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

The Field Study

ISN/Protocol 0819-CL-0201

Version 2.0

Incorporating Substantial Amendment 1 [See Attachment 1]

19 December 2016

NCT03056690

IND 127248

Sponsor:

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

Protocol History:
Version 1.0 [20Oct2016]

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., Protocol authors and contributors, etc.) are located in [Section 15 Sponsor's Signatures]; located at the end of this document.

2. COORDINATING INVESTIGATOR'S SIGNATURE

The Coordinating Investigator's signature can be found in [Section 14 Coordinating Investigator's Signature].

3. INVESTIGATOR'S SIGNATURE

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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Version 2.0 Incorporating Substantial Amendment 1

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I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (dd Mmm yyyy)

Printed Name:----------

<Insert name and qualification of the Investigator>

Address: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See [Section 5.5.6 Reporting of Serious Adverse Events] for SAE Fax Number and Email	**Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Pharmacovigilance** **Fax number: 888-396-3750** **Alternate Fax number: 847-317-1241** **Email: safety-us@astellas.com**
Medical Monitor: Responsible Medical Officer/Medical Expert:	PPD, Medical Affairs & Strategic Consulting, PPD PPD Medical Science Astellas Pharma Global Development (APGD) PPD
Clinical Research Contacts:	PPD, Clinical Science APGD, Astellas Pharma Europe BV (APEB) PPD PPD Clinical Science APGD, APEB PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ACR	American College of Rheumatology
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
ANCOVA	Analysis of covariance
anti-HAV (IgM)	Hepatitis A virus antibodies (immunoglobulin M)
anti-HCV	Hepatitis C virus antibodies
APGD	Astellas Pharma Global Development, Inc.
AST	Aspartate aminotransferase (GOT)
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BMI	Body mass index
BOCF	Baseline observation carried forward
CCSI	Company core safety information
CI	Confidence interval
C_{max}	Maximum concentration
CMSI	Complex Medical Symptoms Inventory
CPAP	Continuous positive airway pressure
CRF	Case report form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A	Cytochrome P450 3A
DBP	Diastolic blood pressure
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
ePRO	Electronic patient reported outcome
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
EU	European Union
FAS	Full analysis set
FDA	Federal Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
FIQR	Fibromyalgia Impact Questionnaire Revised
FMSD	Fibromyalgia Sleep Diary
$GABA_B$	y-aminobutyric acid
GCP	Good clinical practice
GMP	Good manufacturing practices
HADS	Hospital Anxiety and Depression Scale
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
IAP	Interim Analysis Plan
IB	Investigator's brochure

Abbreviations	Description of abbreviations
ICD-10	International Statistical Classification of Diseases and Related Health Problems
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
INR	International normalized ratio
IUD	Intrauterine device
IUS	Intrauterine system
IRB	Institutional review board
ISN	International study number
LA-CRF	Liver abnormality case report form
LFT	Liver function tests
LOAEL	Lowest-observed-adverse-effect level
LOCF	Last observation carried forward
mBOCF	Modified Baseline Observation Carried Forward
M.I.N.I.	Mini-International Neuropsychiatric Interview
MedDRA	Medical Dictionary for Regulatory Activities
mIBS-D	Modified irritable bowel syndrome - diarrhea predominant
MMRM	Mixed model repeated measures
NDA	New Drug Application
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PGx	Pharmacogenomics
PI	Prediction interval
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
PRO	Patient reported outcome
qd	Quaque die (once daily)
QT	time from electrocardiogram Q wave to the end of the T wave
SAE	Serious adverse event
SAF	Safety analysis set
SBP	Systolic blood pressure
SOP	Standard operating procedure
SS	Symptom severity
SUSAR	Suspected unexpected serious adverse reactions
TBL	Total bilirubin level
TEAE	Treatment emergent adverse event
t_{max}	Time of maximum concentration
TSH	Low thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
WPI	Widespread pain index

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Assessments of subjects as they enter a trial before they receive any treatment.
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.
Double-Blind	The study subjects, investigator(s), site staff and Astellas study team will be blinded to treatment.
Early Discontinuation (ED)	The act of concluding participation prior to completion of all protocol-required elements in a trial by an enrolled subject. Four categories of discontinuation are distinguished as follows: a) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); b) Investigator-initiated discontinuation (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) Sponsor-initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis. "Termination" has a history of synonymous use, but it is now considered non-standard.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a trial.
Enroll	The process of registering or entering a subject into a clinical trial. NOTE: Once a subject has signed the informed consent form (ICF), the clinical trial protocol applies to the subject.
End of Study (EOS)	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 (EOT)	The date the last dose of study drug was taken by the enrolled subject.
Electronic Patient Reported Outcomes (ePRO)	An ePRO is a patient-reported outcome that is collected by electronic methods.
Follow-up Period	The weeks following the final dose of study drug for all subjects. This includes a Follow-up visit and an End of Study Phone Call.
Independent Data Monitoring Committee (IDMC)	The Independent Data Monitoring Committee (IDMC) is responsible for the interim futility evaluation of efficacy data defined in the IDMC Charter. Participants in the IDMC include, but may not be limited to an Independent Astellas Statistician who is not on the study team and does not communicate with study team or Site staff. The IDMC will evaluate unblinded data and provide conclusion of futility analysis to Astellas Management.
Intervention	The drug, device, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
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.

Terms	Definition of terms
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening period	Period of time before entering the treatment period, usually from the time when a subject signs the ICF until just before the test drug or comparative drug is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Treatment Period	Time from Day 1, after first study drug administration and through time of last study drug dose. Period of time where major interests of protocol objectives are observed, and where the test drug or placebo is given to a subject, and continues until the last assessment after completing administration of the test drug or placebo.
Washout	Time (post review of safety laboratory assessments) when a subject discontinues use of prohibited medications, as medically indicated and based upon the Investigator's recommendation, to allow for medication to be eliminated from the body. Completed prior to Diary Run-In.

IV. SYNOPSIS

Date and Version No of Protocol Synopsis:	19 December 2016, Version 2.0
Sponsor: Astellas Pharma Global Development Inc (APGD)	**Protocol Number:** 0819-CL-0201
Name of Study Drug: ASP0819	**Phase of Development:** 2a

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

Planned Study Period:
From 1Q2017 to 3-4Q2018

Study Objective(s)**:**
The objectives of the study, conducted in patients with fibromyalgia, are the following:

Primary Objectives

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

Secondary Objectives

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

Exploratory Objectives

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

Planned Total Number of Study Centers and Location(s):
Up to approximately 35 sites in 1 country (United States only)

Study Population:
Male and female subjects between 18 and 80 years of age with fibromyalgia

Number of Subjects to be Enrolled and Randomized:
Approximately 323 subjects are planned to be screened for 178 randomized subjects (89 per arm) (45% screen fail rate).

Study Design Overview:

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 consist of the following study periods:

- Screening period (Day -42 to Day -1)
  Up to 42 days, which includes the completion of screening procedures (Visit 1), wash-out of prohibited medications (if applicable), and a 7-day Baseline Diary Run-In. The wash-out of prohibited medications should be completed prior to the initiation of the Baseline Diary Run-In. The Baseline Diary Run-In may be extended up to 2 days if necessary in the Investigator's opinion. In general, the Screening period should not exceed 42 days. The Investigator should contact the medical monitor if there are circumstances that would cause the subject to exceed 42 days.
- Double-blind randomized treatment period (Day 1 to Day 57 [End of Treatment (EOT)])
  Eight-weeks of treatment with study drug and site visits at Day 1, 15, 29 and 57.
- Follow-up period (Day 58 to Day 85 [End of Study (EOS)])
  Includes a follow-up site visit on Day 71 and an (EOS) phone call on Day 85.

Screening Period:

After signing the informed consent, screening procedures for the subject will start (Visit 1). Subjects will be required to meet both the 1990 and 2010 American College of Rheumatology (ACR) criteria for fibromyalgia. The Investigator or other qualified individual at the site will confirm the diagnosis of fibromyalgia.

Subjects who meet the eligibility criteria [see Section 3.2 Inclusion Criteria] will be instructed, if medically appropriate, to wash-out of any prohibited medications via phone call. At Visit 2 all subjects who continue to meet eligibility criteria will be provided with an electronic diary (e-diary). Subjects will enter a 1-week Baseline Diary Run-In, and during this period, they will record their daily average pain score (0 - 10 Numerical Rating Scale [NRS]) and sleep quality information with the Fibromyalgia Sleep Diary (FMSD) in the e-diary. They will receive instructions regarding its use and begin entering daily scores. Upon awakening, subjects are to rate their sleep quality during the previous night using the e-diary. Each evening before bed, subjects are to rate their average pain during the previous 24 hours using the e-diary. Subjects will need to have a mean daily average pain score ≥ 4 and ≤ 9, and meeting pre-specified criteria for daily average pain scores.

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

After confirmation of eligibility at Visit 3 (Randomization), subjects who meet the mean daily average pain score eligibility requirements at this visit will be randomized. For subjects that meet the entry criteria at Visit 3 (Randomization), additional baseline assessments will be obtained (see Schedule of Assessments).

Double-Blind Randomized Treatment Period (treatment period):

Subjects will enter the treatment period and will be randomized in a 1:1 ratio to receive either ASP0819 or placebo once per day for a period of 8 weeks. Acetaminophen may be used as rescue therapy for intolerable pain due to fibromyalgia during the baseline period and in all subsequent study periods (see rescue medication section). Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used (with the exception of celecoxib) as needed for non-fibromyalgia pain (e.g., headache).

Throughout the treatment period, beginning on Day 1 (Randomization) through Visit 6/Week 8, subjects will record all daily average pain scores (NRS) and any acetaminophen use in the e-diary. Sleep quality scores (FMSD) will be recorded through Visit 6/Week 8. Subjects will take study drug once per day (qd). Subjects randomized to ASP0819 will receive 15 mg (3 capsules of 5 mg each). In order to maintain the study blind, ASP0819 and placebo treated subjects will receive matching capsules.

During the treatment period, subjects will return to the clinic per schedule for safety and efficacy procedures (see Schedule of Assessments for details). Subjects who do not complete the treatment period will be requested to complete EOT visit procedures.

Follow-up Period:

Subjects are encouraged to abstain from any concomitant medications for the treatment of pain prior to Visit 7/Week 10. Rescue medication is allowed during the follow-up period. Subjects will continue to enter their daily average pain score (NRS), sleep quality scores (FMSD) and acetaminophen use into their e-diary and return diaries at Visit 7/Week 10. All subjects will return to the site for a follow-up visit at Day 71, 2 weeks following the EOT visit (Day 57). A follow-up safety phone call will take place approximately 4 weeks post study drug discontinuation (Day 85/EOS).

Inclusion/Exclusion Criteria:

Inclusion

A subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] Authorization for United States [US] sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. A male or female subject between 18 and 80 years of age at the signing of the informed consent.
3. Subject has a body mass index (BMI) ≤ 45 kg/m^2.
4. Female subject must either:
    - Be of nonchildbearing potential:
        - Postmenopausal (defined as at least 1 year without any menses) prior to Screening, or,
        - Documented as surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
    - Or, if of childbearing potential:
        - Agree not to try to become pregnant during the study and for 28 days after the final study drug administration,
        - Have a negative blood pregnancy test at Screening and negative urine test on Day 1, and
        - If heterosexually active, agree to consistently use 1 form of highly effective birth control* starting at Screening and throughout the study period and for 28 days after the final study drug administration.
5. Female subject must agree not to breastfeed at Screening and throughout the study period and for 28 days after the final study drug administration.
6. Female subject must not donate ova starting at Screening, throughout the study period, and for 28 days after the final study drug administration.

7. Male subject must not donate sperm starting at Screening and throughout the study period and for 28 days after the final study drug administration.
8. Male subject with a partner of child-bearing potential, or a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom throughout the study period and for 28 days after the final study drug administration.
9. Subject meets the ACR 1990 fibromyalgia diagnostic criteria at Screening:
    - Widespread pain for at least 3 months, defined as the presence of all of the following:
        - pain on right and left sides of the body,
        - pain above and below the waist, and
        - pain in the axial skeleton (cervical spine or anterior chest or thoracic spine or low back) must be present.
    - Pain in at least 11 of 18 tender point sites on digital palpation.
        - Digital palpation should be performed with an approximate force of 4 kg.
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.
11. Subject has a pain score ≥ 4 on the revised fibromyalgia impact questionnaire (FIQ) pain item at Screening.
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 and agrees to complete daily diaries throughout the duration of the study.
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 e-diary during the Baseline Diary Run-In period, and meeting pre-specified criteria for daily average pain scores.
14. Subject agrees to use only acetaminophen as rescue medication for fibromyalgia pain throughout the course of the trial (up to 1000 mg per dose and not to exceed 3000 mg/day).
15. Subject agrees not to initiate or change any non-pharmacologic interventions (including normal daily exercise routines, chiropractic care, physical therapy, psychotherapy, and massage therapy) during the course of the study. Non-pharmacologic interventions must be stable for a minimum of 30 days prior to Screening. Subject agrees to maintain usual level of activity for the duration of the study.
16. Subject is capable of completing study assessments and procedures, in the opinion of the Investigator.
17. Subject agrees not to participate in another interventional study from Screening through the EOS visit.

* Highly effective forms of birth control include the following:

- Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
- Established intrauterine device (IUD) or intrauterine system (IUS),
- Vasectomy (A vasectomy is a highly effective contraception method if the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used).
- Male is sterile due to a bilateral orchiectomy.

NOTE: The reliability of sexual abstinence for male and/or female subject enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. The investigator is responsible for confirming the subject is continuing to use the protocol-stated contraception requirements.

Waivers to the inclusion criteria will NOT be allowed.

Exclusion

Subject will be excluded from participation if any of the following apply:

1. Subject has received an investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to Screening.
2. Subject has had no meaningful improvement, in the Investigator's opinion, from 2 or more prior treatments (commercially available) for fibromyalgia (in at least 2 pharmacologic classes).
3. Subject has had known hypersensitivity or intolerance to the use of acetaminophen or associated formulation components; known hypersensitivity to the formulation components of ASP0819.
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.
5. Subject has infectious or inflammatory arthritis (e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or gout), autoimmune disease (e.g., systemic lupus erythematosus), or other widespread rheumatic disease other than fibromyalgia.
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.
7. Subject has initiated any non-pharmacologic interventions for the treatment of fibromyalgia or depression within 30 days prior to Screening or during the Screening period.
8. Subject has a history of any psychotic and/or bipolar disorder as assessed by the M.I.N.I.
9. Subject has a Hospital Anxiety and Depression Scale (HADS) score > 14 on the Depression subscale at Screening or at the time of Visit 3 (Randomization).
10. Subject has a history of suicide attempt or suicidal behavior within the last 12 months, or has suicidal ideation within the last 12 months (a response of "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale [C-SSRS]), or who is at significant risk to commit suicide, as assessed by the investigator at Screening and at the time of Visit 3 (Randomization).
11. Subject has clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, or a serum creatinine > 1.5 times the upper limit of normal (ULN) at Screening. These assessments may be repeated once, after a reasonable time period at the investigator's discretion (but within the Screening period).

12. Subject has aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1.5 times the upper limit of the reference range at Screening. These assessments may be repeated once, after a reasonable time period at the Investigator's discretion (but within the Screening period).
13. Subject has a positive test for hepatitis B surface antigen (HBsAg), hepatitis A virus antibodies (immunoglobulin M) (anti-HAV [IgM]), or hepatitis C virus antibodies (anti-HCV)) at Screening or has history of a positive test for human immunodeficiency virus type 1(HIV-1) and/or type 2 (HIV-2).
14. Subject has a resting systolic blood pressure (SBP) > 180 mmHg or < 90 mmHg, and/or a resting diastolic blood pressure (DBP) > 100 mmHg at Screening. These assessments may be repeated once after a reasonable time period at the investigator's discretion (but within the Screening period).
15. Subject has a clinically significant abnormality on 12-lead electrocardiogram (ECG) at Screening or Visit 3 (Randomization). If the ECG is abnormal, based on the investigator's judgment, an additional ECG can be carried out. If this also gives an abnormal result, the subject must be excluded.
16. Subject has a history of myocardial infarction (within 6 months of Screening), unexplained syncope, cardiac arrest, unexplained cardiac arrhythmias or torsade de pointes, structural heart disease or a family history of Long QT Syndrome.
17. Subject has evidence of any clinically significant, uncontrolled cardiovascular, gastrointestinal, endocrinologic (low thyroid stimulating hormone [TSH], but euthyroid is allowed), hematologic, hepatic, immunologic, infectious, metabolic, urologic, pulmonary (including obstructive sleep apnea not controlled by a continuous positive airway pressure [CPAP] device), neurologic, dermatologic, psychiatric, renal and/or other major disease (exclusive of fibromyalgia), as assessed by the investigator.
18. Subject has planned surgery during the study participation.
19. Subject has an active malignancy or a history of malignancy (except for treated non-melanoma skin cancer) within 5 years of Screening.
20. Subject has a positive drug or alcohol test at Screening, Baseline Diary Run-In or prior to Randomization. However, a positive test for tetrahydrocannabinol (THC) and/or opioids is allowed at the Screening visit, but must be confirmed negative prior to Baseline Diary Run-In and Randomization.
21. Subject has a current or recent (within 12 months of Screening) history of a substance use disorder including cannabinoid and/or alcohol abuse disorder. Patient has used opioids for pain for more than 4 days during the week preceding the Screening visit.
22. Subject is currently using protocol-specified prohibited medications and is unable to wash-out [see Section 5.1.3 for Concomitant Medication Restrictions].
23. Subject has filed or is awaiting judgment on a disability claim or has any pending worker's compensation litigation or related monetary settlements.
24. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
25. Subject is an employee of the Astellas Group, the Contract Research Organization (CRO) involved, or the investigator site personnel directly affiliated with this study and/or their immediate families (spouse, parent, child, or sibling, whether biological or legally adopted).

Waivers to the exclusion criteria will NOT be allowed.

Investigational Product(s)**:**
ASP0819 15 mg

Dose(s):
15 mg/3 capsules of 5 mg each

Mode of Administration:
As a single oral dose to be taken preferably in the morning with or without food.

Comparative Drug(s):
Matching placebo for ASP0819 capsules.

Dose(s):
3 placebo capsules to match ASP0819 capsules.

Mode of Administration:
As a single oral dose to be taken preferably in the morning with or without food.

Rescue Therapy:
If a subject experiences intolerable pain due to fibromyalgia during the baseline, treatment or follow-up periods, the subject should be instructed to use acetaminophen (for non-fibromyalgia pain, NSAIDs may be used as needed, refer to [Section 5.1.3 Concomitant medication]).

Subjects are instructed to document all acetaminophen use in the e-diary under rescue medication.

Dose(s):
The maximum amount of acetaminophen is up to 1000 mg per dose, not to exceed 3000 mg/day.

Mode of Administration:
Oral

Concomitant Medication Restrictions or Requirements:
Medications taken for fibromyalgia during the 12 months prior to Screening and other medication taken 28 days prior to the Screening visit and up to the first dose of study medication (treatment period) will be documented in the appropriate case report form (CRF) as prior medication. Subjects taking prohibited medications who are willing to discontinue these medications as medically indicated and based upon the investigator's recommendation, may wash-out over a period of 5 half-lives on a schedule determined by the investigator.

Medications taken after the first dose of study medication and up to EOS will be documented on the appropriate CRF as concomitant medication.

Prior and concomitant medications to be documented include but are not limited to: vitamins, herbal remedies (e.g., St. John's wort, valerian), OTCs and prescription medications. Any medications taken for treatment of pain symptoms will be documented as such on the CRF.

Subjects are instructed not to take any concomitant medication without first consulting the investigator or study coordinator (SC) throughout the duration of the study.

Concomitant Medication for Treatment of Non-Fibromyalgia Pain Symptoms:
NSAIDs will be allowed (with the exception of celecoxib), as needed, for treatment non-fibromyalgia pain, such as headache.

Prohibited Therapies:

Concomitant use of the following medications, therapies or surgical procedures could influence the evaluation of the study drug's efficacy and safety and are prohibited throughout the study (wash-out through the EOS):

- Medications that may have efficacy in reducing pain in fibromyalgia (except for allowed rescue medication), are as follows: gabapentinoids, antidepressants (except for selective serotonin reuptake inhibitors), ketamine, y-aminobutyric acid ($GABA_B$) receptor agonists (including sodium oxybate), opioids, celecoxib, chronic non-narcotic analgesics (with the exception of low dose aspirin for cardioprophylaxis, up to 325 mg daily) and topical pain medications.
- Medications that are sensitive Cytochrome P450 3A (CYP3A) substrates or CYP3A substrates that have a narrow therapeutic range.
- Use of cannabinoids from the Screening visit and throughout the study.
- Procedures that may have efficacy in reducing pain in fibromyalgia (e.g., nerve block, iontophoresis, laser therapy, acupuncture, tender point injections, dry needle injections, spinal cord stimulation therapy and transcutaneous electrical nerve stimulation).
- Hypnotics, other than those specified with restrictions, are listed in the section below, Permitted Medications.
- Tranquilizers, sedating antihistamines (non-sedating antihistamines are permitted), benzodiazepines for sedative, anxiolytic, or sleep aid. In contrast, non-benzodiazepines such as zolpidem are allowed for insomnia as discussed in the Permitted Medications list below.

Permitted Medications:

This list is not all inclusive and the Medical Monitor should be contacted to discuss medications not listed below.

- The following serotonin reuptake inhibitors will be allowed if the patient is on a stable dose 60 days prior to Screening and no changes are anticipated during the course of the study: sertraline, paroxetine, fluoxetine, citalopram, escitalopram, fluvoxamine, vilazodone and vortioxetine.
- The following medications will be allowed if they are stable for at least 30 days prior to Screening and no additional medication is taken for insomnia: zolpidem up to10 mg, eszopiclone up to 1 mg, zaleplon up to 10 mg, zopiclone up to 2 mg and melatonin for sleep.
- Allowed stable medications (i.e., stable dose 30 days prior to Screening and with no changes anticipated during the course of the study): anti-diabetic medications, anti-hypertensive medications, non-sedating antihistamines, lipid-lowering agents, asthma medications, low dose aspirin for cardioprophylaxis, non-sedating treatments for allergic rhinitis, triptans, multivitamins, short-term use of nasal, inhaled and topical corticosteroids.
- NSAIDs will be allowed (with the exception of celecoxib), as needed, for non-fibromyalgia pain, such as headache. However, chronic use of NSAIDs is not allowed (with the exception of low dose aspirin for cardioprophylaxis, up to 325 mg daily)

Permitted Non-Medication Therapy:

The following therapies must be stable for at least 30 days prior to Screening and with no changes anticipated during the course of the study: exercise routines, chiropractic care, physical therapy, psychotherapy and massage therapy.

Duration of Study and Treatment:
Subjects will be treated for a period of up to 8 weeks. Total study duration for a subject is approximately 18 weeks, including a Screening period of up to 6 weeks, an 8-week double-blind treatment period, and a 4-week follow-up period.

Endpoints for Evaluation:

Primary Efficacy

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

Secondary Efficacy

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

Exploratory Efficacy

Treatment Period

- Change from baseline to Weeks 1, 2, 3, 4, 5, 6, 7 and EOT in mean daily average pain score.
- Subject's response defined as achieving various reduction levels (> 0%, ≥ 10%, ≥ 20%, ≥ 40%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, 100%) from baseline to Week 8 and EOT in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.
- Change from baseline to Weeks 2, 4, 8 and EOT in FIQR Total Score.
- Change from baseline to Weeks 2, 4, 8 and EOT in PGIS.
- Subject's response defined as PGIC of very much or much improved at Week 8 and EOT.
- Subject's response defined as achieving ≥ 30 % reduction from baseline in FIQR total score at Week 8 and EOT.
- Subject's composite pain response defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of very much or much improved at Week 8 and EOT.
- Subject's composite syndrome response defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of very much or much improved **and** ≥ 30% reduction from baseline in FIQR total score at Week 8 and EOT.
- Change from baseline to Weeks 1, 2, 3, 4, 5, 6, 7, 8 and EOT in daily in the FMSD, which captures all critical sleep disturbance features of fibromyalgia (8 items).
- Change from baseline to Week 8 and EOT in the HADS depression subscale.
- Change from baseline to Week 8 and EOT in European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L)
- Proportion of days with rescue medication use at Weeks 1, 2, 3, 4, 5, 6, 7, 8 and EOT.
- Incidence of subjects using rescue medication at Weeks 1, 2, 3, 4, 5, 6, 7, 8 and EOT.
- Average daily dosage of rescue medication at Weeks 1, 2, 3, 4, 5, 6, 7, 8 and EOT.

- Change from baseline to Weeks 2, 4, 8 and EOT in Modified Irritable Bowel Syndrome - Diarrhea Predominant (mIBS-D) Symptom Summary Score and abdominal pain, stomach pain, abdominal cramps, abdominal pressure, and bloating as assessed by the mIBS-D Daily Symptom Diary.
- Change from baseline to Week 8 and EOT in neuropathic pain symptoms as assessed by the Neuropathic Pain Symptom Inventory (NPSI).

Follow-Up Period

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

<u>Safety and Tolerability Endpoints</u>

- Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs) from Screening until EOS.
- Safety laboratory tests at Weeks 2, 4, 8 and 10.
- Vital sign measurements at Weeks 2, 4, 8 and 10.
- 12-lead ECG parameters at Weeks 8 and 10.
- Physical examination at Weeks 8 and 10.
- C-SSRS (evaluation of suicidal ideation and behavior) at Weeks 2, 4, 8 and 10.

Statistical Methods:

Sample size justification:

The sample size calculations are based on the primary efficacy endpoint of change from baseline to Week 8 in mean daily average pain NRS. A meta-analysis of the change from baseline in mean daily average pain NRS for pregabalin or duloxetine vs 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 vs placebo, 84 subjects in the ASP0819 and placebo groups 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).

The total number of subjects required for the analysis would be 168 (84:84 subjects in ASP0819: placebo). Assuming approximately 5% of randomized subjects will not contribute to the analysis, and then a total of 178 subjects would be required for randomization using a 1:1 randomization ratio (89:89) subjects for the ASP0819 group and placebo group.

Efficacy:

The primary endpoint is the change from baseline to Week 8 in the mean daily average pain NRS. The baseline mean daily average pain score will be derived from the daily average pain scores (based on the daily NRS recorded in the 7 days before the first day of dosing). The primary analysis population will be the Full Analysis Set (FAS), which will include all randomized subjects who received at least 1 dose of study medication. Unless otherwise stated, all assessments of statistical significance will be one-sided at the 5% significance level, and as such one-sided p-values will be shown.

The primary analysis for the primary endpoint of change from baseline to Week 8 in the mean daily average pain NRS will use a mixed model repeated measures (MMRM) analysis, where the model will include the effects for treatment group, center (pooled where necessary), time (study Week 1 to 8) and treatment-by-time interaction, as well as the covariates of baseline mean daily average pain NRS and baseline pain-by-treatment interaction and subject as a random effect. The unconstrained between-time-point covariance structure will be used. This analysis will utilize observed data, and there will be no imputation for missing data. Least squares estimates for the primary endpoint will be shown for both treatment groups, and for the treatment comparisons of ASP0819 vs placebo (together with 2-sided 90% confidence intervals [CI]). A one-sided 5% significance level will be used for the comparison of ASP0819 vs placebo. This analysis will also display the same estimates for the exploratory endpoints of change from baseline to each Week from Week 1 to 7 in the mean daily average pain NRS. The analysis of change from baseline to EOT in mean daily average pain will use analysis of covariance (ANCOVA), with covariates of baseline average pain NRS score and center (pooled where necessary).

A sensitivity analysis for the primary endpoint will use the same MMRM model as described previously. However, for this secondary analysis, multiple imputation will be used for imputation of any missing data, using the '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 multiple imputation for subjects with missing data for other reasons. An additional sensitivity analysis for the primary endpoint will use modified baseline observation carried forward (mBOCF) for missing data with analysis using ANCOVA, with covariates of baseline mean daily average pain NRS score and center (pooled where necessary). mBOCF is defined as imputation by baseline observation carried forward (BOCF) for subjects who discontinue due to lack of efficacy or AEs, and imputation by last observation carried forward (LOCF) for subjects with missing data at Week 8 for other reasons.

The primary analysis for the secondary endpoints, of mean daily average pain response (≥ 30% and 50% reduction from baseline to Week 8 and to EOT) will be carried out with the Fisher's Exact Test (with one-sided p-value). In addition the percentage of subjects who meet cumulative response levels of > 0% to = 100% will be shown. For the Week 8 analysis subjects with missing data will be classified as non-responders (BOCF), and an additional analysis will use mBOCF. For the EOT analysis, LOCF will be used.

The primary analysis for the change from baseline to Weeks 2, 4 and 8 for the FIQR subscales of Physical Function, Symptoms and Overall Impact will use the same MMRM analysis as described above for the mean daily average pain score.

The primary analysis for the change from baseline to EOT for the FIQR subscales will use the same ANCOVA model as described above.

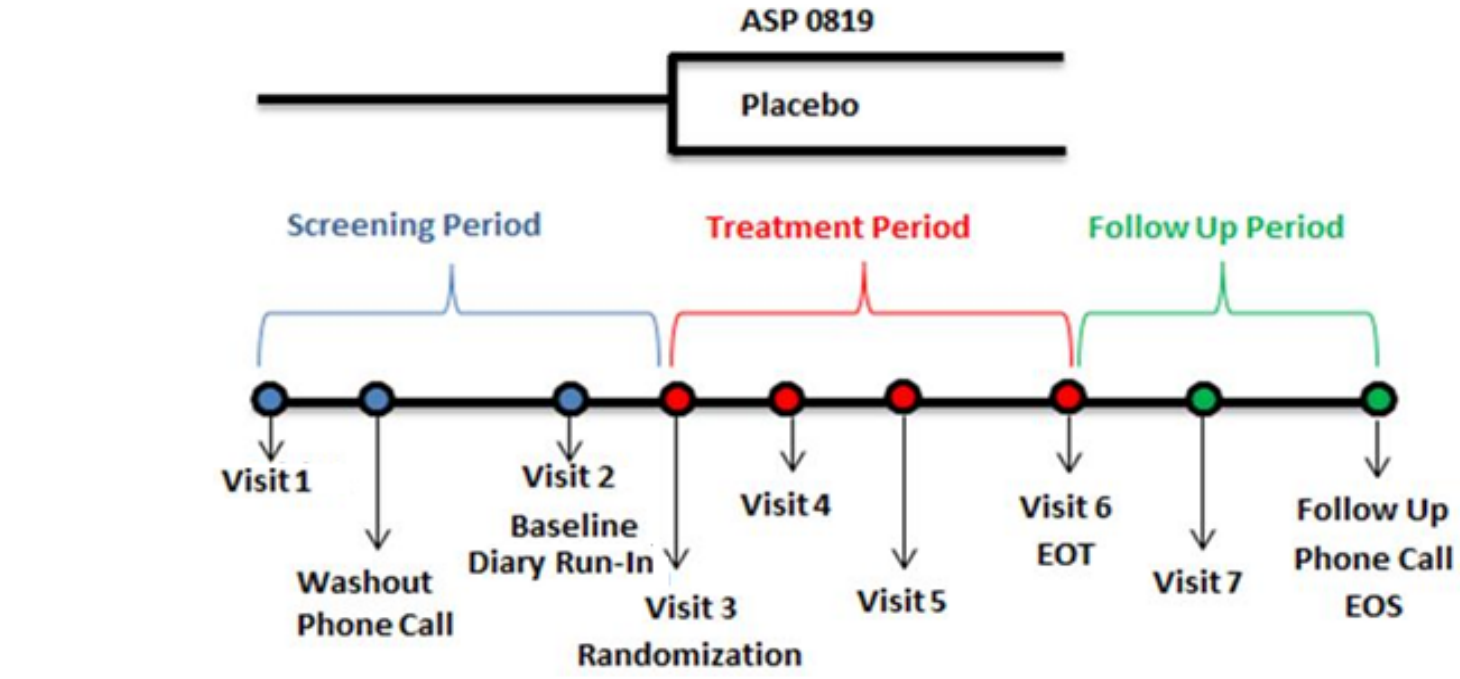
The primary analysis for the PGIC secondary endpoint will use the proportional odds model for ordinal data, with model term for treatment group. In addition, the percentage of subjects who achieve PGIC response (*Improved*, *Very Much Improved*) will be carried out with the Fisher's Exact Test (with one-sided p-value) for binary data.

Safety:
The safety variables will be summarized by descriptive statistics.

Interim analyses:
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 Interim Analysis Plan (IAP).

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



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

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 Patient[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 principal 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.

Footnotes continued on next page

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.

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 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.

Footnotes continued on next page

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.

1 INTRODUCTION

Protocol 0819-CL-0201 is a proof-of-concept study to examine the effects of ASP0819 for the treatment of pain in subjects with fibromyalgia.

1.1 Background

Background on Target Indication

Fibromyalgia is a complex syndrome characterized by chronic widespread musculoskeletal pain often occurring with symptoms of depression, fatigue, sleep disturbances and/or cognitive complaints. Fibromyalgia pain typically includes deep musculoskeletal pain with tender points in the shoulder, girdle, torso, hips and extremities. Fibromyalgia may include various somatic symptoms, such as headache and irritable bowel syndrome. The core diagnostic criteria for fibromyalgia are defined by the 1990 American College of Rheumatology (ACR) [Wolfe et al, 1990]. While the ACR has published new, as well as subsequent amended criteria [Wolfe et al, 2011; Wolfe et al, 2010], the 1990 version is still commonly utilized in clinical trials. The overall prevalence of fibromyalgia in the general population was estimated to be 2.2% in the United States (3.4% and 0.5% in females and males, respectively) [Queiroz, 2013].

Drugs used to treat fibromyalgia (e.g., pregabalin and duloxetine) provide, at best, only modest relief of symptoms and are accompanied by various side effects including sedation, dizziness, cognitive complaints, weight gain, edema and headaches. The approved medications for the treatment of fibromyalgia (United States [US]: pregabalin, duloxetine and milnacipran; Japan: pregabalin) result in only an incremental increase in the percent of subjects (~8% to 13%) with a 30% pain reduction compared to 28% to 34% of subjects with a similar level of improvement on placebo in randomized clinical trials [Häuser et al, 2014]. Despite the available approved medications, novel medications to treat pain, fatigue, sleep disturbances and impaired cognition without intolerable AEs are required to address an unmet medical need for subjects with fibromyalgia.

A pathophysiological mechanism for fibromyalgia has not yet been established. The concept of altered central processing of nociceptive information has dominated the fibromyalgia literature [Woolf, 2011; Staud, 2011]. However, accumulating evidence suggests an abnormality in both peripheral nerve fibers, as well as central pain processing in subjects with fibromyalgia [Serra et al, 2014; Staud & Smitherman, 2002]. Studies have suggested that peripheral abnormalities in sensory nerves may be important in contributing to and/or possibly maintaining fibromyalgia symptoms [Staud, 2006]. Increased spontaneous and evoked firing was observed in fibromyalgia subjects [Serra et al, 2014]; while lidocaine was shown to improve hyperalgesia in fibromyalgia subjects [Staud et al, 2014]. Abnormal (increased) peripheral sensory afferent input may be amplified in the presence of central sensitization (decreased inhibition) [Staud et al, 2014; Staud, 2006].

Furthermore, specific C-fiber abnormalities have been reported in fibromyalgia subjects. Skin biopsies obtained from fibromyalgia subjects showed distinct ultrastructural abnormalities in C-fibers including ballooned Schwann cells (concentrated in tender areas)

and peripheralized small axons of Remak bundles [Kim et al, 2008]. Serra et al. [2014] reported hyperexcitability, as well as structural changes in peripheral nociceptive C-fibers of fibromyalgia subjects, suggesting abnormal peripheral C nociceptor ongoing activity and increased mechanical sensitivity could contribute to the pain and tenderness suffered by fibromyalgia subjects [Serra et al, 2014].

In addition, studies have reported that small-fiber pathology is a contributor to the widespread pain in fibromyalgia subjects [Oaklander et al, 2013; Üçeyler et al, 2013]. Oaklander et al [2013] demonstrated that subjects diagnosed with fibromyalgia have evidence of a neurological cause of their chronic pain and other symptoms, specifically small-fiber polyneuropathy. Further, Üçeyler et al [2013] challenged the concept of fibromyalgia being a form of depression or a psychological disorder, illustrating small-fiber impairment on a psychophysical, neurophysiological and morphological level in fibromyalgia and postulating that small-fiber pathology may be a peripheral nervous system contributor to the complex pathophysiology of pain in fibromyalgia.

Taken together, these findings suggest that some fibromyalgia subjects may have underlying peripheral nerve damage that may contribute to pain symptoms. Given the significant unmet medical need and emerging understanding of peripheral pathophysiology, targeting peripheral mechanisms may be helpful in the treatment of fibromyalgia.

Background on Pharmacological Concept

Ca^{2+}-activated K^+ channels are classified according to their single channel conductance: large conductance channel (K^+ large conductance Ca^{2+}-activated channel, subfamily M, alpha 1 [KCNMA1]), intermediate conductance channel ($K_{Ca}3.1$) and small conductance channel (SK). $K_{Ca}3.1$ is voltage-insensitive and requires only a small increase in intracellular Ca^{2+} to open, subsequently maintaining a negative membrane potential through K^+ efflux [Bradding and Wulff, 2009]. Opening of $K_{Ca}3.1$ results in a period of reduced excitability after each action potential called afterhyperpolarization. The physiological role of $K_{Ca}3.1$ is considered to be regulation of cellular excitability, which suggests it is a potential therapeutic target for various diseases associated with abnormal nerve excitation [Wulff et al, 2007]. For example, the activation of $K_{Ca}3.1$ appears not only to have an analgesic effect on visceral hypersensitivity [McHugh et al, 2008], but also to be involved in the analgesic action of peroxisome proliferator-activated receptor agonists [LoVerme et al, 2006]. The channel is represented in A-delta and C-fiber dorsal root ganglion and axons [Tsantoulas and McMahon, 2014]. Thus, the regulation of $K_{Ca}3.1$ may be a novel target for the treatment of painful disorders associated with neuronal hyperactivity.

Rationale for Clinical Trial with ASP0819

ASP0819 is predicted to lead to hyperpolarization of primary sensory afferent nerves and subsequent decreased firing. This pharmacological action of ASP0819 should reduce peripheral nerve hyperexcitability, thus normalizing the frequency of action potentials and reducing the pain experienced by fibromyalgia subjects.

1.2 Nonclinical and Clinical Data

ASP0819 is an orally available, new molecular entity discovered by Astellas Pharma Inc. ASP0819 has $K_{Ca}3.1$ opening activity that targets peripheral sensory nerves.

ASP0819 pharmacokinetics have been assessed across single doses (1 to 55 mg) and 14-days of multiple once-daily dose (1 to 18 mg) in the same tablet formulation as that tested in the current study. ASP0819 was rapidly absorbed with median t_{max} ranging from 1.03 to 3.03 hours postdose following single and multiple doses. C_{max}, AUC_{inf} and AUC_{tau} increased in a dose-proportional manner showing a low to moderate between-subject variability (12.3% to 41.5%). The average terminal elimination half-life ranged from 38.9 to 54.5 hours with a mean apparent oral clearance varying from 0.196 to 0.285 L/h. Drug accumulation was on average 2.82- to 3.45-fold higher (AUC_{tau}) at steady-state compared to single dose with no clear differences across dose levels. Most of the subjects with once daily doses of ASP0819 appeared to be at steady-state after 8 to 10 days of dosing. The peak to trough ratio was low (1.57 - 1.87 on average), thus suggesting a low degree of fluctuation in the plasma concentrations over the dosing period. The analysis of urine concentrations collected at steady-state showed, that after repeat dosing, ASP0819 excretion in urine was very low ($\leq$ 2%) and not dose dependent. Overall, no sex effect could be observed and the effect of food was clinically insignificant (approximately 20-36% lower following a high-fat meal).

In the phase 1 study, PPD, where single and multiple ascending doses of ASP0819 were assessed, ASP0819 was well tolerated in healthy males and females. There were no deaths, other serious treatment emergent adverse events (TEAEs), or TEAEs leading to discontinuation during the study. In general, the most commonly reported adverse events (AEs) observed across the single ascending dose and multiple ascending dose parts of the study, were constipation and other Gastrointestinal Disorder SOC events; the majority of these events were mild. There were no clinically significant abnormalities in any of the liver or hematologic parameters or other clinical laboratory test results considered related to ASP0819. There were no clinically significant abnormalities in vital signs or electrocardiograms (ECGs); there were no cardiac repolarization (QTcF) intervals greater than 450 msec and no change greater than 30 msec from baseline. There were no clinically significant abnormalities on orthostatic blood pressure changes, with the exception of 1 report of a single brief, mild presyncope following a 55 mg single dose, which was accompanied by a positive orthostatic challenge test (at 18:00 hour, a decrease in DBP of 10.3 mmHg after 3 min standing, and approximately 8 hours post-dosing). Based on a concentration vs change from baseline analysis, ASP0819 showed no clinically significant effects on QTcF.

Please refer to the IB for detailed information from nonclinical and clinical studies.

1.3 Summary of Key Safety Information for Study Drugs

Given the early stage of development, there are currently no expected AEs for ASP0819.

ASP0819 may be associated with TEAEs based on the nonclinical studies. The following were key nonclinical observations: signs of liver abnormality; gastrointestinal atrophy, inflammation; changes in hemoglobin, hematocrit and other red blood cell parameters (Refer to the IB for detailed information).

1.4 Risk Benefit Assessment

No clinical efficacy studies have been conducted to evaluate ASP0819 in the treatment of pain associated with fibromyalgia; therefore, the actual benefit of ASP0819 in the treatment of pain associated with fibromyalgia is unknown. There are no known risks identified with this mechanism of action, as ASP0819 is a first-in-class compound. Based on the safety profile from the phase 1 clinical data, the risks appear to be justified from a risk benefit assessment. An overview of the risk benefit of ASP0819 can be found in the IB, including monitoring and mitigation steps taken to maintain safety of the subjects while on study treatment. Routine risk minimization procedures are planned in this study. Overall, the fibromyalgia subjects that will meet the inclusion and exclusion criteria will be relatively healthy; therefore increased risk is not expected in this population. [See Section 2.2.2 Dose Rationale for safety margins relative to non-clinical toxicology].

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objective(s)

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

2.1.1 Primary Objectives

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

2.1.2 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.

2.1.3 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.

2.2 Study Design and Dose Rationale

2.2.1 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 US in up to approximately 35 sites. Approximately 323 subjects are planned to be screened for 178 randomized subjects (89/arm) (45% screen fail rate).

The study will consist of the following study periods:

- Screening period (Day -42 to Day -1)
  Up to 42 days, which includes the completion of screening procedures (Visit 1), wash-out of prohibited medications (if applicable), and a 7-day Baseline Diary Run-In. The wash-out of prohibited medications should be completed prior to the initiation of the Baseline Diary Run-In. The Baseline Diary Run-In may be extended up to 2 days if necessary in the investigator's opinion. In general, the Screening period should not exceed 42 days. The investigator should contact the medical monitor if there are circumstances that would cause the subject to exceed 42 days.
- Double-blind randomized treatment period (Day 1 to Day 57 [End of Treatment (EOT)])
  Eight-weeks of treatment with study drug and site visits at Day 1, 15, 29 and 57.
- Follow-up period (Day 58 to Day 85 [End of Study (EOS)])
  Includes a follow-up site visit on Day 71, and an (EOS) phone call on Day 85.

Screening Period:

After signing the ICF, screening procedures for the subject will start (Visit 1). Subjects will be required to meet both the 1990 and 2010 ACR criteria for fibromyalgia. The investigator or other qualified individual at the site will confirm the diagnosis of fibromyalgia.

After signing informed consent and during the screening period, study site personnel will check that potential subjects have not already been pre-screened, initiated or completed screening or have been randomized into this study, or another clinical trial, using an independent subject participation database. Independent subject participation databases seek to reduce duplicate enrollment by identifying duplicates before they randomize into the study, and this measure is consistent with exclusion requirement of not participating in another interventional clinical trial during the conduct of the study (inclusion criterion 17). In order to complete this check and per the informed consent, study personnel will request that the subject present a valid picture identification (e.g. driver's license, passport, state issued ID card, etc.) and study personnel may be required to provide certain authorized information

that could potentially be used to identify study subjects identifiers (e.g. date of birth, initials, etc.) so that the match algorithms can be run.

Subjects that meet the inclusion criteria, none of the exclusion criteria, and are not identified as a duplicate subject (e.g. certainly, possible, probably), will be enrolled into the study. Appropriate documentation reflecting the subject's eligibility according to these criteria will be reflective in the subject's source documents.

Subjects who meet the eligibility criteria will be instructed, if medically appropriate, to wash-out of any prohibited medications via phone call from the site. At Visit 2, all subjects who continue to meet eligibility criteria will be provided with an electronic diary (e-diary). Subjects will enter a 1-week Baseline Diary Run-In, and during this period, they will record their daily average pain score (0 – 10 Numerical Rating Scale [NRS]) and sleep quality information with the Fibromyalgia Sleep Diary (FMSD) in the e-diary. They will receive instructions regarding its use and begin entering daily scores. Upon awakening, subjects are to rate their sleep quality during the previous night using the e-diary. Each evening before bed, subjects are to rate their average pain during the previous 24 hours using the e-diary. Subjects will need to have a mean daily average pain score ≥ 4 and ≤ 9 (0-10 NRS), and meet pre-specified criteria for daily average pain scores.

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

Weight, medication history and concomitant medication, physical examination, drug and alcohol screen, vital signs, ECG, pregnancy test, Hospital Anxiety and Depression Scale (HADS), Columbia-Suicide Severity Rating Scale (C-SSRS), Patient Global Impression of Severity (PGIS), European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L), Fibromyalgia Impact Questionnaire Revised (FIQR) and Modified irritable bowel syndrome - diarrhea predominant (mIBS-D) Symptoms Diary should all be obtained and reviewed before Randomization at Visit 3. After confirmation of eligibility, subjects who meet the mean daily average pain score eligibility requirements at this visit will be randomized. For subjects that meet the entry criteria blood samples for laboratory tests and pharmacogenomics will be taken after Randomization and prior to dosing. Pharmacokinetics will be obtained approximately 1 to 4 hour(s) after the first dose.

Rescreening is not allowed. Repeat of screening assessments as mentioned in exclusion criteria 11, 12, 14 and 15 may be done once, after a reasonable timed period at the Investigator's discretion but within the Screening period.

Double-Blind Randomized Treatment Period (treatment period):

Subjects will enter the treatment period and will be randomized in a 1:1 ratio to receive either ASP0819 or placebo once per day for a period of 8 weeks.

Acetaminophen may be used as rescue therapy for intolerable pain due to fibromyalgia during the baseline period and in all subsequent study periods [see Section 4.1.3 Rescue Medication]. Nonsteroidal anti-inflammatory drugs (NSAIDs) will be allowed (with the exception of celecoxib), as needed, for non-fibromyalgia pain, such as headache.

Throughout the treatment period, beginning on Day 1 (Randomization) through Visit 6/Week 8, subjects will record all daily average pain scores (NRS) and any acetaminophen use in the e-diary. FMSD sleep quality scores will be recorded through Visit 6/Week 8. Subjects will take study drug once per day (qd). Subjects randomized to ASP0819 will receive 15 mg (3 capsules of 5 mg each). In order to maintain the study blind, placebo treated subjects will receive matching capsules.

During the treatment period, subjects will return to the clinic per schedule for safety and efficacy procedures (see Schedule of Assessments for details). Subjects who do not complete the treatment period will be requested to complete EOT visit procedures.

Follow-up Period:

Subjects are encouraged to abstain from any concomitant medications for the treatment of fibromyalgia pain prior to Visit 7/Week 10. Rescue medication is allowed during the follow-up period. Subjects will continue to enter their daily average pain score (NRS), FMSD sleep quality scores and acetaminophen use into their e-diary and return diaries at Visit 7/Week 10. All subjects will return to the site for a follow-up visit at Day 71, 2 weeks following the EOT visit (Day 57). A follow-up safety phone call will take place approximately 4 weeks post study drug discontinuation (Day 85/EOS).

Interim Analyses:

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 [see Section 7.7 Interim Analysis]. The plan for the interim analysis may be modified based on the speed of recruitment.

2.2.2 Dose Rationale

The analgesic efficacy of ASP0819 will be assessed at a dose of 15 mg qd over a period of 8 weeks.

Target exposures assessed in this proof-of -concept study are based on efficacious exposures from the rat vagotomy model, which showed significant signs of analgesia with an EC50 (C_{eff}) at 119 ng/mL, and rat reserpine induced myalgia nerve firing model, which showed significant signs of pharmacology at tested exposures ranging from approximately 90 ng/mL to 5000 ng/mL. Based on the Phase 1 human PK data, the predicted mean C_{trough} (95% Prediction Interval [PI]) following 15 mg qd is 2610 ng/mL (1450-3850 ng/mL). All subjects are predicted to have C_{trough} concentrations above the target efficacious exposure (C_{eff} 119 ng/mL).

The predicted mean C_{max} (95%PI) and AUC_{tau} (95%PI) for a 15 mg qd dose of ASP0819 in subjects are 4380 ng/mL (2790–6090 ng/mL) and 76200 ng*hr/mL

(44700-109800 ng*hr /mL), respectively. These predicted mean exposures are below the previously established mean exposure limits; and they are approximately 3-fold or more below the 13-wk rat and dog no-observed-adverse-effect-level C_{max} and AUC_{24}.

The 13-wk lowest-observed-adverse-effect level (LOAELs; 10 mg/kg/day in rat and dog studies) are based on the observations of atrophy in mucosal epithelium in both rats and dogs and necrosis or degeneration in parietal cells in dogs. All findings were reversible. There is approximately a 9-fold safety margin based on the LOAELs from the 13-wk rat and dog toxicology studies to the predicted upper 95% PI for C_{max} and AUC_{24} from a 15 mg qd dose.

Thus, a dose of 15 mg qd should provide exposure within an efficacious target range and below exposures associated with toxicity in nonclinical studies.

2.3 Endpoints

2.3.1 Primary Endpoints

Primary Efficacy Endpoint

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

Safety and Tolerability Endpoints

- TEAEs/serious adverse events (SAEs) from Screening until EOS.
- Safety laboratory tests at Weeks 2, 4, 8 and 10
- Vital sign measurements at Weeks 2, 4, 8 and 10.
- 12-lead ECG parameters at Weeks 8 and 10.
- Physical examination at Weeks 8 and 10.
- C-SSRS (evaluation of suicidal ideation and behavior) at Weeks 2, 4, 8 and 10.

2.3.2 Secondary Endpoints

Secondary Efficacy Endpoints

- Subject's response defined as achieving ≥ 30 % reduction from baseline to Week 8 and EOT in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.
- Subject's response defined as achieving ≥ 50 % reduction from baseline to Week 8 and EOT in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.
- Change from baseline to Weeks 2, 4, 8, and EOT in the FIQR Physical Function, Symptoms, and Overall Impact subscales.
- Overall subject improvement assessed by PGIC at Weeks 2, 4, 8, and EOT.

2.3.3 Exploratory Endpoints

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.
- Subject's response defined as achieving various reduction levels (> 0%, ≥ 10%, ≥ 20%, ≥ 40%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, 100%) from baseline to Week 8 and EOT in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily diary.
- Change from baseline to Weeks 2, 4, 8 and EOT in FIQR Total Score.
- Change from baseline to Weeks 2, 4, 8 and EOT in PGIS.
- Subject's response defined as PGIC of very much or much improved at Week 8 and EOT.
- Subject's response defined as achieving ≥ 30 % reduction from baseline in FIQR total score at Week 8 and EOT.
- Subject's composite pain response defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of very much or much improved at Week 8 and EOT.
- Subject's composite syndrome response defined as achieving ≥ 30% reduction from baseline in mean daily average pain score **and** PGIC of very much or much improved **and** ≥ 30 % reduction from baseline in FIQR total score at Week 8 and EOT.
- Change from baseline to Weeks 1, 2, 3, 4, 5, 6, 7, 8 and EOT in daily in the FMSD, which captures all critical sleep disturbance features of fibromyalgia (8 items).
- Change from baseline to Week 8 and EOT in the HADS depression subscale.
- Change from baseline to Week 8 and EOT in EQ-5D-5L.
- Proportion of days with rescue medication use at Weeks 1, 2, 3, 4, 5, 6, 7, 8 and EOT.
- Incidence of subjects using rescue medication at Weeks 1, 2, 3, 4, 5, 6, 7, 8 and EOT.
- Average daily dosage of rescue medication at Weeks 1, 2, 3, 4, 5, 6, 7, 8 and EOT.
- Change from baseline to Weeks 2, 4, 8 and EOT in Irritable Bowel Syndrome Symptom Summary Score and abdominal pain, stomach pain, abdominal cramps, abdominal pressure, and bloating as assessed by the Irritable Bowel Syndrome-diarrhea predominant (IBS-D) Daily Symptom Diary.
- Change from baseline to Week 8 and EOT in neuropathic pain symptoms as assessed by the Neuropathic Pain Symptom Inventory (NPSI).

Follow-Up Period

- Change from baseline and EOT to Week 10 in mean daily average pain score.
- Change from baseline and EOT to Week 10 in FIQR Physical 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.
- Subject's response defined as 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.

- Subject's response defined as 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.
- Incidence of subjects using rescue medication at Week 10.
- Average daily dosage of rescue medication at Week 10.

3 STUDY POPULATION

3.1 Selection of Study Population

Male and female subjects between 18 and 80 years of age with fibromyalgia.

3.2 Inclusion Criteria

A subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-approved written ICF and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] Authorization for US sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. A male or female subject between 18 and 80 years of age at the signing of the informed consent.
3. Subject has a body mass index (BMI) ≤ 45 kg/m^2.
4. Female subject must either:
    - Be of nonchildbearing potential:
        - postmenopausal (defined as at least 1 year without any menses) prior to Screening, or
        - documented surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
    - Or, if of childbearing potential:
        - agree not to try to become pregnant during the study and for 28 days after the final study drug administration,
        - have a negative blood pregnancy test at Screening and negative urine test on Day 1, and
        - if heterosexually active, agree to consistently use 1 form of highly effective birth control* starting at Screening and throughout the study period and for 28 days after the final study drug administration.
5. Female subject must agree not to breastfeed at Screening and throughout the study period, and for 28 days after the final study drug administration.
6. Female subject must not donate ova starting at Screening, throughout the study period, and for 28 days after the final study drug administration

7. Male subject must not donate sperm starting at Screening and throughout the study period, and for 28 days after the final study drug administration.
8. Male subject with a partner of child-bearing potential, or a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom throughout the study period and for 28 days after the final study drug administration.
9. Subject meets the ACR 1990 fibromyalgia diagnostic criteria at Screening:
    - Widespread pain for at least 3 months, defined as the presence of all of the following:
        - pain on right and left sides of the body,
        - pain above and below the waist, and
        - pain in the axial skeleton (cervical spine or anterior chest or thoracic spine or low back) must be present.
    - Pain in at least 11 of 18 tender point sites on digital palpation.
        - Digital palpation should be performed with an approximate force of 4 kg.
10. Subject meets the ACR 2010 fibromyalgia diagnostic criteria at Screening:
    - Widespread pain index (WPI) ≥ 7 and 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.
11. Subject has a pain score ≥ 4 on the revised fibromyalgia impact questionnaire revised (FIQR) pain item at Screening.
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 and agrees to complete daily diaries throughout the duration of the study.
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 e-diary during the Baseline Diary Run-In period, and meeting pre-specified criteria for daily average pain scores.
14. Subject agrees to use only acetaminophen as rescue medication for fibromyalgia pain throughout the course of the trial (up to 1000 mg per dose and not to exceed 3000 mg/day).
15. Subject agrees not to initiate or change any non-pharmacologic interventions (including normal daily exercise routines, chiropractic care, physical therapy, psychotherapy, and massage therapy) during the course of the study. Non-pharmacologic interventions must be stable for a minimum of 30 days prior to Screening. The subject agrees to maintain usual level of activity for the duration of the study.
16. Subject is capable of completing study assessments and procedures, in the opinion of the investigator.
17. Subject agrees not to participate in another interventional study from Screening through the EOS visit.

* Highly effective forms of birth control include:
  - Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
  - Established intrauterine device (IUD) or intrauterine system (IUS),
  - Vasectomy (A vasectomy is a highly effective contraception method if the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used).
  - Male is sterile due to a bilateral orchiectomy.

  NOTE: The reliability of sexual abstinence for male and/or female subject enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. The investigator is responsible for confirming the subject is continuing to use the protocol stated contraception requirements.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject has received an investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to Screening.
2. Subject has had no meaningful improvement, in the investigator's opinion, from 2 or more prior treatments (commercially available) for fibromyalgia (in at least 2 pharmacologic classes).
3. Subject has had known hypersensitivity or intolerance to the use of acetaminophen or associated formulation components; known hypersensitivity to the formulation components of ASP0819.
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.
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.
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.

7. Subject has initiated any non-pharmacologic interventions for the treatment of fibromyalgia or depression within 30 days prior to Screening or during the Screening period.
8. Subject has a history of any psychotic and/or bipolar disorder as assessed by the M.I.N.I.
9. Subject has a HADS score > 14 on the Depression subscale at Screening or at the time of Visit 3 (Randomization).
10. Subject has a history of suicide attempt or suicidal behavior within the last 12 months, or has suicidal ideation within the last 12 months (a response of "yes" to questions 4 or 5 on the suicidal ideation portion of the C-SSRS), or who is at significant risk to commit suicide, as assessed by the investigator at Screening and at the time of Visit 3 (Randomization).
11. Subject has clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, or a serum creatinine > 1.5 times the ULN at Screening. These assessments may be repeated once, after a reasonable time period at the investigator's discretion (but within the Screening period).
12. Subject has aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1.5 times the upper limit of the reference range at Screening. These assessments may be repeated once, after a reasonable time period at the investigator's discretion (but within the Screening period).
13. Subject has a positive test for hepatitis B surface antigen (HBsAg), hepatitis A virus antibodies (immunoglobulin M) (anti-HAV [IgM]) or hepatitis C virus antibodies (anti-HCV) at Screening or has history of a positive test for human immunodeficiency virus type 1(HIV-1) and/or type 2 (HIV-2).
14. Subject has a resting systolic blood pressure (SBP) > 180 mmHg or < 90 mmHg, and/or a sitting diastolic blood pressure (DBP) > 100 mmHg at Screening. These assessments may be repeated once, after a reasonable time period at the investigator's discretion (but within the Screening period).
15. Subject has a clinically significant abnormality on 12-lead ECG at Screening or Visit 3 (Randomization). If the ECG is abnormal, based on the investigator's judgment, an additional ECG can be carried out. If this also gives an abnormal result, the subject must be excluded.
16. Subject has a history of myocardial infarction (within 6 months of Screening), unexplained syncope, cardiac arrest, unexplained cardiac arrhythmias or torsade de pointes, structural heart disease or a family history of Long QT Syndrome.
17. Subject has evidence of any clinically significant, uncontrolled cardiovascular, gastrointestinal, endocrinologic (low thyroid stimulating hormone [TSH], but euthyroid is allowed), hematologic, hepatic, immunologic, infectious, metabolic, urologic, pulmonary (including obstructive sleep apnea not controlled by a CPAP device)

neurologic, dermatologic, psychiatric, renal and/or other major disease (exclusive of fibromyalgia), as assessed by the investigator or designee.

18. Subject has planned surgery during the study participation.
19. Subject has an active malignancy or a history of malignancy (except for treated non-melanoma skin cancer) within 5 years of Screening.
20. Subject has a positive drug or alcohol test at Screening, Baseline Diary Run-In or prior to Randomization. However, a positive test for tetrahydrocannabinol (THC) and/or opioids is allowed at the Screening visit, but must be confirmed negative prior to Baseline Diary Run-In and Randomization.
21. Subject has a current or recent (within 12 months of Screening) history of a substance use disorder including cannabinoid and/or alcohol abuse disorder. Subject has used opioids for pain for more than 4 days during the week preceding the Screening visit.
22. Subject is currently using protocol specified prohibited medications and is unable to wash-out [see Section 5.1.3 for Concomitant Medication Restrictions].
23. Subject has filed or is awaiting judgment on a disability claim or has any pending worker's compensation litigation or related monetary settlements.
24. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
25. Subject is an employee of the Astellas Group, the Contract Research Organization (CRO) involved or the investigator site executing the study.

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Study Drug

The test drug, ASP0819, will be supplied as 5 mg capsules. The ASP0819 capsules are hard gelatin capsules with a Swedish orange body and yellow cap and contain white powder. For storage conditions, see label text.

4.1.2 Comparative Drug

Matching placebo capsules will be supplied. For storage conditions, see label text.

4.1.3 Rescue Medication

If a subject experiences intolerable pain due to fibromyalgia during the Screening, treatment or follow-up periods, the subject should be instructed to use acetaminophen as a rescue medication for fibromyalgia. Rescue medication use will be captured in the e-diary. NSAIDs

will be allowed, as needed for non-fibromyalgia pain [see Section 5.1.3 Concomitant Medications].

Access to acetaminophen will be arranged by the site according to the local regulations and requirements.

Doses:

The maximum amount of acetaminophen is up to 1000 mg per dose and not to exceed 3000 mg/day.

4.2 Packaging and Labeling

All study drug(s) used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at API/APEBV or Sponsor's designee in accordance with API/APEBV or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

Each carton will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by the investigator/or designee and that:

- Such deliveries are recorded,
- Study drug is handled and stored according to labeled storage conditions,
- Study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- Any unused study drug is returned to the Sponsor.

Study drug inventory and accountability records will be kept by the investigator, head of study site or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator, head of study site or designee agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator, head of study site or designee (i.e., study drug manager) will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by the investigator, head of study site or designee (i.e, study drug manager). The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator, head of study site or designee (i.e., study drug manager) agrees to conduct a final drug supply inventory and

to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned study drug. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.

- The site staff must return study drug to the Sponsor or designee at the end of the study or upon expiration unless otherwise approved by the Sponsor.

4.4 Blinding

4.4.1 Blinding Method

This is a double blind study. Subjects will be randomized to receive ASP0819 or Placebo in a blinded fashion such that neither the investigator, Sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. The randomization number will be assigned based on information obtained from the Interactive Response Technology (IRT).

4.4.2 Confirmation of the Indistinguishability of the Study Drugs

The appearance and the form of both the drug and packaging are identical to those of their matching placebo.

4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list and study medication blind will be maintained by the Interactive Response Technology (IRT) system. Details of steps to maintain treatment blind in the study team during the interim analysis will be described in an Interim Analysis Plan (IAP).

4.4.4 Breaking the Treatment Code for Emergency

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. They must only be requested by the investigator or other persons designated as sub-investigators. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure. Unblinding of the study drug should only be considered for subject safety or when critical therapeutic decisions are contingent upon knowing the blinded study drug assignment. Any unblinding by the investigational staff must be reported immediately to the Sponsor and must include an explanation of why the study drug was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study drug.

4.4.5 Breaking the Treatment Code by the Sponsor

The Sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will

be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

4.5 Assignment and Allocation

All subject numbers will be assigned using the IRT starting at Screening. Randomization will be stratified by site. All subjects will have a unique, 10-digit subject number. The first 5 digits of this number will be the investigator's site number. The second 5 digits assigned will represent the subject's accession number. This will be the number that identifies a subject during the course of the study.

All subjects who meet the eligibility criteria will be randomized. Subjects will be randomized in a 1:1 ratio to ASP0819 or placebo according to the randomization schedule through IRT. The 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.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

Subjects randomized to the ASP0819 group will receive ASP0819 15 mg (3 capsules of 5 mg) qd for the duration of 8 weeks. Subject randomized to the placebo group will receive placebo to match ASP0819 (3 capsules) qd for the duration of 8 weeks.

Doses should be taken in the morning with or without food. In case a subject forgets a dose, the dose should be taken as soon as they remember but prior to bedtime that day. The next day's dose should still be taken as planned. Two doses should not be taken in the same day.

At Randomization and at Visit 4 (Week 2), subjects will receive the assigned treatment sufficient for a period of 2 weeks (including morning dose on the day of the next visit). At Visit 5 (Week 4) subjects will receive the assigned treatment sufficient for a period of 4 weeks.

Pharmacokinetic 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. There are no fasting requirements for the pharmacokinetic samples but date and time of the dose taken prior to collecting the pharmacokinetic sample, as well as the date and time of the last meal in relation to that dose will be captured in the eCRF.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

The dose of 15 mg qd of ASP0819 is less than the highest dose assessed in the phase 1 multiple dose study (18 mg qd). This highest multiple dose of 18 mg was well tolerated and no maximum tolerated dose was determined. Stopping criteria are presented in [Section 6.1 Discontinuation of Subjects]. Study 0819-CL-0201 is a fixed dose, proof-of-concept study. In order to adequately evaluate the hypothesis, it is important to assess efficacy and safety across a common dose; therefore, dose increases and decreases are not allowed.

5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

Concomitant Medication Restrictions or Requirements:

Medications taken for fibromyalgia during the 12 months prior to Screening and other medication taken 28 days prior to the Screening visit and up to the first dose of study medication (treatment period) will be documented in the appropriate CRF as prior fibromyalgia medications or other prior medication. Subjects taking prohibited medications who are willing to discontinue these medications, as clinically indicated and based upon the investigator's recommendation, may wash-out over a period of 5 half-lives on a schedule determined by the investigator.

Medications taken after the first dose of study medication and up to EOS will be documented on the appropriate CRF as concomitant medication.

Prior and concomitant medications to be documented include but are not limited to the following: vitamins, herbal remedies (e.g., St. John's wort, valerian), over-the-counter and prescription medications. Any medications taken for treatment of pain symptoms will be documented as such on the CRF.

Subjects are instructed not to take any concomitant medication without first consulting the investigator or study coordinator throughout the duration of the study.

Concomitant Medication for Treatment of Non-Fibromyalgia Pain Symptoms:

NSAIDs will be allowed (with the exception of celecoxib), as needed, for non-fibromyalgia pain, such as headache. Use in chronic treatment is not allowed (with the exception of low dose aspirin for cardioprophylaxis, up to 325 mg daily). NSAIDs are not to be used as rescue medication for the treatment of pain associated with fibromyalgia. Dosing should be consistent with approved labeling. NSAID use will be captured on the eCRF.

Prohibited Therapies:

Concomitant use of the following medications, therapies or surgical procedures could influence the evaluation of the study drug's efficacy and safety and are prohibited throughout the study (wash-out through the EOS):

- Medications that may have efficacy in reducing pain in fibromyalgia (except for allowed rescue medication), are as follows: gabapentinoids, antidepressants (except for serotonin reuptake inhibitors), ketamine, $GABA_B$ receptor agonists (including sodium oxybate),

opioids, celecoxib, chronic non-narcotic analgesics (with the exception of low dose aspirin for cardioprophylaxis, up to 325 mg daily) and topical pain medications.
- Medications that are sensitive CYP3A substrates or CYP3A substrates that have a narrow therapeutic range.
- Use of cannabinoids from the Screening visit and throughout the study.
- Procedures that may have efficacy in reducing pain in fibromyalgia, for example: nerve block, iontophoresis, laser therapy, acupuncture, tender point injections, dry needle injections, spinal cord stimulation therapy and transcutaneous electrical nerve stimulation.
- Hypnotics other than those specified with restrictions in the following section on Permitted Medications. Tranquilizers, sedating antihistamines (non-sedating antihistamines are permitted), benzodiazepines for sedative, anxiolytic, or sleep aid. In contrast, non-benzodiazepines such as zolpidem are allowed for insomnia as discussed below in the section, Permitted Medication.

Refer to [Appendix 12.1 List of Excluded Concomitant Medications] for a list of drug classes and specific medications that are prohibited during participation in the study.

Permitted Medications:

This list is not all inclusive and the Medical Monitor should be contacted to discuss medications not listed below.

- The following serotonin reuptake inhibitors will be allowed if the subject is on a stable dose 60 days prior to Screening and no changes are anticipated during the course of the study: sertraline, paroxetine, fluoxetine, citalopram, escitalopram, fluvoxamine, vilazodone and vortioxetine.
- The following medications will be allowed if the subject is on a stable dose for at least 30 days prior to Screening and no additional medication is taken for insomnia: zolpidem up to10 mg, eszopiclone up to 1 mg, zaleplon up to 10 mg, zopiclone up to 2 mg and melatonin for sleep.
- Allowed stable medications (i.e., stable dose 30 days prior to Screening and with no changes anticipated during the course of the study): anti-diabetic medications, anti-hypertensive medications, non-sedating antihistamines, lipid-lowering agents, asthma medications, low dose aspirin for cardioprophylaxis, non-sedating treatments for allergic rhinitis, triptans, multivitamins, short-term use of nasal, inhaled and topical corticosteroids. NSAIDs will be allowed (with the exception of celecoxib), as needed, for non-fibromyalgia pain, such as headache. However, chronic use of NSAIDs is not allowed (with the exception of low dose aspirin for cardioprophylaxis, up to 325 mg daily).

Refer to [Appendix 12.2 List of Allowed Anti-depressants and Sleep Aids] for a list of the medications that are permitted during participation in the study.

Permitted Non-Medication Therapy:

The following therapies must be stable for at least 30 days prior to Screening and with no changes anticipated during the course of the study: exercise routines, chiropractic care, physical therapy, psychotherapy, massage therapy. Non-Medication Therapy for fibromyalgia during the 12 months prior to Screening will be documented in the appropriate case report.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study period. Compliance will be verified by the accounting of study drug at each visit after Randomization. When study drug is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at visits. Compliance will be documented.

If compliance is less than 80%, or over 100%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Date of birth, sex, race, ethnicity, height, weight, and BMI will be recorded at Screening (Visit 1). Height will be measured at Screening only. Weight will also be collected prior to Randomization and at Week 8/EOT.

5.2.2 Medical History

A detailed medical history (including psychiatric history) for each subject will be obtained at Screening, including prior medication and contraception use. All relevant past and present conditions, as well as prior surgical procedures will be recorded. Presence of current and/or past major depressive disorder will be captured in the eCRF. Any history of diagnosis of the following disorders will be captured in the eCRF: temporomandibular disorders, irritable bowel syndrome, chronic tension type headache, migraine, chronic low back pain, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, and vulvodynia.

Details on family history of fibromyalgia, depression, bipolar disorder, and Long QT Syndrome will be obtained for each subject.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

The diagnosis fibromyalgia must be confirmed by the investigator and documented in the subject's medical notes (meeting both the 1990 and 2010 American College of Rheumatology clinical classification criteria for fibromyalgia). Duration of fibromyalgia,

date of onset of fibromyalgia symptoms and date of fibromyalgia diagnosis will be recorded in the eCRF.

The number of tender points, WPI and SS score will be completed by the clinician on a tablet device during the Screening visit. Subjects should have a WPI ≥ 7 and SS score ≥ 5 or WPI of 3 to 6 and SS scale score ≥ 9. Tender point examination training of the principal investigator and/or designated site study physician must be documented.

Severity of pain due to fibromyalgia will be assessed through the PGIS and the FIQR and subjects will use a tablet device for completion. Subjects should have a FIQR pain score of ≥ 4 at Visit 1 to be eligible for participation in this study. In addition, the NPSI will be used to characterize the presence of neuropathic pain symptoms.

In order to be eligible for Randomization (Visit 3), subjects will be required to have a mean daily average pain score of ≥ 4 and ≤ 9 on the NRS during the Baseline Diary Run-In period and meeting pre-specified criteria for daily average pain scores.

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, patients 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).

5.2.4 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), and has demonstrated equivalent reliability, validity, and decreased interview time when compared to the Structured Clinical Interview for DSM diagnoses (SCID-P). 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 patients to characterize behavior with “yes” or “no” responses. Some questions contain a recall period (e.g., “Past Two Weeks,” “Past Episode” and “Current Episode”). After completion of the additional questions, the clinician indicates whether or not the diagnostic criteria have been met, based on the instrument scoring criteria [Sheehan et al, 1998; Amorim et al, 1998; Sheehan et al, 1997; Lecrubier et al, 1997].

The M.I.N.I. 7.0 will be completed at Screening by trained site personnel, in accordance with the structured interview requirements.

5.2.5 Hospital Anxiety and Depression Scale

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 moderate to severe symptoms of depression [Snaith, 2003; White et al, 1999; Hermann, 1997; Zigmond & Snaith, 1983].

The HADS depression subscale will be recorded on a tablet device at Screening and at Randomization before dosing. Subjects will be excluded in case they have a score of > 14 at Screening or Randomization. The HADS depression subscale will also be administered at Week 8/EOT.

5.3 Efficacy and Pharmacokinetics Assessments

The subjects will use a handheld device, e-diary, to report daily average pain NRS scores, enter 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 (FIQR, PGIC, PGIS, EQ-5D-5L and mIBS-D Symptoms Diary) will be reported on a tablet device [see also Appendix 12.6]. Efficacy will also be assessed using the HADS depression subscale [see Section 5.2.5 Hospital Anxiety and Depression Scale].

Subjects will receive instructions on how to complete the e-diary/tablet and will be counseled on the importance of completing the e-diary daily and should be retrained on the use of the diary as needed. During the start of Baseline Diary Run-In (Visit 2), the subject will be given sufficient time to practice e-diary completion, supervised by trained site personnel. Questionnaires need to be completed by the subject prior to any other study assessment.

During the Baseline Diary Run-In period, subjects must record daily average pain ratings on a minimum of 5 of 7 days in order to be randomized in the study.

5.3.1 Daily Average Pain Numerical Rating 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. To be eligible for the study subjects should be compliant with daily pain recordings during the Baseline Diary Run-In period, as defined by the completion of a minimum of 5 of 7 daily average pain ratings and agrees to complete daily diaries throughout the duration of the study.

The NRS should be completed by the subject daily for the duration of the study, in the evening and at a consistent time each day. Throughout the study, the subjects should be

counseled on completion of daily e-diary entries and should be retrained on the use of the diary as needed.

The NRS will be collected from the start of the baseline run-in period through Week 10.

5.3.2 Fibromyalgia Sleep Diary

The Fibromyalgia Sleep Diary (FMSD) is an 8-item patient reported outcome (PRO) measure of sleep disturbance specific to fibromyalgia patients, covering the hypothesized domains of Falling Asleep, Staying Asleep, and Sufficient Sleep. Each item is rated on an 11-pt NRS anchored by "0 - not at all" and "10 – extremely." The subject completes the FMSD to rate their quality of sleep during the previous night. The instrument has completed qualitative development in accordance with the Federal Drug Administration (FDA) PRO guidance and ISPOR recommendations, and has established content validity [Kleinman et al, 2014].

The FMSD will be completed on the electronic patient reported outcome (ePRO) device by the subject, daily upon awakening, starting at Baseline Diary Run-In (Visit 2) until Week 10 (Visit 7).

5.3.3 Fibromyalgia Impact Questionnaire Revised

FIQR was developed to capture the total spectrum of problems related to fibromyalgia and the responses to therapy. The original FIQ and FIQR have been extensively used as an index of disease activity and therapeutic efficacy. The 21-item FIQR contains 3 domains: activities of daily living, overall impact, and symptoms. Subjects answer each question on an 11-pt NRS, with anchors appropriate to each question. The recall period is the last 7 days or, for the physical function domain, the last time the activity was performed if not within the 7 day recall period [Bennett et al, 2009].

The FIQR will be completed by the subject on the tablet device at Randomization and at the Week 2, 4, 8/EOT and Week 10 visit. At Screening, the subject only completes the pain item of the FIQR.

5.3.4 Patient Global Impression of Change and Patient Global Impression of Severity

PGIC and PGIS are adaptable global indices that capture the patient's perspective on a defined condition. The PGIC is a self-administered 7-pt Likert scale that asks subjects to evaluate their fibromyalgia relative to baseline. The PGIC is anchored by "very much improved" and "very much worse." The PGIS is a self-administered 6-pt Likert scale that asks subjects to evaluate how their fibromyalgia is now. The PGIS is anchored by "no symptoms" to "very severe".

Both the PGIC and the PGIS will be completed by the subject on the tablet device at the site. The PGIC will be completed at Weeks 2, 4, 8 and 10. The PGIS will be completed at Randomization, Weeks 2, 4, 8 and 10.

5.3.5 Neuropathic Pain Symptom Inventory

The NPSI is a self-report questionnaire specifically designed to evaluate the different symptoms of neuropathic pain [Bouhassira et al, 2004]. 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 = none and 10 = worst imaginable. The NPSI discriminates and quantifies 5 distinct clinically relevant dimensions of neuropathic pain syndromes. The instrument is being used to understand neuropathic pain symptoms that the subjects may have at study entry, and to evaluate any change in symptoms during the study.

The NPSI will be completed by the subject on the tablet device at the site at Randomization and Week 8/EOT.

5.3.6 European Quality of Life-5 Dimensions-5 Levels Questionnaire

The subjects' general health status will be assessed by the EQ-5D-5L. The EQ-5D-5L is an international and standardized nondisease specific (i.e., generic) instrument for describing and valuing health status. It is a multidimensional measure of Health-Related Quality of Life, capable of being expressed as a single index value and specifically designed to complement other health status measures. The EQ-5D-5L has 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. In the newest version, each dimension has 5 response levels (e.g., no problems, slight problems, moderate problems, severe problems and unable to perform the activity). In addition, it has a vertical visual analog scale that elicits a self-rating by the respondent of his/her health status on a scale from 0 (bottom: "The worst health you can imagine") to 100 (top: "The best health you can imagine").

The EQ-5D-5L will be completed on the tablet device by the subject at Randomization (predose), Week 8 and Week 10.

5.3.7 Modified Irritable Bowel Syndrome-Diarrhea Predominant

The mIBS-D is a 5-item questionnaire that assesses the predominant symptoms of IBS-D (abdominal pain, stomach pain, abdominal pressure, bloating, abdominal cramping) on an 11-pt NRS (0 - absence of symptoms to 10- severe symptoms). The items in the mIBS-D are derived from the 7-item IBS-D. The instrument is being used to understand IBS-like symptoms that the subjects may have at study entry, and to evaluate any change in symptoms during the study [Delgado-Herrera et al, 2016; Rosa et al, 2016; Marquis et al, 2014]. Subjects will be asked to complete the questionnaire items while considering 2 distinct recall periods (previous 24 hours and last 7 days).

The mIBS-D Symptoms Diary (5 items) will be completed by the subject on the tablet device at Randomization and at Weeks 2, 4 and 8/EOT.

5.3.8 Pharmacokinetics

Pharmacokinetic 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 eCRF.

Details on sample collection, processing, labeling, storage and shipment procedures are provided in the laboratory manual. Analysis of ASP0819 and any metabolites (if applicable) will be performed using a validated method at a bioanalytical laboratory specified by the Sponsor.

5.4 Safety Assessment

Safety will be assessed through AEs, safety laboratory tests (chemistry, hematology and urinalysis), physical examination, vital signs, 12-lead ECGs and the C-SSRS. Unscheduled assessments will be performed if clinically warranted.

5.4.1 Vital Signs

Single measures of sitting resting blood pressure (SBP and DBP) and pulse rate values will be obtained at each visit (except for Visit 2) and should be conducted prior to blood draws. Blood pressure should always be measured on the same arm of the subject and preferably in the same position (sitting or supine).

Body temperature will be assessed at Screening, Randomization and Week 8/EOT only. The method of recording body temperature must be the same between visits (acceptable methods are oral or tympanic temperature).

Vital signs should be taken before scheduled blood draws.

5.4.2 Adverse Events

See [Section 5.5 Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.3 Liver Safety Monitoring and Assessment] for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function test (LFT) values (e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study. See also the [Table 1 Schedule of Assessments] for study visit collection dates.

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.

Panel	Visits	Parameters to be analyzed
Hematology and Coagulation	Screening, Randomization, Weeks 2, 4, 8/EOT and 10	Hemoglobin Hematocrit Erythrocytes (red blood cell [RBC]) Leukocytes (white blood cell [WBC]) Differential WBC Platelets TSH (only at Screening) PT and INR MCV MCH Reticulocytes
Biochemistry	Screening, Randomization, Weeks 2, 4, 8/EOT and 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
Serology	Screening	Hepatitis B surface antigen (HBsAg) Hepatitis A virus antibodies (immunoglobulin M) (anti-HAV [IgM]) Hepatitis C (HCV) Antibody
Urinalysis	Screening, Randomization, Weeks 2, 4, 8/EOT and 10	Leucocytes Nitrite Protein Glucose pH
Table continued on next page		

Panel	Visits	Parameters to be analyzed
Urinalysis *(continued)*	Screening, Randomization, Weeks 2, 4, 8/EOT and 10	Blood Urobilinogen Bilirubin Ketones Potassium
Drug Screen (urine collection/ urine dip stick)	Screening*, Baseline Diary Run-In (Visit 2), Randomization	Amphetamines Barbituates Benzodiazepines Cannibinoids Cocaine Opioids
Alcohol screen (urine)	Screening, Baseline Diary Run-In (Visit 2), Randomization	Alcohol
Pregnancy test (for applicable females only)	Screening (serum), Randomization (urine), Week 8/EOT (urine), and Week 10 (urine)	β-HCG

*A positive test for tetrahydrocannabinol (THC) and/or opioids is allowed at the Screening visit, but must be confirmed negative prior to Baseline Diary Run-In and Randomization.

Drug and alcohol screen will be analyzed by central lab at Screening.

Central laboratory will provide kits to perform urinary drug and alcohol screening tests to be performed locally at Baseline Diary Run-In and Visit 3 (prior to Randomization).

Results of the urinary drug and alcohol screen tests will be noted in the patient files.

A serum pregnancy test will be performed for all female subjects of child-bearing potential at Screening, A urine pregnancy test will be performed for female subjects of child-bearing potential prior to Randomization and at Week 8/EOT and the Week 10/FU visits.

If the clinical laboratory results are outside the normal range, the investigator will document his/her assessment as clinically significant or not clinically significant.

Unscheduled tests or a repeat of abnormal laboratory test(s) may be performed if clinically indicated and to follow-up on suspected AEs.

5.4.4 Physical Examination

The subject will be examined by a medical doctor or other allied professional at Screening, Randomization (predose), Week 8 and Week 10. Physical examination may also be performed at unscheduled visits if necessary. It includes examination of main body systems, such as cardiovascular system, chest/lungs, abdomen, neurological state and musculoskeletal system.

At the Screening visit (Visit 1) the physical examination will include a tender point exam. For the tender point examination, an incremental pressure with a maximum force of approximately 4 kg will be applied to the 18 possible tender point sites. A positive tender

point count is a response from the subject indicating a subjective feeling of discomfort following pressure ≤ 4 kg.

The medical doctor will conduct the exam, determine findings and assess any abnormalities as to clinical significance and whether any exclusion criteria have been met. After study drug administration, new abnormal findings or a worsening of an ongoing abnormal condition must be recorded as an AE.

5.4.5 Electrocardiogram

A 12-lead ECG will be performed at Screening, Randomization, EOT and FU visits. All ECGs should be taken before any scheduled blood draws. ECGs will be recorded with the subject in the supine position, after the subject has been lying down for approximately 5 minutes. There should be at least 5 minutes between ECG measurements in case a repeat is needed. Any clinically significant adverse changes on the ECG will be reported as AEs. Printouts of all ECGs, marked with the subject number and initials, visit date and visit number should be stored in the subject's source data.

5.4.6 Colombia Suicide Severity Rating Scale

The C-SSRS was developed as a screening tool to identify suicide risk. The interview asks subjects detailed questions regarding suicidal ideation, behaviors, intensity of ideation, and attempts. Response options and recall periods vary in accordance with the nature of the question. The scale requires training to ensure appropriate administration.

The C-SSRS will be performed by trained site staff via interview at Screening, Randomization, and at Weeks 2, 4, 8 and 10. 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. Responses will be reported on the tablet device.

Subjects who have a history of suicide attempt or suicidal behavior within the last 12 months, or has suicidal ideation within the last 12 months (a response of "yes" to questions 4 or 5 on the suicidal ideation domain), will be excluded.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received treatment. AE collection begins after the signing of the informed consent and will be collected until 4 weeks after the last dose of study drug.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical examination) should be defined as an AE only if the abnormality meets 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study drug
- The abnormality or test value is clinically significant in the opinion of the investigator.

5.5.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events (defined in paragraph below)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The Sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious," additional information on the event may be requested.

5.5.3 Special Situations

Special Situations observed in association with the study drug(s) (e.g., test drug, comparator, or background therapy) administered to the subject as part of the study are collected as described in the table below. These Special Situations are not considered AEs but can be associated with or result in an AE. An AE that may be associated with or result from a Special Situation is to be assessed separately from the Special Situation and captured in the eCRF or electronic data source. If the AE meets the definition of serious, these SAEs are to be collected via the

SAE/Special Situation worksheet together with the details of the associated Special Situation and reported as described in [Section 5.5.6 Reporting of Serious Adverse Events].

Special Situation	Collected	
	SAE/Special Situation worksheet	eCRF
Uses other than what is stated in the protocol		X
Overdose* of the medicinal product(s) [see Section 5.5.10 Emergency Procedures and Management of Overdose]	X**	X
Suspected misuse/abuse of the investigational medicinal product(s)	X	X

*Overdose refers to the administration of a quantity of a study drug given per administration or cumulatively, which is above that specific in the protocol. This may be either an accidental or intentional overdose.

**In the event of an intentional overdose, the Special Situation worksheet must be filled out.

5.5.4 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration, which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

5.5.5 Criteria for Defining the Severity of an Adverse Event

The investigator will use the following definitions to rate the severity of each AE:

- Mild: No disruption of normal daily activities
- Moderate: Affects normal daily activities
- Severe: Inability to perform daily activities

5.5.6 Reporting of Serious Adverse Events

The collection of AEs and the expedited reporting of SAEs will start following receipt of the informed consent and will continue to 30 days after the last dose of study drug.

In the case of a SAE, the investigator must contact the Sponsor by fax or email immediately (within 24 hours of awareness), and the study team (CRA and Medical Monitor) should be notified as well within 24 hours of awareness.

The investigator should complete and submit an SAE/Special Situation Worksheet containing all information that is required by local and/or regional regulations to the Sponsor by email or fax immediately (within 24 hours of awareness).

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE/Special Situations Worksheet to:

Astellas Pharma Global Development – United States
Pharmacovigilance
Fax number (888) 396-3750
Alternate fax number: (847) 317-1241
Email: safety-us@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Study Physician or his/her designee [Section II Contact Details of Key Sponsor's Personnel].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/Special Situation Worksheet and on the (e)CRF.

The following minimum information is required:

- International Study Number (ISN)/study number,
- subject number, sex and age,
- the date of report,
- a description of the SAE (event, seriousness criteria), and
- causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports (e.g., IND Safety Reports and Council for International Organizations of Medical Sciences-I) to the regulatory agencies (e.g., FDA, European Medicines Agency) per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB within timelines set by regional regulations (e.g., European Union [EU], electronic Common Technical Document, FDA) where required. Documentation of the submission to and receipt by the IRB of expedited safety reports should be retained by the site.

The Sponsor will notify all investigators responsible for ongoing clinical studies with the study drug of all SUSARs, which require submission per local requirements IRB.

The investigators should provide written documentation of IRB notification for each report to the Sponsor.

The investigator may contact the Sponsor's Medical Monitor/Study Physician for any other problem related to the safety, welfare, or rights of the subject.

5.5.7 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If during AE follow-up, the AE progresses to an "SAE," or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to [Appendix 12.3 Liver Safety Monitoring and Assessment] for detailed instructions on Drug-Induced Liver Injury.

5.5.8 Monitoring of Common Serious Adverse Events

No common SAEs have been identified at this time. Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as “common” are provided in [Appendix 12.4 Common Serious Adverse Events] for reference. The list does NOT change the investigator’s reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert the investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common SAEs” as specified in [Appendix 12.4 Common Serious Adverse Events]. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in [Section 5.5.6 Reporting of Serious Adverse Events].

5.5.9 Procedure in Case of Pregnancy

If a female subject becomes pregnant during the study dosing period or within 28 days from the discontinuation of dosing, the investigator is to report the information to the Sponsor according to the timelines in [Section 5.5.6 Reporting of a Serious Adverse Event] using the pregnancy reporting form and the SAE/Special Situation Worksheet.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 28 days from the discontinuation of dosing and report the information to Sponsor according to the timelines in [Section 5.5.6 Reporting of a Serious Adverse Event] using the pregnancy reporting form and the SAE/Special Situation Worksheet.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus]), the investigator should respond in accordance with [Section 5.5.6 Reporting of Serious Adverse Event]. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned as follows:

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth.
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

5.5.10 Emergency Procedures and Management of Overdose

No information on overdose with ASP0819 in humans is available. Following a suspected overdose, study subjects should be managed with symptomatic and supportive care and observed in a controlled medical setting according to the current standard of care. The Medical Monitor/Expert should be contacted when appropriate.

5.5.11 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all investigators involved in the clinical study, as well as the regulatory authorities. Investigators should inform the IRB of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated informed consent form (ICF) in order to continue in the clinical study.

5.6 Test Drug Concentration

Test drug concentration will be measured to evaluate clinical pharmacokinetics of ASP0819 and any metabolites (if applicable). Pharmacokinetic blood 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 eCRF.

Details on sample collection, processing, labeling, storage, and shipment procedures are provided in the laboratory manual. Analysis will be performed using a validated liquid

chromatography with tandem mass spectrometry method at a bioanalytical laboratory specified by the Sponsor. The remainder of the pharmacokinetic samples might be used in the future to explore the absorption, distribution, metabolism and excretion profile, mode of action and/or safety signals of ASP0819. The samples will be destroyed a maximum of 5 years after clinical study completion.

5.7 Other Measurements, Assessments or Methods

5.7.1 Blood Sample for Future Pharmacogenomics Analysis (Retrospective Pharmacogenomics Analysis) (Optional)

Pharmacogenomics (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues. After Randomization (see schedule of assessments), a 6 mL sample of whole blood for possible retrospective PGx analysis will be collected. Samples will be shipped to a Sponsor designated banking CRO.

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See [Appendix 12.5. Retrospective PGx Sub-study] for further details on the banking procedures.

5.7.2 Subject Training Materials

During the Screening visit, booklets will be provided to the subjects for educational purposes. These booklets will provide the subjects with more information on what to expect while participating in a clinical study and how to accurately report their pain. At the end of each booklet, the subjects will be asked to answer several questions to test their knowledge. These results are not collected in the study database.

5.8 Total Amount of Blood

Total amount of blood collected per subject for laboratory specimens is approximately 130 mL.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation from treatment is a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the subject from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Discontinuation Criteria from Treatment for Individual Subjects:

1. Subject develops unacceptable toxicity
2. Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
3. Subject withdraws consent for further treatment
4. Female subject becomes pregnant
5. Monitoring of liver safety is done to address the potential for liver toxicity (see [Appendix 12.3] for details).

   If an individual subject has an ALT or AST result > 3 x ULN or total bilirubin level (TBL) > 2 x ULN, testing should be repeated within 48 to 72 hours of notification of the test results; and then twice weekly liver safety tests will be performed until normalization or study discontinuation.

   Any subject that meets the following criteria below [outlined in the FDA Guidance for Industry, Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation (July 2009)] should be considered for discontinuation from treatment.

   - ALT or AST > 8 x ULN
   - ALT or AST > 5 x ULN for more than 2 weeks
   - ALT or AST > 3 x ULN and (TBL > 2 x ULN or international normalized ratio [INR] > 1.5)
   - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

Even if a subject discontinues treatment the subject should be asked to continue completion of the EOT, follow-up and EOS visits.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of Astellas Pharma Global Development-United States (APGD-US). A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the first interim lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

In general, all data will be summarized with descriptive statistics (number of subjects, mean, SD, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 Sample Size

The sample size calculations are based on the primary efficacy endpoint of change from baseline to Week 8 in mean daily average pain NRS. A meta-analysis of the change from baseline in mean daily average pain NRS for pregabalin or duloxetine vs 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 vs placebo, 84 subjects in the ASP0819 and placebo groups 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).

The total number of subjects required for the analysis would be 168 (84:84 subjects in ASP0819:placebo groups). Assuming approximately 5% of randomized subjects will not contribute to the analysis, then a total of 178 subjects would be required for randomization using a 1:1 randomization ratio (89:89) subjects for the ASP0819:placebo groups.

7.2 Analysis Sets

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.

7.2.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who are randomized and receive at least 1 dose of study drug. This will be the analysis set for demographic and baseline summaries and all efficacy analyses.

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

7.2.2 Per Protocol Set

The per protocol set (PPS) will consist of 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 will be defined in the 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.

7.2.3 Safety Analysis Set

The safety analysis set (SAF) will consist of all randomized subjects who took at least 1 dose of study drug. The SAF will be used for demographic and baseline characteristic summaries and all safety analyses.

When the SAF is utilized in an analysis, subjects will be presented by the treatment actually received.

7.2.3.1 Pharmacokinetic Analysis Set

The PKAS will consist of the subset of SAF for which at least 1 postdose concentration is available.

7.3 Demographics and Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group and overall for the FAS, SAF and PPS. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoint, and frequency and percentage for categorical endpoint.

7.3.1 Subject Disposition

The number and percentage of subjects who discontinued Screening period and corresponding reasons for discontinuation will be presented for all subjects who signed ICFs. For treatment period and follow-up period, the number and percentage of subjects who discontinued and corresponding reasons for discontinuation will be presented for the FAS and SAF.

7.3.2 Previous and Concomitant Medications

Previous and concomitant medications are coded with World Health Organization Drug Dictionary (WHO-DD) and will be summarized by therapeutic subgroup (Anatomical

Therapeutic Chemical [ATC] second level) and chemical subgroup (ATC fourth level) and preferred WHO name by treatment group and overall for the SAF.

All previous and concomitant medications will also be presented in a listing.

7.3.3 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) by treatment group and overall for the SAF.

Medical history for each subject will also be presented in a listing. Any history of diagnosis of the following: temporomandibular disorders, irritable bowel syndrome, chronic tension type headache, migraine, chronic low back pain, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, and vulvodynia will be captured on eCRF and will be summarized for the SAF.

7.4 Analysis of Efficacy

The efficacy analysis will be conducted using the FAS for all efficacy endpoints and the PPS for the primary efficacy endpoint and select secondary endpoints. The interpretation of results from statistical tests will be based on the FAS. The PPS will be used to assess the robustness of the results from the statistical tests based on the FAS.

Unless otherwise stated, all hypothesis testing will be one-sided at the 5% significance level and two-sided 90% CI will be presented when applicable. Centers will be pooled for analysis when necessary. The center pooling algorithm will be described in detail in the SAP.

7.4.1 Analysis of Primary Endpoint

The primary efficacy endpoint is change from baseline to Week 8 in mean daily average pain score assessed by NRS (0 to 10 scale) in the subject's daily e-diary.

7.4.1.1 Primary Analysis

The primary analysis for the primary endpoint of change from baseline to Week 8 in the mean daily average pain NRS will use a MMRM analysis, where the model will include the effects for treatment group, center (pooled where necessary), time (study Week 1 to 8) and treatment-by-time interaction, as well as the covariates of baseline mean daily average pain NRS and baseline pain-by-treatment interaction and subject as a random effect. The unconstrained between-time-point covariance structure will be used. If this is not feasible, additional covariance structures will be considered and details will be provided in the SAP. This analysis will utilize observed data, and there will be no imputation for missing data. The treatment group contrast for change from baseline to Week 8 will be the primary statistical inference obtained from the MMRM analysis. Least squares estimates for the primary endpoint will be shown for each treatment group, and for the treatment comparisons of ASP0819 vs placebo with 2-sided 90% CIs. A one-sided 5% significance level will be used for the comparison involving ASP0819 vs placebo.

The hypothesis for comparisons is given as follows:

H0: The change from baseline to Week 8 in the mean daily average pain NRS for ASP0819 group is the same as (or worse than) the placebo group.

H1: The change from baseline to Week 8 in the mean daily average pain NRS for ASP0819 group is less than the placebo group.

7.4.1.2 Sensitivity Analysis

The following sensitivity analyses will be conducted for the primary endpoint.

- A sensitivity analysis for the primary endpoint will use the same MMRM model as described in [Section 7.4.1.1 Primary Analysis]. For this sensitivity analysis, multiple imputation 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 multiple imputation for subjects with missing data for other reasons.
- A sensitivity analysis will use modified baseline observation carried forward (mBOCF) for missing data at Week 8 with analysis of covariance (ANCOVA), with covariates of baseline mean daily average pain NRS score and center. mBOCF is defined as imputation by baseline observation carried forward (BOCF) for subjects who discontinue due to lack of efficacy or AEs, and imputation by last observation carried forward (LOCF) for subjects with missing data at Week 8 for other reasons.
- A sensitivity analysis for the primary endpoint will use the same MMRM model as described in [Section 7.4.1.1 Primary Analysis] using the PPS.

7.4.1.3 Subgroup Analysis

Subgroup analysis of primary efficacy endpoint will be considered for following subgroups: sex, age category, category of baseline pain score, with or without depression (current vs no current diagnosis and current/prior diagnosis vs no current/prior diagnosis), and central or peripheral pain etiology (subgroups by CMSI, NPSI). Additional subgroups will be considered as appropriate. More details about subgroup analysis will be provided in the SAP.

7.4.2 Analysis of Secondary Endpoints

The secondary efficacy endpoints are defined in [Section 2.3.2 Secondary Endpoints].

The primary analysis for the secondary endpoints of mean daily average pain score (≥ 30% and 50% reduction from baseline to Week 8 and to EOT) will be carried out with the Fisher's Exact Test. For the Week 8 analysis, subjects with missing data will be classified as non-responders (BOCF group) and an additional analysis will use mBOCF. For the EOT analysis, LOCF will be used.

The primary analysis for the change from baseline to Weeks 2, 4 and 8 for the FIQR subscales of Physical Function, Symptoms and Overall Impact will use the same MMRM analysis as described in [Section 7.4.1.1 Primary Analysis]. The primary analysis for the change from baseline to EOT for the FIQR subscales will use an ANCOVA model, with

covariates of baseline FIQR subscale score and center. An additional ANCOVA analysis will be conducted at Week 8 with mBOCF for subjects with missing data.

The primary analysis for the PGIC will use the proportional odds model for ordinal data with model term for treatment group. The analysis will be used to assess PGIC at Weeks 2, 4, 8 and EOT. For subjects with missing data, the analysis at Weeks 2, 4 and 8 will be conducted using mBOCF. An additional analysis at Weeks 2 and 4 will use LOCF.

7.4.3 Analysis of Exploratory Endpoints

The exploratory efficacy endpoints are defined in [Section 2.3.3 Exploratory Endpoints]. For the treatment period, the following analyses will be performed.

The analysis for the change from baseline to each week from Week 1 to 7 in mean daily average pain is included in the primary analysis of primary endpoint as described in [Section 7.4.1.1 Primary Analysis], which includes data from Week 1 to 8. The change from baseline to EOT in mean daily average pain will be analyzed with an ANCOVA model, with covariates of baseline mean daily average pain and center. In addition, the percentage of subjects who meet cumulative response levels of > 0% to = 100% at Week 8 and EOT will be shown. For the analysis at Week 8, subjects with missing data will be classified as non-responders (BOCF group) and an additional analysis will use mBOCF.

The change from baseline to Weeks 2, 4, 8 in FIQR Total Score and PGIS will be analyzed using the MMRM model as described in [Section 7.4.1.1 Primary Analysis]. The change from baseline to EOT in FIQR total Score and PGIS will be analyzed with an ANCOVA model, with covariates of baseline score and center. An additional ANCOVA analysis for change from baseline to Week 8 will be conducted with mBOCF.

The subject's response defined as achieving ≥ 30% reduction from baseline in FIQR Total score at Week 8 and EOT will be analyzed using the Fisher's Exact Test. For the analysis at Week 8, mBOCF will be used for subjects with missing data.

The percentage of subjects who achieve PGIC response (*Much Improved*, *Very Much Improved*) at Week 8 and EOT will be analyzed using the Fisher's Exact Test. The analyses at Week 8 will be conducted using mBOCF for subjects with missing data.

The subject's composite pain response is defined as achieving ≥ 30% reduction from baseline in mean daily average pain score and PGIC of very much or much improved. The percentage of subjects who achieve composite pain response at Week 8 and EOT will be analyzed using the Fisher's Exact Test. The analysis at Week 8 will be conducted using mBOCF for subjects with missing data.

The subject's composite syndrome response is defined as achieving ≥ 30% reduction from baseline in mean daily average pain score and PGIC of very much or much improved and ≥ 30% reduction from baseline in FIQR total score. The percentage of subjects who achieve composite syndrome response at Week 8 and EOT will be analyzed using the Fisher's Exact Test. The analysis at Week 8 will be conducted using mBOCF for subjects with missing data.

The change from baseline to each week from Week 1 to 8 in FMSD will be analyzed using the MMRM model as described in [Section 7.4.1.1 Primary Analysis]. The change from baseline to EOT in FMSD will be analyzed with an ANCOVA model, with covariates of baseline score and center.

The change from baseline to Week 8 and EOT in HADS depression subscale will be analyzed with an ANCOVA model, with covariates of baseline score and center. The change from baseline to Week 8 and EOT in the EQ-5D-5L (5 dimensions and the subject's health status) will be summarized with descriptive statistics.

The following analyses on rescue medication will be summarized for acetaminophen use. The proportion of days with rescue medication use during each week from Week 1 to 8 and EOT will be analyzed using Negative Binomial Regression model with terms for treatment and center. The incidence of subjects using rescue medication during each week from Week 1 to 8 and EOT will be analyzed using the Fisher's Exact Test. The average daily dose of rescue medication during each week from Week 1 to 8 and EOT will be analyzed using analysis of variance with model terms for treatment and center.

The change from baseline to Weeks 2, 4 and 8 in IBS symptom summary score and abdominal pain, stomach pain, abdominal cramps, abdominal pressure, and bloating as assessed by the mIBS-D daily symptom diary will be analyzed using the MMRM method as described in [Section 7.4.1.1 Primary Analysis]. The change from baseline to EOT in these assessments will be analyzed with an ANCOVA model, with covariates of baseline score and center.

The change from baseline to Week 8 and EOT in the NPSI subscores of burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain and paresthesia/dysesthesia will be analyzed with an ANCOVA model, with covariates of baseline score and center.

For the follow-up period, data will be summarized with descriptive statistics (number of subjects, mean, SD, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints. The following endpoints will be considered and summarized by randomized treatment group.

- Change from baseline and EOT to Week 10 in mean daily average pain score.
- Change from baseline and EOT to Week 10 in FIOR physical 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.
- Subject's response defined as 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.
- Subject's response defined as 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.

- Incidence of subjects using rescue medication at Week 10.
- Average daily dosage of rescue medication at Week 10.

7.5 Analysis of Safety

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

7.5.1 Adverse Events

AEs will be coded using the MedDRA. TEAE is defined as any AE which starts, or worsens, after the first dose of study drug through 30 days after the last dose of study drug.

The number and percentage of subjects with TEAEs, TEAEs leading to discontinuation, serious TEAEs and TEAEs related to study drug as assessed by the investigator will be summarized by system organ class, preferred term and treatment group. In addition, TEAEs will be summarized by relationship to study drug as determined by the investigator and by severity for each treatment group.

All TEAEs will also be listed.

7.5.2 Laboratory Assessments

For quantitative laboratory tests, descriptive statistics will be used to summarize baseline value, post baseline value at each specified time point, and change from baseline to each specified post baseline time point by treatment group. Shifts relative to normal ranges from baseline to each specified post baseline time point in laboratory tests will also be tabulated.

The number and percentage of subjects with potentially clinically significant values in liver enzymes: alkaline phosphatase (ALP), ALT, AST and TBL will be presented by treatment group. Criteria for potentially clinically significant values using the above laboratory tests will be provided in the SAP.

Laboratory test data will also be displayed in listings.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign parameters at baseline value, post baseline value at each specified time point, and change from baseline to each specified post baseline time point by treatment group.

The number and percentage of subjects with potentially clinically significant values in SBP, DBP and pulse rate will be presented by treatment group. Criteria for potentially clinically significant values using the above vital sign parameters tests will be provided in the SAP.

Vital sign parameter data will also be displayed in listings.

7.5.4 Physical Examination

Physical examination will be listed by treatment group.

7.5.5 Electrocardiograms

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

7.5.6 Columbia Suicide Severity Rating Scale

Descriptive statistics and listing of events will be provided for the C-SSRS for each treatment group by time point and for the entire study.

7.5.7 Analysis of Pharmacokinetics

A listing of sample times and concentrations will be provided.

7.6 Protocol Deviations

Protocol deviations as defined in [Section 8.1.7 Protocol Deviations] will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. 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.

7.7 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 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 IAP.

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

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs, concomitant medication, last dose date of double blind study drug and the efficacy data below. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment group, in addition to determining whether an AE is/is not treatment emergent. The imputed date of study drug will be used to calculate duration of

study drug exposure. Listings of the AEs and concomitant medications and study dosing will present the actual partial dates; imputed dates will not be shown.

For one of the sensitive analyses for the primary efficacy endpoint, multiple imputation will used to impute missing data, using *Jump to Reference* algorithm for subjects who discontinue due to lack of efficacy or AEs and standard regression-based multiple imputation for subjects with missing data for other reasons. 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 7.4 Analysis of Efficacy]

See the SAP for details of the definition for windows to be used for analyses by visit.

Centers that do not enroll a sufficient number of subjects will be pooled for statistical analyses, which includes study center according to a pre-specified algorithm in the SAP. The pooling decisions will be made and documented prior to study hard-lock.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture (EDC) system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents, as defined in the Monitoring Plan, and confirm that there are no inconsistencies between them.

Laboratory tests are performed at a central laboratory. Central Laboratory data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The Central laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and Adverse Events will be collected in the eCRF.

8.1.2 Electronic Patient Reported Outcomes

Subject diaries and questionnaires will be completed by the subject on an electronic device. The information completed by the subject on the electronic device will be automatically uploaded into a central website. The investigator or site designee should review the diaries and questionnaire data on the website for correct completion while the subject is at the site. The diary and questionnaire data will be transferred electronically to Sponsor or designee at

predefined intervals during the study. The vendor will provide Sponsor or designee with a complete and clean copy of the data.

8.1.3 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included, but not limited to, in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight);
- Inclusion and exclusion criteria details;
- Participation in main study, PGx sub-study (if applicable) and original signed and dated ICFs;
- Visit dates;
- Medical history and physical examination details;
- Key efficacy and/or and safety data, if applicable (as specified in the protocol);
- AEs and concomitant medication ;
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.);
- Laboratory printouts (if applicable);
- Details of dispensing and return of study drug;
- Reason for premature discontinuation (if applicable);
- Pharmacokinetic sample processing and storage history, including date/time each sample is transferred to the freezer, freezer identification and the temperature log for the freezer (if applicable);
- Pharmacogenomic sample processing and storage history, including date/time each sample is transferred to the freezer, freezer identification and the temperature log for the freezer (if applicable).

8.1.4 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.5 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO, as well as inspections from the IRB and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents [refer

to Section 8.1.3 Specification of Source Documents] when they are requested by the Sponsor monitors and auditors, the IRB, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.6 Data Management

Data Management will be coordinated by the Data Science department of the Sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and WHO-DD, respectively.

8.1.7 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- entered into the study even though they did not satisfy entry criteria,
- developed withdrawal criteria during the study and not withdrawn,
- received wrong treatment or incorrect dose, and
- received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The investigator will also assure that deviations meeting IRB and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB and applicable regulatory authorities will be provided to the Sponsor and maintained within the trial master file.

8.1.8 End of Trial in All Participating Countries

The end of the study is defined as the last visit or follow-up contact of the last subject in the study.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board/Competent Authorities

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the IB, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB. The IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible ethics committees and regulatory agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IRB at appropriate intervals, not exceeding 1 year. The investigator shall make an accurate and adequate final report to the IRB within 90 days after the close-out visit for APGD-sponsored studies, or for APEB/APEL-sponsored studies within 1 year after last subject out or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that all informed consents were obtained prior to any study-related procedures and that the subject received signed copies.

The signed ICFs will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

Subjects must provide separate written consent prior to providing any blood samples that may be used at a later time for genetic analysis as part of the PGx substudy.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update their ICF and submit it for approval to the IRB. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the Sponsor. However, the Sponsor requires the investigator to permit the Sponsor, Sponsor's representative(s), the IRB and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information

Protection Law in Japan and Privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then Sponsor shall serve as the controller of such data, as defined by the EU Data Protection Directive, and the investigator and/or third party shall act only under the instructions of the Sponsor in regard to personal data. If Sponsor is not based in the EEA, Sponsor must appoint a third party to act as its local data protection representative or arrange for a cocontroller established in the EU for data protection purposes in order to comply with the Directive.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the IB and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the clinical study agreement.

8.3.2 Documents and Records Related to the Clinical Study

The Sponsor will provide the investigator and/or institution with the following:

- study protocol (and amendments, where applicable),
- IB (and amendments, where applicable),
- eCRFs,
- study drug with all necessary documentation and
- study contract.

In order to start the study, the investigator and/or study site is required to provide the following documentation to the Sponsor:

- Financial disclosure in compliance with federal regulation 21CFR Part 54,
- signed and dated FDA form 1572,
- signed investigator's statement in this protocol and eCRF,
- current Curricula Vitae of all investigators,
- list of sub-investigators and collaborators,
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (copy documents) and
- study contract.

The investigator will archive all study data (e.g., subject identification code list, source data, CRFs, and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the New Drug Application [NDA] or discontinuation of the Investigational New Drug [IND]). The Sponsor will notify the site/investigator if the NDA/Marketing Authorisation Applications/Japan-NDA is approved or if the IND/Investigational Medicinal Product Dossier/Clinical Trial Notification (CHIKEN TODOKE) is discontinued. The investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes.

All data will be entered on the CRFs supplied for each subject.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the investigator, the regulatory authority, and the IRB (if applicable).

Amendments to this protocol must be signed by the Sponsor and the investigator. Written verification of IRB approval will be obtained before any amendment is implemented, which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB approval, but will be submitted to the IRB for their information, if required by local regulations.

If there are changes to the informed consent, written verification of IRB approval must be forwarded to the Sponsor. An approved copy of the new informed consent must also be forwarded to the Sponsor.

8.3.4 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator (s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the quality assurance and quality control systems and written SOPs of the CRO will be applied.

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, CRFs, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Data Monitoring Committee

The IDMC is responsible for the interim futility evaluation of efficacy data defined in the IDMC Charter. Participants in the IDMC include, but may not be limited to: an Independent Astellas Statistician who is not on the study team, and does not communicate with study team or Site staff. The IDMC will evaluate unblinded data and provide conclusion of futility analysis to Astellas Management [see Section 7.7 Interim Analysis (and Early Discontinuation of the 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 external statistician of the project team, with results reviewed by an IDMC also external to the study team. 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.

10.2 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 List of Excluded Concomitant Medications - Excluded Medications with Efficacy or Potential Efficacy in Fibromyalgia Pain

These lists are not exhaustive. Medications should be considered excluded if taken alone or as part of a combination product. **If in doubt, please contact the Medical Monitor.**

Gabapentenoids		
gabapentin	miragabalin	pregabalin
Antidepressants		
amitriptyline bupropion duloxetine desvenlafaxine levomilnacipran	Monoamine oxidase inhibitors maprotiline milnacipram mianserin mirtazapine	reboxetine trazodone Tricyclic Antidepressants venlafaxine
Opioids		
bezitramide buprenorphine butorphanol dextromoramide dextropropoxyphene dezocine dihydrocodeine fentanyl	hydromorphone ketobemidone meptazinol methadone morphine nalbuphine nicomorphine oxycodone	papaveretum pentazocine pethidine/meperidine phenazocine piritramide tapentadol tilidine tramadol
Others		
baclofen buspirone Cannabinoids Herbals (e.g., St. John's wort, kava kava, kratom)	ketamine mazindol Muscle Relaxants (e.g., carisoprodol, cyclobenzaprine, tizanidine, metaxalone)	sodium oxybate Stimulants celecoxib
Topical and Injectable Pain Medications		
capsaicin	menthol methyl salicylate	Tenderpoint injections with anesthetics or steroids

Excluded P450 CYP3A Substrates

Sensitive Substrates		
alfentanil	ebastine	perospirone
almorexant	eletriptan	quetiapine
alpha-dihydroergocryptine	elvitegravir	ridaforolimus
aplaviroc	eplerenone	saquinavir
aprepitant	everolimus	sildenafil
atazanavir	felodipine	simeprevir
atorvastatin	ibrutinib	simvastatin
avanafil	indinavir	tacrolimus
bosutinib	ivacaftor	terfenadine
brecanavir	levomethadyl (LAAM)	ticagrelor
brotizolam	lomitapide	tilidine
budesonide	lopinavir	tipranavir
buspirone	lovastatin	tolvaptan
capravirine	lumefantrine	triazolam
casopitant	lurasidone	ulipristal
conivaptan	Maraviroc	vardenafil
danoprevir	midazolam	vicriviroc
darifenacin	midostaurin	voclosporin
darunavir	neratinib	
dasatinib	nisoldipine	
dronedarone		
Narrow Therapeutic Range Substrates		
alfentanil	ergotamine	quinidin
cyclosporine	fentanyl	sirolimus
diergotamine	pimozide	tacrolimus

Excluded Central Nervous System Agents

Antipsychotics/Tranquilizers		
amisulpride	fluphenazine	paliperidone
amoxapine	haloperidol	perphenazine
aripiprazole	iloperidone	pimavanserin
asenapine	loxapine	pimozide
brexpiprazole	lurasidone	quetiapine
cariprazine	melperone	risperidone
chlorproethazine	mesoridazine	thioridazine
clozapine	molindone	thiothixene
droperidol	olanzapine	trifluoxperazine
		ziprasidone
Benzodiazepines /Sedatives/Sleep Agents		
alprazolam	diazepam	midazolam
Barbituates	flurazepam	oxazepam
chlordiazepoxide	hydroxyzine	temazepam
clobazam	lorazepam	triazolam
clonazepam	meprobamate	
clorazepate		
Sedating Antihistamines		
alimemazine	Chronic diphenhydramine or use for sleep	ketotifen
chlorpheniramine	cyproheptadine	promethazine
clemastine	hydroxyzine	
Other CNS Medications		
Anti-epileptics (e.g., topiramate, divalproate sodium, carbamazepine, lamotrigine)	Dopamine agonists	Mood stabilizers (e.g., lithium)

12.2 List of Allowed Anti-depressants and Sleep Aids

If in doubt, please contact the Medical Monitor.

Allowed Antidepressants*

Selective Serotonin Reuptake Inhibitors		
citalopram escitalopram fluoxetine	fluvoxamine paroxetine sertraline	vilazodone vortioxetine

*follow prescribing information in package insert

Allowed Sleep Aids*

eszopiclone up to 1 mg melatonin	zaleplon up to 10 mg zolpidem up to10 mg	zopiclone up to 2 mg

*follow prescribing information in package insert

12.3 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases to > 3 × ULN or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 × ULN	or	> 2 × ULN
Severe*	> 3 × ULN	and	> 2 × ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the liver abnormality case report form (LA-CRF) that has been developed globally and can be activated for any study or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to do the following:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases is to be recorded as "AEs" within the (e)CRF. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic patients and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, is to be entered in the (e)CRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including the following:
    - acute viral hepatitis (A, B, C, D, E or other infectious agents),
    - ultrasound or other imaging to assess biliary tract disease,
    - other laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Subject Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if the LFT results are as follows:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5) (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10 to 50% mortality (or transplant). The 2 "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 × ULN ("2 × ULN elevations are too common in treated and untreated patients to be

discriminating"). 2) Cases of increased bilirubin (at least 2 × ULN) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

References

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Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.4 Common Serious Adverse Events

For this protocol, there is no list of common SAEs anticipated for the study population for the purposes of IND safety reporting.

12.5 Retrospective Pharmacogenomics Sub-Study

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx sub-study. As part of this sub-study, subjects must provide written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide 1 approximately 6 mL tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

PHARMACOGENOMICS ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety.

DISPOSAL OF PHARMACOGEMONICS SAMPLES / DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.6 Questionnaires

Questionnaire	Frequency/Visit
Daily Average Pain Numerical Rating Scale (NRS) Score	Daily from Visit 2 onwards, at home, until Visit 7 by subject. Every attempt should be made by the subject to enter the daily NRS score at a consistent time in the evening throughout the study.
Fibromyalgia Sleep Diary (FMSD)	Daily from Visit 2 onwards, at home, until Visit 7 by subject. Every attempt should be made by the subject to enter the daily FMSD score upon awakening in the morning throughout the study.
Mini-International Neuropsychiatric Interview (M.I.N.I.)	Visit 1 at clinic by site personnel
Hospital Anxiety and Depression Scale (HADS)	Visit 1, Visit 3 and Visit 6 at clinic by subject
Columbia-Suicide Severity Rating Scale (C-SSRS)	Visit 1, Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7 at clinic by site personnel.
Complex Medical Symptoms Inventory (CMSI)	Visit 2 by the subject on the electronic patient reported outcomes (ePRO) device
Patient Global Impression of Change (PGIC)	Visit 4, Visit 5, Visit 6 and Visit 7 at clinic by subject
Patient Global Impression of Severity (PGIS)	Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7 at clinic by subject
European Quality of Life-5 Deminsenions-5 Levels (EQ-5D-5L)	Visit 3, Visit 6 and Visit 7 at clinic by subject
Fibromyalgia Impact Questionnaire Revised (FIQR)	Visit 1, Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7 at clinic by subject
Modified Irritable Bowel Syndrome – Diarrhea Predominant (mIBS-D) Symptoms Diary	Visit 3, Visit 4, Visit 5 and Visit 6 at clinic by subject
Neuropathic Pain Symptom Inventory (NPSI)	Randomization and Week 8/End of Treatment

For the daily questionnaires the subject will receive an e-diary that can be taken home. The subject should take the e-diary to the clinic for each study visit. For the questionnaires to be completed at the site the subject will use the tablet that is available at the site.

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 1

I. The purpose of this amendment is:

Substantial Change
1. PoC Fibromyalgia studies 0819-CL-0201 and PPD (see separate submission to PAC) are pilot for including duplicate subject check
DESCRIPTION OF CHANGE:
New screening assessment added to section 2.2.1 : after signing informed consent and during the screening period, study site personnel will check that potential subjects have not already been pre-screened, initiated or completed screening or have been randomized into this study, or another clinical trial, using an independent subject participation database. Independent subject participation databases seek to reduce duplicate enrollment by identifying duplicates before they randomize into the study, and this measure is consistent with exclusion requirement of not participating in another interventional clinical trial during the conduct of the study. In order to complete this check and per the informed consent, study personnel will request that the subject present a valid picture identification (e.g. driver's license, passport, state issued ID card, etc.) and study personnel may be required to provide certain authorized information that could potentially be used to identify study subjects identifiers (e.g. date of birth, initials, etc.) so that the match algorithms can be run. Subjects that meet the inclusion criteria, none of the exclusion criteria, and are not identified as a duplicate subject (e.g. certainly, possible, probably), will be enrolled into the study. Appropriate documentation reflecting the subject's eligibility according to these criteria will be reflective in the subject's source documents. *Note : Protocol wording developed in collaboration with the legal department*
RATIONALE:
➢ Proliferating problem of professional patients (recognized for a.o. US trials)- Websites dedicated to train people on how to get into research studies (e.g. Finance.youngmoney.com) ➢ 6-11% who seek entry are, on another trial, in a lock out period or are attempting to enter at another facility ➢ Incidence of dual enrollment per trial ranges from 2% to 10% according to the therapeutic area and the phase of the study ➢ Certain indications attract "repeat" subjects ➢ Recent study (3662-CL-0049) demonstrated that 3% of subjects were within study duplicates (screened only) at two different sites in a small POC study ➢ Fibromyalgia is a very heterogeneous disease, lacks rigorous standardized and objective diagnostic criteria and relies on patient reported medical history ➢ Implement checking prospectively in new (CNS) clinical trials to maximize the signal to noise ratio and increase chance of detecting effect size.A third party vendor will be used

who is specialized in detecting potential duplicate subjects from a trials database. Subjects will provide informed consent for this verification in the study's ICF.

Non-Substantial Changes
1. Minor Administrative-type changes
DESCRIPTION OF CHANGE:
Wording changes for 8062 protocol also implemented here in the 0819 protocol to align the 2 FM PoC Ph2 studies.
RATIONALE:
To align with the PPD study.
2. Clarification of the number of tender point sites
DESCRIPTION OF CHANGE:
Clarify the expectation that the patient will be eligible if she/he has pain in 'at least' 11 of the 18 tender point sites.
RATIONALE:
The expectation is that a patient is eligible for study participation if he/she has pain in at least 11 of the 18 tender point sites. The wording is only mentioning that the patient has pain in 11 of 18 tender point sites.
3. Update collection of tender points on site tablet instead of CRF
DESCRIPTION OF CHANGE:
The FM diagnosis is confirmed using the ACR criteria: Widespread Pain Index, Symptoms Severity Scale and the Tender Points. WPI and SSS are captured by the investigator on the site tablet. We want to include the tender point assessment here as well instead of capturing it separately in the CRF.
RATIONALE:
Decreasing complexity for the site in keeping the 3 assessments together.

II Amendment Summary of Changes:

2.1 Study Design and Dose Rationale *Section 2.2.1, Study Design*
ADDED**:**
After signing informed consent and during the screening period, study site personnel will check that potential subjects have not already been pre-screened, initiated or completed screening or have been randomized into this study, or another clinical trial, using an independent subject participation database. Independent subject participation databases seek to reduce duplicate enrollment by identifying duplicates before they randomize into the study, and this measure is consistent with exclusion requirement of not participating in another interventional clinical trial during the conduct of the study (inclusion criterion 17). In order to complete this check and per the informed consent, study personnel will request that the subject present a valid picture identification (e.g. driver's license, passport, state issued ID card, etc.) and study personnel may be required to provide certain authorized information that could potentially be used to identify study subjects identifiers (e.g. date of birth, initials, etc.) so that the match algorithms can be run. **Subjects that meet the inclusion criteria, none of the exclusion criteria, and are not identified as a duplicate subject (e.g. certainly, possible, probably), will be enrolled into the study. Appropriate documentation reflecting the subject's eligibility according to these criteria will be reflective in the subject's source documents.**

Table 1 : Schedule of Assessements
WAS:
Verify Eligibility Criteria
IS AMENDED TO:
Verify Eligibility Criteria **(and duplicate subject database check)**

IV Synopsis, Inclusion Criteria and 3 Study Population *3.2 Inclusion Criterion #9*
WAS:
• Pain in 11 of 18 tender point sites on digital palpation.
IS AMENDED TO:
• Pain in **at least** 11 of 18 tender point sites on digital palpation.

1 Background *Background on Target Indication*
WAS:
Despite the available approved medications, novel medications to treat pain, fatigue, sleep disturbances and impaired cognition without intolerable AEs ~~present~~ an unmet medical need for subjects with fibromyalgia.
IS AMENDED TO:
Despite the available approved medications, novel medications to treat pain, fatigue, sleep disturbances and impaired cognition without intolerable AEs **are required to address** an unmet medical need for subjects with fibromyalgia.

2.1 Study Design and Dose Rationale *2.2.1 Study Design*
WAS:
The study will be conducted in the US.
IS AMENDED TO:
The study will be conducted in the US **in up to approximately 35 sites**.

5.2 Demographics and Baseline Characteristics *5.2.3 Diagnosis of the Target Disease, Severity and Duration of Disease*
WAS:
The diagnosis fibromyalgia must be confirmed by the investigator and documented in the subject's medical notes (meeting both the 1990 and 2010 American College of Rheumatology clinical classification criteria for fibromyalgia). Duration of fibromyalgia, date of onset of fibromyalgia symptoms date of fibromyalgia diagnosis ~~and number of tenderpoints~~ will be recorded in the eCRF. ~~Tender point examination training of the principal investigator and/or designated site study physician must be documented~~. The WPI and SS score will be completed by the clinician on a tablet device during the Screening visit. Subjects should have a WPI ≥ 7 and SS score ≥ 5 or WPI of 3 to 6 and SS scale score ≥ 9.
IS AMENDED TO:
The diagnosis fibromyalgia must be confirmed by the investigator and documented in the subject's medical notes (meeting both the 1990 and 2010 American College of Rheumatology clinical classification criteria for fibromyalgia). Duration of fibromyalgia, date of onset of fibromyalgia symptoms and date of fibromyalgia will be recorded in the eCRF. **The number of tender points**, WPI and SS score will be completed by the clinician on a

tablet device during the Screening visit. Subjects should have a WPI ≥ 7 and SS score ≥ 5 or WPI of 3 to 6 and SS scale score ≥ 9. **Tender point examination training of the principal investigator and/or designated site study physician must be documented.**

5.8 Total Amount of Blood
WAS:
Total blood collected for laboratory specimens is approximately 144 mL.
IS AMENDED TO:
Total **amount of** blood collected **per subject** for laboratory specimens is approximately 144 mL.

14 COORDINATING INVESTIGATOR'S SIGNATURE

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

ISN/Protocol 0819-CL-0201

Version 2.0 Incorporating Substantial Amendment 1

19 December 2016

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: _____ _____

<Insert name, department/affiliation, name of institution> Date (dd Mmm yyyy)

Printed Name: PPD

Address:

15 SPONSOR'S SIGNATURES