STATISTICAL ANALYSIS PLAN

Final Version 2.0, dated 10-Apr-2018

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

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Astellas Pharma Global Development, Inc. (APGD)
1 Astellas Way,
Northbrook,
IL 60062

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ACR	American College of Rheumatology
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
APGD	Astellas Pharma Global Development, Inc.
ASCM	Analysis Set Classification Meeting
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BLOQ	Below the limit of quantification
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
CI	Confidence Interval
CMSI	Complex Medical Symptom Inventory
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP3A	Cytochrome P450 3A
DBP	Diastolic Blood Pressure
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	European Quality of Life 5 Dimensions-5 Levels
EQ-VAS	EQ Visual Analog Scale
FAS	Full Analysis Set
FIQR	Fibromyalgia Impact Questionnaire Revised
FM	Fibromyalgia
FMSD	Fibromyalgia Sleep Diary
FU	Follow-up
$GABA_B$	γ-aminobutyric acid
GD-US	Global Development - United States
H	High

Abbreviations	Description of abbreviations
HADS	Hospital Anxiety and Depression Scale
IAP	Interim Analysis Plan
ICD-10	International Statistical Classification of Diseases and Related Health Problems
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
IRT	Interactive Response Technology
L	Low
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward
LS	Least squares
mBOCF	Modified Baseline Observation Carried Forward
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mIBS-D	Modified irritable bowel syndrome - diarrhea predominant
M.I.N.I.	Mini-International Neuropsychiatric Interview
MMRM	Mixed model repeated measures
N	Normal
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug
PCS	Potentially Clinically Significant
PD1-x	Protocol Deviation 1-x
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PKAS	Pharmacokinetics Analysis Set
PPS	Per-Protocol Analysis Set
PRO	Patient reported outcome
PT	Preferred Term
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software

Abbreviations	Description of abbreviations
SBP	Systolic Blood Pressure
SD	Standard deviation
SE	Standard error
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SS	Symptom severity
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
THC	Tetrahydrocannabinol
TLF	Tables, Listings and Figures
ULN	Upper Limit of Normal
US	United States
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary
WPI	Widespread pain index

List of Key Terms

Terms	Definition of terms
Baseline Diary Run-In	7-day period in which subject completes numerical rating scale (NRS) and Fibromyalgia Sleep Diary (FMSD) on handheld device daily beginning at Day -7 through Day -1.
End of Study	End of study for each subject has occurred when the final protocol-defined assessment has been completed. In this study, the last protocol defined assessment is approximately 4 weeks after last study drug dose.
End of Treatment	The date the last dose of study drug was taken by the enrolled subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. Randomization will occur after predose assessments and eligibility criteria have been confirmed at Visit 3.
Treatment-Emergent Adverse Event	Any adverse event which starts, or worsens, after the first dose of study drug through 30 days after the last dose of study drug.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

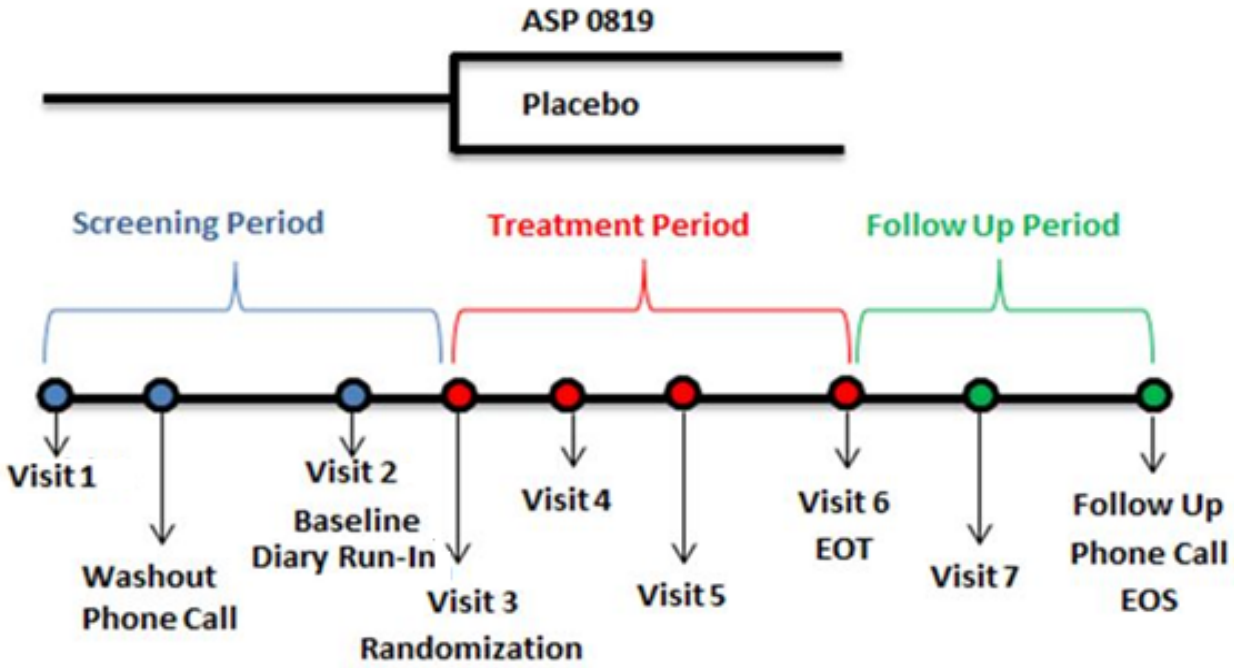
The SAP is finalized and signed prior to database hard lock to ensure lack of bias. Any subsequent changes will be described with justification in an updated version of the SAP (with date of version number).

This statistical analysis is coordinated by the responsible biostatistician of GD-US. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and Tables, Listings and Figures (TLFs) meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 FLOW CHART AND VISIT SCHEDULE

Figure 1 Study flow chart



Visit Day:	-42	-7	1	15	29	57	71	85
Visit Week:	-6 through -1	-1		2	4	8	10	12

EOS: end of study; EOT: end of treatment.

Table 1 Schedule of Assessments

Schedule of Assessments	Screening Period			Randomization	Treatment Period			Follow-Up Period[a]	
	Screening	Wash-out	Baseline Diary Run-In		Treatment			Follow-up Visit	End of Study (EOS) Phone Call
Visit	**1**	**NA**	**2**	**3**	**4**	**5**	**6**	**7**	**N/A**
Week	**-6 through -1**				**2**	**4**	**8/EOT**	**10**	**12**
Day (and Window)	**-42 to -8**		**-7 to -1**	**1**	**15 ± 2**	**29 ± 2**	**57± 2**	**71± 2**	**85± 2**
ASSESSMENTS									
Informed Consent	X								
Demographics	X								
Height and Weight[b]	X			X			X		
Medical/Surgical History	X								
Medication History and Concomitant Medication	X	X	X	X	X	X	X	X	X
Fibromyalgia Diagnosis (ACR 1990 and 2010)[c]	X								
Verify Eligibility Criteria (and duplicate subject database check)	X	X[d]	X[d]	X					
Phone Call to Subject[e]		X							X
e-diary Distribution/Return			X					X	
Physical Examination (including tender point exam at Screening)	X			X			X	X	
Drug and Alcohol Screen[f]	X		X	X					
Randomization[g]				X					
Vital Signs[h]	X			X	X	X	X	X	
Laboratory Tests (Hematology, Biochemistry, Urinalysis)[i]	X			X	X	X	X	X	
Electrocardiogram[j]	X			X			X	X	
Pregnancy Test	X[k]			X[l]			X[l]	X[l]	
Blood Sample for Pharmacogenomics[m]				X					
Blood sampling for Pharmacokinetics[n]				X	X	X	X		
Complex Medical Symptoms Inventory (CMSI)[o]			X						

Table continued on next page

Schedule of Assessments	Screening Period			Randomization	Treatment Period			Follow-Up Period[a]	
	Screening	Wash-out	Baseline Diary Run-In		Treatment			Follow-up Visit	End of Study (EOS) Phone Call
Visit	**1**	**NA**	**2**	**3**	**4**	**5**	**6**	**7**	**N/A**
Week	**-6 through -1**				**2**	**4**	**8/EOT**	**10**	**12**
Day (and Window)	**-42 to -8**		**-7 to -1**	**1**	**15 ± 2**	**29 ± 2**	**57± 2**	**71± 2**	**85± 2**
M.I.N.I.[p]	X								
Hospital Anxiety and Depression Scale (HADS)[q]	X			X			X		
NRS e-diary Collection[r]			←	—	—	—	→		
NPSI[s]				X			X		
PGIC[t]					X	X	X	X	
PGIS[u]				X	X	X	X	X	
EQ-5D-5L[v]				X			X	X	
FMSD e-diary Collection[w]			←	—	—	—	→		
FIQR[x]	X			X	X	X	X	X	
mIBS-D Symptoms Diary[y]				X	X	X	X		
C-SSRS[z]	X			X	X	X	X	X	
Subject Training Materials[aa]	X		X						
Study Drug Dispensed				X	X	X			
Study Drug Dosing[bb]				X	X	X	X		
Study Drug Returned					X	X	X		
Adverse Events[cc]	X	X	X	X	X	X	X	X	X
Rescue Medication (if applicable)			←	—	—	—	—	→	

a) Follow-up visit and phone call will be planned relative to date of last dose (14 and 28 days post last dose).

b) Height will be measured at Screening only. Weight will be collected at Screening, prior to Randomization and Week 8/End of Treatment (EOT).

c) Tender point examination training of the principle investigator and/or designated site study physician must be documented.

d) Continued subject eligibility to be confirmed based on laboratory results prior to having the subject wash-out of current pain medications (site to contact subject via phone call). Continued subject eligibility to be confirmed based on completion of wash-out prior to having the subjects start Baseline Diary Run-In (Visit 2).

e) During Screening period (wash-out): study staff to contact the subject, if necessary, to initiate wash-out of current pain medications after continued eligibility has been confirmed. During follow-up: follow-up phone call 4 weeks (Day 85) post study drug will be required.

f) Subjects will be tested for drugs and alcohol at Screening, Baseline Diary Run-In, and prior to Randomization. A positive screen for tetrahydrocannabinol (THC) and/or opioids is allowed at the Screening visit, however must be confirmed negative prior to Baseline Diary Run-In and Randomization.

Footnotes continued on next page

g) Continued subject eligibility to be assessed and confirmed based on daily average pain scores recorded in the e-diary prior to subject being randomized.

h) Sitting or supine resting blood pressure and pulse rate values will be obtained at each visit (except for Visit 2) and should be conducted prior to blood draws. Body temperature will be assessed at Screening, Randomization and Week 8/EOT only.

i) Blood specimens for scheduled clinical chemistry laboratory tests do not need to be fasted samples.

j) Electrocardiograms are to be conducted prior to blood draws. A single electrocardiogram (ECG) will be obtained at the specified visits, unless, in the investigator's judgment, additional ECG's are required for safety reasons.

k) Serum for females of childbearing potential.

l) Urine for females of childbearing potential. Samples are to be collected prior to Randomization, Week 8/EOT, and the Week 10/FU visits.

m) Sample to be collected 1 time, preferably prior to first dose on Day 1; however, the sample can be collected at any time during the course of the study. A separate pharmacogenomics informed consent form (ICF) will need to be obtained from subject prior to collecting.

n) Pharmacokinetic sampling will occur on Day 1 in the clinic at approximately 1-4 hour(s) after dosing and once at Weeks 2, 4 and 8 at any time point. Date and time of the dose taken prior to collecting the PK sample, as well as the date and time of the last meal in relation to that dose will be captured in the electronic case report form (eCRF).

o) Complex Medical Symptom Inventory (CMSI). Questionnaire will be completed by the subject at Baseline Diary Run-in.

p) Mini-International Neuropsychiatric Interview (M.I.N.I.) will be completed by trained personnel at Screening.

q) Hospital Anxiety and Depression Scale (HADS). Questionnaire will be completed by the subject at Screening, Randomization and the Week 8/EOT visits.

r) Numeric Rating Scale (NRS). Subject is to rate average pain on a daily basis (24-hour recall) by entering pain score (0 - 10) in the e-diary. The NRS should be completed prior to bedtime at a consistent time of day throughout the study starting daily at Diary Run-In until Week 10/FU.

s) Neuropathic Pain Symptom Inventory (NPSI). Questionnaire will be completed by the subject at Randomization and Week 8/EOT visits.

t) Patient Global Impression of Change (PGIC). Questionnaire will be completed by the subject at the Week 2, 4, 8/EOT and Week 10/FU visits.

u) Patient Global Impression of Severity (PGIS). Questionnaire will be completed by the subject at Randomization and the Week 2, 4, 8/EOT and Week 10/FU visits.

v) European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L). Questionnaire will be completed by the subject at Randomization, Week 8/EOT and Week 10/FU visits.

w) Fibromyalgia Sleep Diary (FMSD) during the study starting daily at Baseline Diary Run-In (Visit 2) until Week 10/FU visit. Upon awakening, subject is to rate their quality of sleep (FMSD) during the previous night using the e-diary.

x) Fibromyalgia Impact Questionnaire Revised (FIQR) will be completed by the subject at Screening, Randomization and at the Week 2, 4, 8/EOT and Week 10 visits. At Screening, subject only completes pain item of FIQR.

y) Modified irritable bowel syndrome - diarrhea predominant (mIBS-D) Symptoms Diary will be completed by the subject at Randomization and at Weeks 2, 4 and 8/EOT visits.

z) Columbia Suicide Severity Rating Scale (C-SSRS). Questionnaire will be facilitated by the primary investigator/Site staff, as appropriately trained, at Screening, Randomization and the Weeks 2, 4, 8/EOT and Week 10/FU visits.

aa) Subject training materials are to be distributed and reviewed during the Screening period.

bb) Subjects will begin study drug dosing on Day 1 of the Randomization visit.

cc) Serious Adverse Events (AEs, TEAEs, SAEs and SUSARs) will be collected from the time of signing the ICF through 4 weeks post-last dose.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

The objectives of the study, conducted in subjects with fibromyalgia, are the following:

3.1.1 Primary Objectives

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

3.1.2 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.

3.1.3 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.

3.2 Study Design

This is 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 will be conducted in the United States (US). Approximately 323 subjects are planned to be screened for 178 randomized subjects (45% screen fail rate). Subjects will be randomized in a 1:1 ratio to one of two treatment groups: ASP0819 15 mg or Placebo once per day.

The study will consist of a screening period of up to 6 weeks, which includes the completion of screening procedures, wash-out of prohibited medications (if applicable) followed by a 1-week baseline diary run-in; an 8-week double-blind randomized treatment period (subjects randomized to the ASP0819 group will receive ASP0819 15 mg [3 capsules of 5 mg] once daily; subjects randomized to the placebo group will receive placebo to match ASP0819 [3 capsules] once daily); and a 4-week follow-up period. The total study duration for a subject is approximately 18 weeks.

Acetaminophen may be used as rescue therapy for intolerable pain due to fibromyalgia during the baseline diary run-in and in all subsequent study periods. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used (with the exception of celecoxib) as needed for non-fibromyalgia pain (e.g., headache).

This study design includes a stopping rule for futility. Two interim analyses for futility based on the primary efficacy endpoint will be conducted. The timing of these analyses will be at approximately 35% and 55% of all subjects with Week 8/End of Treatment (EOT) data. The plan for the interim analysis may be modified based on speed of recruitment.

The futility analyses will be conducted by an Astellas statistician, with results reviewed by an Astellas Independent Data Monitoring Committee (IDMC). The Astellas statistician and other members of the Astellas IDMC are external to the study team. No one within the study team will be unblinded to the treatment allocation or interim results. Details of the interim analysis procedure, steps to maintain treatment blind in the study team and criteria for stopping the study will be described in an Interim Analysis Plan (IAP).

3.3 Randomization

All subject numbers will be assigned using the interactive response technology (IRT) starting at screening. All subjects will have a unique, ten-digit subject number. The first five digits of this number will be the investigator's site number. The second five digits assigned will represent the subject's accession number. This will be the number that identifies a subject during the course of the study.

Screening procedures, wash-out of prohibited medications (if applicable) and the baseline-diary run-in will be completed prior to randomization. Only subjects who meet all inclusion criteria and exhibit none of the exclusion criteria will be randomly assigned in a 1:1 ratio to ASP0819 15 mg or placebo according to the randomization schedule through IRT. The randomization will be stratified by site. Site personal will dispense the treatment according to the IRT system's assignment.

If a subject is assigned a randomization number, but does not receive study drug, the randomization number will not be used again.

The randomization schedules that determine subject treatment will be computer-generated by IRT before the beginning of the study. Specific procedures for randomization through the IRT are contained in the study-specific IRT manual.

4 SAMPLE SIZE

In this study, a total of 178 subjects will be randomized in a 1:1 ratio to ASP0819 15 mg once daily (89 subjects) or placebo once daily (89 subjects).

The sample size calculations are based on the primary efficacy endpoint of change from baseline to Week 8 in mean daily average pain assessed by numerical rating scale (NRS). A meta-analysis of the change from baseline in mean daily average pain NRS for pregabalin or duloxetine versus placebo in studies for fibromyalgia indicated an effect size of approximately 0.30.

Using an effect size of 0.39 (30% larger than the meta-analysis result) for the primary efficacy endpoint for the comparison of ASP0819 versus placebo, 84 subjects each in the ASP0819 group and the placebo group (168 subjects in total) would be required to provide

80% power to demonstrate statistical significance using a 1-sided 5% significance level (based on the assumption of normally distributed data, and taking into account the interim analysis for futility).

Assuming approximately 5% of randomized subjects will not contribute to the primary efficacy analysis, a total of 178 subjects are required to be randomized into the study.

5 ANALYSIS SETS

In accordance with International Council for Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications and for the allocation of subjects to analysis sets, except Pharmacokinetic Analysis Set (PKAS), will be determined prior to database hard lock. The allocation of subjects to PKAS will be determined after database hard lock.

5.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all randomized subjects who take at least one dose of study drug.

The FAS will be used for demographic and baseline characteristic summaries and primary summaries and analyses of efficacy variables.

When the FAS is utilized in an analysis, subjects will be presented by the randomized treatment group, i.e. planned treatment group, even if the treatment they received was different.

5.2 Per Protocol Set (PPS)

The per protocol set (PPS) will include a subset of subjects from the FAS who meet criteria based on adherence to the protocol, which may affect the primary efficacy endpoint or select secondary efficacy endpoints. The PPS criteria is defined in Section 5.2.1 of this SAP.

The PPS will be used for demographic and baseline characteristic summaries and for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints outlined in Section 7.4.2

Final judgments on exclusion of subjects from the PPS are to be made at the analysis set classification meeting (ASCM), which will be held prior to database hard lock and unblinding of the study.

5.2.1 Reasons for Exclusion From PPS

A subject who meets any of the criteria described in Table 2 will be completely excluded from the PPS; there will be no partial data exclusion of a specified time point for a subject.

Table 2 Criteria for Assessing Reasons for Exclusion From PPS

Number	Source	Criterion/Criteria
Didn't Satisfy Diary Eligibility Criteria		
1.1	Inclusion Criterion # 12: Subject is 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.	Compliance is not met at baseline i.e. number of days of daily average NRS pain ratings during the baseline diary run-in (from study day -7 to -1) is < 5.
1.2	Inclusion Criterion # 13: Subject has a mean daily average pain score ≥ 4 and ≤ 9 on an 11 point 0 to 10 NRS as recorded in the subject electronic diary (e-diary) during the baseline diary run-in period, and meeting pre-specified criteria for daily average pain scores.	During the baseline diary run-in period (from study day -7 to -1) the subject has: • A mean daily average pain NRS of < 4 or > 9 and/or, • Two or more daily average pain scores of > 9 and/or, • Four or more daily average pain scores of ≤ 3.
Didn't Satisfy Non-Diary Eligibility Criteria		
2.1	Inclusion Criterion # 9: Subject meets the American College of Rheumatology (ACR) 1990 fibromyalgia diagnostic criteria at Screening: • Widespread pain for at least 3 months, defined as the presence of all of the following: o pain on right and left sides of the body, o pain above and below the waist, and o pain in the axial skeleton (cervical spine or anterior chest or thoracic spine or low back) must be present. • Pain in 11 of 18 tender point sites on digital palpation. o Digital palpation should be performed with an approximate force of 4 kg.	Inclusion Criterion # 9 is No and/or pain is in < 11 tender point sites
2.2	Inclusion Criterion # 10: Subject meets the ACR 2010 fibromyalgia diagnostic criteria at Screening: • Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 or WPI 3-6 and SS scale score ≥ 9. • Symptoms have been present at a similar level for at least 3 months. • The subject does not have a disorder that would otherwise explain the pain.	Inclusion criterion #10 is No and/or WPI ≥ 7 and SS scale score < 5 or WPI 3-6 and SS scale score < 9 or WPI < 3.
Table continued on next page		

Number	Source	Criterion/Criteria
2.3	Inclusion Criterion # 11: Subject has a pain score ≥ 4 on the revised fibromyalgia impact questionnaire revised (FIQR) pain item at Screening.	Inclusion criterion #11 is No and/or FIQR pain item score < 4 at Screening.
Met Exclusion Criteria		
3.1	Exclusion Criterion # 4: Subject has pain due to diabetic peripheral neuropathy, post-herpetic neuralgia, traumatic injury, prior surgery, complex regional pain syndrome, or other source of pain that, in the investigator's opinion, would confound or interfere with the assessment of the subject's fibromyalgia pain or require excluded therapies during the subject's study participation.	Exclusion Criterion # 4 is Yes.
3.2	Exclusion Criterion # 5: Subject has infectious or inflammatory arthritis (e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and gout), autoimmune disease (e.g., systemic lupus erythematosus), or other widespread rheumatic disease other than fibromyalgia.	Exclusion Criterion # 5 is Yes.
3.3	Exclusion Criterion # 6: Subject has a current, untreated moderate or severe major depressive disorder as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.). Subject with current, treated major depressive disorder can be included provided that, in the investigator's opinion, it is without clinically significant changes in symptoms while on the same dose of a protocol allowed antidepressant for greater than 60 days prior to Screening.	Exclusion Criterion # 6 is Yes.
3.4	Exclusion Criterion # 8: Subject has a history of any psychotic and/or bipolar disorder as assessed by the M.I.N.I.	Exclusion Criterion # 8 is Yes.
3.5	Exclusion Criterion # 9: Subject has a HADS score > 14 on the Depression subscale at Screening or at the time of Visit 3 (Randomization).	Exclusion Criterion #9 is Yes and/or HADS total score > 14 (using HADS corrected questionnaire) at Screening or Visit 3 (Randomization). Subjects who completed the incorrect version of this questionnaire will be reviewed on a case by case basis.
Error in Study Drug Administration Compared to Treatment Assigned		
4	Received wrong treatment during the double-blind treatment period	A subject will be excluded if the study drug taken at any time during the double-blind treatment period is different from the treatment group assigned at randomization.

Table continued on next page

Number	Source	Criterion/Criteria
Poor Study Drug Compliance		
5	Poor study drug compliance during the double-blind treatment period.	Percent overall compliance is <70% for a subject, calculated over day 1 to Week 8/EOT. Subjects with missing compliance will be reviewed on a case by case basis.
Unblinding of Study Drug		
6	Incorrect unblinding of double-blind study drug.	A subject's treatment for double-blind study drug is incorrectly unblinded. The decision to exclude the subject will be evaluated on a case by case basis.
Use of Prohibited Concomitant Medication		
7	Subject received celecoxib, duloxetine, gabapentin, milnacipran or pregabalin during the double-blind treatment period.	Subject received at least one dose of celecoxib, duloxetine, gabapentin, milnacipran or pregabalin during the double-blind treatment period.

5.3 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all randomized subjects who received at least one dose of study drug.

The SAF will be used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

When the SAF is utilized in an analysis, subjects will be presented by the treatment actually received. Subjects who are randomized to placebo who accidentally receive at least one dose of ASP0819 will be summarized in the ASP0819 treatment group in the SAF.

5.4 Pharmacokinetics Analysis Set (PKAS)

The PKAS will consist of the subset of SAF for which at least one post dose concentration is available.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

The subjects will use a handheld device (an e-diary that will be taken home) to report daily average pain NRS scores, enter Fibromyalgia sleep diary (FMSD) data and to capture rescue medication use. Data will be automatically transmitted to a central database.

The questionnaires on efficacy to be performed during the clinic visits (Fibromyalgia Impact Questionnaire Revised [FIQR], Patient Global Impression of Change [PGIC], Patient Global Impression of Severity [PGIS], European Quality of Life 5 Dimensions-5 Levels [EQ-5D-5L], modified irritable bowel syndrome - diarrhea predominant [mIBS-D] Symptoms Diary) and the Hospital Anxiety and Depression Scale (HADS) depression subscale will be reported on a tablet device that is available at the site. For FIQR, PGIS, EQ-5D-5L, mIBS-D and HADS baseline is defined as the last assessment on or prior to the first dose day (Day 1) of double-blind study drug.

6.1.1 Primary Efficacy Endpoint(s)

The primary efficacy variable is the change from baseline to Week 8 in mean daily average pain score assessed by NRS (0 to 10 scale).

The NRS is a generic instrument for the assessment of pain, consisting of a single question that asks subjects to record their daily average pain on an 11- point scale, where 0 anchors "no pain" and 10 "pain as bad as you can imagine." The recall period is the last 24 hours.

The subject will use the e-diary to report daily average pain NRS scores from the start of the baseline diary run-in period through Week 10. Subjects will be instructed to complete the NRS in the evening and at a consistent time each day (ideally between 6pm and midnight, however can be captured until 2am the next morning). For this reason, any daily average pain score entered onto the e-diary up to 2am the following day will be attributed to the previous study day in the derivation of the mean daily average NRS pain scores. This is described in more detail in Section 7.11.4.3

Mean daily average NRS pain scores will be derived for each subject as follows:

Table 3 Derivation of mean daily average NRS pain score

Analysis Time point	Derivation
Baseline	Arithmetic mean of non-missing daily pain scores from the last 7 days prior to the randomization visit i.e., using the non-missing scores from Study Days -7 to -1. If the pain score is missing on all of these 7 days, then the score will be set to missing.
Treatment period Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, EOT Follow-up period Week 10	Arithmetic mean of non-missing daily pain scores collected within time window per visit windows defined in Section 7.11.4.3 Table 21 If the pain score is missing on all of the days during the time window, then the score for that time point will be set to missing.

EOT: end of treatment

Change from baseline is defined in Section 7.1 A negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome).

6.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Percentage of subjects achieving ≥ 30 % (or ≥ 50%) reduction from baseline to Week 8 in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.
  - A subject with at least 30% (or 50%) reduction in mean daily average pain score (NRS) from baseline to Week 8 will be classified as a responder; otherwise they will be classified as a non-responder.
  - Subjects who do not have Week 8 data will be classified as non-responders.
  - Subjects who do not have baseline data will be classified as non-responders.

- Percentage of subjects achieving ≥ 30 % (or ≥ 50%) reduction from baseline to EOT in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.
  - A subject with at least 30% (or 50%) reduction in mean daily average pain score (NRS) from baseline to EOT will be classified as a responder; otherwise they will be classified as a non-responder.
  - Subjects who do not have EOT data will be classified as non-responders.
  - Subjects who do not have baseline data will be classified as non-responders.

  Percent change from Baseline is defined in Section 7.1. A negative percent change indicates a reduction/improvement from Baseline (i.e., a favorable outcome).
- Change from baseline to Weeks 2, 4, 8 and EOT in the FIQR function, symptoms and overall impact subscales.
  The 21-item FIQR contains 3 subscales: function (9 questions), overall impact (2 questions), and symptoms (10 questions). Subjects answer each question on an 11-point NRS, with anchors appropriate to each question on a tablet device during the clinic visit. The recall period is the last 7 days or, for the function subscale, the last time the activity was performed if not within the 7-day recall period.
  For each subject the items described in Table 4 will be derived. The questionnaire should be considered to be invalid if three or more of the individual questions are unanswered. In this case, all subscales and the total score would be set to missing, even if a particular subscale has no missing items.
  Change from baseline is defined in Section 7.1. A negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome).

Table 4 Derivation of FIQR subscales and total score

Analysis Time point	**FIQR Item**	**Derivation**
Baseline, <u>Treatment period</u> Week 2, Week 4, Week 8, EOT, <u>Follow-up period</u> Week 10	<u>Function subscale score</u> Rate the difficulty of the following activities: 1) Brush or comb your hair 2) Walk continuously for 20 mins 3) Prepare a homemade meal 4) Vacuum, scrub or sweep floors 5) Lift and carry a full bag of groceries 6) Climb one flight of stairs 7) Change bed sheets 8) Sit in a chair for 45 mins 9) Go shopping for groceries	Sum of scores from questions 1 to 9. In the case of missing data, unanswered questions should be compensated using the following "weighting" factor: If only x questions from the Function subscale were answered, the added score of the x questions should be weighed by 9/x. The range of scores will be 0 to 90, with a lower score indicting better (higher) function.
Table continued on next page		

Analysis Time point	FIQR Item	Derivation
	Overall impact subscale score: 10) Fibromyalgia prevented me from accomplishing goals for the week 11) I was completely overwhelmed by my fibromyalgia symptoms	Sum of scores from questions 10 and 11. In the case of missing data, unanswered questions should be compensated using the following "weighting" factor: If only x questions from the Overall impact subscale were answered, the added score of the x questions should be weighed by 2/x. The range of scores will be 0 to 20, with a lower score indicating better (lower) impact.
	Symptoms subscale score: Please rate: 12) Your level of pain 13) Your level of energy 14) Your level of stiffness 15) The quality of your sleep 16) Your level of depression 17) Your level of memory problems 18) Your level of anxiety 19) Your level of tenderness to touch 20) Your level of balance problems 21) Your level of sensitivity to loud noises, bright lights, odors and colds	Sum of scores from questions 12 to 21. In the case of missing data, unanswered questions should be compensated using the following "weighting" factor: If only x questions from the Symptoms subscale were answered, the added score of the x questions should be weighed by 10/x. The range of scores will be 0 to 100, with a lower score indicating a better (lower) level of symptoms.
	Total score	A normalization factor is applied to each of the three subscale scores: the function subscale score is divided by 3, the overall subscale score is divided by 1 (i.e. it is left unchanged), and the symptoms subscale score is divided by 2. The total FIQR score is the sum of the three normalized subscale scores. The range of scores will be 0 to 100, with a lower score indicating a better response.

EOT: end of treatment

- Overall subject improvement assessed by PGIC at Weeks 2, 4, 8, and EOT.
  The PGIC is a self-administered 7-point Likert scale that asks subjects to evaluate their fibromyalgia relative to baseline. This is a single question and the grade ranges from 1 to 7, where 1 anchors "Very Much Improved" and 7 anchors "Very Much Worse". Subjects will complete the questionnaire during the clinic visits on a tablet device.

6.1.3 Exploratory Efficacy Endpoints

Treatment Period

- Change from baseline to Weeks 1, 2, 3, 4, 5, 6, 7 and EOT in mean daily average pain score (see Table 3) assessed by NRS (0 to 10 scale).
- Percentage of subjects achieving > 0%, ≥ 10%, ≥ 20%, ≥ 40%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90% and =100% reduction from baseline to Week 8 and from baseline to 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 FIQR total score (see Table 4).
  Change from baseline to Weeks 2, 4, 8 and EOT in PGIS.
  The PGIS is a self-administered 6-point Likert scale that asks subjects to evaluate how their fibromyalgia is now. This is a single question and the grade ranges from 1 to 6 where 1 anchors "no symptoms" and 6 anchors "very severe". Subjects will complete the questionnaire during the clinic visits on a tablet device.
  Change from baseline is defined in Section 7.1. A negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome).
- Percentage of subjects achieving a PGIC of "Very Much Improved" or "Much Improved" at Week 8 and at EOT.
- Percentage of subjects achieving ≥ 30 % reduction from baseline in FIQR total score at Week 8 and at EOT.
- Percentage of subjects achieving a composite pain response, defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of "Very Much Improved" or "Much Improved" at Week 8 and at EOT.
- Percentage of subjects achieving a composite syndrome response, defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of "Very Much Improved" or "Much Improved" **and** ≥ 30 % reduction from baseline in FIQR total score, at Week 8 and EOT.

Table 5 Summary of responder definition for exploratory endpoints

Analysis Time point	Responder definition	Handling of missing data
Percentage of subjects achieving > 0%, ≥ 10%, ≥ 20%, ≥ 40%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90% and =100% reduction compared to baseline in mean daily average pain score		
Week 8	Except for >0% and 100%, a subject will be classified as a responder if the reduction from baseline to Week 8 is ≥ the specified percentage; otherwise classified as a non-responder. For >0%, a subject will be classified as a responder if the reduction from baseline to Week 8 is >0%; otherwise classified as a non-responder. For 100%, a subject will be classified as a responder if the reduction from baseline to Week 8 is =100%; otherwise classified as a non-responder.	Subjects with missing baseline or Week 8 data will be classified as non-responders.
Week 8 ***using mBOCF[a] for imputation of missing data***	As above.	Subjects with missing baseline or EOT data will be classified as non-responders.
EOT	Except for >0% and 100%, a subject will be classified as a responder if the reduction from baseline to EOT is ≥ the specified percentage; otherwise classified as a non-responder. For >0%, a subject will be classified as a responder if the reduction from baseline to EOT is >0%; otherwise classified as a non-responder. For 100%, a subject will be classified as a responder if the reduction from baseline to EOT is =100%; otherwise classified as a non-responder.	Subjects with missing baseline or EOT data will be classified as non-responders
Percentage of subjects achieving a PGIC of "Very Much Improved" or "Much Improved"		
Week 8 ***using mBOCF[a] for imputation of missing data***	A subject will be classified as a responder if they answer "Very Much Improved" or "Much Improved" at Week 8; whereas if they answer "Minimally Improved", "No Change", "Minimally Worse", "Much Worse" or "Very Much Worse" they will be classified as a non-responder.	Subjects with missing EOT data will be classified as non-responders.
EOT	A subject will be classified as a responder if they answer "Very Much Improved" or "Much Improved" at EOT; whereas if they answer "Minimally Improved", "No Change", "Minimally Worse", "Much Worse" or "Very Much Worse" they will be classified as a non-responder.	Subjects with missing EOT data will classified as non-responders.

Table continued on next page

Analysis Time point	Responder definition	Handling of missing data
Percentage of subjects achieving ≥ 30 % reduction from baseline in FIQR total score		
Week 8 ***using mBOCF[a] for imputation of missing data***	A subject with at least 30% reduction in FIQR total score from baseline to Week 8 will be classified as a responder; otherwise they will be classified as a non-responder.	Subjects with missing baseline or EOT data will be classified as non-responders.
EOT	A subject with at least 30% reduction in FIQR total score from baseline to EOT will be classified as a responder; otherwise they will be classified as a non-responder.	Subjects with missing baseline or EOT data will classified as non-responders
Percentage of subjects achieving a composite pain response		
Week 8 ***using mBOCF[a] for imputation of missing data***	A subject with at least 30% reduction from baseline in mean daily average pain score **and** PGIC of "Very Much Improved" or "Much Improved" at Week 8 will be classified as a responder; otherwise they will be classified as a non-responder.	Subjects with missing baseline or EOT data for any component will be classified as non-responders.
EOT	A subject with at least 30% reduction from baseline in mean daily average pain score **and** PGIC of "Very Much Improved" or "Much Improved" at EOT will be classified as a responder; otherwise they will be classified as a non-responder.	Subjects with missing baseline or EOT data for any component will classified as non-responders
Percentage of subjects achieving a composite syndrome response		
Week 8 ***using mBOCF[a] for imputation of missing data***	A subject with at least 30% reduction from baseline in mean daily average pain score **and** PGIC of "Very Much Improved" or "Much Improved" **and** at least 30 % reduction from baseline in FIQR total score at Week 8 will be classified as a responder; otherwise they will be classified as a non-responder.	Subjects with missing baseline or EOT data for any component will be classified as non-responders.
EOT	A subject with at least 30% reduction from baseline in mean daily average pain score **and** PGIC of "Very Much Improved" or "Much Improved" **and** at least 30 % reduction from baseline in FIQR total score at EOT will be classified as a responder; otherwise they will be classified as a non-responder.	Subjects with missing baseline or EOT data for any component will classified as non-responders

AE: adverse event; EOT: end of treatment; FIQR: Fibromyalgia impact questionnaire revised; mBOCF: modified baseline observation carried forward; PGIC: Patient global impression of change

[a]mBOCF for these binary response endpoints will be implemented as follows: Subjects who discontinue early due to lack of efficacy or adverse events (AEs) will be classified as non-responders whereas subjects who discontinue early due to other reasons will be classified using their responder status at EOT.

- Change from baseline to Weeks 1, 2, 3, 4, 5, 6, 7, 8 and EOT in mean daily FMSD item scores, which captures all critical sleep disturbance features of fibromyalgia.

  The FMSD is an 8-item patient reported outcome (PRO) measure of sleep disturbance specific to fibromyalgia subjects, covering the hypothesized domains of Falling Asleep, Staying Asleep, and Sufficient Sleep. Each item is rated on an 11-point NRS anchored by "0 - not at all" and "10 – extremely." Using the e-diary, the subject completes the FMSD to rate their quality of sleep during the previous night each morning at a consistent time (ideally between 6 am and noon however can be captured until 2 am the next morning). For this reason, any FMSD item entered onto the e-diary up to 2 am the following day will be attributed to the previous study day. This is described in more detail in Section 7.11.4.3

Table 6 Derivation of mean daily score for each FMSD item

Analysis Time point	FMSD Item	Derivation
Baseline Treatment period Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8 EOT, Follow-up period Week 10	Item 1: Difficulty with falling asleep Item 2: Restlessness of sleep Item 3: Difficulty getting comfortable Item 4: Difficulty staying asleep Item 5: Degree of deep sleep Item 6: Degree of being rested when waking up for the day Item 7: Difficulty with beginning the day Item 8: Degree of having enough sleep during the previous night	Score from 0 to 10 for each individual item. To calculate the mean daily FMSD item scores at each analysis timepoint: Arithmetic mean of non-missing FMSD item scores collected within time window per visit windows defined in Section 7.11.4.3, Table 22. If any of the FMSD item scores are missing on all of the days during the time window, then the FMSD item score for that time point will be set to missing.

EOT: end of treatment; FMSD: Fibromyalgia Sleep Diary

Change from baseline is defined in Section 7.1. For FMSD Item 1, Item 2, Item 3, Item 4 and Item 7 a negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome); whereas FMSD Item 5, Item 6 and Item 8 a positive change indicates an improvement in sleep symptoms compared to baseline.

- Change from baseline to Week 8 and EOT in the HADS depression subscale.
  HADS is a 14-item self-report scale developed for the assessment of anxiety and depression in non-psychiatric populations. Each item is rated on a 4-point Likert-type scale with varying level descriptors specific to each item. For the purposes of this study, only the 7-item depression subscale will be administered to monitor subjects for symptoms of depression. Higher scores indicate more severe symptoms of depression.

  Change from baseline is defined in Section 7.1. A negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome). Change from baseline

to Week 8 and to EOT for the HADS depression subscale will only be calculated for subjects who have baseline data captured using the corrected version of the questionnaire. For subjects who have baseline HADS data captured using the original version of the questionnaire that was used at the start of the study change from baseline will not be derived. Data captured using the original version of the questionnaire will be listed only and will not be presented in any tables.

Table 7 Derivation of HADS depression subscale

Analysis Time point	HADS Version	HADS Depression Item	Derivation
Baseline Treatment period Week 8 EOT	Corrected	Depression total score: • I feel as if I am slowed down • I enjoy the things I used to enjoy • I have lost interest in my appearance • I can laugh and see the funny side of things • I look forward with enjoyment to things • I feel cheerful • I can enjoy a good book, radio or television program Note: Reverse scoring has been applied on CRF.	Sum of the non-missing scores from the 7 questions used for depression and yields a score of 0 to 21. The score cannot be calculated if the score is missing for 2 or more of the individual questions. If the score is missing only for 1 question, then it will be imputed with average of the remaining non-missing scores from the 6 questions.
Baseline	Original	Depression total score: 1) I wake early and then sleep badly for the rest of the night. 3) I feel miserable and sad. 5) I have lost interest in things. 7) I have a good appetite. 9) I feel life is not worth living. 10) I still enjoy the things I used to. 13) I feel as if I have slowed down. For items 7 and 10 the scoring is reversed	Sum of the non-missing scores from the 7 questions used for depression and yields a score of 0 to 21. The score cannot be calculated if the score is missing for 2 or more of the individual questions. If the score is missing only for 1 question, then it will be imputed with average of the remaining non-missing scores from the 6 questions.

EOT: end of treatment; HADS: Hospital anxiety and depression scale

- Change from baseline to Week 8 and EOT in EQ-5D-5L.
  EQ-5D-5L consists of 2 parts: 1) the descriptive system and 2) the EQ visual analogue scale (EQ-VAS).
  The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In the newest version, each dimension has 5 response levels: no problems, slight problems, moderate problems, severe problems and unable to perform the activity. There will be no imputation for missing answers on the questions.
  The EQ-VAS is recorded by the subject of his/her health on a vertical, visual analogue scale where the endpoints are labeled 'The best health you can imagine' (=100) and 'The worst health you can imagine' (=0). There will be no imputation for missing answer on

the question.
Change from baseline is defined in Section 7.1 and only applies to the EQ-VAS. A positive change in the EQ-VAS indicates an improvement in health versus baseline.

Table 8 Derivation of EQ-5D-5L items

Analysis Time point	EQ-5D-5L Item	Derivation
Baseline Treatment period Week 8, EOT Follow-up period Week 10	Descriptive system dimension 1) Mobility 2) Self-care 3) Usual activities 4) Pain/discomfort 5) Anxiety/depression	For each dimension, there are 5 response levels of increasing severity: 1) No problems 2) Slight problems 3) Moderate problems 4) Severe problems 5) Unable to perform the activity There will be no imputation for missing answers on the questions.
	EQ-VAS: Visual analogue scale from 0 to 100.	Score from 0 to 100. There will be no imputation for missing answer on the question.

- Proportion of days with rescue medication use at Weeks 1, 2, 3, 4, 5, 6, 7, 8, EOT and Overall double-blind treatment period.
  The number and proportion of days with rescue medication use during each analysis time point will be derived for each subject as shown in Table 9. The number of days with rescue medication use will be utilized to derive the proportion of days with rescue medication use and will be used for summaries of raw proportions. See Section 7.4.3 for formal analysis of this endpoint. Rescue medication use will be derived for acetaminophen use collected from the daily e-diary only.
- Incidence of subjects using rescue medication at Weeks 1, 2, 3, 4, 5, 6, 7, 8, EOT and Overall double-blind treatment period.
- Average daily dosage of rescue medication at Weeks 1, 2, 3, 4, 5, 6, 7, 8, EOT and Overall double-blind treatment period.
  The derivation of average daily dosage of rescue medication use (acetaminophen use only) during each time point for each subject is shown in Table 9.

Table 9 Derivation of rescue medication endpoints

Analysis Time point	Item	Derivation
Baseline, Treatment period Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8 EOT, Overall double-blind treatment period Follow-up period Week 10, Overall follow-up period	Proportion of days with rescue medication use	$\frac{\text{Number of days of rescue medication}}{\text{Total number of days}}$ Number of days of rescue medication: Number of days of acetaminophen use within time window per visit windows defined in Section 7.11.4.3 Table 21 Total number of days: Minimum of (upper bound of the time window, last assessment day from e-diary data) – lower bound of the time window + 1, per visit windows defined in Section 7.11.4.3 Table 21 If no rescue medication is taken on any of the days during the time window, then the proportion of days with rescue medication use for that time point will be zero.
	Incidence of subjects using rescue medication	Percentage of subjects with acetaminophen use within the time window per visit windows defined in Section 7.11.4.3 Table 21
	Average daily dosage of rescue medication (mg)	$\frac{\text{Total dose of rescue medication}}{\text{Total number of days}}$ Total dose of rescue medication: Total dose of acetaminophen within time window per visit windows defined in Section 7.11.4.3 Table 21 If no rescue medication (acetaminophen) is taken on any of the days during the time window, then the total dose will be zero. Total number of days: Minimum of (upper bound of the time window, last assessment day from e-dairy data) – lower bound of the time window + 1, per visit windows defined in in Section 7.11.4.3 Table 21

EOT: end of treatment

- Change from baseline to Weeks 2, 4, 8 and EOT in Irritable Bowel Syndrome Symptom Summary Score and abdominal pain, stomach pain, abdominal cramping, abdominal pressure, and bloating individual items as assessed by the mIBS-D Daily Symptom Diary.
  The mIBS-D is a 5-item questionnaire that assesses the predominant symptoms of IBS-D (abdominal pain, stomach pain, abdominal pressure, bloating, abdominal cramps) on an 11-point NRS (0 - absence of symptoms to 10- severe symptoms). Subjects will be asked to complete the questionnaire items while considering 2 distinct recall periods (previous 24 hours and last 7 days) and will enter their scores on a tablet device during their clinic visit. The Irritable Bowel Syndrome 4-item Symptom Summary Score will

be derived for each subject for each of the 2 distinct recall periods (previous 24 hours and last 7 days) as shown in Table 10

Change from baseline is defined in Section 7.1 A negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome).

Table 10 Derivation of Irritable Bowel Syndrome Symptom Summary Score

Analysis Time point	Derivation
Baseline Treatment period Week 2, Week 4, Week 8, EOT	Symptom summary score: (abdominal pain + abdominal pressure + abdominal cramps + bloating)/4 The score ranges between 0 to 10 with 0 indicating an absence of symptoms and 10 indicating severe symptoms. Apart from abdominal pain (where responses to the stomach pain item for the same time point & recall period may be used) there will be no imputation for missing answers on the questions. The symptom summary score cannot be calculated if data is missing in at least one of the items (apart from abdominal pain which can be replaced with stomach pain)

- Change from baseline to Week 8 and EOT in neuropathic pain symptoms as assessed by the Neuropathic Pain Symptom Inventory (NPSI).
  The NPSI is a self-report questionnaire specifically designed to evaluate the different symptoms of neuropathic pain and will be completed by the subject during clinic visits on a tablet device. The questionnaire comprises a list of 10 descriptors (plus 2 temporal items) reflecting spontaneous, paroxysmal and evoked pain (i.e., mechanical and thermal allodynia/hyperalgesia) and paresthesia/dysesthesia. Each of these items is quantified on a (0–10) numerical scale, with 0 = no pain and 10 = the most intense pain imaginable; and the total score ranges from 0 to 100. The NPSI total score and 5 subscale scores including burning (superficial) spontaneous pain, pressing (deep) spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia will be derived for each subject as shown in Table 11

Table 11 Derivation of Neuropathic Pain Symptom Inventory total score and subscores

Analysis Time point	Derivation
Baseline, Treatment period Week 8, EOT	Burning (superficial) spontaneous pain: Question 1 score Pressing (deep) spontaneous Pain: (Question 2 score + Question 3 score)/2 Paroxysmal pain : (Question 5 score + Question 6 score)/2 Evoked pain : (Question 8 score + Question 9 score + Question 10 score)/3 Paresthesia/dysesthesia : (Question 11 score + Question 12 score)/2 Total score : (Question 1 score + Question 2 score + Question 3 score + Question 5 score + Question 6 score + Question 8 score + Question 9 score + Question 10 score + Question 11 score + Question 12 score) The subscales where data is missing (any item) cannot be scored. The total score cannot be calculated if data is missing in at least one of the subscales.

Follow-Up Period

The following exploratory endpoints during the follow-up period will also be assessed. In the derivation of these endpoints there will be no imputation of missing data as these will be summarized using descriptive summaries only. Change from baseline and change from EOT are defined in Section 7.1. Apart from the EQ-VAS a negative change indicates a reduction/improvement from baseline or EOT. Whereas a positive change indicates an increase/worsening versus baseline or EOT.

- Change from baseline and EOT to Week 10 in mean daily average pain score.
- Change from baseline and EOT to Week 10 in FIQR Function subscale, Symptoms subscale, Overall Impact subscale, and total score.
- Overall subject improvement assessed by PGIC to Week 10.
- Change from baseline and EOT to Week 10 in PGIS.
- Percentage of subjects achieving ≥ 30 % reduction from baseline to Week 10 in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.
- Percentage of subjects achieving ≥ 50 % reduction from baseline to Week 10 in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.
- Change from baseline to Week 10 in EQ-5D-5L.
- Proportion of days with rescue medication use at Week 10 and Overall follow-up period.
- Incidence of subjects using rescue medication at Week 10 and Overall follow-up period.
- Average daily dosage of rescue medication at Week 10 and Overall follow-up period.

6.2 Safety Variables

The schedule of safety assessments is shown in Table 1. Baseline is defined as the last assessment on or prior to the first dose day (Day 1) of double-blind study drug.

6.2.1 Adverse Events

Adverse events will be categorized as those which occur prior to first dose or treatment-emergent as follows:

- Adverse events prior to first dose
  Adverse events prior to first dose is an adverse event which starts prior to the first dose of study drug. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will be considered as an AE prior to first dose. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will not be considered as an AE prior to first dose.
- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).

  TEAE is defined as an adverse event which starts, or worsens, after the first dose of study drug through 30 days after the last dose of study drug. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent.

  TEAE (Treatment period) is an adverse event which starts, or worsens, after the first dose of study drug through to 4 days after the last dose of study drug. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent, unless it worsens in severity after Day 1 (up to day 4 after last dose).

  TEAE (Follow-up period) is an adverse event which starts, or worsens, 5 days after the last dose of study drug through 30 days after the last dose of study drug.

  A drug-related TEAE is defined as any TEAE with a possible or probable relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

For each AE, duration will be calculated in days, using the following formula:

- Duration of AE = End date of AE – Start date of AE +1,

where the start date of AE and the end date of AE are defined as the onset date and end date of the AE, as captured in the eCRF. Imputed dates for the start date or end date may be used to calculate duration (Section 7.11.1).

6.2.2 Clinical Laboratory Variables

Clinical laboratory variables are raw values (i.e., values at each scheduled visit) and changes from baseline for chemistry, hematology and urinalysis parameters at Weeks 2, 4, 8 and Week 10.

6.2.3 Vital Signs

Vital signs variables are raw values (i.e., values at each scheduled visit) and changes from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate at Weeks 2, 4, 8 and Week 10.

6.2.4 Electrocardiograms

The 12-lead electrocardiograms (ECG) scheduled assessments will be made at baseline, Week 8 and Week 10. The results will be recorded as "normal", "abnormal not clinically significant", or "abnormal clinically significant". Electrocardiogram variables are raw values (categorical) at each scheduled visit and changes from baseline (shift from baseline) at Week 8 and Week 10.

6.2.5 Columbia Suicide Severity Rating Scale

The Columbia suicide severity rating scale (C-SSRS) is a questionnaire used for suicide assessment. At screening, the "Screening/Baseline" version is to be used to determine eligibility. During all subsequent visits, the "Since last visit" version is used to monitor on-study suicidal ideation and behavior after the initial assessment. Analysis will mainly focus on two aspects: suicidal ideation and suicidal behavior and they will be derived for each subject as follows using the "Since Last visit" version:

Analysis Time point	C-SSRS Item	Derivation
Baseline Treatment period Week 2, Week 4, Week 8, EOT, Overall double-blind treatment period Follow-up period Week 10, Overall follow-up period	Suicidal ideation	A "yes" answer to any one of the following five questions from suicidal ideation section on the C-SSRS. 1. Wish to be dead 2. Non-specific active suicidal thoughts 3. Active suicidal ideation with any methods (not plan) without intent to act 4. Active suicidal ideation with some intent to act, without specific plan 5. Active suicidal ideation with specific plan and intent If a subject answers "yes" to more than one suicidal ideation question within a visit window at an analysis time point (Section 7.11.5.3, Table 25), the worst case response (i.e., the highest) will be used in any summaries.
Table continued on next page		

Analysis Time point	C-SSRS Item	Derivation
	Suicidal behavior	A "yes" answer to any one of the following five questions from suicidal behavior section on the C-SSRS. 6. Preparatory acts or behavior 7. Aborted attempt 8. Interrupted attempt 9. Actual attempt 10. Completed suicide If a subject answers "yes" to more than one suicidal behavior question within a visit window (Section 7.11.5.3, Table 25), at an analysis time point (the worst case response (i.e., the highest) will be used in any summaries.
	Suicidal ideation or behavior	A "yes" answer to any one of the above ten suicidal ideation or behavior questions on the C-SSRS.
	Self-injurious behavior without suicidal intent	A "yes" answer to the following question from suicidal behavior section on the C-SSRS: "Has subject engaged in Non-Suicidal Self-Injurious Behavior?"

There will be no imputation for missing answers on questions.

6.3 Pharmacokinetic Variables

Pharmacokinetic (PK) sampling will occur on Day 1 in the clinic at approximately 1 to 4 hour(s) after dosing and once (anytime during the visit) at Weeks 2, 4 and 8. Date and time of the dose taken prior to collecting the PK sample, as well as the date and time of the last meal in relation to that dose will be captured in the electronic Case Report Form (eCRF).

Plasma concentrations for ASP0819 and any metabolites (if applicable) will be listed only.

6.4 Other Variables

6.4.1 Exposure

For each subject, duration of exposure (defined as length of time on 8 weeks of treatment period) will be calculated in days, using the following formula:

- Duration of exposure = Date of last dose of study drug – Date of first dose of study drug +1,

where the date of first dose of study drug and the date of last dose of study drug are defined as the first study drug dosing date and the last study drug dosing date, as captured in the eCRF. Imputed dates for the first or last dose of study drug may be used to calculate exposure (Section 7.11.1).

6.4.2 Percent overall compliance

Subjects will be instructed to take 3 capsules once per day.

- Overall compliance (%) = 100 × (total number of capsules actually received during 8 weeks of treatment period / total number of capsules planned to receive during 8 weeks of treatment period).

Where

- Total number of capsules planned to receive during 8 weeks of treatment period = 3 x duration of exposure. Duration of exposure will be calculated as described in Section 6.4.1
- Total number of capsules actually received during 8 weeks of treatment period = total number of capsules dispensed during 8 weeks of treatment period – total number of capsules returned during 8 weeks of treatment period.

Double-blind study drug compliance for the entire double-blind treatment period will be calculated for subjects whose total number of capsules taken and the complete date of the first dose and the last dose of double-blind study drug are known.

6.4.3 Previous and concomitant medication

- Previous and concomitant non-medication therapy
  A previous non-medication therapy (screening/wash-out) is defined as any non-medication therapy administered up to the last day of screening/washout (i.e. prior to the baseline diary run-in).

  A previous non-medication therapy (baseline diary run-in) is defined as any non-medication therapy administered after the last day of screening/washout and before the first dose of double-blind study drug.

  A concomitant non-medication therapy (double-blind treatment period) is defined as any non-medication therapy administered between the first dose (inclusive) of double-blind study drug and the last dose of double-blind study drug (inclusive).

  A concomitant non-medication therapy (follow-up period) is defined as any non-medication therapy administered after the last dose of double-blind study drug.

- Previous and concomitant medication
  A previous medication (screening/wash-out) is defined as any medication taken up to the last day of screening/washout (i.e. prior to the baseline diary run-in).

  A previous medication (baseline diary run-in) is defined as any medication taken after the last day of screening/washout and before the first dose of double-blind study drug.

  A concomitant medication (double-blind treatment period) is defined as any medication taken between the first dose (inclusive) of double-blind study drug and the last dose of double blind study drug (inclusive).

  A concomitant medication (follow-up period) is defined as any medication taken after the last dose day of double-blind study drug.

6.4.4 Time since onset of Fibromyalgia symptoms and time since diagnosis

- Time since onset of FM symptoms (years) = (Informed consent date -date FM symptoms started + 1)/365.25
- Time since FM diagnosis (years) = (Informed consent date – date of FM diagnosis + 1)/365.25.

Imputed dates for the date FM symptoms started and FM diagnosis may be used to calculate both of these endpoints as described in Section 7.11.1

6.4.5 Mini-International Neuropsychiatric Interview

The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I 7.0) is a short, structured diagnostic interview administered by trained personnel. The instrument captures the major Axis I psychiatric disorders in Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and International Statistical Classification of Diseases and Related Health Problems (ICD-10). Each module begins with screening questions that are answered yes or no. A negative response in the screening algorithm advances the interview to the next module, whereas a positive response will prompt additional questions that ask subjects to characterize behavior with "yes" or "no" responses. The final number of YESs or NOs allows the coding a final evaluation per module by Yes/No answer (according to time recall) or severity (according to module): current, in early remission and in remission. The M.I.N.I. 7.0 will be completed at Screening and any diagnosis identified from the M.I.N.I will be captured in the eCRF.

6.4.6 Widespread Pain Index and Symptom Severity Scale score

The Widespread Pain Index (WPI) and Symptom Severity (SS) scale score will be completed by the clinician on a tablet device during the Screening visit.

The WPI is a checklist of 19 non-articular body parts classified in 5 body regions. The body parts are checked if pain/tenderness is observed. The WPI global score is the sum of body parts checked as presence of pain and ranges from 0 to 19.

The SS Scale is comprised of two parts:

- First part: evaluation of 3 key-symptoms (fatigue, waking unrefreshed and cognitive symptoms) over the past week. The severity of these symptoms will be measured on a 4-point response scale (from 0 = no problem to 3 = severe).
  The score for the first part is the sum of the item scores and ranges from 0 to 9.
- Second Part: presence evaluation (1=presence and 0=absence) of 3 other somatic symptoms (headaches, pain/cramps in lower abdomen and depression) during the previous 6 months.
  The score for the second part is the sum of the item scores and ranges from 0 to 3.

The SS Scale score is the sum of the first and the second part scores and ranges from 0 to 12.

6.4.7 Complex Medical Symptoms Inventory

The Complex Medical Symptoms Inventory (CMSI) is designed to aid clinicians in collecting information from fibromyalgia patients regarding their disease-specific symptoms and to characterize the diagnosis. The inventory contains 2 parts: a symptom checklist to be completed by patients, and a diagnostic inventory completed by the clinician. In this study, only the symptom checklist will be utilized.

The symptom checklist contains 39 items (males) or 41 items (females). For each symptom question, subjects mark a box to indicate if the symptom: 1) has occurred for at least

3 months in the past year, and/or 2) has occurred for a 3-month period during their lifetime. Only the boxes that apply should be checked. The CMSI will be completed on the tablet device by the subject at Baseline Diary Run-In (Visit 2). The CMSI total score is the sum of the number of items that the subject checks as either occurring for at least 3 months in the past year and/or has occurred for a 3-month period during their lifetime. The CMSI total score at baseline will be calculated and ranges from 0 to 39 for males and 0 to 41 for females. Baseline is defined as the last assessment on or prior to the first dose day (Day 1) of double-blind study drug.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation (SD) and/or standard error (SE), median, minimum and maximum. When needed, the use of other percentiles (e.g., 10%, 25%, 75% and 90%) will be mentioned in the relevant section. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%.

Summaries based on FAS and PPS (e.g. disposition, baseline and efficacy data) will be presented by planned treatment group, unless specifically stated otherwise. Safety analysis and other summaries based on SAF will be presented by actual treatment received. For summaries which present both absolute values over time and change from baseline values over time the number of subjects used to calculate the descriptive statistics will be those who have non-missing data at each analysis visit and at baseline. For endpoints which include mBOCF, LOCF or mLOCF imputation the descriptive statistics will be calculated after the imputation has been performed.

Unless otherwise specified, statistical comparisons will be made using one-sided tests at the α=0.05 significance level and two-sided 90% confidence intervals (CIs) will be presented when applicable. When two-sided p-values are presented statistical comparisons will be made using an α=0.1 significance level.

The pooled site will be used in all statistical models that include the "center" as a factor. The pooling sites algorithm is provided in Section 7.11.6.

All data, including observed and derived data, will be presented in subject data listings.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher on Unix. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

Calculations of change from baseline or change from EOT:

- **Change from baseline to post-baseline** will be calculated as: post-baseline value – baseline value.
- **Change from EOT to Week 10** will be calculated as: Week 10 – EOT

- **Percent change from baseline to post-baseline** will be calculated as: 100 × (change / baseline value).

Handling of baseline value of 0 in analysis involving percent change is discussed in the TLF Specifications for this study.

Definition of Study Day:

The number of study days relative to the first dose date of study drug (Study Day), is calculated as:

- Study Day = Date of assessment – Date of first dose of study drug +1, when the date of assessment is on or after the date of first dose of study drug
- Study Day = Date of assessment – Date of first dose of study drug, when the date of assessment is before the date of first dose of study drug

where the date of first dose of study drug is defined in Section 6.4.1

The day of the first dose of study drug is defined as Study Day 1, while the day before the date of first dose of study drug (i.e., Randomization visit) is defined as Study Day -1 (there is no Study Day 0).

For daily average pain scores assessed by NRS and FMSD scores, any data captured in the e-diary up to 2 am in the morning of the following day will be assigned to the previous day in the derivation of Study Day.

Definition of Follow-up Day:

The number of study days relative to the last dose date of study drug (Follow-up Day), is calculated as:

- Follow-up Day = Date of assessment – Date of last dose of study drug

where the date of last dose of study drug up is defined in Section 6.4.1

Follow-up Day will equal zero on the day of the last dose of study drug and positive values will indicate days during the follow-up period.

For daily average pain scores assessed by NRS and FMSD scores, any data captured in the e-diary up to 2 am in the morning of the following day will be assigned to the previous day in the derivation of Follow-up Day.

Definition of Treatment Period:

Time from Study Day 1, through to Follow-up Day 4.

Definition of Efficacy Follow-up Period:

Time from Follow-up Day 5 through to Follow-up Day 28.

Definition of Safety Follow-up Period:

Time from Follow-up Day 5 through to Follow-up Day 30.

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number of subjects with informed consent, discontinued during screening/wash-out, entered the baseline diary run-in, discontinued prior to randomization, randomized for all subjects with informed consent ('Total' overall only);
- Number and percentage of subjects who were randomized, took study drug, did not take study drug, in the analysis sets by treatment group and 'Total' over all treatment groups for all randomized subjects;
- Number and percentage of subjects who completed and discontinued the screening/wash-out, and primary reason for discontinuing screening/wash-out for all subjects with informed consent ('Total' overall only);
- Number and percentage of subjects who completed and discontinued prior to randomization, and primary reason for discontinuing prior to randomization for all subjects who came for randomization visit ('Total' overall only);
- Number and percentage of subjects who completed and discontinued treatment, and primary reason for treatment discontinuation by treatment group and 'Total' over all treatment groups for all randomized subjects, SAF and FAS;
- Number and percentage of subjects completed and discontinued the follow-up period, and primary reason for discontinuing the follow-up period by treatment group and 'Total' over all treatment groups for all randomized subjects and SAF;
- Number and percentage of subjects who completed and discontinued treatment at each visit, by primary reason for treatment discontinuation by treatment group and 'Total' over all treatment groups for all randomized subjects, SAF and FAS;
- Number and percentage of subjects excluded from PPS by reason for exclusion defined in Section 5.2.1, by treatment group and 'Total' over all treatment groups for FAS; and
- Number and percentage of subjects for each protocol version by treatment group and 'Total' over all treatment groups for randomized subjects, as well as, number and percentage of subjects for each protocol version for screen failures (subjects who discontinued during screening/wash-out or prior to randomization) and Total Number of subjects enrolled (i.e. including Screen Failures).

A stacked bar plot of cumulative discontinuation rates (colored by primary reason for discontinuation) overall and at each visit by treatment group will be produced for the SAF.

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all randomized subjects. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by treatment group and total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol

deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and li sting. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.2.3 Demographic and Other Baseline Characteristics

No hypothesis testing will be performed comparing treatment groups for demographic and other baseline characteristics.

7.2.3.1 Demographics

Demographic characteristics will be summarized by descriptive statistics for the following variables listed in Table 12. This will be done for all randomized subjects, as well as for the SAF, FAS and PPS by treatment group and 'Total' over all treatment groups.

Table 12 Demographic characteristics

Characteristic	Summarized as	Categories
Age (years)	Continuous	--------
Weight (kg)	Continuous	--------
Height (cm)	Continuous	--------
BMI (kg/m^2)	Continuous	--------
Sex	Categorical	• Male • Female • Unknown
Race	Categorical	• White • Black or African American • Asian • American Indian or Alaska Native • Native Hawaiian or Other Pacific Islander • Other
Ethnicity	Categorical	• Not Hispanic or Latino • Hispanic or Latino
Age group	Categorical	• < 45 years • ≥ 45 to < 65 years • ≥ 65 years
EudraCT Age group	Categorical	• ≥ 18 to ≤ 64 years • ≥ 65 to ≤ 84 years

Table continued on next page

Characteristic	Summarized as	Categories
BMI group 1	Categorical	• < 25 kg/m^2 • ≥ 25 to < 30 kg/m^2 • ≥ 30 kg/m^2
BMI group 2	Categorical	• < 30 kg/m^2 • ≥ 30 kg/m^2

Number and percentage of subjects randomized in each site will be presented by treatment group and 'Total' over all treatment groups for randomized subjects. In addition, number and percentage of pooled sites and the combination of sites into pooled sites will be summarized by treatment group and overall for the FAS.

7.2.3.2 Fibromyalgia and Targeted Medical History

Fibromyalgia and targeted medical history will be summarized by descriptive statistics for the following variables listed in Table 13. This will be done for all randomized subjects, the SAF, FAS and PPS by treatment group and 'Total' over all treatment groups.

Table 13 Fibromyalgia Diagnosis and Targeted Medical History

Characteristic	Summarized as	Categories
Time since FM diagnosis (years)	Continuous	--------
Time since onset of FM symptoms (years)	Continuous	--------
Currently treated for FM	Categorical	• Yes • No
History of Major Depressive Disorder (MDD) as assessed by M.I.N.I.	Categorical	• Yes • No
Ongoing MDD (only for subjects with a History of MDD)	Categorical	• Yes • No
Currently Treated with Medication for MDD (only for subjects with a History of MDD)	Categorical	• Yes • No
HADS Depression total score*	Continuous	--------
HADS Depression group*	Categorical	• Normal (0 to 7) • Mild mood disturbance (8 to 10) • Moderate mood disturbance (11 to 14) • Severe mood disturbance (15 to 21)
C-SSRS Item: • Suicidal ideation • Suicidal behavior • Suicidal ideation or behavior • Self-injurious behavior without suicidal intent	Categorical	For each item: • Yes • No
History of Temporomandibular Disorders	Categorical	• Yes • No
History of Irritable Bowel Syndrome	Categorical	• Yes • No

Table continued on next page

Characteristic	Summarized as	Categories
History of Chronic Tension Type Headache	Categorical	● Yes ● No
History of Migraine	Categorical	● Yes ● No
History of Chronic Low Back Pain	Categorical	● Yes ● No
History of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome	Categorical	● Yes ● No
History of Interstitial Cystitis/Painful Bladder Syndrome	Categorical	● Yes ● No
History of Endometriosis (Females Only)	Categorical	● Yes ● No
History of Vulvodynia (Females Only)	Categorical	● Yes ● No
Alcohol History	Categorical	● Never ● Current ● Former
History of Alcohol Use Disorder (only for subjects with current or former Alcohol History)	Categorical	● Yes ● No
History of Drug Use	Categorical	● Never ● Current ● Former
History of Substance Use Disorder (only for subjects with current or former History of Drug Use)	Categorical	● Yes ● No
First or Second Degree Family History of • Fibromyalgia • Depression • Bipolar disorder	Categorical	For each Family History: ● Yes ● No

C-SSRS: Columbia Suicide Severity Rating Scale, FM: Fibromyalgia, HADS: Hospital Anxiety and Depression Scale, MDD: Major Depressive Disorder, M.I.N.I: Mini-International Neuropsychiatric Interview

*Only for subjects with data captured using the corrected version of the HADS questionnaire.

7.2.3.3 Fibromyalgia related baseline disease characteristics

Fibromyalgia related baseline disease characteristics will be summarized by descriptive statistics for the following variables listed in Table 14. This will be done for all randomized subjects, the SAF, FAS and PPS by treatment group and 'Total' over all treatment groups.

Table 14 Fibromyalgia related baseline disease characteristics

Characteristic	Summarized as	Categories
Baseline mean daily average pain score assessed by NRS	Continuous	--------
Baseline mean daily average pain score assessed by NRS group	Categorical	● No pain: 0 ● Mild: > 0 to < 4 ● Moderate: ≥ 4 to < 7 ● Severe: ≥ 7 to 10

Table continued on next page

Characteristic	Summarized as	Categories
WPI	Continuous	-------
SS scale score	Continuous	-------
Tender point count	Continuous	-------
PGIS	Categorical	• No symptoms • Very mild • Mild • Moderate • Severe • Very severe
CMSI total score at baseline	Continuous	--------
Central pain etiology as defined by CMSI*	Categorical	• More centrally driven FM pain • Non-specific FM pain • More peripherally driven FM pain
NPSI: • Burning (superficial) spontaneous pain subscore • Pressing (deep) spontaneous pain subscore • Paroxysmal pain subscore • Evoked pain subscore • Paresthesia/dysesthesia • Total score	Continuous	-------
Peripheral pain etiology as defined by NPSI: NPSI total score and relevant subscales*	Categorical	• Low • High
FIQR: • Function subscale • Symptoms subscale • Overall impact subscale • Total score	Continuous	-------
mIBS-D within past 24 hours at baseline: • Abdominal pain • Stomach pain • Abdominal cramps • Abdominal pressure • Bloating • Symptom summary score	Continuous	--------
mIBS-D within past 24 hours*: • Abdominal pain • Stomach pain • Abdominal cramps • Abdominal pressure • Bloating • Symptom summary score	Categorical	• Low • Mid • High

CMSI: Complex Medical Symptom Inventory, FIQR: Fibromyalgia Impact Questionnaire Revised, FM: Fibromyalgia; mIBS-D: Modified irritable bowel syndrome - diarrhea predominant, NPSI: Neuropathic Pain Symptom Inventory, NRS: Numerical Rating Scale; PGIS: Patient Global Impression of Severity,

Footnotes continued on next page

SS: Symptom severity, WPI: Widespread pain index.

*CMSI will be split into three groups using the CMSI total score at baseline: more centrally driven FM pain (≤ 1st tertile); non-specific FM pain (> 1st tertile to < 3rd tertile) and more peripherally driven FM pain (≥ 3rd tertile); NPSI total score and subscales will be split into two groups using the scores at baseline: low scores (< median) versus high scores (≥ median); m-IBS items and symptom summary score with past 24 hours will be split into three groups at baseline: low (≤ 1st tertile); mid (> 1st tertile to < 3rd tertile) and high (≥ 3rd tertile). These were defined during blinded data review using the methods described in Section 7.8.1

7.2.3.4 Medical History

Medical history is coded in Medical Dictionary for Regulatory Activities (MedDRA), and will be summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by treatment group and "Total" over all treatment groups for the SAF.

7.2.4 Previous and Concomitant Medications

The following will be presented using the SAF:

- All previous medications prior to the baseline diary run-in,
- All previous medications taken for any pain (i.e., FM pain only or FM pain and Other type of pain or Other type of pain only) prior to the baseline diary run-in,
- All previous medications taken for FM pain (FM pain only or FM pain and Other type of pain) prior to the baseline diary run-in,
- All previous medications during baseline diary run-in,
- All previous medications taken for any pain during baseline diary run-in,
- All previous medications taken for FM pain during baseline diary run-in,
- All concomitant medications during the double-blind treatment period,
- All concomitant medications taken for any pain during the double-blind treatment period,
- All concomitant medications taken for FM pain during the double-blind treatment period,
- All concomitant medications taken during the follow-up period,
- All concomitant medications taken for any pain during the follow-up period, and
- All concomitant medications taken for FM pain during the follow-up period.

Previous and concomitant medications are coded with World Health Organization Drug Dictionary (WHO-DD). Each of the above will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by treatment group and 'Total' over all treatment groups. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups. All previous medications taken for any pain prior to the baseline diary run-in; all previous medications taken for any pain during baseline diary run-in; all concomitant medications taken for any pain during the double blind treatment period and all concomitant medications taken for any pain during the follow-up period will also be summarized by preferred WHO name by treatment group and 'Total' over all treatment groups.

In addition to the above summaries, an overview of previous medications taken prior to the baseline diary run-in and previous medications during the baseline diary run-in taken to treat pain will be produced. This will summarize the number and percentage of subjects in each of the following categories for each treatment group and 'Total' over all treatment groups:

- Any pain (i.e., FM pain only; or FM pain and Other type of pain; or Other type of pain only),
- FM pain (i.e., FM pain only; or FM pain and Other type of pain),
- FM pain only,
- FM pain and Other type of pain,

As with previous medication, concomitant medication (double-blind treatment period) and concomitant medication (follow-up period) taken to treat pain will be summarized for each treatment group and 'Total' over all treatment groups for the above categories.

The listing will only contain data of the subjects who actually used previous and concomitant medications.

7.2.5 Previous and Concomitant Non-Medication Therapy

The following will be presented using the SAF:

- All previous non-medication therapies prior to baseline diary run-in,
- All previous non-medication therapies received for any pain (i.e., FM pain only or FM pain and Other type of pain or Other type of pain only) prior to baseline diary run-in,
- All previous non-medication therapies received for FM pain (FM pain only or FM pain and Other type of pain) prior to baseline diary run-in,
- All previous non-medication therapies received during baseline diary run-in,
- All previous non-medication therapies received for any pain during baseline diary run-in,
- All previous non-medication therapies received for FM pain during baseline diary run-in,
- All concomitant non-medication therapies received during the double-blind treatment period,
- All concomitant non-medication therapies received for any pain during the double-blind treatment period,
- All concomitant non-medication therapies received for FM pain during the double-blind treatment period,
- All concomitant non-medication therapies received during the follow-up period,
- All concomitant non-medication therapies received for any pain during the follow-up period, and
- All concomitant non-medication therapies received for FM pain during the follow-up period.

Each of the above will be summarized by treatment group and 'Total' over all treatment groups for:

- Normal Daily Exercise Routines,
- Chiropractic Care,
- Physical Therapy,

- Psychotherapy,
- Massage therapy, and
- Other.

Subjects receiving the same non-medication therapy multiple times will be counted once per medication and investigational period.

In addition to the above summaries an overview of previous non-medication therapies prior to the baseline diary run-in and previous non-medication therapies during the baseline diary run-in received to treat pain, the number and percentage of subjects with the following categories will be summarized for each treatment group and 'Total' over all treatment groups:

- Any pain (i.e. FM pain only; or FM pain and Other type of pain; or Other type of pain only),
- FM pain (i.e. FM pain only; or FM pain and Other type of pain),
- FM pain only,
- FM pain and Other type of pain,

As with previous non-medication therapy, concomitant non-medication therapy (double-blind treatment period) and concomitant non-medication therapy (follow-up period) will be summarized for each treatment group and 'Total' over all treatment groups for the above categories.

The listing will only contain data of the subjects who actually used previous and concomitant non-medication therapies.

7.3 Study Drugs

7.3.1 Exposure

Duration of exposure will be summarized by treatment group and 'Total' over all treatment groups in three ways for the SAF:

- Descriptive statistics will be presented for the total number of days a subject was exposed to study drug.
- Number and percentage of subjects in each of the following mutually exclusive extent of exposure categories:
  - 1 to 7 days,
  - 8 to 14 days,
  - 15 to 28 days,
  - 29 to 48 days,
  - 49 to 64 days,
  - ≥ 65 days.
- Number and percentage of subjects in the following cumulative extent of exposure time categories:
  - ≥ 1 day,
  - ≥ 8 days;

- ≥ 15 days,
- ≥ 29 days,
- ≥ 49 days,
- ≥ 65 days.

7.3.2 Treatment Compliance

Overall compliance with the dosing schedule will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized by treatment group and 'Total' over all treatment groups in two ways for the SAF:

- Descriptive statistics for percent overall compliance.
- Number and percentage of subjects in the following categories of percent overall compliance:
  - < 50%,
  - ≥ 50% to < 80%,
  - ≥ 80% to < 100%,
  - = 100%,
  - > 100% to < 120%,
  - ≥ 120%.

7.4 Analysis of Efficacy

Efficacy analyses will be performed using the FAS and the PPS where indicated. No formal hypothesis testing of comparison between treatment groups will be performed for the efficacy data during the follow-up period i.e., descriptive statistics will be used to summarize the continuous efficacy variables and frequencies and percentages will be used to summarize the categorical efficacy data.

7.4.1 Analysis of Primary Endpoint(s)

Analysis of the primary efficacy endpoint will be performed on the FAS and the PPS. Table 15 describes the primary analysis and sensitivity analyses that will be performed for the primary efficacy endpoint.

Table 15 Summary of the Primary and Sensitivity Analyses for the Primary Efficacy Endpoint

Variable	Imputation	Analysis Set	Analysis Type
Change from baseline to Week 8 in mean daily average pain score assessed by NRS (Primary Analysis)	None	FAS	MMRM analysis of change from baseline[a]
Change from baseline to Week 8 in mean daily average pain score assessed by NRS (Sensitivity Analysis)	Discontinuation-reason based multiple imputation[b]	FAS	MMRM analysis of change from baseline[a]
Change from baseline to Week 8 in mean daily average pain score assessed by NRS (Sensitivity Analysis)	mBOCF[c]	FAS	ANCOVA analysis of change from baseline
Change from baseline to Week 8 in mean daily average pain score assessed by NRS (Sensitivity Analysis)	None	PPS	MMRM analysis of change from baseline[a]

[a]MMRM analysis uses data from baseline and change from baseline data at Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7 and Week 8 time points.

[b]Discontinuation-reason based multiple imputation (MI) will use a "Jump to Reference" algorithm (where placebo is the reference group) for subjects who discontinue due to lack of efficacy or AEs and standard regression-based MI for subjects with missing data for other reasons.

[c]mBOCF is defined as imputation by baseline observation carried forward for subjects who discontinue due to lack of efficacy or AEs, and imputation by last observation carried forward for subjects with missing data at Week 8 for other reasons.

7.4.1.1 Primary Analysis of Primary Endpoint

The hypothesis for comparison of mean change from baseline between ASP0819 and placebo is shown below:

H_0: The mean change from baseline to Week 8 in mean daily average pain score assessed by NRS (0 to 10 scale) for ASP0819 15 mg once daily group is same as (or higher, i.e. worse than) the placebo group.

H_1: The mean change from baseline to Week 8 in mean daily average pain score assessed by NRS (0 to 10 scale) for ASP0819 15 mg once daily group is less than the placebo group.

The change from baseline in mean daily average pain score to Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7 and Week 8 will be analyzed using a mixed-effect, repeated measures (MMRM) model including treatment, center (pooled where necessary), time (study Week 1 to 8), and treatment-by-time interaction as fixed effects, baseline mean daily average pain score and baseline mean daily average pain score-by-time interaction as covariates. The treatment group contrasts for change from baseline to Week 8 will be the primary statistical inference obtained from this model.

This analysis will utilize observed data, and there will be no imputation for missing data. Parameters will be estimated using restricted maximum-likelihood and the Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust SEs.

An unstructured variance-covariance structure will be used to model the within-subject errors. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: heterogeneous Toeplitz (for efficacy endpoints captured in the e-diary only, i.e. mean daily average pain score assessed by NRS and mean daily average FMSD) followed by compound symmetry. Residual plots of scaled residuals will be used to check the fit of the model and assess whether there is any evidence of non-normality.

From the MMRM model the following results will be presented:

- Least squares (LS) mean estimates, SE and 2-sided 90% confidence interval (CI) for mean change from baseline to each analysis time-point (Week 1 to Week 8) within a treatment group (ASP0819, placebo),
- The difference in LS means for ASP0819 versus placebo, SE for the difference and 2-sided 90% CI for the difference at each analysis time-point,
- One-sided p-value for ASP0819 versus placebo at each analysis time-point, and
- Two-sided p-value for treatment-by time interaction.

An overlay plot will be provided for LS mean change from baseline from the MMRM analysis and mean change from baseline from the follow-up period +/- SE vs analysis time-point by treatment group.

7.4.1.2 Sensitivity Analyses of Primary Endpoint

The following sensitivity analyses will be performed for the primary efficacy endpoint to assess the robustness of the primary analysis.

Discontinuation-reason based multiple imputation

The MMRM analysis that will be used to perform the primary analysis of the primary endpoint assumes that missingness is at random. That is, the model assumes that the trajectory of mean daily average pain scores over time for subjects who withdraw is similar to the trajectory for those observed in their own treatment arm which is valid so long as that assumption is reasonable.

Discontinuation-reason based multiple imputation (MI) will be used to examine the sensitivity of the primary analysis results to departures from that underlying assumption and will assess a situation where data for subjects who discontinue early follow a pattern which is missing not at random. Specifically, MI will be used for imputation of any missing data, using "Jump to Reference" algorithm (where placebo is the reference group) [Carpenter et al. 2013] for subjects who discontinue due to lack of efficacy or AEs and standard regression-based MI for subjects with missing data for other reasons. The analysis will be implemented using the general three-step process (imputation phase, followed by analysis phase, followed by pooling phase) described in O'Kelly and Ratitch, 2014.

1. The imputation phase will implement MI via sequential modelling for both the "Jump to Reference" algorithm and standard regression-based MI. In particular, when implementing the "Jump to Reference" algorithm via sequential modelling, this means

that only baseline values are used in the imputation of missing values for subjects in the ASP0819 15 mg once daily group who discontinue due to lack of efficacy or AEs (this variation of the "Jump to Reference" algorithm is also referred to as the "Unconditional Reference" approach). The imputation phase will generate *M* imputed datasets, where *M*=100.

2. The analysis phase will perform the primary MMRM analysis model of the primary efficacy endpoint as described in Section 7.4.1.1 for each of the *M=100* imputed datasets (which now contain complete data, where missing data have been filled in).
3. Rubin's rules will be used to generate an overall set of pooled results which combines the analysis results from the *M=100* imputed datasets.

The overall set of pooled results will present:

- Least squares (LS) mean estimates, SE and 2-sided 90% confidence interval (CI) for mean change from baseline to Week 8 within a treatment group (ASP0819, placebo),
- The difference in LS means for ASP0819 versus placebo, SE for the difference and 2-sided 90% CI for the difference at Week 8,
- One-sided p-value for ASP0819 versus placebo at Week 8, obtained using the difference in the LS means.
- Descriptive summary statistics at Week 8 will be derived using the mean of the *M=100* imputed datasets.

Descriptive summaries and plots will be used to explore the pattern of missingness are described in Section 7.2.1

Modified baseline observation carried forward

Prior to any analysis mBOCF will be used to impute any missing Week 8 data. Modified baseline observation carried forward is defined as imputation by BOCF for subjects who discontinue due to lack of efficacy or AEs, and imputation by LOCF for subjects with missing data at Week 8 for other reasons. The imputed change from baseline to Week 8 data will be analyzed using ANCOVA with treatment group and center (pooled site) as fixed effects and baseline value as a covariate.

The ANCOVA will present LS mean estimates, SE for the LS means and two-sided 90% CI for change from baseline to Week 8 within a treatment group (ASP0819, placebo). For comparisons between ASP0819 and placebo for the change from baseline to Week 8, the ANCOVA model will present the difference in LS mean estimates, SE and corresponding 2-sided 90% CI. The differences in LS mean estimates will be used to obtain 1-sided p-values for ASP0819 versus placebo.

Per-protocol analysis

The same analysis of the primary efficacy endpoint as described in Section 7.4.1.1 will be repeated using the PPS.

Subgroup analysis

The subgroup analysis of the primary efficacy endpoint is described in Section 7.8.1

7.4.2 Analysis of Secondary Endpoints

Analysis of secondary efficacy endpoints will be performed on the FAS. Analyses of select secondary endpoints will be performed on the PPS as specified in Table 16

Table 16 Summary of the Analyses for the Secondary Efficacy Variables

Variable	Imputation	Analysis Set	Analysis Type
Percentage of subjects achieving ≥ 30% (or ≥ 50%) reduction from baseline to Week 8 in mean daily average pain score assessed by NRS where all subjects with missing Week 8 data are classified as non-responders	BOCF	FAS	Fisher's exact test
Percentage of subjects achieving ≥ 30% (or ≥ 50%) reduction from baseline to Week 8 in mean daily average pain score assessed by NRS (Sensitivity analysis)	mBOCF[c]	FAS	Fisher's exact test
Percentage of subjects achieving ≥ 30% (or ≥ 50%) reduction from baseline to Week 8 in mean daily average pain score assessed by NRS where all subjects with missing Week 8 data are classified as non-responders (Sensitivity analysis)	BOCF	PPS	Fisher's exact test
Percentage of subjects achieving ≥ 30% (or ≥ 50%) reduction from baseline to EOT in mean daily average pain score assessed by NRS	LOCF	FAS	Fisher's exact test
Change from baseline to Week 2, Week 4 and Week 8 for the FIQR function, symptoms and overall impact subscales	None	FAS	MMRM analysis of change from baseline[a]
Change from baseline to Week 8 for the FIQR function, symptoms and overall impact subscales (Sensitivity Analysis)	Discontinuation-reason based multiple imputation[b]	FAS	MMRM analysis of change from baseline[a]
Change from baseline to Week 8 for the FIQR function, symptoms and overall impact subscales (Sensitivity analysis)	None	PPS	MMRM analysis of change from baseline[a]
Change from baseline to Week 8 for the FIQR function, symptoms and overall impact subscales (Sensitivity Analysis)	mBOCF[c]	FAS	ANCOVA analysis of change from baseline
Change from baseline to EOT for the FIQR function, symptoms and overall subscales	LOCF	FAS	ANCOVA analysis of change from baseline
Overall subject improvement assessed by PGIC at Week 2, Week 4 and Week 8	mBOCF[c]	FAS	Proportional odds model
Overall subject improvement assessed by PGIC at Week 2 and Week 4 (Sensitivity analysis)	LOCF	FAS	Proportional odds model
Overall subject improvement assessed by PGIC at EOT	LOCF	FAS	Proportional odds model

[a]MMRM analysis uses data from baseline and change from baseline data at Week 2, Week 4 and Week 8 time points.

Footnotes continued on next page

[b]Discontinuation-reason based multiple imputation (MI) will use a "Jump to Reference" algorithm (where placebo is the reference group) for subjects who discontinue due to lack of efficacy or AEs and standard regression-based MI for subjects with missing data for other reasons.

[c]mBOCF is defined as imputation by baseline observation carried forward for subjects who discontinue due to lack of efficacy or AEs, and imputation by LOCF for subjects with missing data at the specific analysis time point for other reasons.

The following secondary binary response endpoints (responder, non-responder; as defined in Section 6.1.2) will be analyzed using the Fisher's exact test for ASP0819 versus placebo:

- Percentage of subjects achieving ≥ 30% (or ≥ 50%) reduction from baseline to Week 8 in mean daily average pain score assessed by NRS where all subjects with missing Week 8 data are classified as non-responders,
- Percentage of subjects achieving ≥ 30% (or ≥ 50%) reduction from baseline to Week 8 in mean daily average pain score assessed by NRS where mBOCF is used to impute a responder status for subjects with missing Week 8 data, and
- Percentage of subjects achieving ≥ 30% (or ≥ 50%) reduction from baseline to EOT in mean daily average pain score assessed by NRS.

Summary statistics will show the number and percentage of subjects who show response for each treatment group, 2-sided 90% CI for the percentage within each treatment group (ASP0819, placebo) calculated using the exact unconditional approach, difference in percentages, 2-sided 90% CI for ASP0819 versus placebo calculated using the exact unconditional approach, and 1-sided p-value. In addition, the above responder analysis will be repeated in the PPS as a sensitivity analysis of the percentage of subjects achieving ≥ 30% (or ≥ 50%) reduction from baseline to Week 8 in mean daily average pain score assessed by NRS where all subjects with missing Week 8 data are classified as non-responders.

The following secondary endpoints will be analyzed using the MMRM analysis as described in Section 7.4.1.1 for the primary efficacy analysis (however with only analysis time-points Week 2, Week 4 and Week 8 included):

- Change from baseline to Week 2, Week 4 and Week 8 for the FIQR function, symptoms and overall impact subscales (where no explicit imputation is performed).

For each endpoint, standard summaries of the MMRM analysis results will be provided, as described in Section 7.4.1.1. This will include an overlay plot. In addition, the MMRM analysis will be repeated in the PPS and also in the FAS under the assumption that data is MNAR using decision-reason based multiple imputation as sensitivity analyses of the change from baseline to Week 8 for the FIQR function, symptoms and overall impact subscales.

The following secondary endpoints will be analyzed using ANCOVA, as described in Section 7.4.1.2 for the second sensitivity analysis of the primary endpoint:

- Change from baseline to Week 8 in FIQR function, symptoms and overall impact subscale scores where mBOCF is used for imputation of missing data at Week 8. Modified baseline observation carried forward is defined as imputation by BOCF for subjects who discontinue due to lack of efficacy or AEs, and imputation by LOCF for subjects with missing data at Week 8 for other reasons.

- Change from baseline to EOT in FIQR function, symptoms, and overall impact subscale scores.

For each endpoint, standard summaries of the ANCOVA results, as described in Section 7.4.1.2, will be provided.

The following secondary endpoints will be analyzed using a proportional odds model for ordinal data including treatment group as a factor:

- Overall subject improvement assessed by PGIC at Week 2, Week 4 and Week 8 where mBOCF will be used for subjects with missing data,
- Overall subject improvement assessed by PGIC at Week 2 and Week 4 where LOCF will be used for subjects with missing data, and
- Overall subject improvement assessed by PGIC at EOT.

At each time point, the proportion of subjects in each treatment group achieving each level of response (1 = "Very Much Improved", 2 = "Much improved", 3 = "Minimally Improved", 4 = "No Change", 5 = "Minimally Worse", 6 = "Much Worse", 7 = "Very Much Worse"), will be presented, together with the odds ratio, associated 90% CI based on profile likelihood and 2-sided p-value based on likelihood ratio test for ASP0819 vs placebo. The cumulative logit link will be used to specify the proportional odds model in SAS.

7.4.3 Analysis of Exploratory Endpoints

Analysis of exploratory efficacy endpoints during the treatment period will be performed on the FAS and are described in Table 17. As stated previously, no formal hypothesis testing of comparison between treatment groups will be performed for the efficacy data during the follow-up period i.e., descriptive statistics will be used to summarize the continuous efficacy variables and frequencies and percentages will be used to summarize the categorical efficacy data.

Table 17 Summary of the Analyses for the Exploratory Efficacy Variables

Variable	Imputation	Analysis Set	Analysis Type
Treatment period			
Change from baseline to Week 1, Week 2, Week 3, Week 4, Week 5, Week 6 and Week 7 in mean daily average pain score assessed by NRS	None	FAS	MMRM analysis of change from baseline[a]
Change from baseline to EOT in mean daily average pain score assessed by NRS	LOCF	FAS	ANCOVA analysis of change from baseline
Percentage of subjects achieving different levels of reduction from baseline to Week 8 in mean daily average pain score assessed by NRS where all subjects with missing Week 8 data are classified as non-responders	BOCF	FAS	Descriptive statistics only (tabular and graphical)
Table continued on next page			

Variable	Imputation	Analysis Set	Analysis Type
Percentage of subjects achieving different levels of reduction from baseline to Week 8 in mean daily average pain score assessed by NRS where mBOCF (see Table 5) is used to impute a responder status for subjects with missing Week 8 data	mBOCF[c]	FAS	Descriptive statistics only (tabular and graphical)
Percentage of subjects achieving different levels of reduction from baseline to EOT in mean daily average pain score assessed by NRS	LOCF	FAS	Descriptive statistics only (tabular and graphical)
Change from baseline to Week 2, Week 4 and Week 8 for the FIQR total score	None	FAS	MMRM analysis of change from baseline[b]
Change from baseline to Week 8 for the FIQR total score	mBOCF[c]	FAS	ANCOVA analysis of change from baseline
Change from baseline to EOT for the FIQR total score	LOCF	FAS	ANCOVA analysis of change from baseline
Change from baseline to Week 2, Week 4 and Week 8 for PGIS	None	FAS	MMRM analysis of change from baseline[b]
Change from baseline to Week 8 for the PGIS	mBOCF[c]	FAS	ANCOVA analysis of change from baseline
Change from baseline to EOT for PGIS	LOCF	FAS	ANCOVA analysis of change from baseline
Percentage of subjects achieving a ≥ 30% reduction from baseline in FIQR total score at Week 8 and at EOT	mBOCF[c] (Week 8), LOCF (EOT)	FAS	Fisher's exact test
Percentage of subjects achieving a PGIC of "very much improved" or "much improved" at Week 8 and at EOT	mBOCF[c] (Week 8), LOCF (EOT)	FAS	Fisher's exact test
Percentage of subjects achieving a composite pain response, defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of "very much improved" or "much improved" at Week 8 and at EOT	mBOCF[c] (Week 8), LOCF (EOT)	FAS	Fisher's exact test
Percentage of subjects achieving a composite syndrome response, defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of "very much improved" or "much improved" **and** ≥ 30 % reduction from baseline in FIQR total score, at Week 8 and EOT	mBOCF[c] (Week 8), LOCF (EOT)	FAS	Fisher's exact test
Change from baseline to Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7 and Week 8 in mean daily average FMSD	None	FAS	MMRM analysis of change from baseline[a]
Change from baseline to EOT in mean daily average FMSD	LOCF	FAS	ANCOVA analysis of change from baseline
Change from baseline to Week 8 and EOT in the HADS* depression subscale	None (Week 8), LOCF (EOT)	FAS	ANCOVA analysis of change from baseline
Table continued on next page			

Variable	Imputation	Analysis Set	Analysis Type
Change from baseline to Week 8 and EOT in the EQ-VAS scale of the EQ-5D-5L	None (Week 8), LOCF (EOT)	FAS	Descriptive statistics only
Shift from baseline to Week 8 and EOT for each of the 5 dimensions of the EQ-5D-5L	None (Week 8), LOCF (EOT)	FAS	Descriptive statistics only
Proportion of days with rescue medication use at Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, EOT and Overall double-blind treatment period	None	FAS	Negative binomial regression
Incidence of subjects using rescue medication during Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, EOT and Overall double-blind treatment period	None	FAS	Fisher's exact test
Average daily dosage of rescue medication during Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, EOT and Overall double-blind treatment period	None	FAS	ANOVA
Change from baseline to Week 2, Week 4 and Week 8 for the Irritable Bowel Syndrome Symptom Summary Score and abdominal pain, stomach pain, abdominal cramps, abdominal pressure, and bloating individual items within past 24 hours and within past 7 days as assessed by the mIBS-D Daily Symptom Diary	None	FAS	MMRM analysis of change from baseline[b]
Change from baseline to EOT for the Irritable Bowel Syndrome Symptom Summary Score and abdominal pain, stomach pain, abdominal cramps, abdominal pressure, and bloating individual items within the past 24 hours and within past 7 days as assessed by the mIBS-D Daily Symptom Diary	LOCF	FAS	ANCOVA analysis of change from baseline
Change from baseline to Week 8 and EOT in the NPSI total score and NPSI burning pain, pressing pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia subscales	None (Week 8), LOCF (EOT)	FAS	ANCOVA analysis of change from baseline
Follow-up period			
Change from baseline and EOT to Week 10 in mean daily average pain score	None (Baseline), LOCF (EOT)	FAS	Descriptive statistics only
Change from baseline and EOT to Week 10 in FIQR function, symptoms and overall impact subscale scores and total score	None (Baseline), LOCF (EOT)	FAS	Descriptive statistics only
Overall subject improvement assessed by PGIC at Week 10	None	FAS	Descriptive statistics only
Change from baseline and EOT to Week 10 in PGIS	None (Baseline), LOCF (EOT)	FAS	Descriptive statistics only
Percentage of subjects achieving a ≥ 30% (or ≥ 50%) reduction from baseline to Week 10 in mean daily average pain score assessed by NRS	None	FAS	Descriptive statistics only
Table continued on next page			

Variable	Imputation	Analysis Set	Analysis Type
Change from baseline to Week 10 in EQ-VAS scale of the EQ-5D-5L	None	FAS	Descriptive statistics only
Shift from baseline to Week 10 for each of the 5 dimensions of the EQ-5D-5L	None	FAS	Descriptive statistics only
Proportion of days with rescue medication use at Week 10 and Overall follow-up period	None	FAS	Descriptive statistics only
Incidence of subjects using rescue medication at Week 10 and Overall follow-up period	None	FAS	Descriptive statistics only
Average daily dosage of rescue medication at Week 10 and Overall follow-up period	None	FAS	Descriptive statistics only

[a]MMRM analysis uses data from baseline and change from baseline data at Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7 and Week 8 time points.

[b]MMRM analysis uses data from baseline and change from baseline data at Week 2, Week 4 and Week 8 time points.

[c]mBOCF is defined as imputation by baseline observation carried forward for subjects who discontinue due to lack of efficacy or AEs, and imputation by LOCF for subjects with missing data at Week 8 for other reasons.

*Only for subjects with data captured using the corrected version of the HADS questionnaire.

Treatment period

The MMRM analysis and associated summaries and plots for the primary efficacy analysis as described in Section 7.4.1.1 will be used to interpret the exploratory efficacy analyses of change from baseline to Week 1, Week 2, Week 3, Week 4, Week 5, Week 6 and Week 7 in mean daily average pain score assessed by NRS.

Similarly, the following exploratory endpoints will also be analyzed using the MMRM analysis as described in Section 7.4.1.1 for the primary efficacy analysis:

- Change from baseline to Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7 and Week 8 in mean daily average FMSD,
- Change from baseline to Week 2, Week 4 and Week 8 for the FIQR total score (only data from Weeks 2, 4 and 8 will be included in the model),
- Change from baseline to Week 2, Week 4 and Week 8 for PGIS (only data from Weeks 2, 4 and 8 will be included in the model), and
- Change from baseline to Week 2, Week 4 and Week 8 for the Irritable Bowel Syndrome Symptom Summary Score and abdominal pain, stomach pain, abdominal cramps, abdominal pressure, and bloating individual items within past 24 hours and within past 7 days as assessed by the mIBS-D Daily Symptom Diary (only data from Weeks 2, 4 and 8 will be included in the model).

For each endpoint, standard summaries of the MMRM analysis results will be provided, as described in Section 7.4.1.1

The following exploratory endpoints will be analyzed using ANCOVA as described in Section 7.4.1.2 for the second sensitivity analysis of the primary endpoint:

- Change from baseline to EOT in mean daily average pain score assessed by NRS,

- Change from baseline to Week 8 for the FIQR total score where mBOCF is used for imputation of missing data at Week 8,
- Change from baseline to EOT for the FIQR total score,
- Change from baseline to Week 8 for the PGIS where mBOCF is used for imputation of missing data at Week 8,
- Change from baseline to EOT for PGIS,
- Change from baseline to EOT in mean daily average FMSD,
- Change from baseline to Week 8 (note that no imputation will be performed hence the ANCOVA will only include subjects with data at both baseline and Week 8) and EOT in the HADS depression subscale,
- Change from baseline to EOT for the Irritable Bowel Syndrome Symptom Summary Score and abdominal pain, stomach pain, abdominal cramps, abdominal pressure, and bloating individual items within past 24 hours and within past 7 days as assessed by the mIBS-D Daily Symptom Diary,
- Change from baseline to Week 8 (note that no imputation will be performed hence the ANCOVA will only include subjects with data at both baseline and Week 8) and EOT in the NPSI total score and NPSI burning pain, pressing pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia subscales.

Where appropriate for the above endpoints, mBOCF is defined as imputation by BOCF for subjects who discontinue due to lack of efficacy or AEs, and imputation by LOCF for subjects with missing data at Week 8 for other reasons. For each endpoint, standard summaries of the ANCOVA results, as described in Section 7.4.1.2, will be provided.

The following exploratory binary response endpoints will be analyzed using Fisher's exact test as described in Section 7.4.2 for the analysis of the secondary binary response endpoints:

- Percentage of subjects achieving a ≥ 30% reduction from baseline in FIQR total score at Week 8 (where mBOCF is used for imputation of missing data at Week 8) and at EOT,
- Percentage of subjects achieving a PGIC of "very much improved" or "much improved" at Week 8 (where mBOCF is used for imputation of missing data at Week 8) and at EOT,
- Percentage of subjects achieving a composite pain response, defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of "very much improved" or "much improved" at Week 8 (where mBOCF is used for imputation of missing data at Week 8) and at EOT,
- Percentage of subjects achieving a composite syndrome response, defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of "very much improved" or "much improved" **and** ≥ 30 % reduction from baseline in FIQR total score, at Week 8 (where mBOCF is used for imputation of missing data at Week 8) and EOT, and
- Incidence of subjects using rescue medication during Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, EOT and Overall double-blind treatment period.

Refer to Table 5 Section 6.1.3 for the definition of mBOCF for responder variables.

The following exploratory endpoints will be analyzed using a negative binomial regression model with terms for treatment group and center (pooled site):

- Proportion of days with rescue medication use at Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, EOT and Overall double-blind treatment period.

Each analysis time-point will be analyzed separately. The response variable in each model will be the number of days with rescue medication during each analysis time-point, i.e., Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, EOT (the last 7 days on treatment) and Overall double-blind treatment period. The logarithm of the follow-up time within each analysis time-point (apart from the double-blind treatment period this will usually be 7 days, except if the subjects discontinued during that week) will be used as an offset variable in the model and there will be no imputation of missing data.

The estimated treatment effect (i.e., the rate ratio of ASP0819 versus placebo), corresponding 90% confidence interval (CI), and 1-sided p-value for the rate ratio will be presented. In addition, the proportion of days of rescue medication use will be summarized using n, mean, SD, minimum, maximum and median for all analysis time-points (Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, EOT and Overall double-blind treatment period).

The following exploratory endpoints will be analyzed using ANOVA model including $\log_{10}$ average daily dosage of rescue medication during the double-blind treatment period as response (subjects with 0 will have a value of 5 imputed prior to log-transforming) and treatment group and center (pooled site) as fixed effects:

- Average daily dosage of rescue medication during the overall double-blind treatment period.

The analysis will be performed for theoverall double-blind treatment period and there will be no imputation of missing data (note subjects with 0 average daily dosage of rescue medication will have a value of 5 imputed prior to $\log_{10}$-transformation). The ANOVA will present geometric LS mean ($10^{\text{LS Mean}}$) and 2-sided 90% CI ($10^{\text{Lower Confidence Limit of LS Mean}}$, $10^{\text{Upper Confidence Limit of LS Mean}}$) for each treatment group (ASP0819, placebo). The ratio of geometric LS mean of the ASP0819 15mg group divided by the geometric LS mean of the placebo group with corresponding 2-sided 90% CI will be derived. The ratio of the geometric LS mean estimates will be used to obtain 1-sided p-values for ASP0819 versus placebo. At Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8 and at EOT descriptive summaries of the average daily dose of rescue medication will be produced with the addition of the 1st and 3rd quartiles.

For the following exploratory binary response endpoints, descriptive summaries will be produced and there will be no formal hypothesis testing of comparison between treatment groups:

- Percentage of subjects achieving different levels of reduction from baseline to Week 8 in mean daily average pain score assessed by NRS where all subjects with missing Week 8 data are classified as non-responders,
- Percentage of subjects achieving different levels of reduction from baseline to Week 8 in mean daily average pain score assessed by NRS where mBOCF (see Table 5) is used to impute a responder status for subjects with missing Week 8 data, and
- Percentage of subjects achieving different levels of reduction from baseline to EOT in mean daily average pain score assessed by NRS.

For each of the above endpoints, the number and percentage of subjects achieving levels of reduction in mean daily average pain score assessed by NRS from baseline to Week 8 at > 0%, ≥ 10%, ≥ 20%, ≥ 30%, ≥ 40%, ≥ 50%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90% and 100% will be summarized by treatment group. In addition to the above summary, an overlay plot will be presented for each binary response endpoint for different levels of reduction (range is 0 to 100% by 10% i.e, >0%, ≥10% to ≥90% by 10%, and =100%) in each treatment group. Refer to Section 6.1.2 for ≥ 30% and ≥ 50% responder definitions and Section 6.1.3 for >0%, ≥ 10%, ≥ 20%, ≥ 40%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90% and =100% responder definitions. In the plot, the x-axis will display the percentage of improvement i.e., percentage reduction versus baseline in mean daily average pain score and y-axis will be percentage of subjects improved

Descriptive statistics will be used to summarize the change from baseline to Week 8 and EOT in the EQ-VAS scale of the EQ-5D-5L. For the EQ-VAS the baseline value, post-baseline value at each specified time point (Baseline, Week 8 and EOT) and change from baseline to each specified post-baseline time point will be summarized using n, mean, SD, Q1, Q3, minimum, maximum and median by treatment group. For each of the 5 dimensions of the EQ-5D-5L: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, number and percentage of subjects will be summarized for each level by baseline value, post-baseline value at each specified time-point by treatment group. Shift tables from baseline to Week 8, from baseline to EOT and baseline to Week 10 by treatment group will also be produced.

Follow-up period

For the follow-up period, data will be summarized with descriptive statistics (number of subjects, mean, SD, minimum, median and maximum) for continuous endpoints (absolute values at Week 10 analysis timepoint as well as change from baseline to Week 10 and change from EOT to Week 10), and frequency and percentage for categorical endpoints (at the Week 10 analysis time point as well as shift from baseline to Week 10 and shift from EOT to Week 10).

7.4.4 Analysis of Other Variables

Not applicable.

7.5 Analysis of Safety

All analysis of safety will be presented by treatment group for SAF, unless specified otherwise. No hypothesis testing will be performed comparing treatment groups for any safety parameters.

7.5.1 Adverse Events

Summaries and listings of serious adverse events (SAEs) and serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms if any upgrade was done.

Duration of AE will be included in all listings and is calculated as described in Section 6.2.1

The coding dictionary for this study will be MedDRA version 20.0. It will be used to summarize AEs by SOC and PT. Standardised MedDRA query (SMQs) will also be used to identify AEs of interest as described in Section 7.5.2

7.5.1.1 Adverse Events Prior to First Dose

The number and percentage of subjects with AEs prior to first dose, as classified by SOC and PT will be summarized for each treatment group.

7.5.1.2 Treatment Emergent Adverse Events

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug,
- Number of deaths,
- Number of drug abuse related TEAEs, and
- Number of drug withdrawal related TEAEs.

The above summary will be repeated for TEAEs (treatment period) and TEAEs (follow-up period).

7.5.1.3 Treatment Emergent Adverse Events by SOC and/or PT

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized for each treatment group. Summaries will be provided for:

- TEAEs
- TEAEs (treatment period) and TEAEs (follow-up period),
- Drug related TEAEs,
- Serious TEAEs (including number of events),
- Drug related serious TEAEs (including number of events),
- TEAEs leading to permanent discontinuation of study drug,
- Drug related TEAEs leading to permanent discontinuation of study drug,
- TEAEs leading to death (including number of events)
- Drug related TEAEs leading to death (including number of events),
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5% in any treatment group.

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized for each treatment group in decreasing order of frequency within the ASP0819 treatment group.

The number and percentage of subjects with TEAEs (including number of events), as classified by SOC and PT will also be summarized by severity to study drug. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity, then the subject will be counted only once with the worst severity. If any of the severity values are missing then the subject will be counted only once with worst severity, i.e. severe. In the adverse event count, the adverse events will be presented in each category they were classified to.

Drug related TEAEs will be presented in a similar way by severity only. When assessing severity for drug-related TEAEs as reported by the investigator, only drug-related TEAEs will be used in the analysis and the worst grade for severity will be chosen as described above.

7.5.2 Adverse Events of Interest

The number and percent of subjects who have a TEAE within the Drug abuse, dependence and withdrawal SMQ (MedDRA 20.0) will be summarized by treatment group.

Drug abuse related TEAEs

The number and percent of subjects who have a TEAE within the Drug abuse and dependence SMQ (MedDRA 20.0) during the treatment period and follow-up period, as classified by SOC and PT will be summarized by treatment group.

In addition, the number and percent of subjects who have Drug abuse related TEAEs during the treatment period and follow-up period, as defined in Section 10.1 Appendix 1, as classified by PT and lowest level term will be summarized by treatment group.

Drug withdrawal related TEAEs

The number and percent of subjects who have a TEAE within the Drug withdrawal SMQ (MedDRA 20.0) during the treatment period and follow-up period, as classified by SOC and PT will be summarized treatment group.

In addition, the number and percent of subjects who have withdrawal related TEAEs during the treatment period and follow-up period, as defined in Section 10.2 Appendix 2, as classified by SOC and PT will be summarized by treatment group.

7.5.3 Clinical Laboratory Evaluation

The baseline visit is the last measurement taken prior to first dose of study drug.

Quantitative clinical laboratory variables, i.e. hematology & coagulation, and biochemistry will be summarized using mean, SD, minimum, maximum and median for each treatment group at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

The number and percentage of subjects below and above the reference range will be summarized for each treatment group at each visit. For hematology and biochemistry, two types of shift tables will be presented for each treatment group:

- Shift tables of reference range changes from baseline to post-baseline value at each specified time point (low, normal, high), and
- Summary shifts of reference range changes from baseline to post-baseline value at each specified time point (shift from normal or high to low, shift from normal or low to high, categorized increase [shift from low to normal, low to high or from normal to high], categorized no change [value stays in the same reference range], categorized decrease [shift from high to normal, high to low or from normal to low]).

The following list of parameters will be summarized using descriptive statistics and for the shift table.

Lab panel	Analysis Time point	Parameter
Hematology and Coagulation	Baseline <u>Treatment period</u> Week 2, Week 4, Week 8, <u>Follow-up</u> Week 10	Hemoglobin Hematocrit Erythrocytes (Red blood cell [RBC]) Leukocytes (White blood cell [WBC]) Differential WBC Platelets PT and INR MCV MCH Reticulocytes
Table continued on next page		

Lab panel	Analysis Time point	Parameter
Biochemistry	Baseline Treatment period Week 2, Week 4, Week 8, Follow-up Week 10	Sodium Potassium Calcium Chloride Magnesium Glucose Creatine Kinase Creatinine Alkaline Phosphatase (ALP) Lactate dehydrogenase (LDH) Aspartate transaminase (AST) Alanine transaminase (ALT) Gamma glutamyl transpeptidase Total bilirubin (direct and indirect) Total protein Albumin Total cholesterol Triglycerides Uric Acid Blood Urea Nitrogen Inorganic phosphate

All laboratory measurements, including the derived outcomes (change from baseline and flagging of abnormal value with high and low) will be presented in the listing. Urinalysis will be listed only.

7.5.3.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant (PCS) criteria for liver tests – defined as Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin (TBL), Aspartate Transaminase (AST), International Normalized Ratio (INR) and their combination are defined.

Table 18 Potentially Clinically Significant Criteria for Liver Enzymes and Total Bilirubin

Parameter	Criteria
ALT	> 3xULN > 5xULN > 10xULN > 20xULN
AST	> 3xULN > 5xULN > 10xULN > 20xULN
ALT or AST	> 3xULN

Table continued on next page

Parameter	Criteria
TBL	> 2xULN
INR	> 1.5 (Ratio)
ALP	> 1.5xULN
ALT and/or AST **AND** TBL(*)	(ALT and/or AST > 3xULN) **and** TBL > 2xULN
ALT and/or AST **AND** TBL and/or INR(*)	(ALT and/or AST > 3xULN) **and** (TBL > 2xULN and/or INR > 1.5)

(*) Combination of values measured from the samples collected on the same day.

The number and percentage of subjects with PCS values in liver enzyme and total bilirubin tests using the subject's highest value during the double-blind treatment period will be presented by treatment group. Another summary will be created using the subject's highest value during the follow-up period.

In addition to the above summaries the following data will be presented graphically by treatment group:

- Scatter plot of maximum values for ALT or AST and TBL during the double-blind treatment period and follow-up period with ALT or AST values on x-axis and TBL values on y-axis [Senior, 2014], and
- Individual display of liver enzymes and TBL for selected subjects experiencing potentially clinically significant criteria of ALT > 3xULN or AST > 3xULN or TBL > 2xULN during double-blind treatment period or follow-up period.

7.5.3.2 Potentially Clinically Significant Laboratory Criteria

Potentially clinically significant laboratory criteria for other laboratory variables are provided in Section 10.3 Appendix 3. The number and percentage of subjects with PCS values using the subject's highest and/or lowest value (depending on the direction of interest) during the double-blind treatment period will be presented by treatment group. Another summary will be created using the subject's highest and/or lowest value (depending on the direction of interest) during the follow-up period.

7.5.4 Vital Signs

The baseline visit is the last measurement taken prior to the first dose of study drug.

Vital signs (SBP, DPB and pulse rate) will be summarized using mean, SD, minimum, maximum and median by treatment group and visit. Additionally, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit. Table 19 describes PCS criteria for vital signs. The number and percentage of subjects with PCS values in vital signs using the subject's worst value during double-blind treatment period will be presented by each treatment group. Another summary will be created using the subject's worst value during the follow-up period.

Table 19 Potentially Clinically Significant Criteria for Vital Signs

Vital Sign Parameter	Criteria	Worst Value
SBP	• <90 mmHg • Decrease of ≥ 20 mmHg from baseline • >180 mmHg • Increase of ≥20 mmHg from baseline	Lowest Lowest Highest Highest
DBP	• <40 mmHg • Decrease of ≥ 20 mmHg from baseline • >100 mmHg • Increase of ≥ 20 mmHg from baseline	Lowest Lowest Highest Highest
Pulse rate	• <50 bpm • Decrease of ≥ 20 bpm from baseline • <50 bpm and decrease of ≥ 20 bpm from baseline (*) • >100 bpm • Increase of ≥ 20 bpm from baseline • >100 bpm and increase of ≥ 20 bpm from baseline (*)	Lowest Lowest Lowest Highest Highest Highest

(*) Combination of values from the same time point.

7.5.5 Electrocardiograms

The baseline visit is the last measurement taken prior to the first dose of study drug.

The number and percentage of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the 12-lead ECG will be tabulated by treatment group at each treatment visit and time point (Baseline, Week 8, EOT and Week 10).

Number and percent of subjects with 12-lead ECG abnormalities as well as number and percent of subjects whose 12-lead ECG reading changed from normal at baseline to abnormal will be tabulated by treatment group at each treatment visit and time point (Baseline, Week 8, EOT and Week 10)

A shift table of the finding at baseline ('normal', 'abnormal - not clinically significant' and 'abnormal - clinically significant') to the worst finding during the double-blind treatment period and follow-up period will be presented by treatment group.

7.5.6 Physical Examination Findings

Physical examination findings will be listed by treatment group.

7.5.7 Columbia Suicide Severity Rating Scale

Number and percentage of subjects in each of the categories of C-SSRS described in Section 6.2.5 will be summarized at each analysis time point (Baseline, Week 2, Week 4, Week 8, EOT and Week 10) by treatment group. For each analysis time point, if a subject answers "yes" to more than one question within a category, the worst finding will be used.

For the overall during the double-blind treatment period and the overall during the follow-up period, a subject's worst finding during that period will be used.

All C-SSRS assessments will be listed only for subjects with at least one event of suicidality (suicidal ideation and/or suicidal behavior).

7.5.8 Pregnancies

A detailed listing of all pregnancies will be provided.

7.6 Analysis of PK

A listing of sample times and concentrations will be provided.

7.7 Analysis of PD

Not applicable.

7.8 Subgroups of Interest

7.8.1 Subgroup Analysis for Primary Endpoint

In order to evaluate homogeneity of treatment effect across subject groups, subgroup analyses of the primary efficacy variable (change from baseline in mean daily average pain score as assessed by NRS) will be performed. Separate analyses will be performed for each distinct level of a subgroup.

For each subgroup, the primary efficacy endpoint will be summarized descriptively using n, mean, SD, minimum, maximum and median by treatment group. For subgroups where there are more than 20 subjects across both treatment groups for each distinct level, an analysis of the primary efficacy endpoint will be performed using the MMRM model as described in Section 7.4.1.1. Since the study is not designed to detect a treatment effect within each subgroup category p-values will be excluded from the summaries of these analyses.

The following subgroups will be assessed:

- Sex,
- Age group,
- Category of baseline mean daily average pain score as assessed by NRS,
- Central pain etiology as assessed by CMSI total score,
- Peripheral pain etiology as assessed by NPSI total score and relevant subscales,
- mIBS-D within past 24 hours at baseline: Symptom summary score, abdominal pain, stomach pain, abdominal cramps, abdominal pressure and bloating, and
- Depression as assessed by M.I.N.I: Current/prior diagnosis versus no current/prior diagnosis.

Table 20 describes the subgroups defined on the basis of the categorized variables that will be used to summarize the primary efficacy endpoint.

Table 20 Grouping variables for Subgroup Analysis for Primary Endpoint

Subgroup	Subgroup Category
Sex	Female Male
Age group	<45 years ≥45 to < 65 years ≥ 65 years
BMI	< 30 kg / m^2 ≥ 30 kg / m^2
Baseline mean daily average pain score as assessed by NRS	≥4 to < 7 (Moderate) ≥ 7 (Severe)
Central pain etiology as defined by CMSI	More centrally driven FM pain Non-specific FM pain More peripherally driven FM pain
Peripheral pain etiology as defined by NPSI: NPSI total score and relevant subscales	Low High
mIBS-D within past 24 hours at baseline: • Abdominal pain • Stomach pain • Abdominal cramps • Abdominal pressure • Bloating • Symptom summary score	Low Mid High
Depression as assessed by M.I.N.I: Current/Prior versus No current/Prior	Current/Prior (History of MDD = 'Yes') No current/Prior (History of MDD = 'No')

BMI: Body mass index; CMSI: Complex Medical Symptoms Inventory; FM: Fibromyalgia; mIBS-D: Modified irritable bowel syndrome - diarrhea predominant; M.I.N.I.: Mini-International Neuropsychiatric Interview; NPSI: Neuropathic Pain Symptom Inventory; NRS: Numerical rating scale.

There is no pre-defined cut-point which can be used to categorize subjects into those that have more centrally driven FM pain versus those who may have more peripherally driven FM pain as assessed by baseline CMSI total score. Similarly, there are no cut-points which can be used to split the subjects into those with lower scores on total and/or subscales of the NPSI at baseline versus those with higher scores. This also applies to the mIBS-D symptom summary score and individual items.

During blinded data review, for each endpoint scatterplots versus change from baseline to Week 8 in mean daily average pain score assessed by NRS were used to assess the most appropriate cut-point. For CMSI total score and mIBS-D symptom summary score and individual items a decision was made to split subjects into three subgroups using tertiles of the measurements at baseline as the cut-point. For NPSI subscales and NPSI total score a decision was made to split subjects into two subgroups using the median of the measurements at baseline as the cut-point.

7.8.2 Subgroup Analysis for Exploratory Endpoint FMSD

To further assess the impact on changes in sleep the FMSD question "How rested were you when you woke up" at baseline will be used to categorize subjects into two subgroups using the median as a cut-point.

For each subgroup, the exploratory endpoint of change from baseline to Week 8 for the two FMSD questions "How restless was your sleep?" and "How rested were you when you woke up?", will be summarized using n, mean, SD, minimum, maximum and median by treatment group.

7.9 Other Analyses

No additional analyses are planned.

7.10 Interim Analysis (and Early Discontinuation of the Clinical Study)

Two interim analyses for futility based on the primary efficacy endpoint will be conducted. The timing of these analyses will be at approximately 35% and 55% of all subjects with Week 8/EOT data. The plan for the interim analysis may be modified based on speed of recruitment. These analyses will be conducted by an Astellas statistician, with results reviewed by an Astellas IDMC. The Astellas statistician and other members of the Astellas IDMC are external to the study team. No one within the study team will be unblinded to the treatment allocation or interim results. Details of the interim analysis procedure, steps to maintain treatment blind in the study team and criteria for stopping the study will be described in an IAP.

7.11 Handling of Missing Data, Outliers, Visit Windows, and Other Information

7.11.1 Missing Data

As a general principle, no imputation of missing data for other variables will be done. Exceptions are the onset date of AE, start and stop dates of non-medication therapy, start and stop dates of previous and concomitant medication, onset date of FM symptoms, date of FM diagnosis and first/last dose date of double-blind study drug. In the listings of AEs, non-medication therapy, previous and concomitant medication and onset date of FM symptoms, diagnosis of FM, the first dose/last dose date of double-blind study drug will present the actual partial dates; imputed dates will not be shown.

For one of the sensitivity analyses for the primary efficacy endpoint and one of the sensitivity analysis for the FIQR secondary endpoint, multiple imputation will be used to impute missing data, using a discontinuation reason-based approach as described in Section 7.4.1.2. For analyses of selected efficacy endpoints, mBOCF, BOCF and/or LOCF will be used to impute the missing data. More details are described in Section 6.1 and Section 7.4.

Imputation of Adverse Event Onset Date

For AEs, a missing or incomplete onset date will be imputed according to the following conventions:

If an onset date is missing or only the year is known, the imputed onset date will be the **latest** of the following non-missing dates:

- First dose date of double-blind study drug
- Randomization date + 1 day

If only the month and year is known for onset date, set the surrogate onset date to the first day of that month and then apply the following rules:

1. If the month and year of the onset date is prior to the month and year of the first dose of double-blind study drug, then the surrogate onset date will be the imputed onset date.
2. If the month and year of the onset date is on or after the month and year of the first dose of double-blind study drug, then the imputed onset date will be the **latest** of the following non-missing dates:
   - First dose date of double-blind study drug
   - Randomization date + 1 day
   - Surrogate onset date

If the imputed onset date is after a complete adverse event end date, the imputed onset date will be the same as the complete adverse event end date.

Imputation of Adverse Event End Date

For AEs, a missing or incomplete end date will be imputed according to the following conventions:

If only the day is missing for end date, set the surrogate end date to the last day of the month.

If the day and the month are missing for end date, set the surrogate end date month to December and set the day to the last day of the month (31).

If the year or the entire end date is missing, end date will not be imputed.

If an AE end date has been imputed, then apply the following rule:

1. If this imputed date falls after the end of participation in the study, then the surrogate end date will be set to the date of end of participation.

If the AE is ongoing (outcome is "NOT RECOVERED/NOT RESOLVED" or "RECOVERING/RESOLVING") then the end date will remain missing.

Imputation of Start and Stop Dates of Non-Medication Therapy and Previous and Concomitant Medication Dates

For Non-Medication Therapy and Previous and Concomitant Medications, a missing or incomplete start and stop dates will be imputed according to the following conventions:

If start date is missing or partial:

- if month is missing, use January
- if day is missing, use the first day of the month under consideration
- if year is missing, use year of the informed consent date

- if entire date is missing, use informed consent date

If stop date is missing or partial and medication or therapy is not ongoing:

- if month is missing, use December
- if day is missing, use the last day of the month under consideration
- if year or the entire date is missing, set to December 31st, 2099

If the imputed start date is after the stop date, then the imputed start date will be one day prior to the stop date.

If the medication or therapy is ongoing, the stop date will remain missing.

Missing Onset Date of FM Symptoms and Date of FM diagnosis

An incomplete onset date of FM Symptoms or date of FM diagnosis will be imputed according to the following conventions:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year.
- Missing year, but day and month are present: No imputations will occur, and the subject will be excluded from all summaries related to time since FM symptoms and diagnosis.
- Missing day, month and year: No imputations will occur, and the subject will be excluded from all summaries related to time since FM symptoms and diagnosis.
- If any such imputed date falls after the informed consent date, then the onset date will be taken as equal to the informed consent date.

Imputation of Study Drug Start Date Double-Blind Treatment Period

For subjects who are randomized to double-blind study drug, the first dose date of double-blind study drug will be imputed if both of the following criteria are met:

- There is a missing or partial date for the first dose of double-blind study drug AND
- The number of capsules dispensed does not equal the number of capsules returned (including missing values).

If the first dose date of double-blind study drug is missing or partial, the first dose date of double-blind study drug is defined as the non-missing dispense date at randomization.

Imputation of Study Drug End Date Double-Blind Treatment Period

For subjects who are randomized to double-blind study drug, the last dose date of double-blind study drug will be imputed if both of the following criteria are met:

- There is a missing or partial date for the last dose of double-blind study drug AND
- The number of capsules dispensed does not equal the number of capsules returned (including missing values).

If only the day is missing for the last dose date of double-blind study drug, the last day of the month under consideration will be used.

If the month and/or year are missing for the last dose date of double-blind study drug, then the **latest** of the following non-missing dates will be used:

1. last dispense date + 1 day OR
2. the date of the last vital sign measurement during the double-blind treatment period OR
3. the date of the first dose of double-blind study drug in the double-blind treatment period + 1 day

7.11.2 Outliers

All values will be included in the analyses.

7.11.3 Values below limit of quantification (BLOQ)

For quantitative laboratory variables, values recorded as "<X" or "<=X" or ">Y" or ">=Y" will be imputed by "X" and "Y" respectively for descriptive statistics. This will be documented in a footnote to all summary tables and all output where such a replacement was performed.

7.11.4 Visit Windows for Efficacy Variables

7.11.4.1 Duplicate Values

For daily average pain scores assessed by NRS and FMSD scores any data captured in the e-diary up to 2am in the morning of the following day will be assigned to the previous day in the derivation of Study Day (Section 7.1).

For all efficacy variables (either recorded in the e-diary or the tablet device), if more than one value is measured/recorded on the same Study Day, then the first of the values will be used. This should be applied before implementing the visit windows as described in Section 7.11.4.3

7.11.4.2 Post Dosing Efficacy Observations

For efficacy variables, observations will not contribute to the efficacy analyses during the treatment period if the subject's last dose of double-blind study drug is as follows:

Any diary days or non-diary days which are > 4 days after the last dose of double-blind study drug will not be included in the analysis related to on-treatment time points and the EOT time point. This should be applied before implementing the visit windows in Section 7.11.4.3

7.11.4.3 Visit Windows

Subjects do not always adhere strictly to the visit timing in the protocol. Therefore, the designation of time points will be based on Study Day and Follow-Up Day (as defined in Section 7.1) rather than the nominal visit recorded in the eCRF.

To assign a measurement to a Week t during the double-blind treatment period, the first step consists of selecting all measurements falling within the double-blind treatment period as defined above. To further determine the Week t measurement, mutually exclusive relative day windows are used.

These day windows are defined to provide derived time points that correspond to the post baseline time points specified in the protocol.

Table 21 provides day windows for daily average pain scores assessed by NRS and rescue medication data. Table 22 provides day windows for the FMSD questionnaire data. Table 23 provides day windows for FIQR, PGIS, PGIC and mIBS-D questionnaire data. Table 24 provides day windows for HADS, EQ-5D-5L and NPSI questionnaire data.

Table 21 Day Windows: NRS questionnaire and rescue medication

Analysis Time point	Visit Window (Day)
Baseline	Study days -7 to -1
Week 1	Study days 2 to 7
Week 2	Study days 8 to 14
Week 3	Study days 15 to 21
Week 4	Study days 22 to 28
Week 5	Study days 29 to 35
Week 6	Study days 36 to 42
Week 7	Study days 43 to 49
Week 8	Study days 50 to 56
EOT	Study day 2 to 56, where post-baseline data from the last 7 calendar days on or prior to the last NRS score will be used. If there is no post-baseline data available EOT will be imputed using the baseline measurement.
Double-blind treatment period[a]	Study days 2 to 56
Week 10	Follow-up days 7 to 13
Follow-up period[a]	Follow-up days 5 to 28

[a]Only applicable to rescue medication.

Table 22 Day Windows: FMSD questionnaire

Analysis Time point	Visit Window (Day)
Baseline	Study days -6 to 1
Week 1	Study days 3 to 8
Week 2	Study days 9 to 15
Week 3	Study days 16 to 22
Week 4	Study days 23 to 29
Week 5	Study days 30 to 36
Week 6	Study days 37 to 43
Week 7	Study days 44 to 50
Week 8	Study days 51 to 57
EOT	Study day 3 to 57, where post-baseline data from the last 7 calendar days on or prior to the last FMSD scores will be used. If there is no post-baseline data available EOT will be imputed using the baseline measurement.
Week 10	Follow up days 8 to 14

Table 23 Day Windows: FIQR, PGIS, PGIC and mIBS-D questionnaires

Analysis Time point	Target Day	Visit Window (Day)
Week 2	Study day 15	Study days 2 to 22
Week 4	Study day 29	Study days 23 to 43
Week 8	Study day 57	Study day 44 to 71
EOT[a]	Not applicable	Study day 2 to Follow-up day 4
Week 10[b]	Follow-up day 14	Follow-up day 5 to 28

Apart from PGIC, baseline is defined as the last assessment on or prior to the first dose day (Day 1) of double-blind study drug.

[a] EOT value is the last available non-missing post-baseline measurement within the visit window. If there is no post-baseline data available EOT will be imputed using the baseline measurement.

[b] mIBS-D is not collected at Week 10

Table 24 Day Windows: HADS, EQ-5D-5L and NPSI questionnaires

Analysis Time point	Target Day	Visit Window (Day)
Week 8	Study day 57	Study day 44 to 71
EOT[a]	Not applicable	Study day 2 to Follow-up day 4
Week 10	Follow-up day 14	Follow-up days 5 to 28

Baseline is defined as the last assessment on or prior to the first dose day (Day 1) of double-blind study drug.

[a] EOT value is the last available non-missing post-baseline measurement within the visit window. If there is no post-baseline data available EOT will be imputed using the baseline measurement.

For efficacy variables recorded in the e-diary (NRS questionnaire, rescue medication and FMSD questionnaire data), the following rule will apply:

- Measurements recorded on all valid diary days which fall within the Day Range for a specified visit as defined in Table 21 (NRS questionnaire and rescue medication) and Table 22 (FMSD questionnaire) will be used to calculate the average.

For efficacy variables recorded in the tablet device, the following rule will apply:

- If a subject has more than one time point with a measurement included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the scheduled day, the later assessment will be used. In case of ties located on the same side of the scheduled day (i.e. more than one value for the same day), the first value will be used.

7.11.5 Visit Windows for Safety Variables

7.11.5.1 Duplicate Values

For safety laboratory data and vital signs, if more than one value is reported on the same day, then the mean of the values will be used. This needs to be done before creating the analysis time points.

7.11.5.2 Post Dosing Safety Observations

For safety variables, observations will not contribute to the safety analyses during the treatment period if the subject's last dose of double-blind study drug is as follows:

Any days which are > 4 days after the last dose of double-blind study drug will not be included in the analysis related to on-treatment time points and the EOT time point. This needs to be done before creating the analysis time points.

7.11.5.3 Visit Windows

Table 25 provides day windows for safety laboratory variables, vital sign variables and C-SSRS. Table 26 provides day windows for the categorical ECG assessment.

Table 25 Day Windows: Laboratory, Vital Sign Variables and C-SSRS

Analysis Time point	Target Day	Visit Window (Day)
Week 2	Study day 15	Study days 2 to 22
Week 4	Study day 29	Study days 23 to 43
Week 8	Study day 57	Study days 44 to 71
EOT[a]	Not applicable	Study day 2 to Follow-up day 4
Double-blind treatment period[b]	Not applicable	Study day 2 to Follow-up day 4
Week 10	Follow up day 14	Follow-up days 5 to 28
Follow-up period[b]	Not applicable	Follow-up day 5 onwards

Baseline is defined as the last assessment on or prior to the first dose day (Day 1) of double-blind study drug.

[a] EOT value is the last available non-missing post-baseline measurement within the visit window.

[b]Only applicable to potentially clinically significant laboratory parameters, potentially clinically significant vital signs and C-SSRS.

Table 26 Day windows: Categorical ECG assessment

Analysis Time point	Target Day	Visit Window (Day)
Week 8	Study day 57	Study days 44 to 71
EOT[a]	Not applicable	Study day 2 to Follow-up day 4
Double-blind treatment period	Not applicable	Study day 2 to Follow-up day 4
Week 10	Follow-up day 14	Follow-up days 5 to 28
Follow-up period	Not applicable	Follow-up day 5 onwards

Baseline is defined as the last assessment on or prior to the first dose day (Day 1) of double-blind study drug.

[a] EOT value is the last available non-missing post-baseline measurement within the visit window.

For safety variables, the following rules will apply:

1. For laboratory and vital sign variables, if a subject has more than one visit with a measurement included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the scheduled day, the later assessment will be used. In case of ties located on the same side of the target day (i.e., more than one value for the same day), the mean of the values will be used.

2. For the categorical ECG assessment, if a subject has more than one result with a measurement included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the later assessment will be used in the analyses. In case of ties located on the same side of the scheduled day (i.e. more than one value for the same day), the worst-case parameter value (where 'abnormal - clinically significant' is considered worse than 'abnormal - not clinically significant', which in turn are both considered worse than 'normal') will be used.
3. For the C-SSRS, if a subject answers "yes" to more than one question within a window, the worst-case response (within a category) will be used irrespective of whether this is closest to the target day.

7.11.6 Pooling Sites Algorithm

Approximately 178 subjects will be enrolled in approximately 35 sites. When "center" is included as a factor in a statistical model, sites that have less than 10 FAS subjects in total will be identified and then combined for statistical analysis purpose according to the following algorithm:

Step 1. Divide the sites into 2 groups with Group 1 including all sites that have at least 10 FAS subjects in total and Group 2 including all remaining sites. Sort each group in ascending order by total sample size and site number.

Step 2. Starting at the top of the Group 2 list (i.e., the first site with the smallest total sample size), combine the minimum number of sites required to achieve a "study site" that has at least 10 FAS subjects in total. Continue forming "center" in this manner until all Group 2 sites have been grouped or it is no longer possible to form a "center" with at least 10 FAS subjects in total.

Step 3. If there is a site (or several sites) left after step 2, combined the site(s) with the last pooled site that is created. For the situation where no previous pooled site is created, combine the site(s) with the first site on the sorted Group 1 list.

Pooled sites will be assigned names PoolSite01, PoolSite02, etc.

For all sites that have been combined into pooled sites, the assigned pooled site will be used instead of the original site identification in all statistical models that include "center" as a factor. However, the original site identification will be used in all summaries of subject disposition or discontinuation by site and in all data listings.

8 DOCUMENT REVISION HISTORY

Version	**Date**	**Changes**	**Comment/rationale for change**
1.0	10-Mar-2017	NA	Document finalized
2.0	10-Apr-2018	Page 1: Changed "Subjects" to "Patients" in study title.	Typographical error.
2.0	10-Apr-2018	Section 5.2.1 Table 2: Updated criteria to criterion where appropriate. Additional text included for FIQR inclusion criteria: '**Inclusion criterion #11 is No and/or** FIQR pain item score < 4 at Screening.' Percent overall compliance is <70% for a subject, calculated over day 1 to Week 8/EOT. **Subjects with missing compliance will be reviewed on a case by case basis.** Additional text included for HADS exclusion criteria: **Exclusion Criterion #9 is Yes and/or** HADS total score > 14 **(using HADS corrected questionnaire)** at Screening or Visit 3 (Randomization). **Subjects who completed the incorrect version of this questionnaire will be reviewed on a case by case basis.**	Typographical errors. Criterion numbering updated and additional text included for clarification to match classification specification
2.0	10-Apr-2018	Section 6.1: Additional sentence added: 'For FIQR, PGIS, EQ-5D-5L, mIBS-D and HADS baseline is defined as the last assessment on or prior to the first dose day (Day 1) of double-blind study drug.	Clarification of derivation of baseline for questionnaires captured on the tablet at site.
2.0	10-Apr-2018	Section 6.1.3 Table 5: 'Baseline' removed from the description of 'Handling of missing data' column for the 'Percentage of subjects achieving a PGIC of "Very Much Improved" or "Much Improved" at Week 8 and EOT' rows	Typographical error

Version	**Date**	**Changes**	**Comment/rationale for change**
2.0	10-Apr-2018	Section 6.1.3: Additional text added to FMSD section: 'Change from baseline is defined in Section 7.1. For FMSD Item 1, Item 2, Item 3, Item 4 and Item 7 a negative change indicates a reduction/improvement from baseline (i.e., a favorable outcome); whereas FMSD Item 5, Item 6 and Item 8 a positive change indicates an improvement in sleep symptoms compared to baseline.'	Clarification that direction of change differs for different FMSD Items.
2.0	10-Apr-2018	Section 6.1.3: Additional text added to HADS depression subscale 'Change from baseline to Week 8 and to EOT for the HADS depression subscale will only be calculated for subjects who have baseline data captured using the corrected version of the questionnaire. For subjects who have baseline HADS data captured using the original version of the questionnaire that was used at the start of the study change from baseline will not be derived. Data captured using the original version of the questionnaire will be listed only and will not be presented in any tables.'	Clarification that change from baseline for the HADS depression subscale total score will only be calculated for subjects with baseline data captured using the corrected version of this questionnaire.
2.0	10-Apr-2018	Section 6.1.3 Table 7: Additional row added for the derivation of the HADS depression subscale total score using the corrected version of the HADS questionnaire. Additional column added to distinguish the derivations required for the original and corrected HADS questionnaire. Post-baseline analysis visits removed from the original HADS questionnaire.	Section updated to include the corrected version of the HADS questionnaire and derivation of the HADS depression subscale total score. Analysis timepoints for the original version of the HADS questionnaire updated to include baseline only.
2.0	10-Apr-2018	Section 6.1.3: Additional text has been to the following sentence: 'Change from baseline is defined in Section 7.1 **and only applies to the EQ-VAS**.'	Clarification that change from baseline only applies to the EQ-VAS.
2.0	10-Apr-2018	Section 6.1.3 Table 9: Total Number of days replaced with 'Minimum of (upper bound of the time window, last assessment day from e-dairy data) – lower bound of the time window + 1'	Additional text included to define the denominator for each week (Total number of days) for subjects who discontinue early or who come in early for their last visit (but within the designated window in the protocol.)

Version	**Date**	**Changes**	**Comment/rationale for change**
2.0	10-Apr-2018	Section 6.4.7: Additional sentences added to the end of this section: 'The CMSI total score at baseline will be calculated and ranges from 0 to 39 for males and 0 to 41 for females. Baseline is defined as the last assessment on or prior to the first dose day (Day 1) of double-blind study drug.'	Extra clarification regarding derivation of CMSI total score and definition of baseline.
2.0	10-Apr-2018	Section 7.1: Additional sentences added to the end of the following paragraph: 'Summaries based on FAS and PPS (e.g. disposition, baseline and efficacy data) will be presented by planned treatment group, unless specifically stated otherwise. Safety analysis and other summaries based on SAF will be presented by actual treatment received. **For summaries which present both absolute values over time and change from baseline values over time the number of subjects used to calculate the descriptive statistics will be those who have non-missing data at each analysis visit and at baseline**. **For endpoints which include mBOCF, LOCF or mLOCF imputation the descriptive statistics will be calculated after the imputation has been performed.**' Unless otherwise specified, statistical comparisons will be made using one-sided tests at the α=0.05 significance level and two-sided 90% confidence intervals (CIs) will be presented when applicable. **When two-sided p-values are presented statistical comparisons will be made using an α=0.1 significance level.**	Extra clarification regarding the number of subjects which will be presented in summary tables. Significance level added for 2-sided p-values.

Version	**Date**	**Changes**	**Comment/rationale for change**
2.0	10-Apr-2018	Section 7.2.4: Additional paragraph added: All previous medications for taken for any pain prior to the baseline diary run-in; all previous medications taken for any pain during baseline diary run-in; all concomitant medications taken for any pain during the double blind treatment period and all concomitant medications taken for any pain during the follow-up period will also be summarized by preferred WHO name by treatment group and 'Total' over all treatment groups.	Description of extra summaries of previous medications and concomitant medications for any pain added.
2.0	10-Apr-2018	Section 7.2.3.2, Table 13: Footnote added: *Only for subjects with data captured using the corrected version of the HADS questionnaire.	Clarification that HADS depression subscale total score will only be calculated for subjects with data captured using the corrected version of this questionnaire.
2.0	10-Apr-2018	Section 7.2.3.3, Table 14: Additional group added to each of CMSI total score and NPSI total score and subscales. Footnote regarding definition of cut-points for CMSI total score, NPSI total score and subscales and mIBS-D summary score and individual items updated.	Decision made to split CMSI total score into three groups; NPSI total score and subscales into two groups; mIBS-D summary score and individual items into three groups based on assessment of scatterplots during blind data review.
2.0	10-Apr-2018	Section 7.4.2: In the section describing the proportional odds analysis of overall subject improvement assessed by PGIC the text has been updated to: At each time point, the proportion of subjects in each treatment group achieving each level of response (1 = "Very Much Improved", 2 = "Much improved", 3 = "Minimally Improved", 4 = "No Change", 5 = "Minimally Worse", 6 = "Much Worse", 7 = "Very Much Worse"), will be presented, together with the odds ratio, associated 90% CI **based on profile likelihood** and **2**-sided p-value **based on likelihood ratio test** for ASP8062 vs placebo. The cumulative logit link will be used to specify the proportional odds model in SAS.	p-value updated to 2-sided rather than 1-sided. Additional detail provided regarding methods used for calculation of CI and p-value.

Version	**Date**	**Changes**	**Comment/rationale for change**
2.0	10-Apr-2018	Section 7.4.1.1: In the description of the MMRM model the text 'baseline mean daily average pain score-by-treatment interaction' has been replaced by 'baseline mean daily average score-by-**time** interaction' and subject as a random effect has been removed from the model	Typographical error 'treatment' replaced with 'time'. Subject as a random effect has been removed from model due to issues with convergence.
2.0	10-Apr-2018	Section 7.4.3, Table 17: Footnote added: *Only for subjects with data captured using the corrected version of the HADS questionnaire.	Clarification that HADS depression subscale total score will only be calculated for subjects with data captured using the corrected version of this questionnaire.
2.0	10-Apr-2018	Section 7.4.3, Table 17: Additional rows for shifts from baseline to Week 8 and to EOT for the Treatment Period and from baseline to Week 10 for the Follow-up Period for each of the 5 dimensions of the EQ-5D-5L have been added.	As EQ-5D-5L dimensions are categorical have replaced summary tables of change from baseline with shift tables
2.0	10-Apr-2018	Section 7.4.3 Table 17: NPSI total score added to the list of exploratory analyses: 'Change from baseline to Week 8 and EOT in the **NPSI total score and** NPSI burning pain, pressing pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia subscales'	Typographical error
2.0	10-Apr-2018	Section 7.4.3: NPSI total score added to list of exploratory analyses: • Change from baseline to Week 8 (note that no imputation will be performed hence the ANCOVA will only include subjects with data at both baseline and Week 8) and EOT in the **NPSI total score** and NPSI burning pain, pressing pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia subscales.	Typographical error

Version	**Date**	**Changes**	**Comment/rationale for change**
2.0	10-Apr-2018	Section 7.4.3: ANOVA analysis of average daily dose of rescue medication updated to specify that this will be performed for the overall double-blind treatment period only. In addition, the response variable will be log10 transformed and values of 0 imputed as 5 prior to analysis.	Normality assumptions reviewed during blind data review and judged invalid for ANOVA at Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8 and EOT. Upon log10 transformation normality assumptions deemed acceptable for average daily dose of rescue medicine during the double-blind treatment period.
2.0	10-Apr-2018	Section 7.4.3: Additional text added to clarify that descriptive summaries of change from baseline apply to EQ-VAS only. Additional text included to describe the shift tables that will be produced for the EQ-5D-5L 5 dimensions.	As EQ-5D-5L dimensions are categorical have replaced summary tables of change from baseline with shift tables. Clarification provided that change from baseline summaries apply to EQ-VAS only.
2.0	10-Apr-2018	Section 7.5.1.3: Text updated so that AEs with missing severity will be imputed with worst severity, i.e severe rather than treated as missing.	Updated to comply with latest version of Astellas standards
2.0	10-Apr-2018	Section 7.5.3: Bullet point describing summary shifts of laboratory parameters so that 'low to high' is included as a categorized increase and 'high to low' is included as a categorized decrease.	Study team feedback provided that these extra conditions should be included in these definitions.
2.0	10-Apr-2018	Section 7.5.4 Table 19: Criteria for SBP absolute worst lowest value changed from <100 mmHg to **<90 mmHg** Criteria for SBP absolute worst highest value changed from >160 mmHg to **>180 mmHg**	Updates to absolute worst lowest and highest criteria definition for SBP per study team feedback.
2.0	10-Apr-2018	Section 7.8.1: Text updated to describe updates to the cut-points being used to split the CMSI total score, NPSI total score and subscales and mIBS-D summary score and individual items into subgroups.	Decision made to split CMSI total score into three groups; NPSI total score and subscales into two groups; mIBS-D summary score and individual items into three groups based on assessment of scatterplots during blind data review.

Version	**Date**	**Changes**	**Comment/rationale for change**
2.0	10-Apr-2018	Section 7.11.4.3: Tables 21 and 22 Imputation of EOT updated to specify that baseline is carried forward when there are no measurements post baseline. Tables 23 and 24 Extra footnote providing the definition of baseline and imputation of EOT when there are no post-baseline measurements added.	Extra clarification regarding imputation at EOT timepoint provided for NRS, FMSD, FIQR, PGIS, PGIC mIBS-D, HADS, EQ-5D-5L and NPSI questionnaires. Definition of baseline provided for FIQR, PGIS, mIBS-D, HADS, EQ-5D-5L and NPSI questionnaires.
2.0	10-Apr-2018	Section 7.11.5.3: Extra footnote providing definition of baseline added to Tables 25 and 26.	Extra clarification regarding definition of baseline for laboratory parameters, vital signs variables, C-SSRS questionnaire and ECG assessments.
2.0	10-Apr-2018	Appendix 10.1: MedDRA version updated to 20.0. List of Lower Level Terms updated to reflect update to MedDRA v2.0. Lower Level Codes added to table.	Table updated to reflect change to MedDRA v20.0
2.0	10-Apr-2018	Appendix 10.2: MedDRA version updated to 20.0. List of Lower Level Terms updated to reflect update to MedDRA v2.0. Lower Level Codes added to table.	Table updated to reflect change to MedDRA v20.0
2.0	10-Apr-2018	Section 6.1, 7.2 and 7.4: “FIQR physical function” was changed to “FIQR function” wherever it was mentioned.	Typographical error.

9 REFERENCES

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10 APPENDICES

10.1 Appendix 1: Drug Abuse Related Adverse Events

Abuse related adverse events of interest (MedDRA 20.0) that are explicitly referenced in the 2010 draft guidance

System Organ Class	Higher Level GT	Higher Level Term	Preferred term	Lowest Level Term	Lower Level Code
Psychiatric disorders	Mood disorders and disturbances NEC	Emotional and mood disturbances NEC	Euphoric Mood	Euphoria	10015533
				Euphoric	10015534
				Euphoric mood	10015535
				Exaggerated well-being	10015584
				Feeling high	10016333
				Felt high	10016382
				High	10020044
				High feeling	10020063
				Hyperthimic	10020847
				Hyperthimic state	10020849
				Laughter	10024042
				Mood elevated	10027949
			Mood altered	Affect alteration	10054199
				Affect altered	10001439
				Altered mood	10001850
				Bad mood	10004064
				Mood alteration NOS	10027937
				Mood altered	10027940
				Mood change	10027941
		Affect alterations	Inappropriate affect	Elation inappropriate	10014339
				Exhilaration inappropriate	10015672
				Exhiliration inappropriate	10015673
				Inappropriate affect	10021588
				Inappropriate crying	10021589
				Inappropriate elation	10021592
				Inappropriate exhilaration	10021593
				Inappropriate laughter	10021595
				Inappropriate mood elevation	10021596
				Mood elevation inappropriate	10027950

Table continued on next page

System Organ Class	Higher Level GT	Higher Level Term	Preferred term	Lowest Level Term	Lower Level Code
Psychiatric disorders	Disturbances in thinking and perception	Perception disturbances	Hallucination	Drug-induced hallucinosis	10013761
				Hallucinating	10019062
				Hallucination	10019063
				Hallucination NOS	10019066
				Hallucinations	10019077
				Hallucinations aggravated	10019078
				Kinesthetic hallucination	10023450
				Organic hallucinosis syndrome	10031079
				Pseudohallucination	10066297
				Sensory hallucinations	10040028
				Stump hallucination	10042263
			Hallucination, auditory	Auditory hallucinations	10003785
				Hallucination auditory	10019064
				Hallucination, auditory	10019070
				Verbal hallucinations	10069415
			Hallucination, visual	Hallucination visual	10019068
				Hallucination with color	10055527
				Hallucination with colour	10019069
				Hallucination, visual	10019075
				Visual hallucinations	10047570

Table continued on next page

System Organ Class	Higher Level GT	Higher Level Term	Preferred term	Lowest Level Term	Lower Level Code
General disorders and administration site conditions	General system disorders NEC	Feelings and sensations NEC	Feeling drunk	Drunk-like effect	10013767
				Drunkenness feeling of	10013769
				Feeling drunk	10016330
			Feeling abnormal	Cotton wool in head	10011221
				Feeling abnormal	10016322
				Feeling bad	10016324
				Feeling dazed	10050462
				Feeling floating	10016331
				Feeling lifeless	10016340
				Feeling miserable	10016342
				Feeling stoned	10070679
				Feeling strange	10016366
				Feeling weightless	10016372
				Feels awful	10016375
				Feels bad	10016376
				Feels poorly	10016377
				Felt like a zombie	10016384
				Floating feeling	10016782
				Foggy feeling head	10016876
				Funny episode	10017552
				Fuzzy	10017565
				Fuzzy head	10017566
				Muzzy head	10028405
				Neck strange feeling of	10028844
				Soft feeling	10041286
				Spaced out	10041374
				Thick head	10043428
				Unstable feeling	10046253
				Weird feeling	10047904

The AE term of sedation is mentioned in the 2010 Draft Guidance but is not included in this table.

10.2 Appendix 2: Drug Withdrawal Related Adverse Events

Drug Withdrawal – Related Adverse Events Occurring Following Drug Discontinuation (Preferred Terms; MedDRA 20.0)

System Organ Class	Higher Level GT	Higher Level Term	Preferred Term	Preferred Term Code
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety symptoms	Agitation	10001497
Nervous system disorders	Neurological disorders NEC	Neurological signs and symptoms NEC		10001497
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Anhedonia	10002511
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety symptoms	Anxiety	10002855
Musculoskeletal and connective tissue disorders	Muscle disorders	Muscle related signs and symptoms NEC	Chills	10008531
Musculoskeletal and connective tissue disorders	Muscle disorders	Feelings and sensations NEC		10008531
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Depressed mood	10012374
Psychiatric disorders	Depressed mood disorders and disturbances	Depressive disorders	Depression	10012378
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea (excl infective)	Diarrhoea	10012735
Psychiatric disorders	Mood disorders and disturbances	Emotional and mood disturbances NEC	Dysphoria	10013954
Nervous system disorders	Sleep disturbances (incl subtypes)	Sleep disturbances NEC	Dyssomnia	10061827
Psychiatric disorders	Sleep disorders and disturbances	Dyssomnias		10061827
Psychiatric disorders	Depressed mood disorders and disturbances	Depressive disorders	Persistent depressive disorder	10077804
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Feeling of despair	10016344
Nervous system disorders	Headaches	Headaches NEC	Headache	10019211

Table continued on next page

System Organ Class	Higher Level GT	Higher Level Term	Preferred Term	Preferred Term Code
Skin and subcutaneous tissue disorders	Skin appendage conditions	Apocrine and eccrine gland disorders	Hyperhidrosis	10020642
General disorders and administration site conditions	General system disorders NEC	General signs and symptoms NEC		10020642
Psychiatric disorders	Sleep disorders and disturbances	Disturbances in initiating and maintaining sleep	Insomnia	10022437
Nervous system disorders	Sleep disturbances	Disturbances in initiating and maintaining sleep		10022437
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Morose	10027977
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms	Nausea	10028813
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Negative thoughts	10058672
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety symptoms	Nervousness	10029216
Psychiatric disorders	Anxiety disorders and symptoms	Obsessive-compulsive disorders and symptoms	Obsessive thoughts	10029897
General disorders and administration site conditions	General system disorders NEC	Pain and discomfort NEC	Pain	10033371
Nervous system disorders	Sleep disturbances (incl subtypes)	Sleep disturbances NEC	Poor quality sleep	10062519
Psychiatric disorders	Sleep disorders and disturbances	Dyssomnias		10062519
Cardiac disorders	Cardiac disorder signs and symptoms	Cardiac signs and symptoms NEC	Syncope	10042772
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	Circulatory collapse and shock		10042772
Nervous system disorders	Neurological disorders NEC	Disturbances in consciousness NEC		10042772
Psychiatric disorders	Sleep disorders and disturbances	Disturbances in initiating and maintaining sleep	Terminal insomnia (lower level term of interest: early morning awakening)	10068932
Nervous system disorders	Sleep disturbances	Disturbances in initiating and maintaining sleep		10068932

Table continued on next page

System Organ Class	Higher Level GT	Higher Level Term	Preferred Term	Preferred Term Code
Nervous system disorders	Movement disorders (incl parkinsonism)	Tremor (excl congenital)	Tremor	10044565
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms	Vomiting	10047700

10.3 Appendix 3: Potentially Clinically Significant Laboratory Criteria

Potentially Clinically Significant Laboratory Criteria					
Laboratory Parameter	Low PCS criteria (Classical unit)	High PCS criteria (Classical unit)	Conv. factor	Low PCS criteria (SI unit)	High PCS criteria (SI unit)
Hematology and Coagulation					
Hemoglobin	< 7.0 g/dL	> 20.0 g/dL	10	< 70 g/L	> 200 g/L
Hematocrit	< 20.0 %	> 60.0 %	0.01	< 0.200 v/v (Fraction)	> 0.600 v/v (Fraction)
Leukocytes (White Blood Cell Count)	< 2.00 $x10^3/\mu L$	> 30.00 $x10^3/\mu L$	1	< 2.00 $x10^9$ /L	> 30.00 $x10^9$ /L
Platelets	< 40 $x10^3/\mu L$	> 1000 $x10^3/\mu L$	1	< 40 $x10^9$ /L	> 1000 $x10^9$ /L
International Normalized Ratio (INR)	No lower limit	> 2 (Ratio)	1	No lower limit	> 2.00 (Ratio)
Other Biochemistry*					
Sodium	< 120 mEq/L	> 160 mEq/L	1	< 120 mmol/L	> 160 mmol/L
Potassium	< 2.8 mEq/L	> 6.2 mEq/L	1	< 2.8 mmol/L	> 6.2 mmol/L
Calcium	< 6.0 mg/dL	> 13.0 mg/dL	0.25	< 1.50 mmol/L	> 3.25 mmol/L
Chloride	< 80 mEq/L	> 120 mEq/L	1	< 80 mmol/L	> 120 mmol/L
Magnesium	< 0.98 mg/dL	> 4.74 mg/dL	0.4114	< 0.400 mmol/L	> 1.950 mmol/L
Glucose	< 40 mg/dL	> 450 mg/dL	0.0555	< 2.22 mmol/L	> 24.98 mmol/L
Creatinine	No lower limit	> 5.00 mg/dL	88.4	No lower limit	> 442.0 µmol/L
Uric Acid	No lower limit	> 13.0 mg/dL	59.48	No lower limit	> 773 µmol/L
Blood Urea Nitrogen (BUN)	No lower limit	> 80 mg/dL	0.357	No lower limit	> 28.6 mmol/L

Source: Tietz. Textbook of Clinical Chemistry and Molecular Diagnostics, 4th Edition. Elsevier Saunders, 2006, section VII, chapter 56, pages 2317-2318.

Conv.: Conversion; PCS: Potentially Clinically Significant; SI: International System of Units.

* PCS criteria for Liver Enzymes and Total Bilirubin are provided in Table 18, Section 7.5.3.1

10.4 Appendix 4: Key contributors and Approvers

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

Primary author (s)

PPD	PPD

Contributors and Reviewers

PPD	Data Science
PPD	Medical Science
PPD	Data Science

Author and Approver Signatories

Authored by: _____ _____

PPD

Date (DD Mmm YYYY)

(E-signatures are attached at end of document)

PPD, Data Science, Astellas Pharma Global Development, Inc. was the biostatistics peer reviewer of this Statistical Analysis Plan

This Statistical Analysis Plan was approved by:

PPD, Data Science,
Astellas Pharma Global Development, Inc.

This Statistical Analysis Plan was approved by:

PPD
Medical Science,
Astellas Pharma Global Development, Inc.