Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (APGD)		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP0819		

SYNOPSIS

Title of Study: A Phase 2a, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess the Analgesic Efficacy and Safety of ASP0819 in Patients with Fibromyalgia

Investigators/Coordinating Investigator: ███████████████, MD

Study Centers: The study was conducted at 24 sites in the US.

Publication Based on the Study: Not applicable

Study Period: 1Q2017 – 1Q2018

Study Initiation Date (Date of First Enrollment): 20 Mar 2017

Study Completion Date (Date of Last Evaluation): 27 Feb 2018

Phase of Development: 2a

Objectives:

The objectives of this study, conducted in subjects with fibromyalgia, were to:

Primary Objectives:

- Assess analgesic efficacy of ASP0819 relative to placebo.
- Assess the safety and tolerability of ASP0819 relative to placebo.

Secondary Objectives:

- Assess treatment differences in physical function of ASP0819 relative to placebo.
- Assess the improvements in overall subject status (e.g., fibromyalgia symptoms, global functioning) of ASP0819 relative to placebo.

Exploratory Objectives:

- Assess the time course of efficacy of ASP0819.
- Assess treatment differences in sleep disturbance.
- Assess treatment differences in depression.
- Assess treatment differences in quality of life.
- Assess the use of rescue medication.
- Assess treatment differences in responder rate based on composite endpoint definition.
- Assess treatment differences in gastrointestinal symptoms.

- Assess relationship between gastrointestinal symptoms and analgesic effect.
- Assess relationship between neuropathic symptoms and analgesic effect.

Methodology:

This was a phase 2a, randomized, double-blind, placebo-controlled parallel group study to assess analgesic efficacy and safety of ASP0819 in subjects with fibromyalgia.

The study consisted of the following study periods:

- Screening period (day -42 to day -1)

Up to 42 days, which included the completion of screening procedures (visit 1), wash-out of prohibited medications (if applicable), and a 7-day baseline diary run-in. The wash-out of prohibited medications was completed prior to the initiation of the baseline diary run-in. The baseline diary run-in could have been extended by up to 2 days if necessary in the investigator's opinion. In general, the screening period did not exceed 42 days. The investigator was to contact the medical monitor if there were circumstances that would cause the subject to exceed 42 days.

- Double-blind randomized treatment period; day 1 to day 57 (End of Treatment [EOT])

Eight weeks of treatment with study drug and site visits at days 1, 15, 29 and 57.

- Follow-up period; day 58 to day 85 (End of Study [EOS])

Including a follow-up site visit on day 71 and an EOS phone call on day 85.

Screening Period:

After signing the informed consent form, screening procedures for the subject started (visit 1). Subjects had to meet both the 1990 and 2010 American College of Rheumatology (ACR) criteria for fibromyalgia, confirmed by the investigator or other qualified individual at the site.

Screening procedures included: weight, medication history and concomitant medication, physical examination, drug and alcohol screen, clinical laboratory tests, vital signs, electrocardiogram (ECG), pregnancy test (if applicable), Hospital Anxiety and Depression Scale (HADS), Columbia-Suicide Severity Rating Scale (C-SSRS), Patient Global Impression of Severity (PGIS), European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L), Fibromyalgia Impact Questionnaire Revised (FIQR) and Modified Irritable Bowel Syndrome - diarrhea predominant (mIBS-D) symptoms diary.

Subjects who met the eligibility criteria were instructed to washout any prohibited medications, if medically appropriate. At visit 2, all subjects who continued to meet eligibility criteria were provided with an electronic diary (e-diary). Subjects entered a 1 week baseline diary run-in; during this period, they recorded their daily average pain score (0 - 10 numerical rating scale [NRS]) and sleep quality information with the Fibromyalgia Sleep Diary (FMSD) in the e-diary. They received instructions regarding its use and began entering daily scores. Upon awakening, subjects had to rate their sleep quality during the previous night using the e-diary. Each evening before bed, subjects had to rate their average pain during the previous 24 hours using the e-diary. Subjects needed to have a mean daily average pain score ≥ 4 and ≤ 9 (0 to 10 NRS), and meet prespecified criteria for daily average pain scores.

A subject who did not meet the required mean daily average pain score or who was not compliant with e-diary entries by completing at least 5 of 7 days in the baseline run-in was considered a screen failure and was not allowed to repeat the pain assessments nor rescreen for the study.

After confirmation of eligibility, subjects who met the mean daily average pain score eligibility requirements were randomized at visit 3 (day 1).

Double-Blind Randomized Treatment Period:

Subjects who entered the treatment period were randomized in a 1:1 ratio to receive either ASP0819 15 mg (3 capsules of 5 mg each) or matching placebo once per day for a period of 8 weeks.

Throughout the treatment period, beginning on day 1 (randomization) through visit 6/week 8, subjects recorded all daily average pain scores and any rescue medication use in the e-diary. FMSD sleep quality scores were also recorded through visit 6/week 8. Subjects returned to the study center for safety and efficacy assessments at weeks 2, 4 and 8.

Follow-up Period:

Subjects were encouraged to abstain from any concomitant medications for the treatment of fibromyalgia pain prior to visit 7/week 10. Rescue medication was allowed during the follow-up period. Subjects continued to enter their daily average pain score and rescue medication use into their e-diary and return diaries at visit 7/week 10. All subjects returned to the site for a follow up visit at day 71 and received a follow-up safety phone approximately 4 weeks post study drug discontinuation (day 85/EOS).

Rescue Medication:

If a subject experienced intolerable pain due to fibromyalgia during the screening, treatment or follow-up periods, the subject was instructed to use acetaminophen as a rescue medication for fibromyalgia. Nonsteroidal antiinflammatory drugs were allowed as needed for nonfibromyalgia pain.

Number of Subjects (Planned, Enrolled and Analyzed):

It was planned that 178 subjects would be randomized into the study using a 1:1 randomization ratio with 89 subjects in both the ASP0819 and placebo groups.

A total of 406 subjects provided written informed consent and 186 subjects were randomized to receive ASP0819 (91 subjects) or placebo (95 subjects). Two subjects (one in each treatment group) did not take study drug. Therefore, 184 randomized subjects were included in the safety analysis set (SAF) and the full analysis set (FAS). The per protocol analysis set (PPS) included 173 subjects while the pharmacokinetic data set included 90 subjects.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects aged 18 to 80 years with a body mass index (BMI) ≤ 45 kg/m^2. Subjects had to have a diagnosis of fibromyalgia that met both the ACR 1990 fibromyalgia diagnostic criteria at screening:

- Widespread pain for at least 3 months, defined as the presence of all of the following:
    - Pain on right and left sides of the body,
    - Pain above and below the waist, and
    - Pain in the axial skeleton (cervical spine or anterior chest or thoracic spine or low back) must have been present.

- Pain in at least 11 of 18 tender point sites on digital palpation.
  - Digital palpation was performed with an approximate force of 4 kg.

and the ACR 2010 fibromyalgia diagnostic criteria at screening:

- Widespread pain index (WPI) $\geq$ 7 and symptom severity (SS) scale score $\geq$ 5 or WPI 3 to 6 and SS scale score $\geq$ 9.

- Symptoms had to have been present at a similar level for at least 3 months.

- The subject did not have a disorder that would otherwise explain the pain.

Subjects also had to have a pain score $\geq$ 4 on the FIQR pain item at screening and be compliant with daily pain recordings during the baseline diary run-in period, as defined by the completion of a minimum of 5 of 7 daily average pain ratings and agreed to complete daily diaries throughout the duration of the study. In addition, they had to have a mean daily average pain score $\geq$ 4 and $\leq$ 9 on an 11-point 0 to 10 NRS as recorded in the subject e-diary during the baseline diary run-in period, and met prespecified criteria for daily average pain scores. Subjects had to agree to use only acetaminophen as rescue medication for fibromyalgia pain throughout the course of the study (up to 1000 mg per dose and not to exceed 3000 mg/day).

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

ASP0819 was supplied as 5 mg capsules. Batch numbers used were: ███████, ██████ and ██████ for secondary packed / final product; the general batch number was ████████.

ASP0819 was administered orally in the morning, with or without food.

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

Subjects were treated once daily for a period of up to 8 weeks

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

Placebo was provided as matching capsules to ASP0819. Batch numbers used were: ███████, ██████ and ██████ for secondary packed / final product; the general batch number was ████████.

Placebo was administered orally in the morning, with or without food.

Criteria for Evaluation:

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

- Subject's response defined as achieving $\geq$ 30 % reduction from baseline to week 8 and EOT in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.

- Subject's response defined as achieving $\geq$ 50 % reduction from baseline to week 8 and EOT in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.

- Change from baseline to weeks 2, 4, 8 and EOT in the FIQR physical function, symptoms and overall impact subscales.

- Overall subject improvement assessed by Patient Global Impression of Change (PGIC) at weeks 2, 4, 8 and EOT.

Exploratory endpoints included assessment of the time course of efficacy of ASP0819; treatment differences in sleep disturbance, depression, quality of life, gastrointestinal symptoms and responder rate based on composite endpoint definition; the use of rescue medication; and the relationship between neuropathic symptoms, gastrointestinal symptoms and analgesic effect.

Safety and Tolerability Endpoints

- Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs).
- Safety laboratory tests.
- Vital signs.
- Physical examination.
- 12-lead ECG parameters.
- C-SSRS (evaluation of suicidal ideation and behavior).

Statistical Methods:

Efficacy

The efficacy analysis was conducted using the FAS for all efficacy endpoints and the PPS for the primary efficacy endpoint and select secondary endpoints. The interpretation of results from statistical tests was based on the FAS. The PPS was used to assess the robustness of the results from the statistical tests based on the FAS. Unless otherwise stated, all hypothesis testing was 1-sided at the 5% significance level and 2-sided 90% confidence interval (CI) was presented when applicable. Centers were pooled for analysis when necessary.

Primary Efficacy Endpoint

The primary analysis for the primary endpoint of 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 fixed effects for treatment group, center (pooled where necessary), time (study week 1 to 8) and treatment−by−time interaction, with baseline mean daily average pain NRS and baseline mean daily average pain NRS−by−time interaction as covariates. The unconstrained between-timepoint covariance structure was used. If this was not feasible, additional covariance structures were to be considered. This analysis was to utilize observed data, and there was to be no imputation for missing data. The treatment group contrast for change from baseline to week 8 was the primary statistical inference obtained from the MMRM analysis. Least squares (LS) mean estimates for the primary endpoint were shown for each treatment group, and for the treatment comparisons of ASP0819 versus (vs) placebo with 2-sided 90% CIs. A 1-sided 5% significance level was used for the comparison involving ASP0819 vs placebo.

The hypotheses for comparisons were given as follows:

H_0: The mean change from baseline to week 8 in the mean daily average pain NRS for ASP0819 group was the same as or higher (i.e., smaller reduction) than the placebo group.

H_1: The mean change from baseline to week 8 in the mean daily average pain NRS for ASP0819 group was less (i.e., larger reduction) than the placebo group.

A sensitivity analysis for the primary endpoint used the same MMRM model as described previously. However, for the secondary analysis, multiple imputation was used for imputation of any missing data, using the 'Jump to Reference' algorithm (where placebo is the reference group) for subjects who discontinued due to lack of efficacy or AEs and standard regression-based multiple imputation for subjects with missing data for other reasons. An additional sensitivity analysis for the primary endpoint used modified baseline observation carried forward (mBOCF) for missing data with analysis using analysis of covariance (ANCOVA), with covariates of baseline mean daily average pain NRS score and center (pooled where necessary). mBOCF was defined as imputation by baseline observation carried forward (BOCF) for subjects who discontinued due to lack of efficacy or AEs, and imputation by last observation carried forward (LOCF) for subjects with missing data at week 8 for other reasons.

Secondary Efficacy Endpoints

The primary analysis for the secondary endpoints of mean daily average pain score ($\geq$ 30% and 50% reduction from baseline to week 8 and to EOT) was carried out with the Fisher's Exact Test. For the week 8 analysis, subjects with missing data were classified as nonresponders (BOCF group) and an additional analysis used mBOCF. For the EOT analysis, LOCF was used.

The primary analysis for the change from baseline to weeks 2, 4 and 8 for the FIQR subscales of physical function, symptoms and overall impact used the same MMRM analysis as described previously. 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. An additional ANCOVA analysis was conducted at week 8 with mBOCF for subjects 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 subjects with missing data, the analysis at weeks 2, 4 and 8 was conducted using mBOCF. An additional analysis at weeks 2 and 4 used LOCF.

Safety

Safety analysis was conducted using the SAF, unless otherwise specified. No hypothesis testing was performed comparing treatment groups for any safety parameters.

Adverse Events

AEs were coded using the Medical Dictionary for Regulatory Activities   (MedDRA) version 20.0. A TEAE was 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 subjects with TEAEs, TEAEs leading to discontinuation, serious TEAEs and TEAEs related to study drug, as assessed by the investigator, were summarized by system organ class, preferred term and treatment group. In addition, TEAEs were summarized by relationship to study drug as determined by the investigator and by severity for each treatment group.

Other Safety Variables

For quantitative laboratory tests, descriptive statistics were used to summarize baseline value, postbaseline value at each specified timepoint, and change from baseline to each specified postbaseline timepoint by

treatment group. Shifts relative to normal ranges from baseline to each specified postbaseline timepoint in laboratory tests were tabulated. The number and percentage of subjects with potentially clinically significant values in liver enzymes: alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and total bilirubin level were presented by treatment group.

Descriptive statistics were used to summarize vital sign parameters at baseline value, postbaseline value at each specified timepoint, and change from baseline to each specified postbaseline timepoint by treatment group. The number and percentage of subjects with potentially clinically significant values in systolic blood pressure, diastolic blood pressure and pulse rate were presented by treatment group.

For ECG parameters, a shift table of the finding at baseline (normal, not clinically significant normal and clinically significant normal) to the worst finding during treatment period and follow-up period was presented by treatment group.

Descriptive statistics and listing of events were provided for the C-SSRS for each treatment group by timepoint and for the entire study.

Summary of Results/Conclusions:

Populations

Subject classification and analysis sets can be found in [Table 1].

Demographic characteristics were relatively similar across treatment groups [Table 2]. The majority of subjects in the SAF were female (177 [96.2%] subjects) and White (151 [82.1%] subjects). The age of the subjects ranged from 20 to 80 years, with an overall mean age of 49.3 years. Overall mean weight of subjects was 86.32 kg, mean height was 163.9 cm and mean BMI was 32.0 kg/m^2. There were no meaningful differences in demographics between the placebo and ASP0819 treatment groups.

Efficacy and Pharmacokinetic Results:

Primary Efficacy Endpoint

The results of the primary analysis of the primary endpoint of change from baseline to week 8 in mean daily average pain score using MMRM demonstrated a reduction (improvement) from baseline in mean daily average pain score at week 8, which was numerically greater in magnitude in the ASP0819 treatment group compared with the placebo group, but was not statistically significant (P = 0.086) [Table 3] and [Figure 1].

The result of the primary analysis was shown consistent by the sensitivity analyses using discontinuation-reason based multiple imputation (LS mean difference: -0.34; P = 0.091) and mBOCF imputation (LS mean difference: -0.37; P = 0.060).

Secondary Efficacy Endpoints

Responder Analysis

The responder analysis of change from baseline to EOT in mean daily average pain score demonstrated numerically higher response rates (30% or 50% reduction) in the ASP0819 treatment group compared with the placebo group but these were not statistically significant [Table 4] and [Figure 2]. Consistent results were generally seen in the FAS for the change from baseline to week 8 using BOCF imputation and mBOCF imputation.

FIQR Function, Symptoms and Overall Impact Subscales

For the FAS, a numerically higher improvement from baseline in FIQR function, symptoms and overall impact subscales was seen at all timepoints in the ASP0819 treatment group compared with the placebo group Figure 3 Figure 4 and Figure 5 . However, a statistically significant greater improvement in the ASP0819 treatment group compared with the placebo group was seen only in the symptoms subscale and overall impact subscale at week 4 (LS mean difference: -3.73; P = 0.039 and LS mean difference: -1.34; P = 0.018, respectively), but not in FIQR function (LS mean difference: -2.97; P = 0.103).

The reduction (improvement) from baseline in FIQR function, symptoms and overall impact subscales was numerically greater in magnitude at week 8 in the ASP0819 treatment group compared with the placebo group, but was not statistically significant Table 5 . The result of this analysis was shown consistent using discontinuation-reason based multiple imputation.

For the PPS, the ANCOVA of change from baseline in FIQR showed statistically significant greater improvement for the ASP0819 treatment group vs the placebo group at week 8 using mBOCF imputation in symptoms (LS mean difference: -3.74; P = 0.041) and overall impact subscales (LS mean difference: -1.08; P = 0.049), and at EOT using LOCF imputation in overall impact subscale (LS mean difference: -1.08; P = 0.049).

PGIC

The analysis of overall subject improvement assessed by PGIC demonstrated that subjects in the ASP0819 treatment group were more likely to have better overall improvement compared with the placebo group at EOT but the treatment difference was not statistically significant Table 6 . Similar results were observed at weeks 2, 4 and 8 using mLOCF imputation and at weeks 2 and 4 using LOCF imputation.

Exploratory Efficacy Endpoints

There was also a trend for an improvement in favor of ASP0819 over placebo in multiple exploratory endpoints, but most of them did not reach the threshold for statistical significance. However, several of the exploratory sleep measures and the total FIQR score did show consistent statistically significant improvement for ASP0819 compared to placebo.

Safety Results:

ASP0819 administered at a dose of 15 mg once daily over a period of 8 weeks was safe and well tolerated compared to placebo in subjects with fibromyalgia.

There were no deaths or SAEs during the study Table 7 . Overall, 53 (56.4%) subjects in the placebo group and 62 (68.9%) subjects in the ASP0819 treatment group reported TEAEs. Drug-related TEAEs were reported for 29 (30.9%) subjects in the placebo group and 22 (24.4%) subjects in the ASP0819 treatment group. The subjects treated with ASP0819 reported more TEAEs (159 events) than the subjects treated with placebo (139 events). However, more drug-related TEAEs were reported by subjects treated with placebo (67 events) than those treated with ASP0819 (40 events).

Four subjects experienced TEAEs leading to withdrawal of treatment; 3 (3.2%) subjects in the placebo group and 1 (1.1%) subject in the ASP0819 treatment group.

The majority of the TEAEs were reported during the double-blind treatment period Table 8 .

The most common (≥ 10% in either treatment group) system organ classes for the TEAEs were 'nervous system disorders' (20.2% subjects [placebo]; 24.4% subjects [ASP0819]), 'infections and infestations' (19.1% subjects [placebo]; 20.0% subjects [ASP0819]), 'gastrointestinal disorders' (16.0% subjects [placebo]; 18.9% subjects [ASP0819]); 'musculoskeletal and connective tissue disorders' (10.6% subjects [placebo]; 22.2% subjects [ASP0819]) and 'injury, poisoning and procedural complications' (6.4% subjects [placebo]; 13.3% subjects [ASP0819]). The most commonly reported TEAE in the study was headache, which was reported by 11 (11.7%) subjects in the placebo group and by 12 (13.3%) subjects in the ASP0819 treatment group   Table 9 . Headache was also the most commonly reported drug-related TEAE reported for 8 (8.5%) subjects in the placebo group and 5 (5.6%) subjects in the ASP0819 treatment group.

The majority of TEAEs were considered by the investigator to be mild or moderate in severity. Severe TEAEs were reported by 3 (3.2%) subjects in the placebo group and 1 (1.1%) subject in the ASP0819 treatment group. These events were gastroenteritis viral, headache and syncope in the placebo group and insomnia in the ASP0819 treatment group.

Severe drug-related TEAEs were reported by 1 (1.1%) subject in each treatment group. These events were headache in the placebo group and insomnia in the ASP0819 treatment group.

There were no clinically relevant changes observed with the clinical laboratory analyses of hematology and biochemistry that would indicate an ASP0819-related effect.

No subjects met the drug induced liver injury criteria during the study and only 1 subject had a potentially clinically significant laboratory value during the study. This subject was in the ASP0819 treatment group and had an isolated international normalized ratio > 2.

No safety concerns were raised for the vital signs or ECG parameters.

No single event of suicidal ideation or suicidal behavior was reported during the double-blind treatment period.

CONCLUSIONS:

- The study did not achieve its primary endpoint (LS mean treatment difference of -0.34; P = 0.086 at week 8).
- There was evidence of moderate activity as seen by LS mean treatment differences between ASP0819 and placebo of -0.37 (P = 0.030), -0.42 (P = 0.033), -0.45 (P = 0.026), and -0.34 (P = 0.086) at weeks 2, 6, 7 and 8, respectively, in change from baseline in mean daily average pain.
- Safety and tolerability in ASP0819 was comparable to placebo.

Date of Report: 21 Aug 2018

Table 1   **Analysis Sets - All Randomized Subjects**

Analysis Set	Placebo (N = 95) n (%)	ASP0819 15 mg (N = 91) n (%)	Total (N = 186) n (%)
Randomized	95 (100.0)	91 (100.0)	186 (100.0)
Subjects who took study drug	94 (98.9)	90 (98.9)	184 (98.9)
Subjects who did not take study drug	1 (1.1)	1 (1.1)	2 (1.1)
SAF†	94 (98.9)	90 (98.9)	184 (98.9)
FAS‡	94 (98.9)	90 (98.9)	184 (98.9)
PPS§	87 (91.6)	86 (94.5)	173 (93.0)
PKAS¶	0	90 (98.9)	90 (48.4)

FAS: full analysis set; PKAS: pharmacokinetic analysis set; PPS: per protocol set; SAF: safety analysis set.

† All randomized subjects who took at least 1 dose of study drug. When the SAF is utilized in an analysis, subjects are presented by the treatment actually received. Subjects randomized to placebo who have accidentally received at least 1 dose of ASP0819 are summarized in the ASP0819 treatment group.

‡ All randomized subjects who took at least 1 dose of study drug. When the FAS is utilized in an analysis, subjects are presented by the randomized treatment group, i.e., planned treatment group, even if the treatment they received was different.

§ A subset of subjects from the FAS who meet criteria based on adherence to the protocol, which may have affected the primary efficacy endpoint or select secondary efficacy endpoints.

¶ The subset of SAF for which at least 1 postdose concentration was available.

Source: Table 12.1.1.2

Table 2   Summary of Demographic Characteristics (SAF)

Parameter Category/Statistic	Placebo (N = 94) n (%)	ASP0819 15 mg (N = 90) n (%)	Total (N = 184) n (%)
Sex, n (%)			
Male	5 (5.3)	2 (2.2)	7 (3.8)
Female	89 (94.7)	88 (97.8)	177 (96.2)
Ethnicity, n (%)			
Not Hispanic or Latino	81 (86.2)	80 (88.9)	161 (87.5)
Hispanic or Latino	13 (13.8)	10 (11.1)	23 (12.5)
Race, n (%)			
White	73 (77.7)	78 (86.7)	151 (82.1)
Black or African American	16 (17.0)	10 (11.1)	26 (14.1)
Asian	1 (1.1)	0	1 (0.5)
American Indian or Alaska Native	3 (3.2)	0	3 (1.6)
Native Hawaiian or Other Pacific Islander	1 (1.1)	1 (1.1)	2 (1.1)
Other	0	1 (1.1)	1 (0.5)
Age (years)			
Mean (SD)	49.8 (12.5)	48.7 (12.1)	49.3 (12.3)
Median	50.5	49.0	50.0
Min - Max	20 - 80	21 - 75	20 - 80
Weight (kg)			
Mean (SD)	86.89 (18.94)	85.73 (19.86)	86.32 (19.35)
Median	83.60	85.66	84.01
Min - Max	51.9 - 130.2	44.1 - 132.1	44.1 - 132.1
Height (cm)			
Mean (SD)	163.8 (7.1)	164.0 (6.9)	163.9 (7.0)
Median	162.6	162.8	162.6
Min - Max	150 - 185	150 - 183	150 - 185
BMI (kg/m^2)			
Mean (SD)	32.18 (6.22)	31.81 (6.62)	32.00 (6.40)
Median	31.96	31.28	31.75
Min - Max	19.7 - 44.5	17.2 - 44.9	17.2 - 44.9

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

Source: Table 12.1.2.1.2

Table 3 **MMRM Analysis of Change from Baseline to Week 8 in Mean Daily Average Pain Score (FAS)**

	Placebo (N = 94)	ASP0819 15 mg (N = 90)
Baseline		
Mean (SD)	6.32 (1.02)	6.32 (1.01)
Change from baseline to week 8		
LS mean (SE)†	-1.26 (0.18)	-1.60 (0.18)
Treatment difference (SE)‡ (ASP0819 - placebo)		-0.34 (0.25)
2-sided 90% CI for difference		(-0.76, 0.07)
1-sided P value for difference§		0.086

CI: confidence interval; FAS: full analysis set; LS mean: least squares mean; MMRM: mixed model repeated measures.
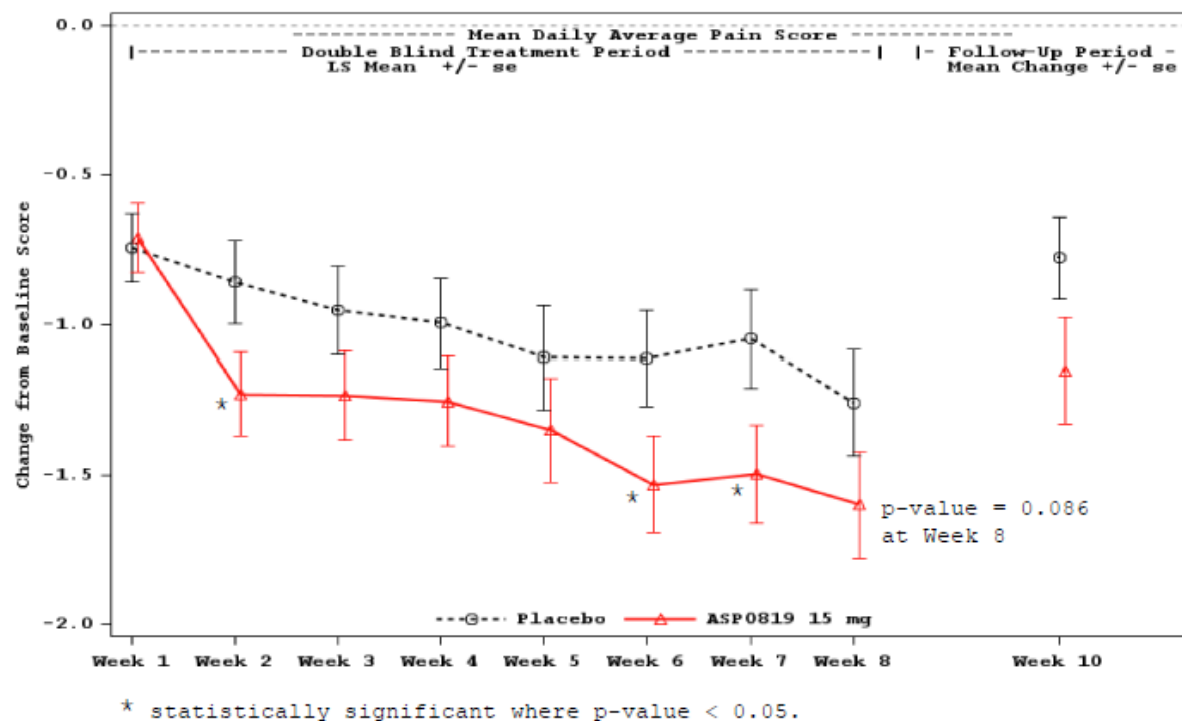
† A negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome).

‡ Differences are calculated by subtracting the LS mean of placebo group from the LS mean of ASP0819 15 mg group.

§ P value is for comparison of ASP0819 15 mg with placebo from the above described MMRM model.

Source: Table 12.3.1.1.1

Figure 1 **MMRM Analysis: LS mean Change from Baseline during Double-blind Treatment Period and Follow-up Period (FAS)**

FAS: full analysis set; LS mean: least squares mean; MMRM: mixed model repeated measures.

This figure was edited.

Source: Table 12.3.1.1.1 and Figure 12.3.1.1

Table 4 **Responder Analysis of Change from Baseline to EOT in Mean Daily Average Pain Score: LOCF Imputation (FAS)**
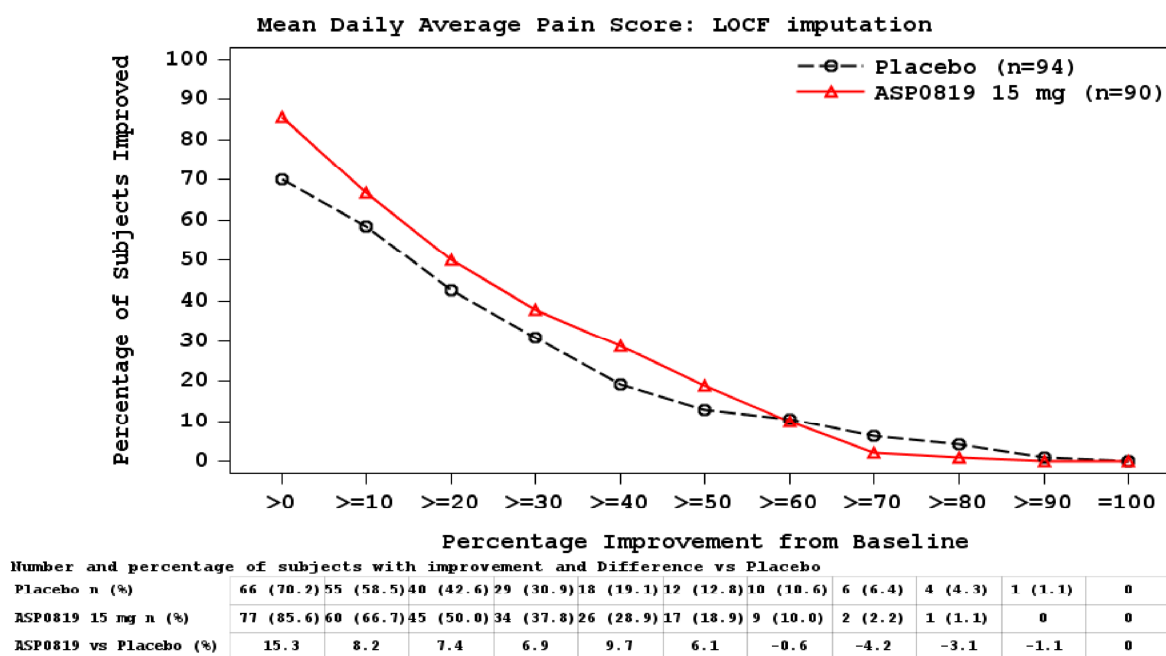
Responder Criteria	Statistic	Placebo (N = 94)	ASP0819 15 mg (N = 90)
≥ 30% reduction from baseline to EOT	Responders	29 (30.9)	34 (37.8)
	Treatment difference (ASP0819 vs placebo)		6.9
	2-sided 90% CI for difference		(-5.2, 19.1)
	1-sided P value for difference†		0.202
≥ 50% reduction from baseline to EOT	Responders	12 (12.8)	17 (18.9)
	Treatment difference (ASP0819 vs placebo)		6.1
	2-sided 90% CI for difference		(-6.2, 18.1)
	1-sided P value for difference†		0.174

CI: confidence interval; EOT: end of treatment; FAS: full analysis set; LOCF: last observation carried forward; vs: versus.

† P value is for comparison of ASP0819 15 mg with placebo using Fisher's Exact method.

Source: Table 12.3.1.3.4

Figure 2 **Subjects Achieving Different Levels of Reduction in Mean Daily Average Pain Score from Baseline to EOT: LOCF Imputation (FAS)**

EOT: end of treatment; FAS: full analysis set; LOCF: last observation carried forward; vs: versus.

Source: Figure 12.3.1.4

Table 5   **MMRM Analysis of Change from Baseline to Week 8 in FIQR Function, Symptoms and Overall Impact Subscales and Total Score (FAS)**

	Placebo (N = 94)	ASP0819 15 mg (N = 90)
Function Subscale		
Baseline		
Mean (SD)	47.82 (15.00)	48.03 (14.74)
Change from baseline to week 8		
LS mean (SE)†	-11.45 (1.79)	-14.04 (1.82)
Treatment difference (SE)‡ (ASP0819 - placebo)		-2.59 (2.53)
2-sided 90% CI for difference		(-6.78, 1.60)
1-sided P value for difference§		0.154
Symptoms Subscale		
Baseline		
Mean (SD)	56.52 (11.85)	57.03 (13.45)
Change from baseline to week 8		
LS mean (SE)†	-11.14 (1.65)	-14.20 (1.68)
Treatment difference (SE)‡ (ASP0819 - placebo)		-3.06 (2.34)
2-sided 90% CI for difference		(-6.93, 0.81)
1-sided P value for difference§		0.097
Overall Impact Subscale		
Baseline		
Mean (SD)	11.79 (3.91)	11.59 (4.06)
Change from baseline to week 8		
LS mean (SE)†	-3.80 (0.49)	-4.66 (0.50)
Treatment difference (SE)‡ (ASP0819 - placebo)		-0.86 (0.70)
2-sided 90% CI for difference		(-2.02, 0.30)
1-sided P value for difference§		0.111
Total Score		
Baseline		
Mean (SD)	55.99 (12.00)	56.12 (13.17)
Change from baseline to week 8		
LS mean (SE)†	-13.15 (1.74)	-16.42 (1.77)
Treatment difference (SE)‡ (ASP0819 - placebo)		-3.27 (2.46)
2-sided 90% CI for difference		(-7.34, 0.80)
1-sided P value for difference§		0.093

CI: confidence interval; FAS: full analysis set; FIQR: Fibromyalgia Impact Questionnaire Revised; LS mean: least squares mean; MMRM: mixed model repeated measures.
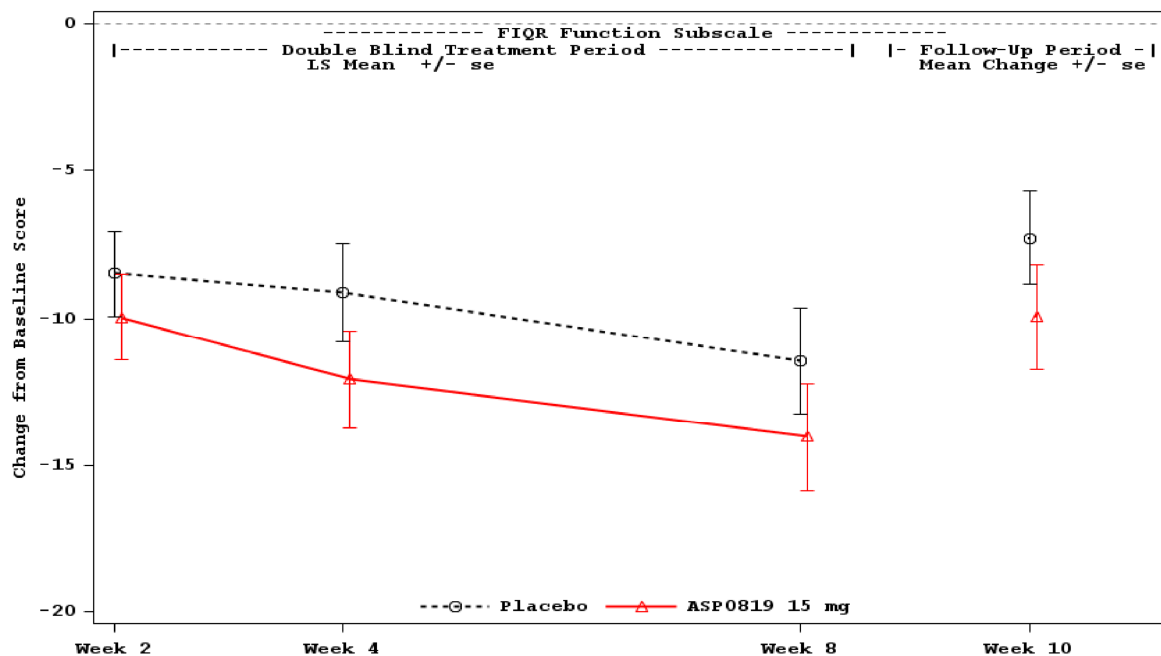
† A negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome).

‡ Differences are calculated by subtracting the LS mean of placebo group from the LS mean of ASP0819 15 mg group.

§ P value is for comparison of ASP0819 15 mg with placebo from the above described MMRM model.

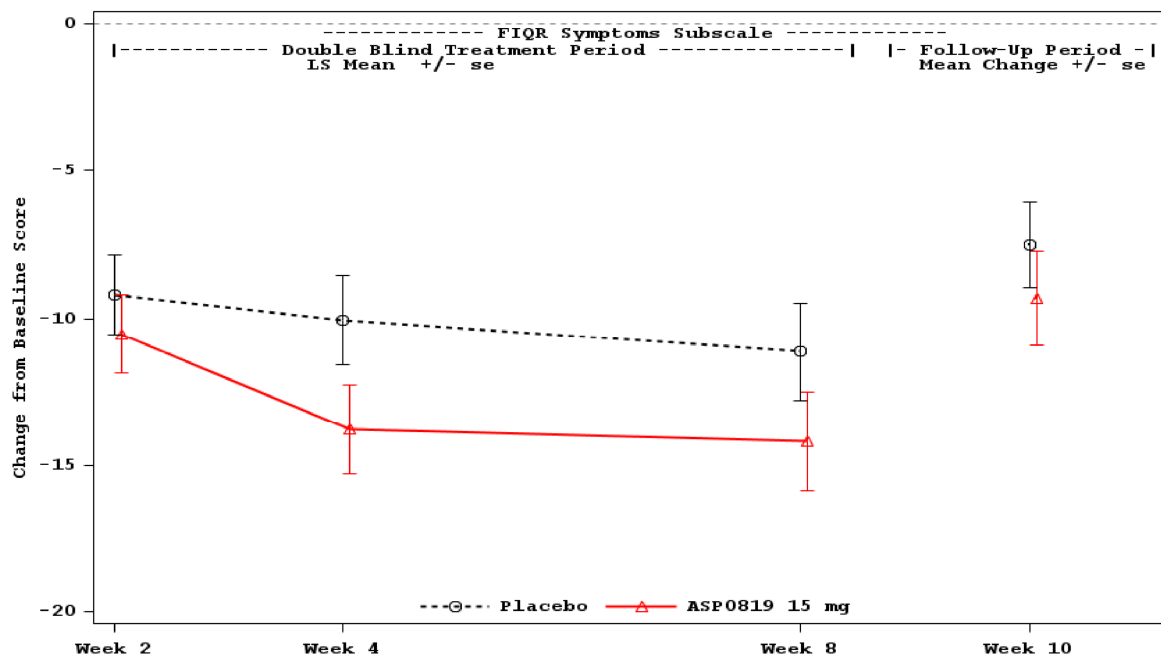Source: Table 12.3.2.1 and Table 12.3.4.1

Figure 3   MMRM Analysis: LS mean Change from Baseline during Double-blind Treatment Period and Follow-up Period in FIQR Function Subscale (FAS)

FAS: full analysis set; FIQR: Fibromyalgia Impact Questionnaire Revised; LS mean: least squares mean; MMRM: mixed model repeated measures.

Source: Figure 12.3.2

Figure 4   **MMRM Analysis: LS mean Change from Baseline during Double-blind Treatment Period and Follow-up Period in FIQR Symptoms Subscale (FAS)**

FAS: full analysis set; FIQR: Fibromyalgia Impact Questionnaire Revised; LS mean: least squares mean; MMRM: mixed model repeated measures.
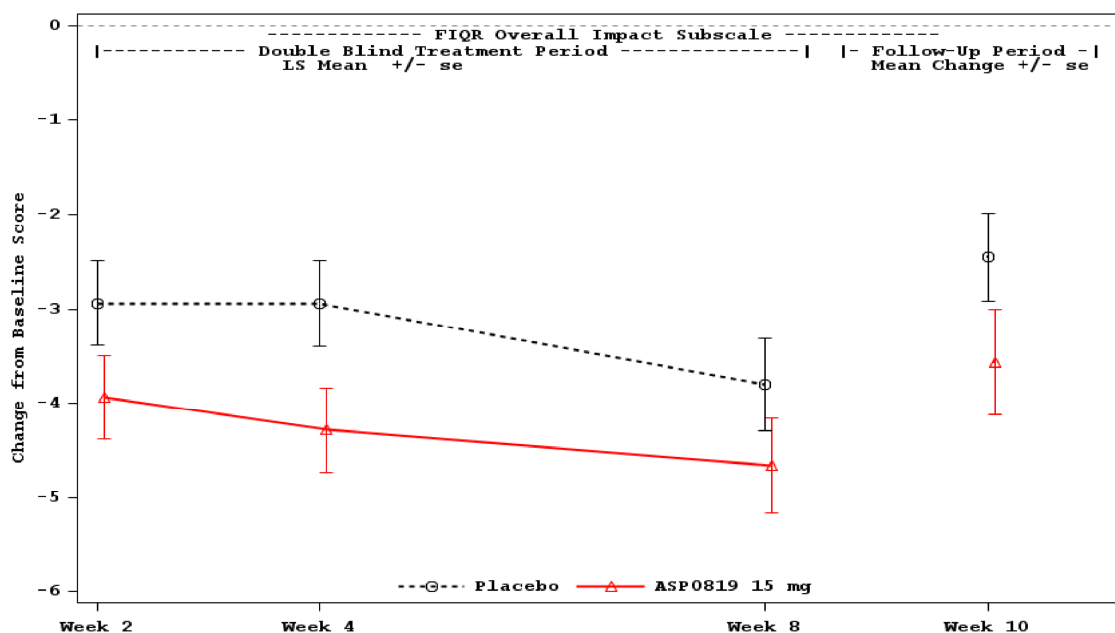
Source: Figure 12.3.2

Figure 5   **MMRM Analysis: LS mean Change from Baseline during Double-blind Treatment Period and Follow-up Period in FIQR Overall Impact Subscale (FAS)**

FAS: full analysis set; FIQR: Fibromyalgia Impact Questionnaire Revised; LS mean: least squares mean; MMRM: mixed model repeated measures.

Source: Figure 12.3.2

Table 6   Overall Subject Improvement at EOT Assessed by PGIC: LOCF Imputation (FAS)

PGIC Category	Placebo (N = 94)	ASP0819 15 mg (N = 90)
1 – Very much improved	6 (6.4)	9 (10.0)
2 – Much improved	17 (18.1)	19 (21.1)
3 – Minimally improved	25 (26.6)	19 (21.1)
4 – No change	36 (38.3)	36 (40.0)
5 – Minimally worse	8 (8.5)	3 (3.3)
6 – Much worse	2 (2.1)	3 (3.3)
7 – Very much worse	0	1 (1.1)
Odds ratio: ASP0819 vs placebo		1.20
90% 2-sided CI†		(0.78, 1.87)
2-sided P value‡		0.486

CI: confidence interval; EOT: end of treatment; FAS: full analysis set; LOCF: last observation carried forward; PGIC: patient global impression of change; vs: versus.

† The 90% 2-sided CI is based on profile likelihood and 2-sided P value is based on likelihood test.

‡ P value is for the comparison of ASP0819 15 mg with placebo from the above described proportional odds model.

Source: Table 12.3.3.3

Table 7   Overview of TEAEs (SAF)

	Placebo (N = 94) n (%) E	ASP0819 15 mg (N = 90) n (%) E
Any TEAE	53 (56.4) 139	62 (68.9) 159
Drug-related† TEAE	29 (30.9) 67	22 (24.4) 40
Serious TEAE‡	0	0
Drug-related† serious TEAE‡	0	0
TEAE leading to withdrawal of treatment	3 (3.2) 6	1 (1.1) 1
Death§	0	0
TEAE within the drug abuse, dependence and withdrawal SMQ¶	0	0
TEAE within the drug abuse and dependence SMQ¶	0	0
TEAE within the drug withdrawal SMQ¶	0	0
Drug abuse related TEAEs††	0	0
Drug withdrawal related TEAEs††	21 (22.3) 26	22 (24.4) 33

AE: adverse event; E: number of events; MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event; SAF: safety analysis set; SAP: statistical analysis plan; SMQ: Standardized MedDRA Query; TEAE: treatment emergent adverse event.

TEAE is defined as an AE that starts, or worsens, after the first dose of study drug through 30 days after the last dose of study drug.

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

‡ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.

§ All reported deaths after the first study drug administration.

¶ MedDRA v20.0.

†† As defined by predefined Adverse Events of Interest search strategy [SAP, Appendices 1 and 2].

Source: Table 12.6.1.1.1

Table 8   **Overview of TEAEs by Investigational Period (SAF)**

	Treatment Period		Follow-up Period‡‡	
	Placebo (N = 94) n (%) E	ASP0819 15 mg (N = 90) n (%) E	Placebo (N = 93) n (%) E	ASP0819 15 mg (N = 90) n (%) E
Any TEAE	52 (55.3) 112	61 (67.8) 152	16 (17.2) 27	7 (7.8) 7
Drug-related† TEAE	29 (30.9) 63	22 (24.4) 39	3 (3.2) 4	1 (1.1) 1
Serious TEAE‡	0	0	0	0
Drug-related† serious TEAE‡	0	0	0	0
TEAE leading to withdrawal of treatment	3 (3.2) 6	1 (1.1) 1	0	0
Death§	0	0	0	0
TEAE within the drug abuse, dependence and withdrawal SMQ¶	0	0	0	0
TEAE within the drug abuse and dependence SMQ¶	0	0	0	0
TEAE within the drug withdrawal SMQ¶	0	0	0	0
Drug abuse related TEAEs††	0	0	0	0
Drug withdrawal related TEAEs††	20 (21.3) 23	21 (23.3) 32	3 (3.2) 3	1 (1.1)

E: number of events; MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event; SAF: safety analysis set; SMQ: Standardized MedDRA Query; TEAE: treatment-emergent adverse event.

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

‡ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.

§ All reported deaths after the first study drug administration.

¶ MedDRA v20.0.

†† As defined by predefined Adverse Events of Interest search strategy [SAP, Appendices 1 and 2].

‡‡ N is the number of subjects who entered the follow-up period.

Source: Table 12.6.1.1.2

Table 9   **TEAEs (≥ 5% in Any Treatment Group) (MedDRA v20.0) by Preferred Term (SAF)**

MedDRA v20.0 Preferred Term	Placebo (N = 94) n (%)	ASP0819 15 mg (N = 90) n (%)
Overall	**53 (56.4)**	**62 (68.9)**
Headache	11 (11.7)	12 (13.3)
Arthralgia	3 (3.2)	5 (5.6)
Nausea	2 (2.1)	5 (5.6)
Pain in extremity	3 (3.2)	5 (5.6)
Upper respiratory tract infection	4 (4.3)	5 (5.6)
Viral upper respiratory tract infection	5 (5.3)	4 (4.4)
Diarrhoea	6 (6.4)	2 (2.2)

MedDRA: Medical Dictionary for Regulatory Activities; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.18