced by these patients with dizziness were headache and nausea (6 and 4 patients administered ASP8062, respectively). In the placebo group, 2 TEAEs of dizziness were reported with mild and moderate severity and were considered possibly and probably related to study drug, respectively.

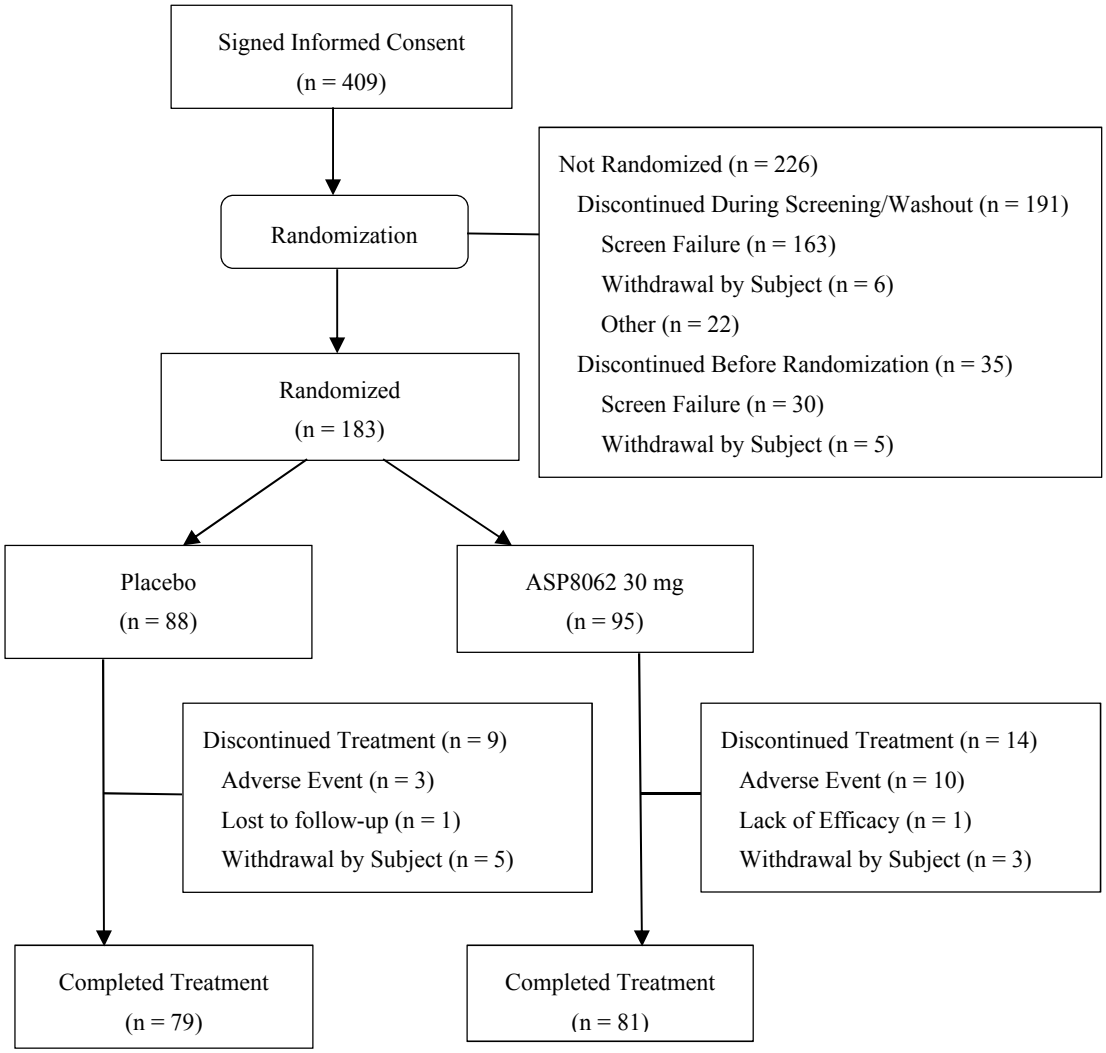
- The other most commonly reported TEAEs in both ASP8062 and placebo groups were headache (14 [14.7%] and 10 [11.4%] patients, respectively) and nausea (6 [6.3%] and 4 [4.5%], respectively).
- There were no TEAEs within the drug abuse and dependence standardized MedDRA query (SMQ) and no TEAE within the drug withdrawal SMQ.
- There were no patients who had laboratory values that met the potentially clinically significant criteria for hepatotoxicity or had concomitant elevations in alanine aminotransferase or aspartate aminotransferase with total bilirubin or that required further liver function investigation.
- No clinically relevant changes in vital signs were observed. Potentially clinically significant orthostatic vital sign changes were reported by a few patients in both treatment groups but without a clear difference between the 2 treatment arms.
- No clinically significant ECG abnormalities were observed.

CONCLUSIONS:

The efficacy of ASP8062 in reducing the mean daily average pain score was not statistically shown. The most commonly reported TEAE with morning dosing of ASP8062 was dizziness. Other than dizziness, ASP8062 was safe and well tolerated.

Date of Report: 10 Aug 2018

Figure 1 **Disposition of Subjects**



Source: Tables 12.1.1.1, 12.1.1.3.1, 12.1.1.3.2 and 12.1.1.4.1

Table 1 Patient Disposition and Analysis Sets (All Randomized Patients)

Analysis Set [n (%)]	Placebo (n = 88)	ASP8062 30 mg (n = 95)	Total (n = 183)
Randomized	88 (100.0%)	95 (100.0%)	183 (100.0%)
Patients who took study drug	88 (100.0%)	95 (100.0%)	183 (100.0%)
Patients who did not take study drug	0	0	0
Safety analysis set†	88 (100.0%)	95 (100.0%)	183 (100.0%)
Full analysis set‡	88 (100.0%)	95 (100.0%)	183 (100.0%)
Per protocol set§	87 (98.9%)	93 (97.9%)	180 (98.4%)
Pharmacokinetic analysis set¶	0	95 (100.0%)	95 (51.9%)
Completed treatment	79 (89.8%)	81 (85.3%)	160 (87.4%)
Study drug discontinuation	9 (10.2%)	14 (14.7%)	23 (12.6%)
Adverse event	3 (3.4%)	10 (10.5%)	13 (7.1%)
Lack of efficacy	0	1 (1.1%)	1 (0.5%)
Lost to follow-up	1 (1.1%)	0	1 (0.5%)
Withdrawal by patient	5 (5.7%)	3 (3.2%)	8 (4.4%)

† All randomized patients who took at least 1 dose of study drug. When the safety analysis set is utilized in an analysis, patients are presented by the treatment actually received.

‡ All randomized patients who took at least 1 dose of study drug. When the full analysis set is utilized in an analysis, patients are presented by the randomized treatment group.

§ A subset of patients from the full analysis set who met criteria based on adherence to the protocol, which may affect the primary efficacy endpoint or select secondary efficacy endpoints.

¶ The subset of safety analysis set for which at least 1 postdose ASP8062 plasma concentration is available.

Source: Tables 12.1.1.2 and 12.1.1.4.1

Table 2 Summary of Demographics and Baseline Characteristics (Safety Analysis Set)

Parameter Category/ Statistics	Placebo (n = 88)	ASP8062 30 mg (n = 95)	Total (n = 183)
Sex, n (%)			
Male	5 (5.7%)	2 (2.1%)	7 (3.8%)
Female	83 (94.3%)	93 (97.9%)	176 (96.2%)
Ethnicity, n (%)			
Not Hispanic or Latino	71 (80.7%)	77 (81.1%)	148 (80.9%)
Hispanic or Latino	17 (19.3%)	18 (18.9%)	35 (19.1%)
Race, n (%)			
White	69 (78.4%)	70 (73.7%)	139 (76.0%)
Black or African American	15 (17.0%)	20 (21.1%)	35 (19.1%)
Asian	3 (3.4%)	1 (1.1%)	4 (2.2%)
American Indian or Alaska Native	0	3 (3.2%)	3 (1.6%)
Other	1 (1.1%)	1 (1.1%)	2 (1.1%)
Age, years			
Mean (SD)	51.3 (12.9)	52.5 (11.9)	51.9 (12.3)
Median	50.5	54.0	53.0
Min - Max	19 - 80	20 - 78	19 - 80
Age group, n (%)			
< 45 years	30 (34.1%)	21 (22.1%)	51 (27.9%)
≥ 45 to < 65 years	44 (50.0%)	59 (62.1%)	103 (56.3%)
≥ 65 years	14 (15.9%)	15 (15.8%)	29 (15.8%)
EudraCT age category, n (%)			
≥ 18 to ≤ 64 years	74 (84.1%)	80 (84.2%)	154 (84.2%)
≥ 65 to ≤ 84 years	14 (15.9%)	15 (15.8%)	29 (15.8%)
Weight, kg			
Mean (SD)	85.17 (19.56)	86.19 (20.09)	85.70 (19.79)
Median	82.45	86.00	83.91
Min – Max	44.3 - 140.0	50.5 - 145.1	44.3 - 145.1
Height, cm			
Mean (SD)	163.9 (8.2)	162.9 (6.9)	163.4 (7.6)
Median	164.8	162.6	162.6
Min – Max	149 - 190	147 - 185	147 - 190
BMI, kg/m^2			
Mean (SD)	31.53 (6.41)	32.33 (6.78)	31.94 (6.60)
Median	31.23	31.88	31.28
Min – Max	18.0 - 45.0	20.6 - 48.3	18.0 - 48.3
BMI group 1, n (%)			
< 25 kg/m^2	15 (17.0%)	15 (15.8%)	30 (16.4%)
≥ 25 to < 30 kg/m^2	22 (25.0%)	27 (28.4%)	49 (26.8%)
≥ 30 kg/m^2	51 (58.0%)	53 (55.8%)	104 (56.8%)
BMI group 2, n (%)			
< 30 kg/m^2	37 (42.0%)	42 (44.2%)	79 (43.2%)
≥ 30 kg/m^2	51 (58.0%)	53 (55.8%)	104 (56.8%)

All patients who received at least 1 dose of study drug (safety analysis set).

BMI: body mass index (weight [kg]/height [m^2]); Max: maximum; Min: minimum

Source: Table 12.1.2.1.2

Table 3 MMRM Analysis of Change from Baseline in Mean Daily Average Pain Score at Week 8 (Full Analysis Set)

Analysis Visit Statistic	Placebo (n = 88)	ASP8062 30 mg (n = 95)
Baseline		
n	88	95
Mean (SD)	6.49 (1.03)	6.54 (0.97)
Median	6.43	6.57
Min – Max	4.3 to 9.0	4.4 to 8.5
Week 8		
n	78	80
Mean (SD)	4.97 (1.66)	5.15 (1.83)
Median	5.00	5.38
Min – Max	0.1 to 8.6	1.0 to 8.3
Change from Baseline†		
n	78	80
Mean (SD)	-1.41 (1.62)	-1.45 (1.97)
Median	-1.29	-0.86
Min – Max	-6.7 to 2.0	-7.3 to 1.7
LS Mean Change from Baseline†		
LS Mean (SE)	-1.42 (0.19)	-1.36 (0.19)
90% 2-sided CI	(-1.74, -1.11)	(-1.67, -1.06)
Difference in LS Means‡: ASP8062 30 mg vs Placebo		
LS Mean (SE)	--	0.06 (0.26)
90% 2-sided CI	--	(-0.38, 0.50)
1-sided P value§	--	0.590

All patients who received at least 1 dose of study drug (full analysis set).

MMRM analysis model is performed with change from baseline (weeks 1, 2, 3, 4, 5, 6, 7 and 8) as response; treatment, center (pooled where necessary), time (study weeks 1 to 8) and treatment*time as fixed effects, baseline and baseline*time as covariates.

n is the number of patients with nonmissing scores at the analysis visit and at baseline.

--: not applicable; CI: confidence interval; LS: least squares; Max: maximum; Min: minimum; MMRM: mixed model repeated measures

† A negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome).

‡ Differences are calculated by subtracting the LS mean of placebo group from the LS mean of ASP8062 30 mg group.

§ P value is for comparison of ASP8062 30 mg with placebo from the above described MMRM model.

Source: Table 12.3.1.1.1

Table 4 Incidence of Common Treatment-emergent Adverse Events Occurring in ≥ 3% of Patients in Any Treatment Group (Safety Analysis Set)

MedDRA v20.0 System Organ Class Preferred Term [n (%)]	Placebo (n = 88)	ASP8062 30 mg (n = 95)
Overall	**43 (48.9%)**	**67 (70.5%)**
Eye Disorders	**2 (2.3%)**	**5 (5.3%)**
Vision blurred	1 (1.1%)	3 (3.2%)
Gastrointestinal Disorders	**15 (17.0%)**	**23 (24.2%)**
Diarrhoea	3 (3.4%)	2 (2.1%)
Nausea	4 (4.5%)	6 (6.3%)
Toothache	3 (3.4%)	1 (1.1%)
General Disorders and Administration Site Conditions	**4 (4.5%)**	**8 (8.4%)**
Fatigue	3 (3.4%)	3 (3.2%)
Infections and Infestations	**20 (22.7%)**	**16 (16.8%)**
Gastroenteritis	3 (3.4%)	1 (1.1%)
Sinusitis	3 (3.4%)	1 (1.1%)
Upper respiratory tract infection	2 (2.3%)	3 (3.2%)
Urinary tract infection	5 (5.7%)	3 (3.2%)
Viral upper respiratory tract infection	3 (3.4%)	2 (2.1%)
Injury, Poisoning and Procedural Complications	**6 (6.8%)**	**1 (1.1%)**
Contusion	3 (3.4%)	0
Musculoskeletal and Connective Tissue Disorders	**8 (9.1%)**	**12 (12.6%)**
Back pain	0	4 (4.2%)
Fibromyalgia	2 (2.3%)	3 (3.2%)
Muscle spasms	2 (2.3%)	4 (4.2%)
Nervous System Disorders	**15 (17.0%)**	**41 (43.2%)**
Dizziness	2 (2.3%)	28 (29.5%)
Headache	10 (11.4%)	14 (14.7%)
Somnolence	1 (1.1%)	4 (4.2%)
Psychiatric Disorders	**6 (6.8%)**	**10 (10.5%)**
Insomnia	1 (1.1%)	3 (3.2%)
Respiratory, Thoracic and Mediastinal Disorders	**4 (4.5%)**	**9 (9.5%)**
Dyspnoea	0	3 (3.2%)
Oropharyngeal pain	1 (1.1%)	3 (3.2%)

All patients who received at least 1 dose of study drug (safety analysis set).

A TEAE was defined as any AE that started or worsened after the first dose of study drug through 30 days after the last dose of study drug.

AE: adverse event; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.2.1