Clinical Trial Protocol: APD371-004

Study Title: A Randomized, Open-label, Parallel, Phase 2a Study to Determine the Tolerability, Pharmacokinetics, and Efficacy of APD371 in Subjects with Crohn's disease experiencing Abdominal Pain

Study Number: APD371-004

Study Phase: 2a

Product Name: APD371

Indication: Acute and chronic inflammatory pain

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SYNOPSIS

Protocol Number:	APD371-004
Title:	A Randomized, Open-label, Parallel, Phase 2a Study to Determine the Tolerability, Pharmacokinetics, and Efficacy of APD371 in Subjects with Crohn's disease experiencing Abdominal Pain
Study Phase:	2a
Name of Drug:	APD371
Indication:	Acute and chronic inflammatory pain
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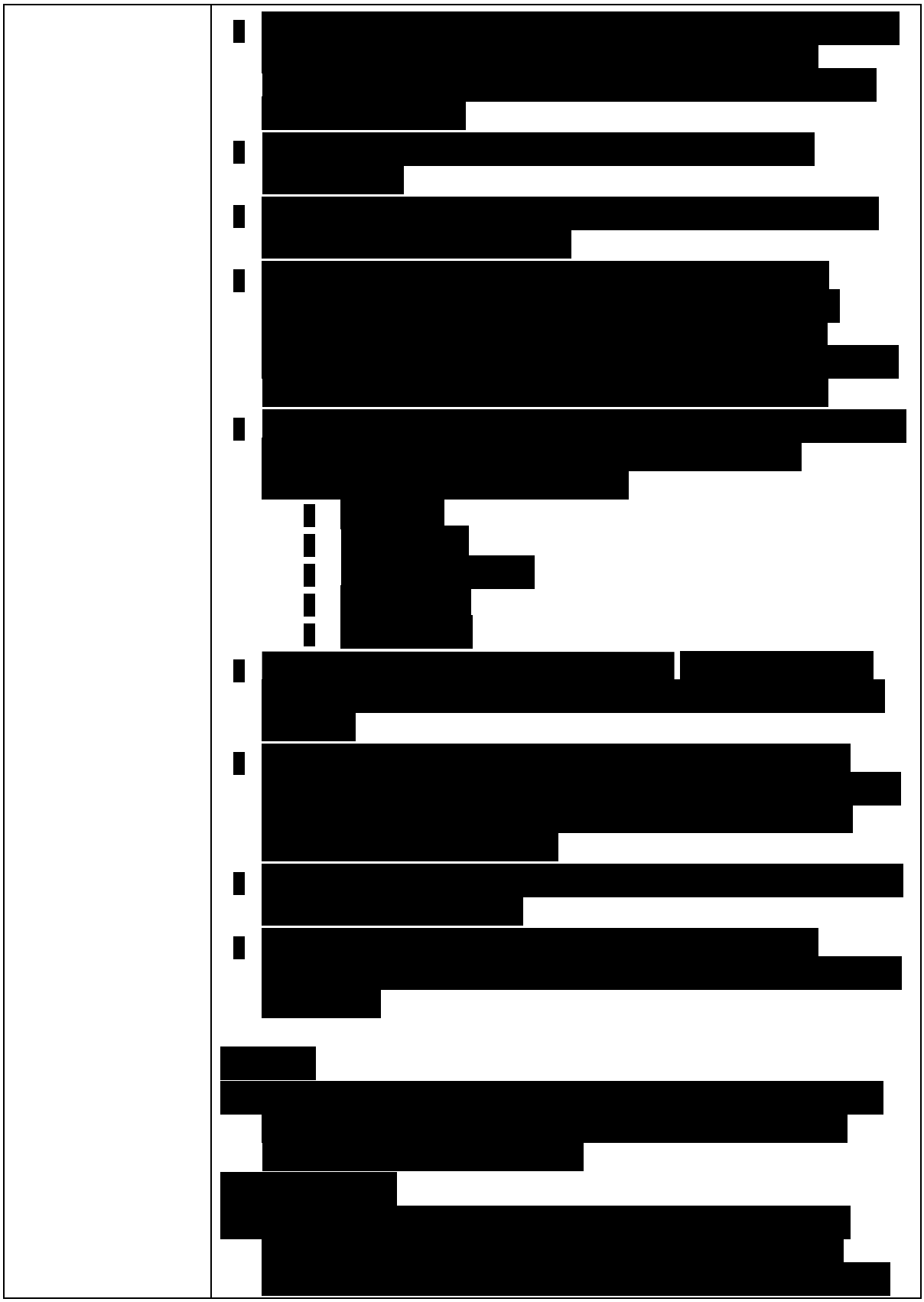
Dosage:	APD371 dosed at 25 mg or 100 mg three times daily (TID) at approximately 07:00 ± 2 hr, 15:00 ± 2 hr and 23:00 ± 2 hr for 8 weeks (Wk).
Concurrent Control:	Intra-subject screening (baseline)

Route and Formulation:	Oral, capsules which are identical for each dose
Objectives:	Key Objective • To assess the tolerability and safety of two doses of APD371 in subjects with Crohn's Disease (CD) experiencing abdominal pain treated for up to 8 Wk. Exploratory Objectives: • Determination of pharmacokinetic (PK) profiles (including metabolites) and average PK parameters (C_{max}, t_{max}, AUC_{0-8}) of two doses of APD371 TID • Change in abdominal pain score (APS) from pre-dose (trough) to 1.5 hr post-dose (peak) following the first of 3 daily doses of APD371; assessed daily to Day 56 and averaged weekly to Wk 8 • Change in average abdominal pain score (AAPS) from baseline to Wk 8 (averaged weekly to Wk 8) • Proportion of subjects who are weekly responders • Proportion of subjects who are end-of-treatment responders • Number of pain-free days per week, based on responses to the Abdominal Pain Severity [redacted] [redacted] • Pain medication use • Effect of APD371 treatment on reduction in C-reactive protein (CRP) and other biomarkers at week 4 and week 8 • Effect of APD371 treatment on reduction in fecal calprotectin at week 4 and week 8 [redacted] [redacted]
Study Design:	A randomized, open label, parallel group, multi center, comparison of two doses of APD371. Eligible subjects will enter a screening period of up to 4 weeks and will then be randomized in a 1:1 ratio to receive APD371 in doses of 25 mg or 100 mg TID for 8 weeks.

	Randomization will be stratified by sex.
Study Population:	The study population will consist of adult male and female subjects aged 18 to 80 years who are diagnosed with abdominal pain due to quiescent to mildly active CD, as defined by a weekly average abdominal pain score (AAPS) ≥ 4 over one week (0 [no pain] to 10 [worst possible]), with minimal intestinal inflammation, confirmed with a simple endoscopic score (-CD) score <10 or fecal calprotectin (FCP) <500 mcg/g. Endoscopy results obtained within 1 month prior to screening may be utilized. Concomitant therapy may include all anti-inflammatory therapy for CD, including 5-aminosalicylates, antibiotics, immunomodulators, and oral or topical corticosteroids (prednisone ≤20 mg/day, budesonide at a dose ≤9 mg/day, or equivalent steroid) on stable maintenance doses. Subjects who have received/are currently receiving anti-tumor necrosis factor-α or other biologic therapy will be allowed to continue on these therapies if the dose/regimen has been stable for at least 8 weeks prior to screening and no intended change in these therapies during the study is anticipated.
Inclusion criteria	[redacted] 6. A clinical diagnosis of CD for at least 3 months prior to screening corroborated by prior endoscopic and histopathologic documentation consistent with CD. 7. Quiescent to mildly active inflammatory CD defined with a total SES-CD score of < 10 or FCP < 500 mcg/g within 4 weeks before screening. 8. Moderate to severe abdominal pain as defined by average abdominal pain score (AAPS) of ≥ 4 points on 7 consecutive days of the screening period up to Day -2. AAPS will be based on the 11-point numeric rating scale where 0 (no abdominal pain) to 10 (worst possible abdominal pain) [redacted]



	[redacted]
Exclusion criteria	General Exclusion Criteria [redacted] 2. Female subjects who are lactating or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 prior to study drug administration [redacted]

	[redacted] 8. Recent history (within 6 months of screening visit) of cerebrovascular disease, Acute Coronary Syndrome, Cerebrovascular accident, Transient ischemic attack, Myocardial infarction, unstable angina [redacted] 12. Other significant chronic pain conditions that in the opinion of the investigator may influence the abdominal pain score [redacted] <u>Gastrointestinal Exclusion Criteria</u> [redacted] 15. Extensive colonic resection, subtotal or total colectomy [redacted] 17. History of >3 small bowel resections or diagnosis of short bowel syndrome or who have undergone bowel resection within 6 months prior to randomization [redacted]

	[redacted] Infectious Disease Exclusion Criteria 30. Chronic active hepatitis B within the last year (unless shown at the time of study entry to be hepatitis B antigen negative) or any history of hepatitis C [redacted] 33. Evidence of current GI infection (bacterial or parasitic) or significant infection within 45 days of Screening [redacted]
Duration per Subject:	Each subject will receive study treatment for up to 8 weeks
Subject Assignment:	Eligible subjects will be randomized in a 1:1 ratio to receive APD371 25 mg TID or 100 mg TID.

Sample Size:	It is planned to treat and complete safety and tolerability assessments in approximately 16 subjects. Since subjects maybe replaced if they are withdrawn due to major protocol violations, it is estimated a maximum of 20 subjects maybe be dosed. These numbers will be appropriate for a preliminary evaluation of safety and tolerability, provision of PK profiles of APD371 at two doses and exploratory analysis of efficacy end points.
Safety Assessments:	• Adverse event reporting to include; Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reaction (SUSARs) • Clinical laboratory tests to include; hematology, serum chemistry, and urinalysis • Physical examinations • Vital sign measurements • 12-lead electrocardiograms (ECGs)
Pharmacokinetic Assessments:	Blood samples for the assay of APD371 and metabolites M1 [redacted], M2 [redacted], and M4 [redacted] will be collected at the following time points: • Wk 0 (Day 1): prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9, 10 and 24 hours post first daily dose. • Wk 2, 4, and 6: prior to first daily dose • Wk 8 (Day -1, last day dosing): prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose),. • An additional blood sample for PK analysis will be collected, if possible, at the time of any intolerable AE or SAE.
Efficacy assessments:	• The analgesic effect of APD371 on abdominal pain will be scored by subjects in a diary using the APS. The score will be based on the 11-point numeric rating scale from 0 [no abdominal pain] to 10 [worst possible abdominal as follows; During Screening Twice daily for at least 7 consecutive days; 1. Early morning, approximately 06:00 - 08:00 2. Late evening, approximately 20:00 - 22:00. During Treatment Three times a day every day (Day1 to 56); 1. Before the morning dose and any other study procedures 2. At 1.5 hours after the morning dose 3. Before the evening dose. • Additional efficacy assessments will include achievement of clinical improvement [defined as a two- component PRO score (Stool frequency and abdominal pain) of <11], clinical response from baseline to Wk 8, and change from baseline in CRP and fecal calprotectin at week 4 and 8.

Data Analyses:	Safety and tolerability data reported will include incidence of withdrawals and incidence and proportion of subjects with TEAEs, SAEs and SUSARs by dose and by duration of treatment. Compliance with treatment will be determined by tablet counts. The following parameters will be calculated from APD371 plasma concentrations on Wk 0 (Day 1) and Wk 8 (Day -1, last day): C_{max}, t_{max} and AUC_{0-8} Plasma concentration data from predose samples collected during Wk 2, 4, 6, and 8 will be used to determine C_{trough}. Parameter estimates for C_{max} and AUC_{0-8} will be evaluated to assess dose-proportionality. The following parameters will be calculated from plasma concentration data for M1 [redacted], M2 [redacted], and M4 [redacted] on Wk 0 (Day 1) and Wk 8 (Day -1): C_{max}, t_{max} and AUC_{0-8} The ratio of each metabolite to APD371 will be calculated for C_{max}, AUC_{0-8}. The analgesic effect of two doses of APD371 will be reported using summary statistics as a change from baseline in AAPS at each week for trough, peak and combined assessments. Differences between trough and peak APS scores will also be assessed by summary statistics and appropriate non-parametric methods. The proportion of subjects with clinical improvement/response will be determined for each dose and combined at Wk 8 and be compared between 2 doses.
Date	10 August 2017

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAPS	average abdominal pain score
ADL	activities of daily living
AE	adverse event
APS	abdominal pain score
ASA	acetyl salicylic acid
AUC	area under the plasma concentration-time curve
AUC_{0-8}	area under the plasma concentration-time curve from time zero to 8 hr postdose
CB_1	cannabinoid-1 (receptor)
CB_2	cannabinoid-2 (receptor)
CD	Crohn's Disease
[redacted]	[redacted]
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CRO	contract research organization
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	plasma concentration observed before treatment administration during repeated dosing
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
FCP	fecal calprotectin
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GPCR	G protein-coupled receptor
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation

IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MIA	monosodium iodoacetate
min	minute
6-MP	6 mercaptopurine
MTD	maximum tolerated dose
NSAID	non-steroidal anti-inflammatory
OTC	over-the-counter
[redacted]	[redacted]
PI	Principal Investigator
PK	pharmacokinetic(s)
PRO	patient reported outcome
QTc	Q and T wave (interval)
RDC	remote data capture
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SES	simple endoscopic score
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
THC	Tetrahydro cannabinol
TID	3 times a day
t_{max}	time of maximum plasma concentration
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
USA	United States of America
WBC	white blood cell (count)
WHO	World Health Organization
WK	week

1 INTRODUCTION

The two main types of inflammatory bowel disease (IBD) are ulcerative colitis (UC), which is limited to the colon, and Crohn's disease (CD), which can affect any segment of the gastrointestinal tract. In both types the most common symptoms are diarrhea and abdominal pain. Treatments for pain associated with IBD that are currently available have been borrowed from other pain conditions and are not specific for abdominal pain. They include opioids that have the potential for developing tolerance/tachyphylaxis, addiction and abuse, and potentially fatal respiratory depression, gabapentinoids that are safer than opioids but also produce adverse cognitive effects, tricyclic antidepressants that show some efficacy but can also produce somnolence, hypotension, and arrhythmias, and non-steroidal anti-inflammatories (NSAIDs; drugs such as ibuprofen and naproxen) which when administered long term may be associated with an increased risk of gastrointestinal injury/bleeding, cardiac events, hypertension, kidney injury, and death. Due to the limitations and side-effects of currently available treatments for abdominal pain, there is a need for an alternative approach to targeted pain management, especially for abdominal pain, that is poorly managed in IBD due to limited specific options. New research suggests the etiology of abdominal pain in IBD arises from dysregulation of the endocannabinoid system, offering the promise of a novel therapeutic target.

APD371 is a new chemical entity developed by Arena Pharmaceuticals, Inc. for the treatment of abdominal pain due to IBD which includes CD. APD371 is an orally available, selective cannabinoid-2 (CB_2) receptor agonist.

The CB_2 receptor is a member of a family of G protein-coupled receptors (GPCRs) that mediate the effects of several structurally related endocannabinoids such as anandamide and 2-arachidonolglycerol.[1,2] Although expression of CB_2 was initially thought to be predominantly restricted to immune cells in the periphery, recent data suggests that this receptor is also expressed in the nervous system in perivascular microglial cells and in brainstem neurons. CB_2 is up-regulated in both dorsal root ganglia and peripheral neurons following injury.[3] Preclinical data using CB_2 agonists and receptor knockout mice has validated the receptor as a potential target for the treatment of pain and neuro-inflammation.[4,5] However, the therapeutic utility of non-selective, brain penetrable cannabinoid agonists is limited by undesirable psychotropic effects associated with activation of the cannabinoid-1 receptor (CB_1). Such side-effects are not apparent upon CB_2 receptor activation. Selectivity for CB_2 activation over CB_1 activation is thus an essential feature needed for therapeutic compounds directed at CB_2.

The binding affinity, potency, and selectivity of APD371 for recombinant CB_2 receptors were determined using radioligand binding assays and GPCR signaling assays. APD371 was shown to be a full agonist of the CB_2 receptor with a K_i of 6 nM for human CB_2 and EC_{50} values between 6 nM and 8 nM for the human, rat, and dog receptors.[6,7] At test concentrations up to 10 µM, APD371 did not interact with recombinant human, rat, or dog CB1 receptors, indicating a >1000-fold selectivity across these species.[8,9]

The efficacy of APD371 in alleviating pain was evaluated in multiple rodent models of chronic pain, including the monosodium iodoacetate (MIA)-induced model of osteoarthritic joint pain, which shares similar pathophysiology with clinical osteoarthritis in humans. When administered to rats by acute and subchronic oral dosing or by continuous subcutaneous infusion, APD371 significantly suppressed allodynia induced with MIA. APD371-induced analgesia was maintained after animals were pretreated with rimonabant (CB_1 receptor antagonist) or naloxone (μ-opioid receptor inverse agonist) but not with [redacted] (CB_2 receptor antagonist), demonstrating on-target selectivity of APD371 *in vivo*.[6] Subchronic and continuous-infusion dosing with APD371 did not induce tachyphylaxis. The efficacy of APD371 in alleviating pain was also demonstrated in the paclitaxel-induced rodent model of neuropathic pain and the painful peripheral neuropathy rodent models of type 1 and type 2 diabetes.

1.1 Rationale for Proposed Clinical Study

The Cannabinoid system in IBD is dysregulated[1] and the enzymes that breakdown endocannabinoids (e.g., fatty acid amide hydrolase -FAAH) are increased in active inflammatory Crohn's disease. The enzymes that synthesize endocannabinoids (e.g., *N* -acyl-phosphatidylethanolamine-specific phospholipase -NAPE-PLD) are decreased in active inflammatory Crohn's disease and some endocannabinoids are decreased in active inflammatory IBD.

The CB_2 receptors are located in the target tissue gastrointestinal (GI) cells and local immune cells in both humans and in rodents[10] and are found in epithelial cells, immune cells, and in enteric neurons where CB_2 mediated sensitivity is observed at visceral afferent nerve endings[10].

The CB_2 receptor is increased in the ulcerative margin in Crohn's disease,[10] and cannabinoids have been shown to be effective in clinical trials for Crohn's pain. For example, cannabis has been demonstrated to induce a clinical response in patients with Crohn's disease in a prospective placebo-controlled study,[11] and treatment of Crohn's disease with cannabis in an observational study showed improvements in the pain score.[12]

Several preclinical animal studies support these observations which suggest that CB_2 activation can alleviate abdominal pain without the unwanted cognitive effects of CB1 receptor activation. A CB_2 agonist has been shown to block mesenteric nerve firing and this effect is blocked in CB_2 knockouts[13]. Similarly, a reduction of intestinal pain by probiotic *Lactobacillus Acidophophilis* (LCFM) administration in a butyrate-induced model of colonic hypersensitivity is blocked by a CB_2 receptor Antagonist[14].

Arena has completed two phase 1 studies with APD371. The aim of both studies was to assess the safety, tolerability, and pharmacokinetics of APD371 across a range of

escalating doses in healthy subjects aged 18-45. [redacted]

Based on these two safety studies in human volunteers, a safety and tolerability study in CD subjects with abdominal pain treated with maintenance doses of APD371 ranging from 25 mg to 100 mg TID for 8 weeks is proposed.

1.2 Ethics and Regulatory Considerations

The study will be conducted in compliance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), Title 22 of the United States (US) Code of Federal Regulations (CFR) Part 50 (21CFR §50 [Protection of Human Subjects], 22 CFR §56 [Institutional Review Boards (IRB)], and 22 CFR §312 [Investigational New Drug (IND)]) and applicable regulatory requirements, the study protocol, and where applicable, Sponsor and/or Contract Research Organization (CRO) Standard Operating Procedures (SOPs). The protocol and informed consent will be submitted for consideration by the appropriate IRB and written approval from the Chair or designated deputy of the IRB/IEC is required before clinical activities of the study can commence.

The IRB must be notified promptly by the Investigator of the following:

- Deviations from, or changes to, the protocol to eliminate immediate hazards to the trial subjects;
- Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial;
- All adverse events (AE)s that meet the definition of a serious adverse event (SAE);
- New information that may adversely affect the safety of the subjects or the conduct of the trial.

Any changes to the protocol will be made by means of a formal written protocol amendment. All amendments will require IRB approval before implementation except when changes to the protocol are required immediately to eliminate hazards to the trial subjects.

2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the tolerability and safety of two doses of APD371 in subjects with Crohn's Disease (CD) experiencing abdominal pain treated for up to 8 weeks.

2.2 Exploratory Objectives

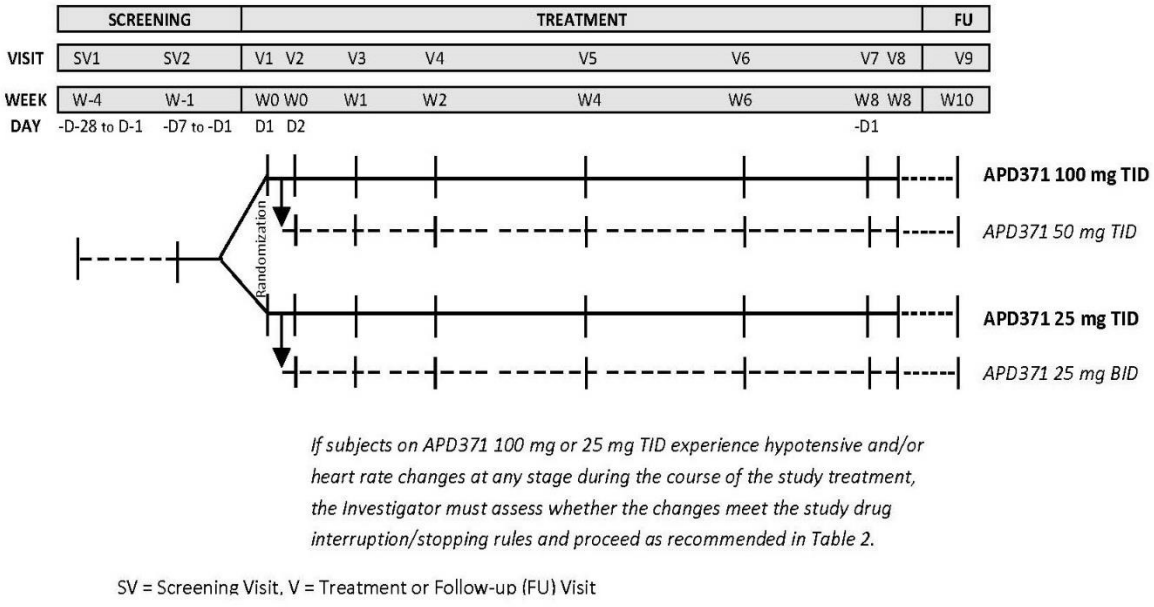
- To determine pharmacokinetic (PK) profiles (including metabolites) and average PK parameters (C_{max}, t_{max}, AUC_{0-8}) of two doses of APD371 TID.
- To assess change in abdominal pain score (APS) from pre-dose (trough) to 1.5 hr post-dose (peak) following the first of 3 daily doses of APD371; assessed daily to Day 56 and averaged weekly to Wk 8
- To assess change in average abdominal pain score (AAPS) from Screening to Wk 8 (averaged weekly to Wk 8)
- To determine the proportion of subjects who are weekly responders
- To determine the proportion of subjects who are end-of-treatment responders
- To determine the number of pain-free days per week in each treatment cohort, based on responses to the APS
- [redacted]
- [redacted]
- To assess pain medication use in each treatment cohort
- To assess the effect of APD371 treatment on reduction in CRP and other biomarkers at week 4 and week 8
- To assess the effect of APD371 treatment on reduction in fecal calprotectin at week 4 and week 8
- [redacted]
- [redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2a study in subjects diagnosed with abdominal pain due to quiescent to mildly active CD. The study design is a randomized, multi center, open-label, group comparison consisting of two cohorts dosed with APD371 in approximately 16 subjects (8 subjects in each cohort). Randomization will be stratified by sex. A study plan is provided in Figure 1.

Figure 1. APD371-004 Study plan



SV = Screening Visit, V = Treatment or Follow-up (FU) Visit

Subjects will enter a screening period of up to 28 days during which they will record their APS on a diary card. If their AAPS is >4 and they satisfy all other eligibility criteria, they will be randomized in a 1:1 ratio to receive APD371 doses of 25 mg or 100 mg capsules TID for 8 weeks (until Day 56).

Eligible subjects will be randomized and on Day 1 subjects will arrive at the study site in the early morning will undertake study evaluations and will stay overnight for safety monitoring until discharge 6 hrs after first dose on Day 2. Following the first day of treatment subjects will return for weekly safety and tolerability assessments for the first two weeks and then once every other week until the end of the treatment period. Safety assessments will include physical examinations, AE reporting, vital signs, 12-lead electrocardiograms (ECGs) and clinical laboratory tests including blood sampling.

Subjects will record their APS during Screening twice daily for at least 7 consecutive days within the Screening period (Day -28 to Day-1); early morning and late evening,

approximately (06:00 - 08:00 and 20:00 - 22:00). During treatment, subjects will record their APS three times a day on each treatment Day (Day 1 to Wk 8), before the morning dose, at 1.5 hours after the morning dose and before the evening dose.

They will also record their stool frequency on a daily basis.

There will be two serial PK assessments; one at the beginning of the study Wk 0 (Day 1, 2) and another at the end of the study Wk 8 (Day -1) and Wk 8. A single PK collection will be performed in the clinic prior to the subject's first daily dose on Wks 2, 4 and 6. A final PK sample collection will be performed at the follow-up visit will occur on Wk 10. If subjects discontinue the study (Early Termination), a final PK sample will be collected.

3.2 Study Duration and Dates

For each subject, the study duration will last a total of approximately 14 weeks consisting of a screening period of up to 4 weeks, a treatment period of 8 weeks and a follow-up period of two weeks.

Subjects will undergo Screening procedures within 29 days prior to dosing. If eligibility is confirmed, subjects will be checked-in at the study site early morning on Day 1, they will overnight at the study site on Day 1 during which they will be randomized, treated with their first dose of APD371 and assessed for safety, tolerability, PK and efficacy. They will then be allowed to return home 6 hours after the first dose of APD371 on Day 2.

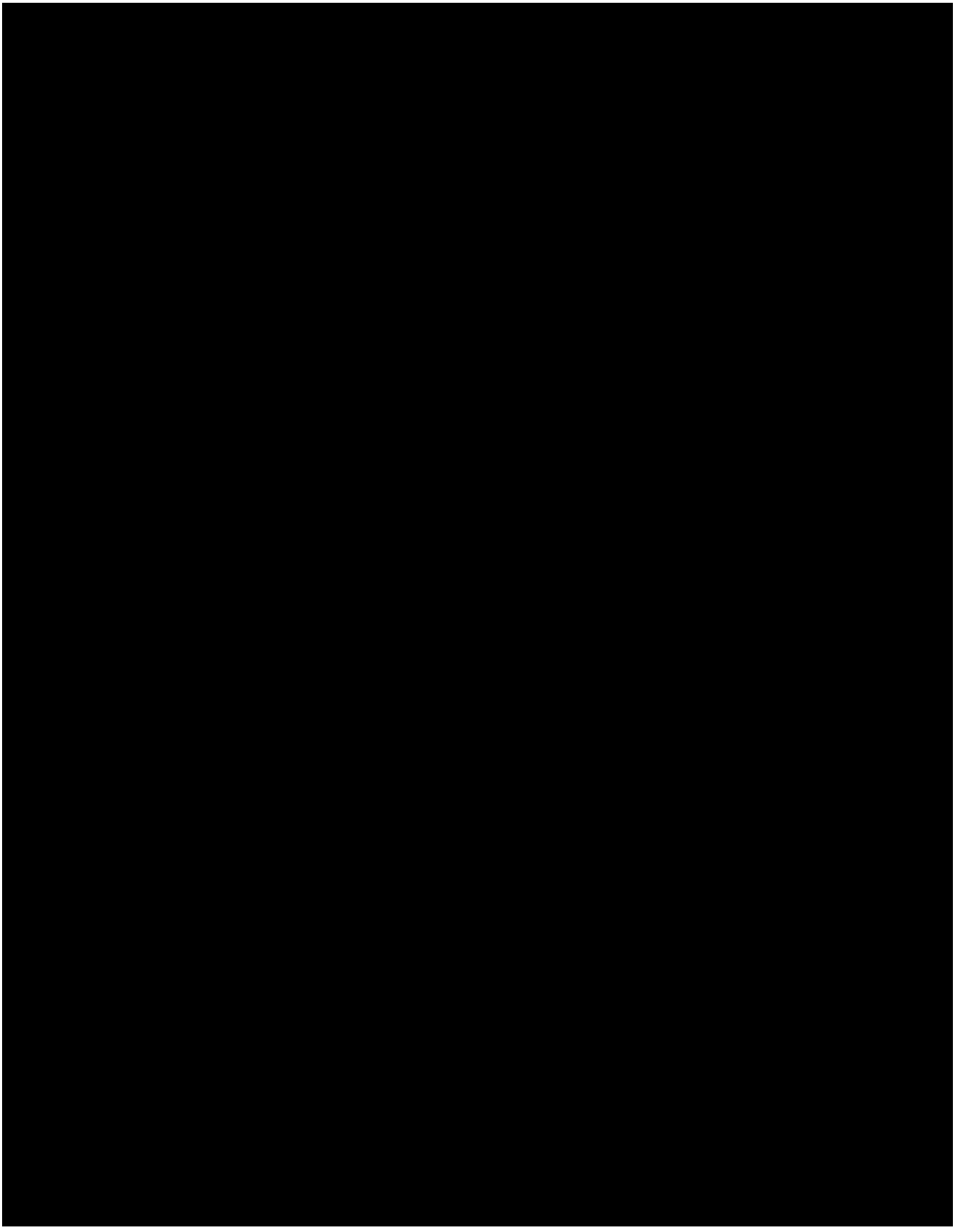
The schedule of procedures and visits for the study is provided in Table 1.

3.3 Rationale for Study Design

As described in Section 1.1, APD371 has previously been administered to healthy adult subjects at single doses of up to 400 mg and in multiple dose of up to 200 mg for 10 days TID. This proposed multiple-dose study is primarily designed to evaluate the safety, tolerability, and PK of two oral doses of APD371 in patients with CD with abdominal pain in order to provide reliable safety, tolerability, and PK data that will guide drug dose and therapeutic regimen choices in subsequent clinical studies.

[redacted]

[redacted]



[redacted]

3.4 Study Population

The study population will consist of adult male and female subjects aged 18-80 years who are diagnosed with abdominal pain due to quiescent to mildly active CD, as defined by an AAPS ≥4 over one week (0 [no pain] to 10 [worst possible]), with minimal intestinal inflammation, confirmed with a total simple endoscopic score (SES-CD) score < 10 or ileal SES-CD < 4 or fecal calprotectin (FCP) < 500. Endoscopy results obtained within 4 weeks prior to screening may be utilized.

Eligible subjects must meet all entry criteria prior to being randomized to receive study medication as outlined below.

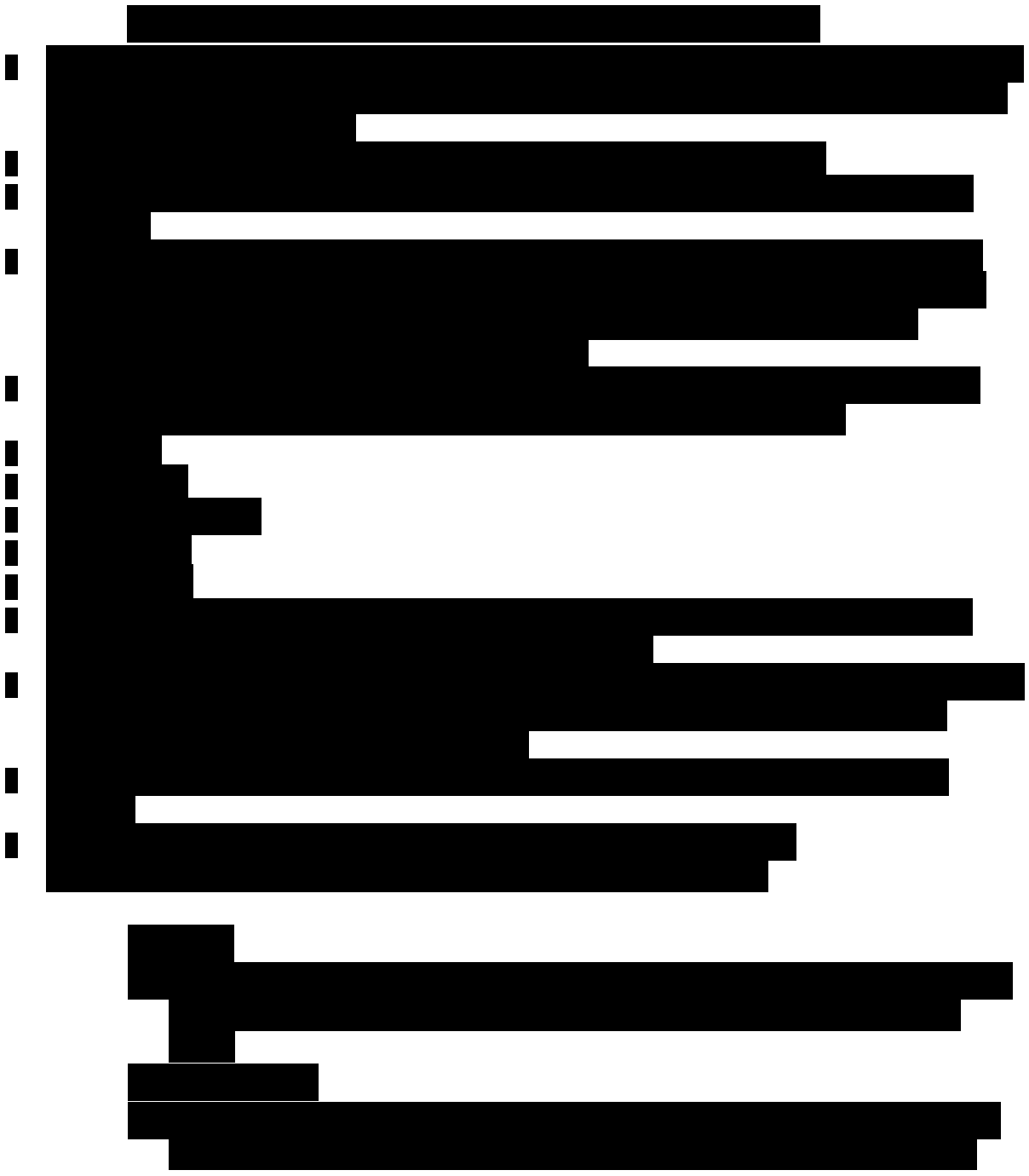
Exceptions to eligibility criteria will not be granted by the Investigator unless approved in advance by the Sponsor.

3.5 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

[redacted]

6. A clinical diagnosis of CD for at least 3 months prior to screening corroborated by prior endoscopic and histopathologic documentation consistent with CD.
7. Quiescent to mildly active inflammatory CD defined with a total SES-CD score of < 10 or FCP < 500 mcg/g within 4 weeks before Screening
8. Moderate to severe abdominal pain as defined by average abdominal pain score (AAPS) of ≥4 points on 7 consecutive days of the screening period up to Day -2. AAPS will be based on the 11-point numeric rating scale where 0 (no abdominal pain) to 10 (worst possible abdominal pain)



[redacted]

3.6 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

General Exclusion Criteria

[redacted]

2. Female subjects who are lactating or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 prior to study drug administration

[redacted]

[redacted]

8. Recent history (within 6 months of screening visit) of cerebrovascular disease, Acute Coronary Syndrome, Cerebrovascular accident, Transient ischemic attack, Myocardial infarction, unstable angina

[redacted]

13. Other significant chronic pain conditions that in the opinion of the Investigator may influence the abdominal pain score

[redacted]

Gastrointestinal Exclusion Criteria

[redacted]

16. Extensive colonic resection, subtotal or total colectomy

[redacted]

18. History of >3 small bowel resections or diagnosis of short bowel syndrome or who have undergone bowel resection within 6 months prior to randomization

[redacted]

[redacted]

Infectious Disease Exclusion Criteria

31. Chronic active hepatitis B within the last year (unless shown at the time of study entry to be hepatitis B antigen negative) or any history of hepatitis C

[redacted]

34. Evidence of current GI infection (bacterial or parasitic) or significant infection within 45 days of Screening

[redacted]

4 STUDY TREATMENTS

4.1 Test Article

The Sponsor will provide adequate supplies of APD371 25 mg, 50 mg and 100 mg active drug capsules. APD371 25 mg and 100 mg strengths will have the same appearance, as will 50 mg strength If subjects in the 100 mg cohort require a 75 mg dose they will be administered one 50 mg and one 25 mg capsule, and a 50 mg dose will include dosing of one 50 mg capsule only.

4.2 Treatments Administered

[redacted]

APD371 drug substance (active) and bulk drug product (capsules) were manufactured under Current Good Manufacturing Practice compliance at Arena Pharmaceuticals, San Diego, CA. Bulk drug product will be packaged and labeled [redacted] and shipped to participating clinical study sites prior to the study start.

4.3 Packaging, Labeling and Storage

25 mg and 100 mg APD371 capsules will be packaged 30 count in 60-cc HDPE bottles with a heat induction seal and child resistant screw cap. Each subject will be provided with 8 bottles of APD371 packaged drug product for the duration of the study, two bottles being dispensed on Day 1, Day 15, Day 29 and Day 43, respectively. If subjects in the 100 mg cohort are titrated down to a 50 mg dose they may receive additional bottles.

The 50 mg APD371 capsules will also be packaged 30 count in 60-cc HDPE bottles with heat induction seal and child resistant screw cap.

Subjects returning for assessment at the end of Wks 2, 4, 6 should take their morning APD371 medication from their newly dispensed bottles for treatment periods Wks 3-4, 5-6 and 7-8, respectively.

4.4 Test Article Accountability

The Investigator will maintain accurate records of the receipt of all study medication. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Study medication will be reconciled by the Sponsor monitor or contracted designee. The Investigator agrees to provide sufficient access to study medication as required for the reconciliation process to be completed in a timely fashion.

4.5 Investigational Product Retention at Study Site

At completion of the study, all study medication will be reconciled by the Sponsor's monitor and then returned at the direction of the Sponsor to be retained or destroyed according to applicable USA regulations. Prior to any action being taken with study medication after the study is completed, the Investigator will contact the Sponsor Contact listed in the Synopsis for approval of such action.

4.6 Dosage and Administration

Investigational product will be dispensed to the subjects under the supervision of the Investigator or his/her designee as determined by the randomization schedule. Dispensing will occur every two weeks at Wks 0, 2, 4 and 6.

Subjects should not crush, break, chew, or dissolve the capsules. There are no food restrictions around dosing with the exception of ingestion of grapefruit juice or prune juice.

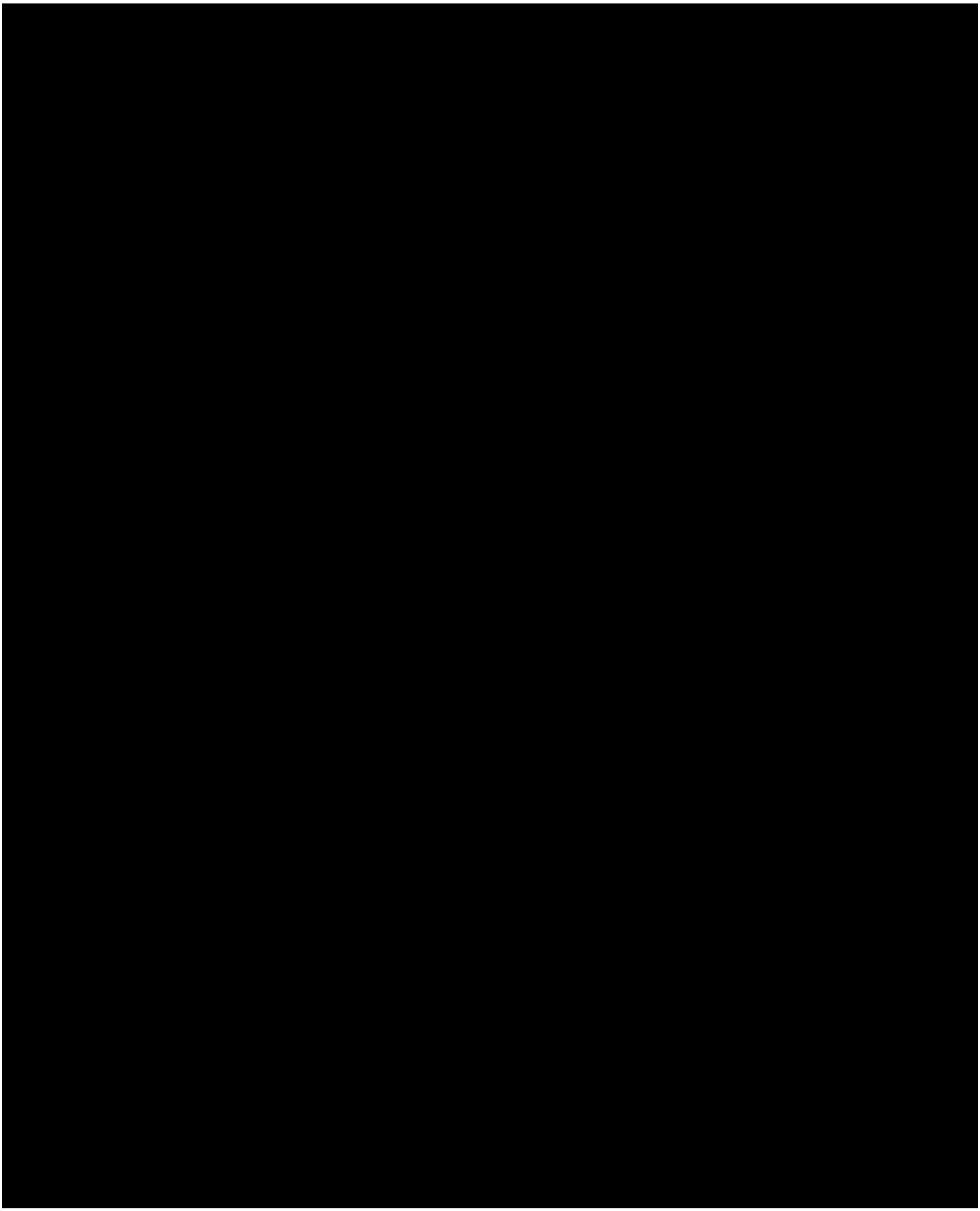
For each of the planned dose cohorts (APD371 25 mg and 100 mg) subjects will self-administer study treatment TID [redacted] on Days 1 to 56. Subjects will be requested not to take their morning dose of study medication on the day of a planned study visit schedule [redacted] until instructed to do so by the Investigator or his/her designee. There will be a total of 8 subjects randomized to each dose cohort.

4.6.1 Dose Interruption and Stopping Rules

Adverse Events (AEs) of supine SBP decrease, supine DBP decrease, postural BP decrease, HR increase and HR decrease will be closely monitored. If such an AE occurs in patients taking the study drug, the Investigator must assess whether the AE meets the study drug interruption/stopping rules and proceed as recommended in the below table.

If the study drug is interrupted due to the criteria described in the table, the patient will be evaluated as part of an unscheduled visit to assess their status and the Investigator will determine next course of action. If necessary, subsequent visits to assess the outcome of the event will be scheduled. Once the re-start criteria are met, study drug will be re-started under medical supervision. Additional visits may be scheduled at the investigator's discretion to more closely monitor patient status.

Any patient that develops postural hypotension will not be discharged from the study site with study drug until the event completely resolves and safety and tolerability of the reduced dose in the patient is confirmed.



4.7 Method of Assigning Subjects to Treatment Groups

A computer-generated block randomization schedule generated by the Sponsor. or a nominated designee will randomly assign [redacted] in a 1:1 ratio to either the APD371 25 mg or APD371 100 mg treatment groups. The randomization code will be held by the hospital pharmacist who will use this to sequentially randomize eligible subjects.

4.8 Randomization and Blinding

4.8.1 Randomization

Subjects will be randomized after the Investigator has verified that they are eligible per criteria in Section 3.5 and Section 3.6. Subjects will then be enrolled into this study and assigned to APD371 25 mg TID or 100 mg TID according to a randomization schedule. Subjects will be randomized based on gender.

Randomization will take place across all study sites using a centralized master list held by the study manager. When a site is ready to enroll a subject, they will contact the study manager to get the appropriate dose group assignment and unique subject number. The subject's identification number will be used on all of that subject's case report forms (CRF). Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment. All subjects must start treatment within 1 week of randomization.

4.8.2 Blinding

For each dose cohort, the Sponsor, CRO, Study safety medical monitors, subjects, and personnel involved with the conduct of the study will be unblinded to the identity of study medication.

4.8.3 Maintenance of Randomization Codes

All personnel directly related to this study (i.e., Investigators, site personnel, monitors, CRO personnel, Sponsor personnel) will remain unblinded.

4.9 Concomitant Medications

All concomitant medications (over-the-counter [OTC] and prescribed) that are taken by subjects and all procedures that are performed during the Screening period and during the study will be documented in the electronic case report form (eCRF) with start date/time and stop date/time, if known.

Stable doses of non-narcotic prescription medications required for treatment of current medical conditions other than pain (e.g., hypertension, thyroid disease, diabetes) may be continued during the screening and study period. Doses may be adjusted as appropriate per usual standards of care.

4.9.1 Not permitted

- Hormonal contraceptives for pain relief within 30 days prior to the Screening Visit, during the Screening period, and for the duration of the study.
- Moderate or strong CYP3A4/5 inducers or inhibitors

4.9.2 Permitted

- Pain rescue medications during screening or the treatment period including:
  - For an inflammatory flare: prednisone at a dose of 40 mg orally daily, to be tapered by 5 mg per week.
  - For severe pain: hyoscyamine at a dose of 0.25 mg tid prn pain
- Pain relief medications such as NSAIDs, narcotic analgesics, or acetaminophen/paracetamol given at stable doses for at least 2 weeks prior to screening and for the duration of the study
- Stable dose of oral or topical 5-ASA for at least two* weeks prior to randomization; stable dose to be maintained on the 5-ASA compound at a constant dose at least through end of study
- Mesalamine or sulfasalazine for at least 4 weeks prior to randomization
- Azathioprine or 6-MP, or methotrexate for at least 8 weeks prior to screening
- Oral corticosteroid therapy (prednisone at a stable dose of 30 mg/day, budesonide at a dose ≤ 9 mg/day, or equivalent steroid) provided that the dose has been stable for the 2 weeks immediately prior to screening or for the two weeks immediately prior to randomization if corticosteroids are being tapered
- Dose regimens within the ranges approved by the FDA and stable for at least 8 weeks prior to screening for the following monoclonal anti-inflammatory drugs:
  - Infliximab
  - Adalimumab
  - Certolizumab pegol
  - Ustekinumab
  - Vedolizumab
- Probiotics (e.g., *Culturelle, Saccharomyces boulardii*) provided that the dose has been stable for the 2 weeks immediately prior to randomization
- Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
- Antibiotics used for the treatment of CD (i.e., ciprofloxacin, metronidazole) provided that the dose has been stable for the two weeks immediately prior to randomization and will remain stable throughout study participation

4.10 Restrictions

4.10.1 Fluid and Food Intake

There are no food restrictions around dosing with the exception of grapefruit and prune juice. Subjects will be provided standardized meals (breakfast, lunch, dinner, snacks) per the Investigating site's SOPs while housed in the clinic. 240 mL of water will be administered with study medication in the clinic at the time of dosing on Day 1 and Week 8 when the PK profile will be obtained. Water may be provided at all other times as needed.

4.10.2 Activity

Subjects will not engage in strenuous activity at any time during study participation.

5 STUDY PROCEDURES

5.1 Informed Consent

For any subject to be screened the Investigator will obtain a signed Informed Consent Form (ICF). The ICF must be reviewed and approved by the Investigator's designated IRB and by the Sponsor. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

All subjects will be informed in writing of the nature of the protocol and investigational therapy and its possible hazards, and of their right to withdraw at any time, before they will be permitted to sign the ICF. The subject's medical record should contain written documentation indicating that informed consent was obtained.

5.2 Medical History

During the Screening Visit, a complete medical history and a social history, including smoking, caffeine, and alcohol use, will be collected by subject interviewer. Concomitant medications, recent blood donations, illnesses, and participation in other investigational drug studies will also be recorded. A review of the subjects screening medical history will be performed at the time of presentation on Day 1 (pre-treatment) to update findings including the requirement for a AAPS ≥ 4 (from a subject diary) and to document any pre-treatment AEs.

5.3 Physical Examination

Body measurements (height and weight) will be taken at the timepoints indicated in the Schedule of Events (Table 1). A complete physical examination including weight will be performed at the initial Screening visit. Abbreviated physical examinations (includes body weight and evaluation of changes to previously observed abnormal findings) will be completed at the time of presentation to the clinic prior to initial dose administration, at the Follow-up Visit Wk 10 and at early termination noting changes in any body system since the previous examination.

5.4 Vital Signs

Supine blood pressure, pulse rate, temperature, and respiratory rate will be measured after the subject has been resting in the supine position for 5 minutes at the timepoints indicated in the Schedule of Events (Table 1). All once daily vital sign assessments are take place before morning dosing or equivalent times when not dosed at approximately 08:00. Vitals signs will be measured after any 12-lead ECG measurement but prior to any blood draw that is scheduled at the same timepoint. Pulse rate will be measured with a pulse oximeter.

Active-Standing Test

The Active-Standing Test[15] that measures BP and heart rate before and after changing the position from supine to standing will also be performed. The test will be performed by the

bedside by measuring blood pressure (BP) and heart rate after the subject has been resting in the supine position for 5 minutes and then after 1 and 3 minutes of standing.

The test will be performed at the following timepoints:

- Day 1: pre-dose, 2, 4, 6, 8 and 10 hours after first dose
- Day 2: 2, 4 and 6 hours after the first dose
- Week 1, 2, 4, 6, and 8 visits 2 hours after the first dose

The active-standing test will be performed if subjects discontinue the study (Early Termination).

5.5 Abdominal Pain assessment

5.5.1 Abdominal Pain Score and Average Abdominal Pain Score

The abdominal pain score (APS) is a PRO using an NCR rating scale which is recorded in a subject diary. The 11 point NCR scale ranges from 0 [no abdominal pain] to 10 [worst possible abdominal pain] will be recorded by subjects in a diary as follows;

During Screening. Twice daily for at least 7 consecutive days within the initial Screening period (Day -28 to Day-1), at the following times;

1. Early morning, approximately 06:00 - 08:00
2. Late evening, approximately 20:00 - 22:00.

The Screening assessment of AAPS will be based on the average of the last (most recent) 7 days of morning and evening diary records within the screening period.

During Treatment. Three times a day on each treatment Day (Day 1 to 56) at the following times;

1. Before the morning dose and before any other morning dose study procedures
2. Approximately at 1.5 hours after the morning dose
3. Before the evening dose.

Note: Subjects will also be required to complete the diary before their first morning dose on Wk 0 (Day 1), and at the End-of-Treatment Visit at Wk 8 in the early morning (06:00 - 08:00). If a subject discontinues the study, Early Termination, the APS score will be assessed.

The average abdominal pain Score (AAPS) is the average of the APS score over each weekly assessment period (Wk 1 to Wk 8). These average scores will be determined automatically in the eCRF from the diary cards records inserted into the eCRF.

If a subject changes dose during the course of the study, they will maintain their daily APS scoring.

[redacted]

5.8 Electrocardiography

5.8.1 12-lead Safety Electrocardiograms

Safety 12-lead ECGs will be recorded from an ECG machine and will be printed and reviewed on site by the Investigator or designee. Typically, all 12-lead ECGs will be obtained as single tracings, with the exception of the pre-treatment ECG obtained on Day -1, which will be a triplicate recording. If a 12-lead ECG shows an abnormality, then two additional ECGs should be obtained as soon as possible for confirmation. Abnormalities of particular interest include increased PR or corrected QT (QTc) intervals, either absolute prolongations or clinically noteworthy increases from baseline values.

Electrocardiograms will be recorded with subjects resting in the supine position. Subjects will have been in the supine position for 10 minutes prior to ECG recording, which will be performed prior to any vital sign measurement and/or blood draw that may be scheduled at the same time point.

Intervals to be provided on the confirmed read for each 12-lead ECG are: RR, PR, QRS, QT, QTc, QTcB, and QTcF. All interval measurements will be made from a single lead (lead II). If lead II is unsuitable for measurement, the following lead progression will be used: I, V4, V5, V3, any suitable lead.

The Investigator will be responsible for review and interpretation of 12-lead ECGs on site and for determining if the ECG is normal, abnormal clinically insignificant, or abnormal clinically significant. Findings will be documented in the eCRF. This information will be used in the ongoing safety review during the conduct of the study.

A 12-lead ECGs will be collected at Screening; at the start of Wk 0 (Day 1) and at Wk 8 (Day -1) prior to and 1.5 hours after the first daily dose; and at the Follow-up Visit at Wk 10. 12-lead ECGs will be collected prior to any vital sign measurement and/or blood draw that is scheduled at the same time point.

5.9 Clinical Laboratory Tests

Protocol-required laboratory testing will be collected during initial screening to determine eligibility. Clinical laboratory tests will be repeated at pre-treatment on Wk 0 (Day 1), pre-treatment at the end of Wk 4 and 8 (Day -1), at the Follow-up visit (Wk 10) and in the event of early termination.

All details regarding clinical laboratory sample collection, preparation, and shipment are included in the laboratory manual provided by the local or central laboratory and the PK sample collection manual provided by the Sponsor.

In the event of abnormal clinical laboratory values, the Investigator will make a judgment whether or not the abnormality is clinically significant.

5.9.1 Laboratory Parameters

Clinical laboratory tests will include the following:

Serum Chemistry
Aspartate transaminase
Alanine transaminase
Alkaline phosphatase
Gamma-glutamyl transferase
Bicarbonate
Magnesium
Sodium
Potassium
Chloride
Calcium
Inorganic phosphate
Glucose
Amylase
Bilirubin (total)
Creatinine
Blood urea nitrogen
Total protein
Albumin
Creatine kinase and MB subtype (if elevated)
Lactate dehydrogenase
Lipase
Total Cholesterol
Triglycerides

Hematology
White blood cell count (WBC)
Red blood cell count
Hemoglobin
Hematocrit
Mean cell volume
Mean cell hemoglobin
Platelet count
Differential WBC

Urinalysis
Appearance
Color
Specific gravity
pH
Protein
Glucose
Ketones
Leukocyte esterase
Blood
Bilirubin
Urobilinogen

Coagulation
Prothrombin time
Activated partial thromboplastin time

Other
Serum/urine pregnancy test (females only), Thyroid function tests [(TSH, T4, and free T4) - Screening only], Hs CRP

5.9.2 Virology

Human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) Screening tests will be performed at the Screening Visit only.

5.9.3 Drugs of Abuse Screen

A drugs of abuse screen will be completed according to the laboratory manual provided by the local or central laboratory and according to the Schedule of Events (Table 1).

The drugs of abuse screen will include cotinine, alcohol, amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.

5.9.4 C-reactive Protein and other Biomarkers

Separate blood samples (a total of 20 mL) for high sensitivity analysis of CRP will be collected at screening, pre-dose at Day 1, Week 4 and Week 8 (Day -1), and Week 10 (Follow-up). [redacted]

5.9.5 Sample Collection, Storage, and Shipping

Blood samples for hematology, serum chemistry, coagulation, HIV and hepatitis screens, drugs of abuse screens, and serum hCG will be collected according to the laboratory manual provided by the local or central laboratory and according to the Schedule of Events (Table 1).

5.9.6 Blood Volume

Total blood volume for clinical laboratory tests will be approximately 205 mL.

5.10 Stool Sample

A stool sample will be collected during screening and at Weeks 4 and 8 (Day -1) for the analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity.

5.11 Pharmacokinetic Assessments

Pharmacokinetic samples for the assay of APD371 and metabolites M1 [redacted], M2 [redacted], and M4 [redacted] will be collected will be collected at the visit time points indicated in the Schedule of Events (Table 1) and detailed in Pharmacokinetic sampling, Table 3.

Table 3. Pharmacokinetic sampling

Study Day	Blood sampling assessments*
Wk 0 (Day 1)	Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9 and 10 hours post first daily dose.
Wk 0 (Day 2)	24 hours post dose first daily dose on Day 1

Wk 2	Prior to first daily dose
Wk 4	Prior to first daily dose
Wk 6	Prior to first daily dose
Wk 8 (Day -1)	Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose).
Wk 8 (End-of-Treatment)	8 hours post dose first daily dose on Wk 8 (Day-1)

* Allowable windows for sample collection:

- time points up to 4 hours: ± 5 mins
- time points after 4 hours: ± 15 mins

Approximately 4 mL of blood will be collected at each timepoint. Blood samples will be processed for collection of plasma fractions for determination of APD371 and metabolite M1 [redacted], M2 [redacted], and M4 [redacted] plasma concentrations. In addition, a blood sample for PK analysis should be collected if possible at the time of any SAE.

Total blood volume collected for PK samples will be approximately 100 ml.

A PK sample collection manual will be provided to instruct on the type of anticoagulant to be used, the material supplies, and the sample processing, storage, and shipping procedures.

Plasma samples will be stored at the local laboratory and shipped to the analytical lab for analysis.

At the end of each cohort, biological samples (e.g. plasma) should be packed, labeled, and shipped on dry ice to the designated bioanalytical CRO for analysis. Samples should be shipped in accordance with the hospital SOPs or guidance, and only on a Monday, Tuesday or Wednesday, to minimize the possibility of the samples being in transit over a weekend. If duplicate samples are being shipped, confirmation should be obtained of arrival at the analytical lab of one set of samples before the second set is shipped.

5.12 Adverse Events Assessments

Adverse events will be recorded and reported in accordance with ICH GCP and 22 CFR§312.32. The definitions of AEs and SAEs will be as given in the ICH Topic E2A, ICH Guideline "Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting."

5.12.1 Adverse Event Reporting

Subjects will be instructed that they may report AEs at any time. Adverse events will be regarded as 'pre-treatment' if they occur between the Screening Visit and the time of administration of the first dose of study medication. All events reported following study medication administration will be recorded as TEAEs.

Monitoring of AEs will be continued up to 30 days after the last study medication administration. In the event that an AE is not resolved or stabilized by this time, the Sponsor in consultation with the Investigator will decide whether to continue to monitor the AE or close-out the event in the database if no further follow-up is necessary.

For this study, an AE is defined as: "Any untoward medical occurrence in a study subject administered any dose of study medication (APD371) and which does not necessarily have to have a causal relationship with this treatment." An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study medication, whether or not related to the product. AEs can be any of the following:

- Unfavorable changes in general condition;
- Subjective or objective signs/symptoms;
- Concomitant disease or accident;
- Clinically relevant adverse changes in laboratory parameters observed in a subject in the course of a clinical study;
- Pre-existing conditions which worsen in severity or frequency or which have new signs/symptoms associated with them.

Adverse events may be elicited by asking the question: "Since you were last asked, have you felt unwell or different from usual in any way?" Any adverse or unexpected events, signs and symptoms, will be fully recorded on the AE Form including details of severity, onset, duration, outcome and relationship to the drug as determined by the Investigator. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (e.g., self-limited fever, runny nose, cough, and scratchy throat should be captured as an upper respiratory infection rather than by the individual signs and symptoms). Adverse events may also be reported at any time. The type and duration of follow-up of subjects after AEs will be documented.

5.12.2 Serious Adverse Events and Expedited Reporting of Adverse Events

An SAE is any untoward medical occurrence that at any dose results in the following outcomes:

- Death;
- Is life-threatening;
- Required/prolonged hospitalization;
- Disability/incapacity;
- Congenital anomaly/birth defect;
- Important medical event.

All SAEs will be captured from the time of Screening to 30 days after the dose of study drug, and will be monitored until resolution or stabilization.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such a medical event includes allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias, or convulsions that do not result in in-subject hospitalization, or the development of drug dependency or drug abuse.

Elective hospitalization and/or surgery for clearly pre-existing conditions (for example a surgery that has been scheduled prior to the subject's entry into the study) will not be reported as an SAE. All other hospitalizations, including elective hospitalizations for any condition that was not pre-existing, will be reported as a SAE.

Any AE considered serious by the investigator or which meets SAE criteria must be reported to PPD Pharmacovigilance (PVG) the remote data capture (RDC) system within 24 hours from the time study site personnel first learn about the event. The following contact information is to be used for SAE reporting:

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PPD Medical Affairs/Pharmacovigilance
PPD PVG Hotline: [redacted]
PPD PVG Fax line: [redacted]

In the event that the RDC entry is not possible (e.g., system failure or access problems), the study site should complete the paper SAE report form and fax the form to PPD PVG within 24 hours of awareness of the event. The RDC system should be updated as soon as it is available.

A full description of every serious adverse event will need to be provided to PPD PVG (this may be supported by source documentation such as laboratory reports or a discharge summary should the patient be hospitalized).

Other situations as defined in ICH Topic E2A, ICH Guideline, 22 CFR§ 312.32, and EU Volume 10, may also qualify for expedited reporting. In these situations, the process will be as detailed for SAEs above:

- SAEs which could be associated with the trial procedures;
- SAEs and AEs of special interest including Suspected Unexpected Serious Adverse reactions (SUSARs) that could materially influence the benefit-risk assessment of a medicinal product, such as: a clinically important increase in the rate of a serious suspected adverse reaction over that listed in the Investigator Brochure.

Subjects who become pregnant during the study will be discontinued immediately. Although not considered an SAE or AE, pregnancies occurring during the period of study drug administration (Day 1 to Day 11) until 30 days after the last dose of study drug should be reported to the Sponsor Contact and IRB in the same manner as an SAE.

Pregnancies will be followed every trimester through the first well baby visit. For female partners who become pregnant by male study subjects during the course of the study, reasonable efforts will be made to collect information on the partner's pregnancy through the first well baby visit as provided by the male study subject.

5.12.3 Assessment of Adverse Event Severity

The severity of each AE will be assessed at onset by a nurse and/or physician. When recording the outcome of the AE the maximum severity of the AE experienced will also be recorded. The severity of the AE will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03[17] definitions, listed below:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*;

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**;

Grade 4: Life-threatening consequences; urgent intervention indicated;

Grade 5: Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

5.12.4 Assessment of Adverse Event Relationship to Study Medication

The relationship of an AE to investigational product(s) will be classified using modified World Health Organization (WHO) criteria (Edwards and Biriell, World Health Organization Collaborating Centre for International Drug Monitoring 1994) as follows.

Related: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition; or an event that could also be explained by concurrent disease or other drugs or chemicals where information on drug withdrawal may be lacking or unclear.

Not related: a clinical event, including laboratory test abnormality, with sufficient evidence to accept that there is no causal relationship to drug administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; proof of other cause; etc.); or an event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

5.12.5 Assessment of Adverse Event Outcome

Outcome of AEs will be defined based on ICH Topic E2B, ICH Guideline.

- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Not Recovered/Not Resolved
- Fatal
- Unknown

5.12.6 Action Taken for Adverse Event

Action taken for AEs will be documented in the eCRF according to the following:

- Concomitant medication or other treatment
- Withdrawal from study

5.12.7 Action Taken for Study Drug

Any action taken with study drug will be defined based on ICH Topic E2B, ICH Guideline and documented in the eCRF according to the following:

- Drug Withdrawn
- None (not changed)
- Dose Reduced
- Unknown
- Not Applicable

5.12.8 Collection of Extra Laboratory Samples/Investigations

In the event of a clinically important AE, a suitable sample may be collected for drug assay or for additional laboratory tests. The Investigator must ensure that the sample is properly labeled and stored. The Investigator and others responsible for care of the subjects should institute any supplementary investigations of significant AEs based on the clinical judgment of the likely causative factor. This may include seeking a further opinion from a specialist in the field of the AE. The Sponsor (or designee) may suggest special tests based on expert advice.

5.12.9 Follow-up of Adverse Events Present at Last Scheduled Study Visit

Adverse events present at the last study day (Wk8) that require follow-up or a repeat laboratory test will be assessed at the last Follow-up visit (Wk 10) and if still present will

continue to be followed-up for 30 days after the last day of study treatment, according to the CRO's procedures for AE follow-up.

Adverse events that have not resolved or stabilized at 30 days after the last subject's last study dose, will be reviewed with the Sponsor on an individual basis to determine if the database will be locked and subsequently updated once the events of ongoing AEs are resolved or if database lock will be held.

5.13 Concomitant Medications and Procedures

All medications (OTC and prescribed) that are taken by subjects and all procedures that are performed during the Screening period and during the study must be recorded in the eCRF with start date/time and stop date/time, if known.

5.14 Removal of Subjects from the Trial or Study Drug

The study will be terminated early if, in the opinion of the Sponsor, Investigator, or IRB, an unacceptable risk to the safety and welfare of subjects is posed by the continuation of the study in light of review of the key safety data.

Subjects will be informed that they are free to withdraw from the study at any time for any reason should they so wish. The Investigator may remove a subject if, in his/her opinion, it is in the best interest of the subject. A subject may be withdrawn from the study for any of the following reasons:

- Deviation/noncompliance with the protocol;
- A serious or intolerable AE occurs;
- The Sponsor or Investigator terminates the study; or
- Withdrawal of consent - any subject may withdraw his/her consent from the study at any time. The Investigator should make a reasonable attempt to document the specific reason why consent is withdrawn.

5.14.1 Handling of Withdrawals

Although a subject is not obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subject's rights. If there is a medical reason for withdrawal, the subject will remain under the supervision of the study physician until in satisfactory health. Reasonable efforts will be made to contact a subject who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

If a subject is prematurely discontinued from this study, the procedures described in Section 6.4 must be followed.

5.14.2 Replacements

Randomized and treated subjects who discontinue the study will not be replaced. Subjects who are randomized but are not treated or are withdrawn due to non-compliance or a major protocol deviation may be replaced.

5.15 Allowable Visit and Procedure Windows

The following are allowable windows for study visits and procedures:

- Study visits:
  - Wks 2, 4, 6, 8 and 10 (Follow-up): ± 2 days

- Vital signs and Active-Standing Test:
  - Pre-dose timepoint: - 15 mins
  - Post-dose timepoints: ± 15 min

6 STUDY ACTIVITIES

6.1 Screening Visits Wk -4 to Wk -1 (Days –28 to -1)

Subjects with a signed ICF and undergoing planned screening will be allocated a sequential 4 digit screening number starting X001 by the investigator or designee.

Within 29 days and up to Day -1 before administration of the first dose of study medication, all Screening activities necessary to define eligibility for entry into the study will be conducted and consist of the following**:**

- Collection of demographic data (sex, age, race/ethnicity)
- Completion of medical and social history (to include tobacco, alcohol, and caffeine use)
- Body measurements
- Physical examination (complete examination) at initial screening visit
- Abbreviated physical exam (includes body weight and evaluation of changes to previously observed abnormal findings) at final screening visit
- Vital signs
- 12-lead ECG
- Virology screen (HBsAg, HIV antibodies, and HCV antibodies*)*
- Drugs of abuse screen
- Serum hCG pregnancy test (females only) at the initial screening visit
- Urine pregnancy test (females only) at the final screening visit
- Clinical laboratory tests to include hematology, serum chemistry, coagulation, HsCRP, thyroid function tests (TSH, T4, and free T4 at initial Screening visit only) and urinalysis**.**
- Stool sample for fecal calprotectin
- Total Simple Endoscopic Score (SES-CD) score < 10 or FCP < 500 mcg/g. Endoscopy results obtained within 1 month prior to screening may be utilized
- Abdominal Pain Assessment scores to be conducted on at least 7 consecutive days twice daily
- [redacted]
- Monitor and document any pre-treatment AEs
- Concomitant medications assessment

At the end of Day -1 all subjects will have undergone screening assessments and final confirmation or otherwise of eligibility.

Subjects who are deemed eligible for the study will be randomized and then report to the study site on the morning of Wk 0 (Day 1) ready for an overnight stay. They will undergo pre-treatment assessments and then the first dose of study medication will be given in the morning at the study site.

6.2 Screening Failures

A Screening failure is defined as a subject who has signed the ICF, but does not meet all the entry criteria as outlined in this protocol and has not been randomized or received study medication. A Screening log will be maintained by the Investigator or designee, indicating the reason for the Screening failure.

6.3 Treatment Period Wk 0 to 8 (Day 1 to Day 56)

Subjects will self-administer APD371 TID for 56 consecutive days according to the randomization schedule. Study procedures will be conducted at the time points indicated in the Schedule of Events (Table 1) and include the following assessments;

6.3.1 Wk 0 (Day 1) Pre-treatment

- Vital signs and Active-Standing Test
- 12-lead ECG
- Abdominal Pain Score within 60 min prior to first morning dose
- PK Blood sample for the analysis of APD371 and metabolite plasma concentrations will be collected within 60 min prior to the first morning dose
- Clinical laboratory tests (to include hematology, serum chemistry, coagulation, HsCRP, [redacted] and urinalysis)
- [redacted]
- Record AEs
- Record concomitant medications
- Study medication will be dispensed before the first dose (Week 1-2)

6.3.2 Wk 0 (Day 1) Post treatment

- Vital signs and Active-Standing Test
- 12-lead ECG at 1.5 hours after initial Day 1 dose
- Abdominal Pain Score at 1.5 hr after first morning dose

- PK Blood samples for the analysis of APD371 and metabolite plasma concentrations 0.5, 1, 2, 4, 6 and 8 hr after the first daily dose (prior to second daily dose) and 9 and 10 hr.
- Record AEs;
- Record concomitant medications

6.3.3 Wk 0 (Day 2)

- Vital signs and Active-Standing Test
- Abdominal Pain Scores
- A PK Blood sample for the analysis of APD371 and metabolite plasma concentrations will be collected 24 hr post first daily dose on Day 1 and before the first daily dose on Day 2
- Record AEs
- Record concomitant medications

6.3.4 Wk 0 to 8 (Day -1) (Days 1 to 56)

- Abdominal Pain Scores will be determined three times a day.

6.3.5 End of Wk 1, 2, 4, 6

- Vital signs and Active-Standing Test
- Abdominal Pain Scores
- PK blood samples will also be taken immediately before the first daily dose (**Week 2, 4 and 6 only**)
- Clinical laboratory tests (to include hematology, serum chemistry, coagulation, HsCRP, [redacted] and urinalysis) prior to first morning dose, **Wk 4 only**
- Study medication will be dispensed before the first daily dose for Wk 0 (Day 1), 2, 4 and 6
- Compliance will be assessed based on all returned bottles and treatment duration at Wks 2, 4, 6 and 8
- Record AEs
- Record concomitant medications
- Stool sample for fecal calprotectin (**Wk 4 only)**
- [redacted]

It is important that subjects do not take their morning study medication prior to instruction by the investigation team on Wk 0 (Day 1 and Day 2), 2, 4 and 6.

6.3.6 Wk 8 (Day -1)

- Vital signs and Active-Standing Test
- 12-lead ECG
- Clinical laboratory tests (to include hematology, serum chemistry, coagulation, HsCRP, [redacted] and urinalysis) prior to first morning dose
- Abdominal Pain Score
- PK Blood samples for the analysis of APD371 and metabolite plasma concentrations will be collected prior to and at 0.5, 1, 2, 4, 6 and 8 hr after the first daily dose (prior to second daily dose)
- Stool sample for fecal calprotectin
- [redacted]
- Colonoscopy for total Simple Endoscopic Score (SES-CD) score (optional)
- Record AEs
- Record concomitant medications

6.3.7 Wk 8 End of Treatment

- Vital signs and Active-Standing Test
- Abdominal Pain Score
- [redacted]
- A PK Blood samples for the analysis of APD371 and metabolite plasma concentrations will be collected 8 hr post first daily dose on Wk 8 (Day -1)
- Record AEs
- Record concomitant medications

Each subject will be evaluated continuously by the Investigator and Sponsor with regards to safety, and then the decision will be made on a case-by-case basis on whether the subject needs to stay overnight at Week 8 to be assessed for safety, including blood pressure and heart rate. If the decision to remove the Visit 8 (Wk 8) overnight stay has been determined, all scheduled evaluations still must be done, including serial PK collections vital signs, active-standing test, APS, [redacted] detailed in the diary cards.

6.4 Early Termination Procedures

- Physical examination (abbreviated examination including body weight and evaluation of changes to previously observed abnormal findings)
- Vital signs and Active-Standing Test
- 12-lead ECG
- Serum hCG pregnancy test (females only)
- Final PK blood sample
- Clinical laboratory tests (to include hematology, serum chemistry, coagulation, HsCRP, [redacted] and urinalysis)
- Abdominal Pain Score
- [redacted]
- Record AEs
- Record concomitant medications

6.5 Wk 10 Follow-up Visit Procedures

Subjects will return to the study site on an outpatient basis for a Follow-up Visit.

- Physical exam (abbreviated examination including body weight and evaluation of changes to previously observed abnormal findings)
- Vital signs and Active-Standing Test
- 12-lead ECG
- Serum hCG pregnancy test (females only)
- Clinical laboratory tests (to include hematology, serum chemistry, coagulation, HsCRP, [redacted] and urinalysis)
- Record AEs
- Record concomitant medications

The Principal Investigator and study site staff should exert every effort to secure subject attendance to the Follow-Up visit. Three attempted telephone contacts should be documented by study personnel before a subject can be considered lost to follow-up. Furthermore, key research personnel should mail a certified letter to the subject's address if no response to 3 telephone contacts remain unanswered. If the subject or a family member does not respond, the certified letter receipt should be filed in the individual's research record with a copy of the letter sent.

7 DATA MANAGEMENT

7.1 Data Collection

All data will be collected according to the Sponsor or CRO's SOPs.

Upon database lock, to include resolution of all queries, the CRO, if applicable, will provide SAS Transport Files (SAS XPT) datasets to the Sponsor and to the biostatistician for analysis using secure electronic data transfer per the Sponsor's specifications.

7.2 Data Coding

7.2.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 18.0 or later) and tabulated, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, maximum severity, causal relationship to study medication, and action taken. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (e.g., self-limited fever, runny nose, cough, and scratchy throat should be captured as an upper respiratory infection rather than by the individual signs and symptoms). Adverse events will be regarded as 'pre-treatment' if they occur between Screening and the time of administration of the first dose of study medication. All other AEs that occur after the first dose of study medication will be considered to be 'treatment-emergent'.

7.2.2 Concomitant Medications

Due to the variability in how medications are recorded, a standard naming convention is required in order to tabulate this data effectively. A common method of standardization is to categorize medications by their preferred term. In order to do this, medications will be coded using the WHO Drug Dictionary, Format C.

7.2.3 Medical History

Medical history will be coded using MedDRA (version 18.0 or later).

8 PLANNED STATISTICAL METHODS

The statistical analysis of the data obtained from this study will be the responsibility of the Sponsor or designated CRO. Full details of the statistical analyses will be written in a separate statistical analysis plan (SAP) which will be finalized prior to database lock. Any changes made to the pre-specified statistical analysis plan, will be listed in the Clinical Study Report along with an explanation as to why they occurred.

8.1 General Considerations

This is a proof-of-concept study design and there are no formal hypothesis tests being specified, Descriptive statistics for proportion based and continuous variables will be reported. Subgroup analysis by randomization stratification factor sex will be performed to assess potential safety and efficacy differences between males and females. Non-inferential between dose cohort comparisons for main study endpoint measures will be performed using parametric or non-parametric methods as appropriate and nominal p-values (2-sided) will be reported. The 95% confidence intervals for main study endpoint measures will also be reported.

8.2 Determination of Sample Size

No formal sample size and power calculation were performed. For this initial study in subjects it is planned to treat and complete safety and tolerability assessments in approximately 16 subjects, which is reasonable to assess the main study endpoints. Since subjects maybe replaced if they are withdrawn due to major protocol violations, a maximum of 20 subjects will be randomized in the study. It is expected that this number of subjects will provide guidance for the assessment of tolerability in this population and quantify the extent of abdominal pain relief.

8.3 Analysis Populations

The Safety Population will include all randomized subjects who received at least 1 dose of study medication.

The PK Completers Population will be defined as all subjects who receive APD371 and have at least 5 of the 9 scheduled PK collections on Wk 0 (Day 1), Wk 0 (Day 2) - 2 or Wk 8 (Day -1) and Wk 8, including the pre-dose sample.

The Efficacy population will include all randomized subjects who received at least 1 dose of study medication and have completed at least one consecutive week of APS up to Week 4.

8.4 Demographics and Baseline Characteristics

All screening subject characteristics of demographic data (age, height, weight, race/ethnicity), social history (smoking status, caffeine intake, alcohol intake), medical

history (abnormalities only), physical examination (abnormalities only), and concomitant medications at study entry will be listed for all subjects.

8.4.1 Demographics

Demographic data will be summarized and tabulated. Continuous variables will be summarized using number of observations (n), mean, standard deviation, median, minimum, and maximum. Frequencies and percentages will be reported for all categorical data.

8.5 Pharmacokinetic Variables

The PK analysis will be conducted by the Sponsor's representative or designated CRO employing noncompartmental methods [redacted]. Only subjects who are given active APD371 drug and have evaluable plasma concentration-time profiles will be included in the analysis.

Individual APD371 and metabolites M1 [redacted], M2 [redacted], and M4 ([redacted] plasma concentrations at specified timepoints will be listed for each subject and will be summarized by dose level. Individual plasma concentration-time profiles of APD371 and metabolites M1, M2 and M4 will be plotted on both a linear and a semi-logarithmic scale for each dose level. Mean values will also be presented graphically for each dose level.

Pharmacokinetic parameters of APD371 and metabolites M1, M2, and M4 may be listed for each subject and summarized by dose level. The following PK parameters may be determined for APD371 and metabolites unless otherwise specified:

Wk 0 (Day 1) and Wk 8 (Day -1)	
C_{max}	maximum plasma concentration
t_{max}	time of maximum plasma concentration
AUC_{0-8}	area under the plasma concentration-time curve over dosing interval (8 hours)
Wk 0 (Day 2), 2, 4, 6, 8	
C_{trough}	plasma concentration observed before treatment administration during repeated dosing

The individual elapsed sampling times will be used for all plasma PK parameters. For the purpose of calculating descriptive statistics and PK parameters, plasma concentrations below the lower limit of quantification (LLOQ) will be set to zero. After the peak, any measurable concentrations observed after two or more consecutive concentrations below the LLOQ will be considered anomalous and excluded from the PK analyses. Any quantifiable concentrations at pre-treatment on Day 1 will be set to zero.

Unrounded data will be used for estimation of summary statistics and PK analysis. Data will be rounded for reporting purposes only, with data presented to 3 significant figures for

numbers less than or equal to 1,000 and to the nearest integer for numbers greater than 1,000. Fold increases will be reported to two decimal places.

The ratio of each metabolite to APD371 will be calculated for C_{max} and AUC_{0-8}.

Summary statistics for continuous variables will include arithmetic mean, arithmetic SD, coefficient of variation, geometric mean, median, minimum and maximum; t_{max} will be summarized using median, minimum and maximum values. The effect of multiple doses of APD371 on PK parameters will be assessed with an analysis of variance model with treatment as factor. Appropriate transformations will be applied to the variables.

C_{trough} APD371 will be summarized by treatment period for each subject.

8.6 Safety Analysis

8.6.1 Adverse Events

Adverse events will be coded using MedDRA v18.0 and tabulated by dose cohort, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, maximum severity, causal relationship to study medication, and action taken. AEs will be regarded as 'pre-treatment' if they occur between Screening and the time of administration of the first dose of study medication.

8.6.2 Physical Examinations

Physical examination results (abnormalities only) will be listed and summarized by dose cohort.

8.6.3 Vital Signs

Individual vital sign measurements will be listed by treatment and measurement time, and summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in vital sign measurements by dose cohort.

8.6.4 Clinical Laboratory Values

Individual lab values will be listed by treatment and visit, and summarized by dose cohort using descriptive statistics. Summary statistics will also be provided for change from baseline in lab values. Shift tables from baseline to the last visit will also be produced for the laboratory assessments based on the categories of Low, Normal, and High.

8.6.5 12-lead ECGs

Individual 12-lead ECG values will be listed by dose cohort and visit, and summarized using descriptive statistics by dose cohort. Intervals to be provided for each ECG are: RR, PR, QRS, QT, QTc, QTcB, and QTcF. Any clinically significant change from baseline may be recorded as an AE if deemed appropriate by the Investigator or Sponsor.

8.7 Efficacy Analysis

8.7.1 Abdominal pain score (APS)

The change in APS scores between morning dose (trough) and 1.5 hr post-treatment first daily dose (peak) assessments will be summarized across all days of treatment and compared by dose cohort and overall. Difference between dose cohort will be reported.

8.7.2 Average abdominal pain score (AAPS)

AAPS will be summarized for the screening period and for each week of treatment before morning dose (trough) assessments and 1.5 hr post-treatment first daily dose (peak) assessments, by study cohort. Statistical comparisons of AAPS will be made between screening and WK 4 and at Wk 8, trough and peak assessments, by dose cohort and overall. Difference between dose cohort will be reported.

8.7.3 Pain relief responders

Proportion of subjects in each treatment cohort who are weekly responders will be summarized and difference between dose cohort will be reported.

Proportion of subjects in each treatment arm who are end-of-treatment responders will be summarized and difference between dose cohort will be reported.

[redacted]

Other exploratory efficacy measure listed in Section 2.2 will be summarized and difference between dose cohort will be reported:

- The number of pain-free days per week in each treatment cohort, based on responses to the APS
- Pain rescue medication use in each dose arm

8.7.5 C-reactive Protein

Change from baseline in level of CRP at week 4 and week 8 (Day-1) will be measured by a high-sensitivity assay (HsCRP), summarized and difference between dose cohort will be reported.

8.7.6 Fecal calprotectin

Change from baseline in level of fecal calprotectin at week 4 and week 8 (Day-1) will be summarized and difference between dose cohort will be reported.

9 REGULATORY REQUIREMENTS

9.1 Pre-study Documentation

The Sponsor or designee must receive the following documentation prior to initiation of the study:

- Protocol signature page signed by the PI
- Food and Drug Administration (FDA) form 1572 signed by the PI
- Curriculum vitae of the PI and Sub-investigators, updated within two years
- Current medical licenses for the PI and all Sub-investigators
- Financial disclosure form signed by the PI and all Sub-investigators listed on the FDA Form 1572
- Copy of the IRB approval letter for the study and approved voluntary ICF
- IRB Membership List.

9.2 Investigator Obligations

The PI is responsible for ensuring that all study site personnel, including Sub-investigators and other study staff members, adhere to all FDA regulations and guidelines regarding clinical trials, including guidelines for GCP (including the archiving of essential documents), both during and after study completion. The PI will be responsible for the subject's compliance to the study protocol. The PI is responsible for providing the Sponsor an adequate final report shortly after he/she completes participation in the study, in accordance with 22 CFR §312.64.

9.3 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. This is detailed in the written information provided to the subject. An agreement for disclosure of any such information will be obtained in writing and is included in both copies of the ICF signed by the subject. The study data shall not be disclosed to a third party without the written consent of the Sponsor.

9.4 Informed Consent

According to the ICH guideline for GCP (E6), the PI (or designee) will obtain and document informed consent for each subject screened for this study. All subjects will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures. The subject's medical record should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the Investigator's designated IRB and by the Sponsor. The ICF

should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

9.5 Institutional Review Board

This protocol and relevant supporting data are to be submitted to the appropriate IRB for review and approval before the study can be initiated. Amendments to the protocol will also be submitted to the IRB prior to implementation of the change. The Sponsor must receive a letter documenting the IRB approval prior to initiation of the study. The PI is also responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The IRB must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the PI. The PI must notify the IRB in writing of any SAE or any unexpected AE according to ICH guidelines.

10 PROTOCOL MANAGEMENT AND ADMINISTRATIVE CONSIDERATIONS

10.1 Study Documentation

The PI and study staff have the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by the Sponsor, representatives of the Sponsor, the IRB, and regulatory authorities (i.e., FDA or international regulatory authorities) at any time, and should consist of the following elements:

Subject files, containing the completed eCRFs, supporting source documentation from the medical record including laboratory data and the ICF.

Regulatory files, containing the protocol with all amendments and Investigator signature pages, copies of all other regulatory documentation, and all correspondence between the site and the IRB and Sponsor; and Drug accountability files, including a complete account of the receipt and disposition of the study medication (test article).

Records are to be available for two years after marketing application approval, or if the application is not approved or never submitted, two years after the last shipment and delivery of the material and the appropriate competent regulatory authorities are notified. The Sponsor will provide written notification when it is appropriate for the Investigator(s) to discard the study-specific documents referenced above.

10.2 Protocol Interpretation and Compliance

To ensure accurate interpretation and implementation of the study, the procedures and endpoints defined in the protocol will be carefully reviewed by the PI and his or her staff prior to the time of study initiation. The Sponsor and PI will follow all reasonable means to resolve any differences of opinion of matters of eligibility, toxicity and other endpoints. In the event that a resolution cannot be reached then one or both parties may seek to terminate the study following the provisions outlined in the Clinical Trials Agreement.

10.3 Study Monitoring

The Sponsor or a contracted monitor will visit the study center periodically to monitor adherence to the protocol, compliance with ICH guidelines, adherence to applicable FDA regulations, and the maintenance of adequate and accurate clinical records. Case report forms will be reviewed to ensure that key safety and efficacy data are collected and recorded as specified by the protocol. The monitor will be permitted to access subjects' complete medical records, laboratory data, and other source documentation as needed to monitor the study appropriately.

11 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study as outlined in the protocol entitled, "A Randomized, Open-label, Parallel, Phase 2a Study to Determine the Tolerability, Pharmacokinetics, and Efficacy of APD371 in Subjects with Crohn's disease experiencing Abdominal Pain" in accordance with the guidelines and all applicable government regulations including Part 54: Financial Disclosure by Clinical Investigators. These guidelines and regulations include, but are not limited to:

- Permission to allow the Sponsor, or designee, and the FDA or other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality. If this study is to be inspected by a regulatory agency, the Sponsor and CRO should be notified as soon as possible.
- Submission of the proposed clinical investigation, including the protocol and the consent form, to a duly constituted IRB for approval, and acquisition of written approval for each prior to the use of the study drug.
- Use of written informed consent that is obtained prior to administration of study drug or any non-routine procedures that involve risk, and that contains all the elements of consent as specified in the federal regulations and has been previously approved by the Sponsor and the IRB.
- Submission of any proposed change in the protocol to the IRB using a signed formal amendment document approved by the Sponsor. Any proposed changes to the protocol require that the informed consent also reflect such changes and that the revised informed consent be approved as determined by the IRB.
- Documentation and explanation of individual protocol deviations on the appropriate eCRF page or in letters to the Sponsor.
- Submission of reports of SAEs to **PPD Medical Affairs/ Pharmacovigilance** within 24 hours after the Investigator's initial receipt of the information.
- Submission of written reports of SAEs, as outlined in the protocol, to the IRB within 15 calendar days of their disclosure.
- Submission of timely progress reports to the IRB and Sponsor at appropriate intervals on a schedule determined by the IRB.
- Maintenance of appropriate records: Federal regulations require an Investigator to prepare and maintain adequate and an accurate case history designed to record all observations and other data (such as study drug accountability) pertinent to the investigation on each individual enrolled in the study. These records must be maintained by the Investigator until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

In addition, I agree to provide all the information requested in the eCRF in a manner to assure legibility and accuracy. To this end, I shall carefully follow the instructions for completing eCRFs.

I also agree that all information provided to me by the Sponsor, including protocols, eCRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be related in confidence to the IRB. I also understand that reports of information about the study or its progress will not be provided to anyone not involved in the study other than to the PI, or in confidence to the IRB or to the FDA or other legally constituted authority.

Principal Investigator **Date**

Printed Name

12 REFERENCES

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UserName: [redacted]
Title: Sr. Manager, Medical Writer
Date: Thursday, 10 August 2017, 02:22 PM Pacific Daylight Time
Meaning: Author Approval
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UserName: [redacted]
Title: Vice President, Regulatory Affairs and Quality
Date: Thursday, 10 August 2017, 04:19 PM Pacific Daylight Time
Meaning: Approval
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UserName: [redacted]
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Meaning: Approval
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UserName: [redacted]
Title: Vice President, Clinical Development
Date: Friday, 11 August 2017, 07:45 AM Pacific Daylight Time
Meaning: Approval
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APD371-004 AMENDMENT 02
SUMMARY OF CHANGES

Protocol Number: APD371-004 Protocol Amendment 02

Protocol Title: A Randomized, Open-label, Parallel, Phase 2a Study to Determine the Tolerability, Pharmacokinetics, and Efficacy of APD371 in Subjects with Crohn's disease experiencing Abdominal Pain

Amendment Date: 10 August 2017

PAGE(S)	PROTOCOL CHANGE DESCRIPTION	RATIONALE
Throughout	Minor administrative and formatting changes were made	Not applicable
1	**TITLE PAGE –Sponsor Contact** *Previously read:* [redacted] Associate Director, Clinical Operations Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, CA 92121, USA Phone: [redacted] Email: [redacted] *Now reads:* [redacted] Head of Clinical Operation Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, CA 92121, USA Phone: [redacted] Email: [redacted]	Administrative change
1	**TITLE PAGE** *Added:* Amendment 02 08 August 2017	Administrative change
2	**SYNOPSIS – Name of Sponsor Medical Contact** *Previously read:* [redacted] MD Arena Pharmaceuticals Development GmbH Gotthardstrasse 3 6300 Zug, Switzerland Phone: [redacted] Email: [redacted]	Administrative change

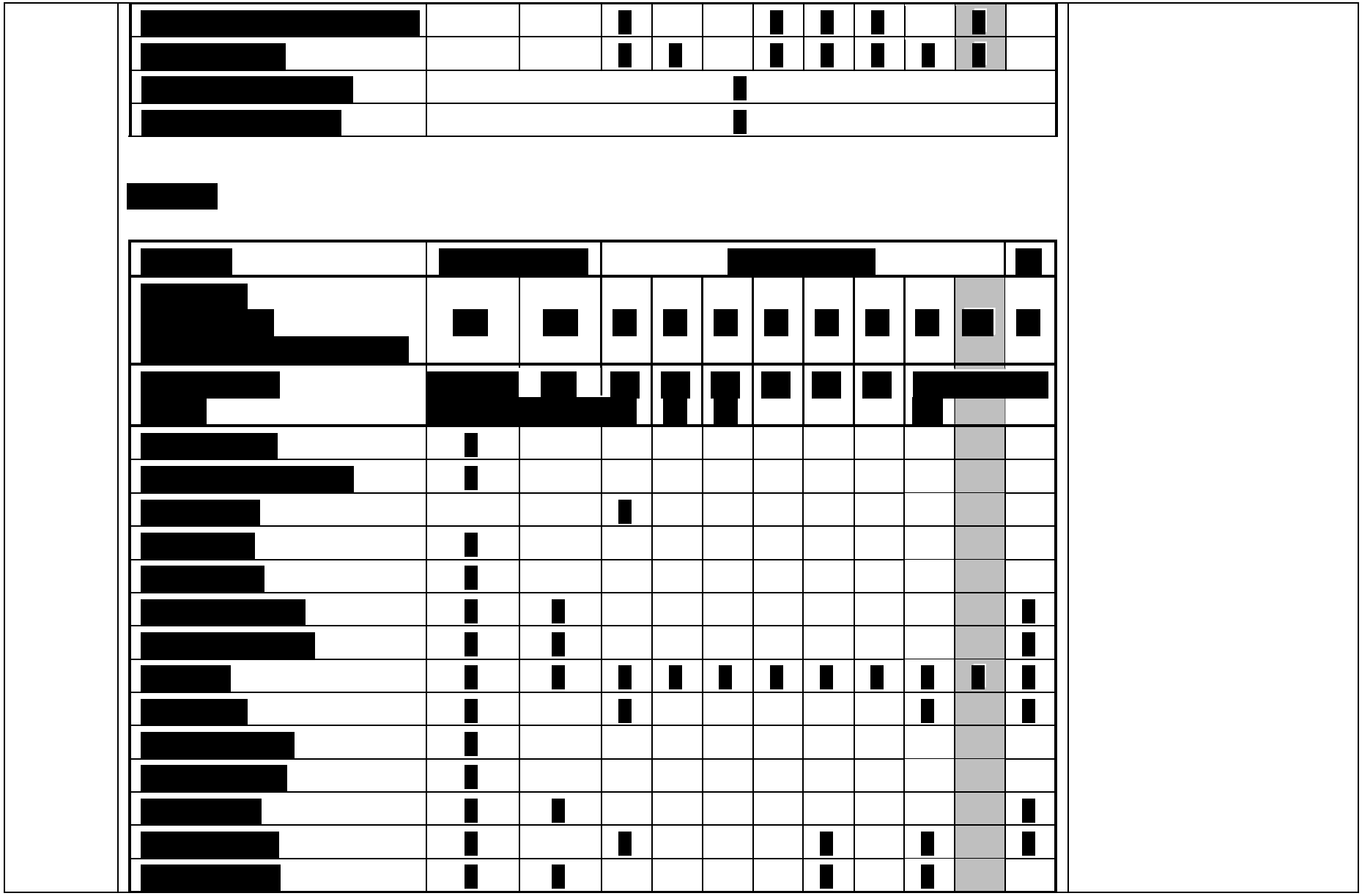
	Now reads: [redacted], MD, PhD Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121 United States of America (USA) Phone: [redacted] Email: [redacted]	
3 and 20	**SYNOPSIS – Objectives, Exploratory Objectives** and **2.2 Exploratory Objectives** *Added:* [redacted]	[redacted]
3 and 20	**SYNOPSIS – Objectives, Exploratory Objectives** and **2.2 Exploratory Objectives** *Previously read:* • Pain rescue medication use *Now reads:* • Pain medication use	Use of standard of care pain medication, including narcotics, is being allowed in this protocol amendment (see Inclusion Criteria #9). A decrease in the use of pain medication will be considered one of the exploratory efficacy endpoints for APD371.
3 and 20	**SYNOPSIS – Objectives, Exploratory Objectives** and **2.2 Exploratory Objectives** *Previously read:* • Effect of APD371 treatment on reduction in C-reactive protein (CRP) at week 4 and week 8 *Now reads:* • Effect of APD371 treatment on reduction in C-reactive protein (CRP) and other biomarkers at week 4 and week 8	Since the CB2 receptor is mainly expressed in immune cells, additional immune and inflammation-related biomarkers will be evaluated to help understand the mechanism of action of APD371.
3 and	**SYNOPSIS – Objectives, Exploratory Objectives** and **2.2 Exploratory Objectives** *Added:*	[redacted]

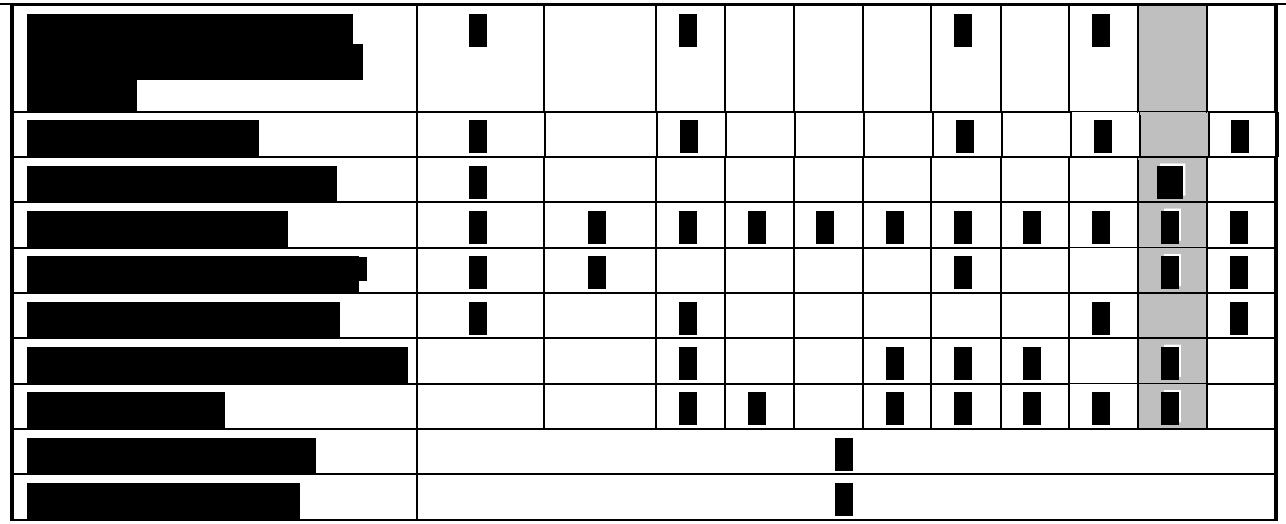
20	[redacted]	[redacted]
3 and 20	**SYNOPSIS – Objectives, Exploratory Objectives** and **2.2 Exploratory Objectives** *Added:* [redacted]	[redacted]
4	**SYNOPSIS – Study Population** *Previously read:* The study population will consist of adult male and female subjects aged 18 to 80 years who are diagnosed with abdominal pain due to quiescent to mildly active CD, as defined by a weekly average abdominal pain score (AAPS) >5 over one week (0 [no pain] to 10 [worst possible]), with minimal intestinal inflammation, confirmed with a simple endoscopic score (-CD) score <6 or ileal SES-CD <4 or fecal calprotectin <300 mcg/g. *Now reads:* The study population will consist of adult male and female subjects aged 18 to 80 years who are diagnosed with abdominal pain due to quiescent to mildly active CD, as defined by a weekly average abdominal pain score (AAPS) ≥4 over one week (0 [no pain] to 10 [worst possible]), with minimal intestinal inflammation, confirmed with a simple endoscopic score (-CD) score <10 or fecal calprotectin (FCP) <500 mcg/g.	The study entry criteria have been amended to revise inclusion and exclusion criteria that were unnecessarily restrictive.
4 and 26	**SYNOPSIS – Inclusion Criteria** and **3.5 Inclusion Criteria #7** *Previously read:* 7. Quiescent to mildly active inflammatory CD defined with a total SES-CD score of < 6 or ileal SES-CD < 4 or FCP < 300 mcg/g at Screening *Now reads:* 7. Quiescent to mildly active inflammatory CD defined with a total SES-CD score of < 10 or FCP < 500 mcg/g within 4 weeks before screening	The study entry criteria have been amended to revise inclusion and exclusion criteria that were unnecessarily restrictive.

4 and 27	**SYNOPSIS – Inclusion Criteria** and **3.5 Inclusion Criteria #8** *Previously read:* 8. Moderate to severe abdominal pain as defined by average abdominal pain score (AAPS) of >5 points on 7 consecutive days of the screening period up to Day -2. AAPS will be based on the 11-point numeric rating scale where 0 (no abdominal pain) to 10 (worst possible abdominal pain) *Now reads:* 8. Moderate to severe abdominal pain as defined by average abdominal pain score (AAPS) of ≥ 4 points on 7 consecutive days of the screening period up to Day -2. AAPS will be based on the 11-point numeric rating scale where 0 (no abdominal pain) to 10 (worst possible abdominal pain)	The study entry criteria have been amended to revise inclusion and exclusion criteria that were unnecessarily restrictive.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
9	**SYNOPSIS – Sample size** And **3.5 Overall study design and plan** *Previously read:* It is planned to treat and complete safety and tolerability assessments in at least 16 subjects. *Now reads:* It is planned to treat and complete safety and tolerability assessments in approximately 16 subjects.	Clarification of sample size.
9	**SYNOPSIS – Pharmacokinetic Assessments** *Previously read:* Blood samples for the assay of APD371 and metabolites M1 [redacted], M2 [redacted], and M4 [redacted] will be collected at the following time points: • Wk 8 (Day -1, last day dosing): prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9, 10 and 24 hr post first daily dose. *Now reads:* Blood samples for the assay of APD371 and metabolites M1 [redacted], M2 [redacted], and M4 [redacted] will be collected at the following time points: • Wk 8 (Day -1, last day dosing): prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose).	Based on PK analysis, AUC0-8 will be an important index for comparison between Week 0 (Day 1) and Week 8 (Day -1) as per section 8.5 (Pharmacokinetic Variables). Samplings at 9, 10 and 24 hours are not required.
15-16	**List of Abbreviations and Definitions of Terms** *Added:* [redacted]	Addition of abbreviations

	THC Tetrahydro cannabinol	
[redacted]	[redacted]	[redacted]



		
		
26	**3.4 Study Population** *Previously read:* The study population will consist of adult male and female subjects aged 18-80 years who are diagnosed with abdominal pain due to quiescent to mildly active CD, as defined by an AAPS >5 over one week (0 [no pain] to 10	The study entry criteria have been amended to revise inclusion and exclusion criteria that were unnecessarily restrictive.

	[worst possible]), with minimal intestinal inflammation, confirmed with a total simple endoscopic score (SES-CD) score < 6 or ileal SES-CD < 4 or fecal calprotectin (FCP) < 300. Endoscopy results obtained within 4 weeks prior to screening may be utilized. *Now reads:* The study population will consist of adult male and female subjects aged 18-80 years who are diagnosed with abdominal pain due to quiescent to mildly active CD, as defined by an AAPS ≥4 over one week (0 [no pain] to 10 [worst possible]), with minimal intestinal inflammation, confirmed with a total simple endoscopic score (SES-CD) score < 10 or ileal SES-CD < 4 or fecal calprotectin (FCP) < 500. Endoscopy results obtained within 4 weeks prior to screening may be utilized.	
26	**3.4 Study Population** *Previously read:* Exceptions to eligibility criteria will not be granted by the Investigator or the Sponsor. *Now reads:* Exceptions to eligibility criteria will not be granted by the Investigator unless approved in advance by the Sponsor.	Revised to allow for exceptions to eligibility criteria.
32	**4.6 Dosage and Administration** *Previously read:* There are no food restrictions around dosing with the exception of ingestion of grapefruit juice, prune juice or poppy seeds or poppy seed containing items. *Now reads:* There are no food restrictions around dosing with the exception of ingestion of grapefruit juice or prune juice.	The restriction on ingestion of poppy seeds or poppy seed containing items was unnecessarily restrictive and has been removed.
35	**4.9 Concomitant Medications** *Previously read:* Stable doses of non-narcotic prescription medications required for treatment of current medical conditions other than pain (e.g., hypertension, thyroid disease, diabetes) may be continued during the screening and study period with the exception of medications known to be moderate or strong CYP3A4/5 inducers or inhibitors. Doses may be adjusted as appropriate per usual standards of care. *Now reads:*	Administrative change (see 4.9.1 Not Permitted)

	Stable doses of non-narcotic prescription medications required for treatment of current medical conditions other than pain (e.g., hypertension, thyroid disease, diabetes) may be continued during the screening and study period. Doses may be adjusted as appropriate per usual standards of care.	
35	**4.9 Concomitant Medications – 4.9.1 Not Permitted** *Previously read:* • Prescription and OTC medications for pain relief (for exceptions, see Section 4.9.2 – Permitted) • Hormonal contraceptives for pain relief within 30 days prior to the Screening visit, during the Screening period, and for the duration of the study. • Dietary supplements (vitamin, herbal, and mineral supplements), unless deemed appropriate by the Investigator for the treatment of an AE. *Now reads:* • Hormonal contraceptives for pain relief within 30 days prior to the Screening Visit, during the Screening period, and for the duration of the study. • Moderate or strong CYP3A4/5 inducers or inhibitors	Not permitted Medications have been amended to revise criteria that were unnecessarily restrictive.
36	**4.9 Concomitant Medications – 4.9.2 Permitted** *Previously read:* • Pain relief medications such as NSAIDs or acetaminophen/paracetamol given at stable doses for at least 2 weeks prior to screening and for the duration of the study *Now reads:* • Pain relief medications such as NSAIDs, narcotic analgesics, or acetaminophen/paracetamol given at stable doses for at least 2 weeks prior to screening and for the duration of the study	Patients with moderate to severe abdominal pain need to be on standard-of-care pain medications, including narcotics, during the study.
36	**4.10 Restrictions – 4.10.1 Fluid and Food Intake** *Previously read:* There are no food restrictions around dosing with the exception of grapefruit, prune juice and poppy seeds or poppy seed containing items. *Now reads:* There are no food restrictions around dosing with the exception of grapefruit and prune juice.	The restriction on ingestion of poppy seeds or poppy seed containing items was unnecessarily restrictive and has been removed.
37	**4.10 Restrictions – 4.10.2 Smoking** *Removed:*	It is common that Crohn's Disease patients that experience abdominal pain are smokers - therefore this restriction was

	Subjects who smoke, have a history of smoking or nicotine use, or use of nicotine-containing products within 90 days prior to dosing will not be allowed into the study. Smoking or use of nicotine-containing products is not allowed during study participation.	unnecessarily restrictive and has been removed.
41	**5.9 Clinical Laboratory Tests – 5.9.4 C-Reactive Protein and other Biomarkers** *Previously read:* Blood samples for analysis of C-reactive protein (CRP) will be collected at screening, pre-dose at Day 1, Week 4 and Week 8 (Day -1), and Week 10 (Follow-up). *Now reads:* Separate blood samples (a total of 20 mL) for analysis of C-reactive protein (CRP) will be collected at screening, pre-dose at Day 1, Week 4 and Week 8 (Day -1), and Week 10 (Follow-up). [redacted]	[redacted]
42	**5.9 Clinical Laboratory Tests – 5.9.6 Blood Volume** *Previously read:* Total blood volume for clinical laboratory tests will be approximately 185 mL. *Now reads:* Total blood volume for clinical laboratory tests will be approximately 205 mL.	Blood volume increased to accommodate additional biomarker testing
42	**5.11 Pharmacokinetic sampling** *Previously read:* Pharmacokinetic samples for the assay of APD371 and metabolites M1 [redacted] M2 [redacted], and M4 [redacted] will be collected will be collected at the visit time points indicated in the Schedule of Events (Table 1) and detailed in Pharmacokinetic sampling, Table 3. **Table 3. Pharmacokinetic sampling** **Study Day** / **Blood sampling assessments*** Wk 0 (Day 1) / Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9 and 10 hours post first daily dose. Wk 0 (Day 2) / 24 hours post dose first daily dose on Day 1 Wk 2 / Prior to first daily dose Wk 4 / Prior to first daily dose	Based on PK analysis, AUC0-8 will be an important index for comparison between Week 0 (Day 1) and Week 8 (Day -1) as per section 8.5 (Pharmacokinetic Variables). Sampling at 9, 10 and 24 hours is not required.

	<table><tr><td>Wk 6</td><td>Prior to first daily dose</td></tr><tr><td>Wk 8 (Day -1)</td><td>Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9, 10 post first daily dose.</td></tr><tr><td>Wk 8 (End-of-Treatment)</td><td>24 hours post dose first daily dose on Wk 8 (Day-1)</td></tr></table> *Now reads:* Pharmacokinetic samples for the assay of APD371 and metabolites M1 [redacted], M2 [redacted], and M4 [redacted] will be collected will be collected at the visit time points indicated in the Schedule of Events (Table 1) and detailed in Pharmacokinetic sampling, Table 3. **Table 3. Pharmacokinetic sampling** <table><tr><th>Study Day</th><th>Blood sampling assessments*</th></tr><tr><td>Wk 0 (Day 1)</td><td>Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9 and 10 hours post first daily dose.</td></tr><tr><td>Wk 0 (Day 2)</td><td>24 hours post dose first daily dose on Day 1</td></tr><tr><td>Wk 2</td><td>Prior to first daily dose</td></tr><tr><td>Wk 4</td><td>Prior to first daily dose</td></tr><tr><td>Wk 6</td><td>Prior to first daily dose</td></tr><tr><td>Wk 8 (Day -1)</td><td>Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose)</td></tr><tr><td>Wk 8 (End-of-Treatment)</td><td>8 hours post dose first daily dose on Wk 8 (Day-1)</td></tr></table>* Allowable windows for sample collection: - time points up to 4 hours: ± 5 mins - time points after 4 hours: ± 15 mins	
50	**6 STUDY ACTIVITIES – 6.1 Screening Visits Wk -4 to Wk -1 (Days -28 to -1)** *Previously read:* • Total Simple Endoscopic Score (SES-CD) score < 6 or ileal SES-CD < 4 or FCP < 300 mcg/g. Endoscopy results obtained within 1 month prior to screening may be utilized. *Now reads:* • Total Simple Endoscopic Score (SES-CD) score < 10 or FCP < 500 mcg/g. Endoscopy results obtained within 1 month prior to screening may be utilized.	The study entry criteria have been amended to revise inclusion and exclusion criteria that were unnecessarily restrictive.
53	**6 STUDY ACTIVITIES – 6.3.6 Wk 8 (Day -1)** *Previously read:* • PK Blood samples for the analysis of APD371 and metabolite plasma concentrations will be collected prior to and at 0.5, 1, 2, 4, 6 and 8 hr after the first daily dose (prior to second daily dose) and 9 and 10 hr	Based on PK analysis, AUC0-8 will be an important index for comparison between Week 0 (Day 1) and Week 8 (Day -1) as per section 8.5 (Pharmacokinetic

	Now reads: • PK Blood samples for the analysis of APD371 and metabolite plasma concentrations will be collected prior to and at 0.5, 1, 2, 4, 6 and 8 hr after the first daily dose (prior to second daily dose)	Variables). Sampling at 9, 10 and 24 hours is not required.
53	**6 STUDY ACTIVITIES – 6.3.7 Wk 8 End of Treatment** *Previously read:* • A PK Blood samples for the analysis of APD371 and metabolite plasma concentrations will be collected 24 hr post first daily dose on Wk 8 (Day -1) *Now reads:* • A PK Blood samples for the analysis of APD371 and metabolite plasma concentrations will be collected 8 hr post first daily dose on Wk 8 (Day -1)	Based on PK analysis, AUC0-8 will be an important index for comparison between Week 0 (Day 1) and Week 8 (Day -1) as per section 8.5 (Pharmacokinetic Variables). Sampling at 9, 10 and 24 hours is not required.

APD371-004 AMENDMENT 1 SUMMARY OF CHANGES

Protocol Number: APD371-004 Protocol Amendment 01

Protocol Title: A Randomized, Open-label, Parallel, Phase 2a Study to Determine the Tolerability, Pharmacokinetics, and Efficacy of APD371 in Subjects with Crohn's disease experiencing Abdominal Pain

Amendment Date: 24 March 2017

APD371-004 Protocol Amendment 01 Summary of Changes

Page(s)	Protocol Change Description	Rationale
Throughout	Minor administrative and formatting changes were made	Not applicable
1	**TITLE PAGE – Title** *Previously read:* A Randomized, Open-label, Parallel Group, Phase 2a Study to Determine the Tolerability, Pharmacokinetics, and Efficacy of APD371 in Subjects with Crohn's disease experiencing Abdominal Pain *Now reads:* A Randomized, Open-label, Parallel, Phase 2a Study to Determine the Tolerability, Pharmacokinetics, and Efficacy of APD371 in Subjects with Crohn's disease experiencing Abdominal Pain	Consistency with protocol title
1 and 2	**TITLE PAGE - Indication** and **SYNOPSIS** *Previously read:* Acute and chronic inflammatory and neuropathic pain *Now reads:* Acute and chronic inflammatory pain	The company decided to focus on inflammatory visceral pain and remove neuropathic pain as a target for the study.
1	**TITLE PAGE –Sponsor Contact** *Previously read:* [redacted] Director, Clinical Operations Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, CA 92121, USA Phone : [redacted], ext. [redacted] Email: [redacted] *Now reads:* [redacted] Associate Director, Clinical Operations Arena Pharmaceuticals, Inc.	Administrative change

	6154 Nancy Ridge Drive San Diego, CA 92121, USA Phone: [redacted] Email: [redacted]	
1	**TITLE PAGE** *Added:* Amendment 01 24 March 2017	Administrative change
2	**SYNOPSIS – Name of Sponsor Medical Contact** *Previously read:* [redacted] MD, CPI Principal, Pacific Pharma Group, LLC 1402 S. Brookside Terrace Tacoma, WA 98465-1210, USA. Phone: [redacted] Mobile: [redacted] Email: [redacted] *Now reads:* [redacted] MD Arena Pharmaceuticals Development GmbH Gotthardstrasse 3 6300 Zug, Switzerland Phone: [redacted] Email: [redacted]	Administrative change
2	**SYNOPSIS – Medical Monitor** *Added*: [redacted] MD, CPI Principal, Pacific Pharma Group, LLC 1402 S. Brookside Terrace Tacoma, WA 98465-1210, USA. Phone: [redacted] Mobile: [redacted] Email: [redacted]	Administrative change
3 and	**SYNOPSIS – Objectives, Exploratory Objectives** and **2.2 Exploratory Objectives** *Previously read:*	Simplification and wording consistency with other objectives

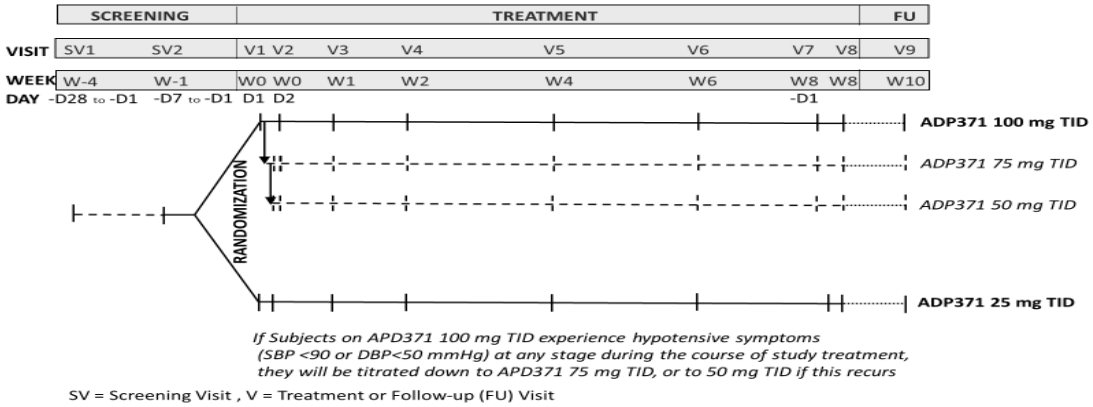
20	• Proportion of subjects in each treatment cohort who are weekly responders *Now reads:* • Proportion of subjects who are weekly responders	
3 and 20	**SYNOPSIS – Objectives, Exploratory Objectives** and **2.2 Exploratory Objectives** *Previously read:* • Proportion of subjects in each treatment cohort who are end-of treatment responders *Now reads:* • Proportion of subjects who are end-of-treatment responders	Simplification and wording consistency with other objectives
3	**SYNOPSIS – Study Design** *Previously read:* A randomized, open label, parallel group, multi center, comparison of two doses of APD371. Eligible subjects will enter a screening period of up to 4 weeks and will then be randomized into an open-label, study, receiving APD371 in doses of 25 mg or 100 mg capsules for 8 weeks. Treatment cohorts will consist of daily doses of 25 mg or 100 mg APD371 TID. Subjects will be randomized in a 1:1 ratio, with random assignment to active study drug 25 mg or 100 mg. Randomization will be stratified by sex. *Now reads:* A randomized, open label, parallel group, multi center, comparison of two doses of APD371. Eligible subjects will enter a screening period of up to 4 weeks and will then be randomized in a 1:1 ratio to receive APD371 in doses of 25 mg or 100 mg TID for 8 weeks. Randomization will be stratified by sex.	To remove redundancy and incorrect information
4	**SYNOPSIS – Section descriptor** *Previously read:* Subject Population *Now reads:* Study Population	Consistency throughout the protocol.
4	**SYNOPSIS – Subject Population** *Previously read:*	Revised for consistency with Section 3.4 and provide the

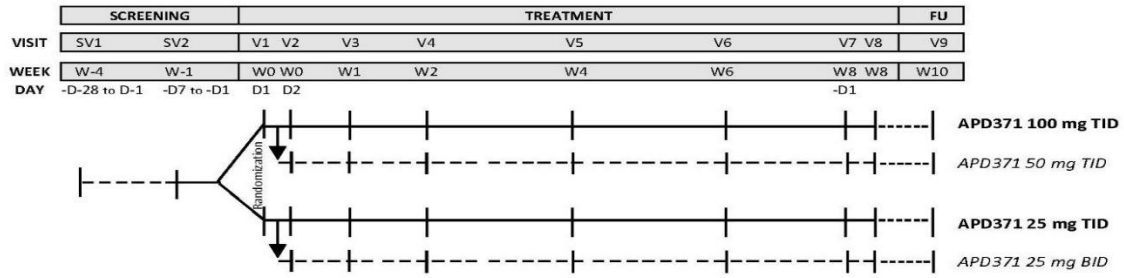
	The study population will consist of adult male and female subjects aged 18 to 80 years who are diagnosed with abdominal pain due to quiescent to mildly active CD, as defined by a weekly average abdominal pain score (AAPS) >5 over one week (0 [no pain] to 10 [worst possible]), with minimal intestinal inflammation, confirmed with a simple endoscopic score (-CD) score <5 or fecal calprotectin <300. Endoscopy results obtained within 1 month prior to screening may be utilized. *Now reads:* The study population will consist of adult male and female subjects aged 18 to 80 years who are diagnosed with abdominal pain due to quiescent to mildly active CD, as defined by a weekly average abdominal pain score (AAPS) >5 over one week (0 [no pain] to 10 [worst possible]), with minimal intestinal inflammation, confirmed with a simple endoscopic score (-CD) score <6 or ileal SES-CD <4 or fecal calprotectin <300 mcg/g. Endoscopy results obtained within 1 month prior to screening may be utilized.	appropriate units for fecal calprotectin.
4 and 26	**SYNOPSIS – Inclusion Criteria** and **3.5 Inclusion Criteria** *Previously read:* 7. Quiescent to mildly active inflammatory CD defined with a total SES-CD score of < 6 or ileal SES-CD < 4 or FCP < 300 at Screening *Now reads:* 7. Quiescent to mildly active inflammatory CD defined with a total SES-CD score of < 6 or ileal SES-CD < 4 or FCP < 300 mcg/g at Screening	Addition of appropriate units for FCP assessment results
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

7 and 29	**SYNOPSIS – Exclusion Criteria** and **3.5 Exclusion Criteria – General Exclusion Criteria** *Previously read:* 13. Other significant chronic pain conditions that in the opinion of the investigator may influence the pain score *Now reads:* 13. Other significant chronic pain conditions that in the opinion of the Investigator may influence the abdominal pain score	Clarification of which pain score.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

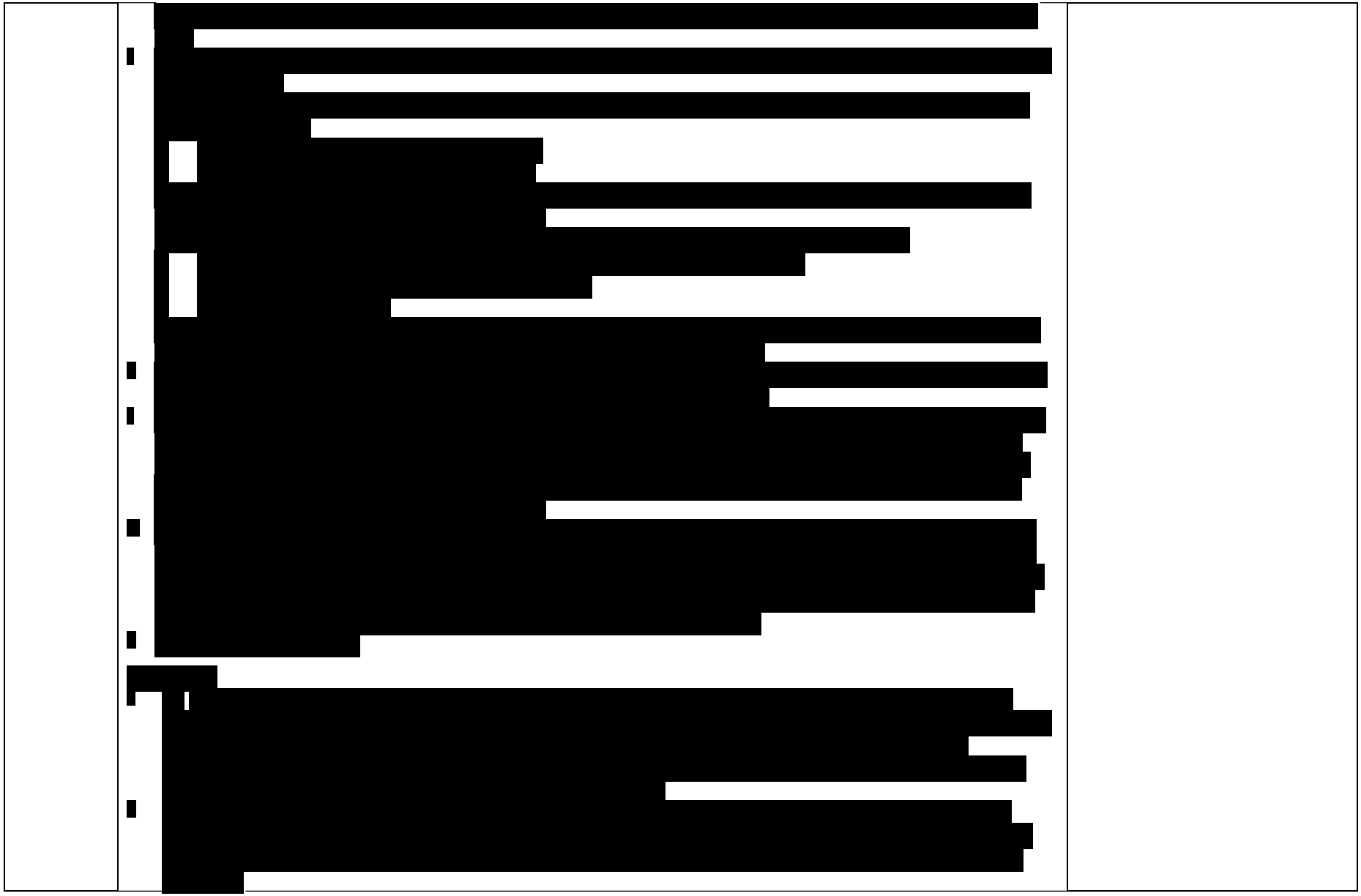
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
8	**SYNOPSIS – Subject Assignment** *Previously read:* Eligible subjects will be randomized in a 1:1 ratio to receive APD371 25 mg TID or 100 mg TID. If subjects on 100 mg TID experience hypotensive symptoms of SBP <90 or DBP<50 mmHg, they will be titrated down to 75 mg TID, or to 50 mg TID if this recurs. *Now reads:* Eligible subjects will be randomized in a 1:1 ratio to receive APD371 25 mg TID or 100 mg TID.	Deleted original dose reduction parameters and added more defined dose reduction parameters in Section 3.1 Overall Study Design and Plan.
14	**List of In-Text Tables** *Previously read:* [redacted] *Now reads:* [redacted] Table 3. Pharmacokinetic sampling..... 42	[redacted]
16	**List of Abbreviations and Definitions of Terms** *Added:* PRO Patient Reported Outcome	Clarification
18	**1.1 Rationale for Proposed Clinical Study** *Previously read:*	Revised to correct protocol number for the second study, the minimal dose tested in that study

	[redacted] *Now reads:* [redacted]	and add units to the lowest dose in this study.
19	**1.2 Ethics and Regulatory Considerations** *Previously read:* The IRB must be notified promptly by the Investigator of the following: • Deviations from, or changes to, the protocol to eliminate immediate hazards to the trial volunteers; • Changes increasing the risk to volunteers and/or affecting significantly the conduct of the trial; • All adverse events (AE)s that meet the definition of a serious adverse event (SAE); • New information that may adversely affect the safety of the volunteers or the conduct of the trial. Any changes to the protocol will be made by means of a formal written protocol amendment. All amendments will require IRB approval before implementation except when changes to the protocol are required immediately to eliminate hazards to the volunteer. *Now reads:* The IRB must be notified promptly by the Investigator of the following: • Deviations from, or changes to, the protocol to eliminate immediate hazards to the trial subjects; • Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial; • All adverse events (AE)s that meet the definition of a serious adverse event (SAE); • New information that may adversely affect the safety of the subjects or the conduct of the trial. Any changes to the protocol will be made by means of a formal written protocol amendment. All amendments will require IRB approval before implementation except when changes to the protocol are required immediately to eliminate hazards to the trial subjects.	Revised to correctly identify the study population (e.g., volunteers vs subjects) in this study.

20	**2.2 Exploratory Objectives** *Previously read:* • To assess change in abdominal pain score (APS) from pre-dose (trough) to 1.5 hr post-dose (peak) following the first of 3 daily doses of APD371; assessed daily to Day 56 *Now reads:* • To assess change in abdominal pain score (APS) from pre-dose (trough) to 1.5 hr post-dose (peak) following the first of 3 daily doses of APD371; assessed daily to Day 56 and averaged weekly to Wk 8	Revised for consistency with synopsis exploratory objectives.
21	**3.1 Overall Study Design and Plan – Figure 1. APD371-004 Study Plan** *Previously read:*  *Now reads:*	Figure revised to reflect clarification of dose adjustment parameters.

	 *If subjects on APD371 100 mg or 25 mg TID experience hypotensive and/or heart rate changes at any stage during the course of the study treatment, the Investigator must assess whether the changes meet the study drug interruption/stopping rules and proceed as recommended in Table 2.* SV = Screening Visit, V = Treatment or Follow-up (FU) Visit	
21	**3.1 Overall Study Design and Plan** *Previously read:* Subjects will enter a screening period of up to 28 days during which they will record their APS on a diary card. If their AAPS is >5 and they satisfy all other eligibility criteria, they will be randomized in a 1:1 ratio to receive APD371 doses of 25 mg or 100 mg capsules TID for 8 weeks (until Day 56). If subjects on APD371 100 mg TID experience hypotensive symptoms (SBP <90 or DBP<50 mmHg) at any stage during the course of study treatment, they will be titrated down to APD371 75 mg TID, or to 50 mg TID if this recurs. *Now reads:* Subjects will enter a screening period of up to 28 days during which they will record their APS on a diary card. If their AAPS is >5 and they satisfy all other eligibility criteria, they will be randomized in a 1:1 ratio to receive APD371 doses of 25 mg or 100 mg capsules TID for 8 weeks (until Day 56).	Deleted original dose reduction parameters and added more defined dose reduction parameters in Section 3.1 Overall Study Design and Plan.
22	**3.1 Overall Study Design and Plan** *Previously read:* There will be two PK assessment days at the beginning of the study Wk 0 (Day 1, 2) and two at the end of the study Wk 8 (Day -1) and Wk 8. A final follow-up visit will occur on Wk 10. *Now reads:* There will be two serial PK assessments; one at the beginning of the study Wk 0 (Day 1, 2) and another at the end of the study Wk 8 (Day -1) and Wk 8. A single PK collection will be performed in the clinic prior to the subject's first daily dose on Wks 2, 4 and 6. A final PK sample collection will be performed at the follow-up visit will occur on Wk 10. If subjects discontinue the study (Early Termination), a final PK sample will be collected.	Revised for additional clarification on composition of the PK sample collections and timing of the collections.
22	**3.1 Overall Study Design and Plan** *Deleted:*	Removed option for discontinuing overnight stay parameters and

	Following review of safety and tolerability of the first 6 subjects the Investigator may at their discretion; 1. Remove the Day 1 CRU overnight stay following TID treatment and discharge subjects from the CRU following completion of the last 10 hr post first dose (2hr post second dose) PK sample and vital sign evaluation. 2. Remove Visit 2 (Wk 0, Day 2); including all evaluations with the exception of APS assessments detailed by the subject at home in diary cards. 3. Remove Visit 8 (Wk 8); including all evaluations with the exception of APS and CDActivity index/stool frequency assessments (morning only) detailed in diary cards by the subject at home. These evaluations should be collected at a later date up to the follow-up visit, together with the return of study drug for compliance assessment.	noted clarification in Table 1, Schedule of Events.
22	**3.2 Study Duration and Dates** *Previously read:* Subjects will undergo Screening procedures within 29 days prior to dosing. If eligibility is confirmed, subjects will be checked-in at the clinical research unit (CRU) early morning on Day 1 they will overnight at the CRU on Day 1 during which they will be randomized, treated with their first dose of APD371 and assessed for safety, tolerability, PK and efficacy. They will then be allowed to return home 4 hours after the first dose of APD371 on Day 2. *Now reads:* Subjects will undergo Screening procedures within 29 days prior to dosing. If eligibility is confirmed, subjects will be checked-in at the clinical research unit (CRU) early morning on Day 1, they will overnight at the CRU on Day 1 during which they will be randomized, treated with their first dose of APD371 and assessed for safety, tolerability, PK and efficacy. They will then be allowed to return home 6 hours after the first dose of APD371 on Day 2.	Revised to update time when subject may return home on Day 2.
[redacted]	[redacted]	[redacted]



		
26	**3.4 Study Population** *Added:* Exceptions to eligibility criteria will not be granted by the Investigator or the Sponsor.	Clarification of no exceptions for eligibility.
31	**4.3 Packaging, Labeling and Storage** *Previously read:* 25 mg and 100 mg APD371 capsules will be packaged 30 count in 60cc HDPE bottles with a heat induction seal and child resistant screw cap. Each subject will be provided with 8 bottles of APD371 packaged drug product for the duration of the study, two bottles being dispensed on Day 1, Day 15, Day 29 and Day 43, respectively. If subjects in the 100 mg cohort are titrated down to a 75mg dose or to a 50 mg dose they may receive additional bottles. The 75 mg dose will be supplied by a combination of 50 mg and 25 mg capsules. A two week dispensation will consist of two bottles of 25 mg and two bottles of 50 mg APD371 drug product (4 bottles in total). 50 mg APD371 capsules will also be packaged 30 count in 40-cc HDPE bottles with heat induction seal and child resistant screw cap. Subjects returning for assessment at the end of Wk 2, 4, 6 should take their morning APD371 medication from their newly dispensed bottles for treatment periods Week 3-4, 5-6 and 7-8 respectively. *Now reads:*	Revised to accommodate potential dose reductions and clarification of 50 mg packaging size.

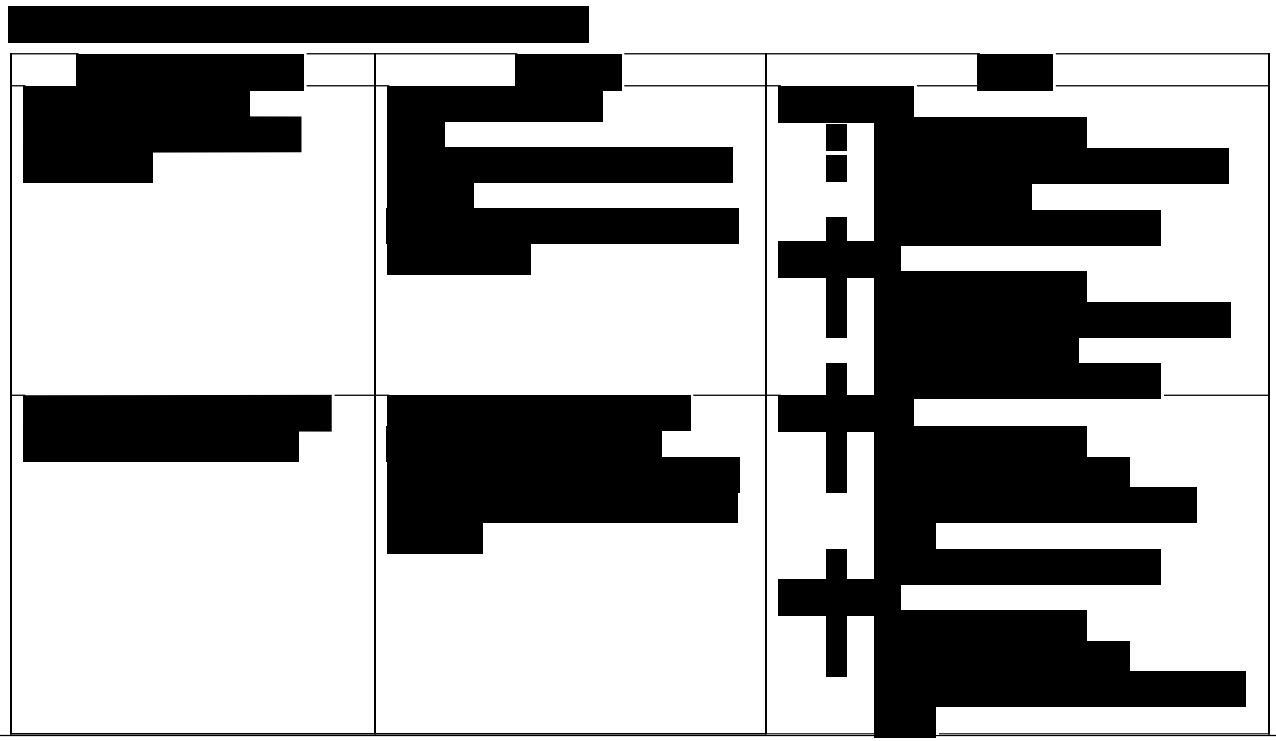
	25 mg and 100 mg APD371 capsules will be packaged 30 count in 60-cc HDPE bottles with a heat induction seal and child resistant screw cap. Each subject will be provided with 8 bottles of APD371 packaged drug product for the duration of the study, two bottles being dispensed on Day 1, Day 15, Day 29 and Day 43, respectively. If subjects in the 100 mg cohort are titrated down to a 50 mg dose they may receive additional bottles. The 50 mg APD371 capsules will also be packaged 30 count in 60-cc HDPE bottles with heat induction seal and child resistant screw cap. Subjects returning for assessment at the end of Wks 2, 4, 6 should take their morning APD371 medication from their newly dispensed bottles for treatment periods Wks 3-4, 5-6 and 7-8, respectively.	
32	**4.6 Dosage and Administration** *Previously read:* Investigational product will be dispensed to the subjects under the supervision of the Investigator or his/her designee as determined by the randomization schedule. Dispensing will occur every two weeks at Wk 0, 2, 4 and 6. Subjects should not crush, break, chew, or dissolve the capsules. There are no food restrictions around dosing with the exception of ingestion of grapefruit juice, prune juice or poppy seeds. For each of the planned dose cohorts (APD371 25 mg and 100 mg) subjects will self-administer study treatment TID (at approximately 07:00 ± 2 hr, 15:00 ± 2 hr and 23:00 ± 2 hr for 8 Wk) on Days 1 to 56. Subjects will be requested not to take their morning dose of study medication on the day of a planned study visit schedule (Wk 0 (Day 1 and Day 2), 2, 4, 6 and Wk 8 (Day-1)) until instructed to do so by the Investigator or his/her designee. There will be a total of 8 subjects randomized to each dose cohort. If subjects in the APD371 100 mg TID cohort experience hypotension, they will be titrated down to APD371 75 mg TID, or to 50 mg TID if this recurs. *Now reads:* Investigational product will be dispensed to the subjects under the supervision of the Investigator or his/her designee as determined by the randomization schedule. Dispensing will occur every two weeks at Wks 0, 2, 4 and 6. Subjects should not crush, break, chew, or dissolve the capsules. There are no food restrictions around dosing with the exception of ingestion of grapefruit juice, prune juice or poppy seeds or poppy seed containing items. For each of the planned dose cohorts (APD371 25 mg and 100 mg) subjects will self-administer study treatment TID (at approximately 07:00 ± 2 hr, 15:00 ± 2 hr and 23:00 ± 2 hr for 8 Wk) on Days 1 to 56. Subjects will be requested not to take their morning dose of study medication on the day of a planned study visit schedule (Wk 0 (Day 1 and Day 2), 2, 4, 6 and Wk 8 (Day-1)) until instructed to do so by the Investigator or his/her designee. There will be a total of 8 subjects randomized to each dose cohort.	Section amended to include dose adjustments, study drug stopping rules and safety measures to address adverse events, including hypotension and pulse.

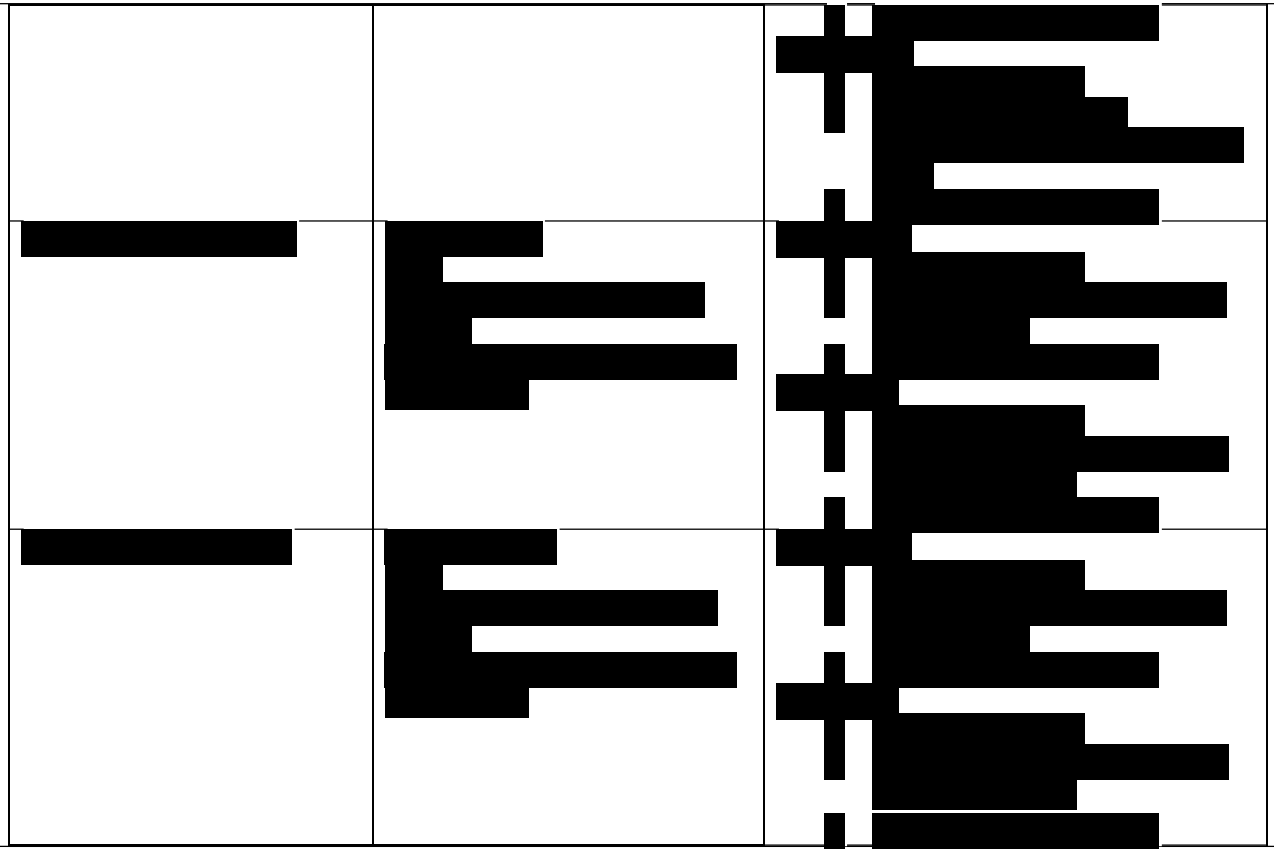
4.6.1 Dose Interruption and Stopping Rules

Adverse Events (AEs) of supine SBP decrease, supine DBP decrease, postural BP decrease, HR increase and HR decrease will be closely monitored. If such an AE occurs in patients taking the study drug, the Investigator must assess whether the AE meets the study drug interruption/stopping criteria and proceed as recommended in the below table.

If the study drug is interrupted due to the criteria described in the table, the patient will be evaluated as part of an unscheduled visit to assess their status and the Investigator will determine next course of action. If necessary, subsequent visits to assess the outcome of the event will be scheduled. Once the re-start criteria are met, study drug will be re-started under medical supervision. Additional visits may be scheduled at the investigator's discretion to more closely monitor patient status.

Any patient that develops postural hypotension will not be discharged from the clinical research unit with study drug until the event completely resolves and safety and tolerability of the reduced dose in the patient is confirmed.



		
35	**4.8.1 Randomization** *Previously read:* A sealed envelope containing the randomization code stratified by sex will be held by the Principal Investigator (PI) and the Arena Medical monitor in a secure yet accessible environment in case of emergency. *Now reads:* Subjects will be randomized after the Investigator has verified that they are eligible per criteria in Section 3.5 and Section 3.6. Subjects will then be enrolled into this study and assigned to APD371 25 mg TID or 100 mg TID according to a randomization schedule. Subjects will be randomized based on gender. Randomization will take place across all study sites using a centralized master list held by the study manager. When a site is ready to enroll a subject, they will contact the study manager to get the appropriate dose group assignment and unique subject number. The subject's identification number will be used on all of that subject's case report forms	Revised to clarify the randomization process across multiple sites.

	(CRF). Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment. All subjects must start treatment within 1 week of randomization.	
35	**4.8.3 Maintenance of Randomization Codes** *Previously read:* All personnel directly related to this study (i.e., Investigators, site personnel, monitors, CRO personnel, Sponsor personnel) will remain unblinded. If a subject experiences hypotensive symptoms (SBP <90 or DBP<50 mmHg) during the course of study drug treatment the investigator can instruct the pharmacy to dispense a APD371 75 mg dose. If hypotension still persists after treatment a APD371 50 mg dose can be dispensed. In either situation all other study medication should be returned to the pharmacy *Now reads:* All personnel directly related to this study (i.e., Investigators, site personnel, monitors, CRO personnel, Sponsor personnel) will remain unblinded.	Deleted dose reduction specifics now incorporated in 4.6.1.
35	**4.9 Concomitant Medications** *Added:* Stable doses of non-narcotic prescription medications required for treatment of current medical conditions other than pain (e.g., hypertension, thyroid disease, diabetes) may be continued during the screening and study period with the exception of medications known to be moderate or strong CYP3A4/5 inducers or inhibitors. Doses may be adjusted as appropriate per usual standards of care.	Amended to clarify acceptable use of non-narcotic medications during screening and study period and allowed adjustments.
35	**4.9 Concomitant Medications – 4.9.1 Not Permitted** *Previously read:* The following concomitant medication restrictions will apply: • **No prescription medications or hormonal contraceptives** are allowed within **30 days** prior to the Screening Visit, during the Screening period, and for the duration of the study. • No OTC medications are allowed, including analgesics or dietary supplements (vitamin, herbal, and mineral supplements) during the Screening period and for the duration of the study unless deemed appropriate by the Investigator for the treatment of an AE *Now reads:* • Prescription and OTC medications for pain relief (for exceptions, see Section 4.9.2 – Permitted) • Hormonal contraceptives for pain relief within 30 days prior to the Screening visit, during the Screening period, and for the duration of the study.	Amended to provide clarification on the use of medications for pain relief and hormonal contraceptions.

	• Dietary supplements (vitamin, herbal, and mineral supplements), unless deemed appropriate by the Investigator for the treatment of an AE.	

36	**4.9 Concomitant Medications – 4.9.2 Permitted**
	Previously read:
	The following medications are allowed in addition to pain relief medications for subjects who still have a AAPS>5;
	Now reads:
	• Pain rescue medications during screening or the treatment period including:
	  • For an inflammatory flare: prednisone at a dose of 40 mg orally daily, to be tapered by 5 mg per week.
	  • For severe pain: hyoscyamine at a dose of 0.25 mg tid prn pain
	• Pain relief medications such as NSAIDs or acetaminophen/paracetamol given at stable doses for at least 2 weeks prior to screening and for the duration of the study
		Amended to clarify the permitted use of pain relief medications and consistency with synopsis.

36	**4.9 Concomitant Medications – 4.9.2 Permitted** *Moved:* • Stable doses of NSAIDs or acetaminophen/paracetamol for at least 2 weeks prior to screening and to remain stable for the duration of the study	Removed pain relief medications from list of rescue mediations. Information added to section introduction.
36	**4.9 Concomitant Medications – 4.9.2 Permitted** *Previously read:* • Oral corticosteroid therapy (prednisone at a stable dose ≤ 20 mg/day, budesonide at a dose ≤ 9 mg/day, or equivalent steroid) provided that the dose has been stable for the 2 weeks immediately prior to screening or for the two* weeks immediately prior to randomization if corticosteroids are being tapered *Now reads:* • Oral corticosteroid therapy (prednisone at a stable dose of 30 mg/day, budesonide at a dose ≤ 9 mg/day, or equivalent steroid) provided that the dose has been stable for the 2 weeks immediately prior to screening or for the two weeks immediately prior to randomization if corticosteroids are being tapered.	Clarification of stable dose for prednisone that is more in-line with the clinical setting and removal of asterisk (*) referencing deleted comment.
36	**4.9 Concomitant Medications – 4.9.2 Permitted** *Deleted:* Corticosteroids ,Immunosuppressive agents, TNF α- antagonists, Integrin antagonists: See Appendix A for further details of use in screening	Information included in previous bullet points
36	**4.9 Concomitant Medications – 4.9.2 Permitted** *Deleted:* *All AAPS should be based on a stable dose of pain relief medication for the screening and treatment periods.	Clarification for stable doses incorporated into the individual bullet points.

36	**4.10 Restrictions – 4.10.1 Fluid and Food Intake** *Previously read:* There are no food restrictions around dosing with the exception of grapefruit, prune juice and poppy seeds. Subjects will be provided standardized meals (breakfast, lunch, dinner, snacks) per the Investigating site SOPs while housed in the clinic. Water, other than 240 mL administered with study medication, will not be permitted from 1 hour before until 1 hour after dosing, but will be allowed at all other times. *Now reads:* There are no food restrictions around dosing with the exception of grapefruit, prune juice and poppy seeds or poppy seed containing items. Subjects will be provided standardized meals (breakfast, lunch, dinner, snacks) per the Investigating site SOPs while housed in the clinic. 240 mL of water will be administered with study medication in the clinic at the time of dosing on Day 1 and Week 8 when the PK profile will be obtained. Water may be provided at all other times as needed.	Provide clarification on ingestion of poppy seed containing items and hydration during PK assessments and while on study.
37	**4.10 Restrictions – 4.10.2 Smoking** *Previously read:* Subjects who smoke, have a history of smoking or nicotine use, or use of nicotine containing products within 90 days prior to dosing will not be allowed into the study. Smoking or use of nicotine-containing products is not allowed during the inpatient period. *Now reads:* Subjects who smoke, have a history of smoking or nicotine use, or use of nicotine-containing products within 90 days prior to dosing will not be allowed into the study. Smoking or use of nicotine-containing products is not allowed during study participation.	Clarifying duration of smoking restriction.
37	**4.10 Restrictions – 4.10.3 Activity** *Previously read:* Subjects will not engage in strenuous activity at any time during the inpatient period. *Now reads:* Subjects will not engage in strenuous activity at any time during study participation.	Clarifying duration of activity restriction.
38	**5.2 Medical History** *Previously read:* During the Screening Visit, a complete medical history and a social history, including smoking, caffeine, and alcohol use, will be collected by subject interviewer. Concomitant medications, recent blood donations, illnesses, and participation in other investigational drug studies will also be recorded. A partial examination will be performed at Check-in to the CRU to update findings since the Screening Visit including the requirement for a AAPS >5 from a subject diary and to document any pre-treatment AEs. *Now reads:*	Clarification identifying review of subjects status prior to randomization.

	During the Screening Visit, a complete medical history and a social history, including smoking, caffeine, and alcohol use, will be collected by subject interviewer. Concomitant medications, recent blood donations, illnesses, and participation in other investigational drug studies will also be recorded. A review of the subjects screening medical history will be performed at the time of presentation on Day 1 (pre-treatment) to update findings including the requirement for a AAPS > 5 (from a subject diary) and to document any pre-treatment AEs.	
38	**5.3 Physical Examination** *Previously read:* Body measurements (height and weight) will be taken at the timepoints indicated in the Schedule of Events (Table 1). A complete physical examination including weight will be performed at the initial Screening visit. Abbreviated physical examinations will be completed at the final Screening visit and at the Follow-up Visit Wk 10. *Now reads:* Body measurements (height and weight) will be taken at the timepoints indicated in the Schedule of Events (Table 1). A complete physical examination including weight will be performed at the initial Screening visit. Abbreviated physical examinations (includes body weight and evaluation of changes to previously observed abnormal findings) will be completed at the time of presentation to the clinic prior to initial dose administration, at the Follow-up Visit Wk 10 and at early termination noting changes in any body system since the previous examination.	Amended to clarify timing of full and abbreviated examinations and review requirements for post initial screening exam.
38	**5.4 Vital Signs** *Previously read:* Supine blood pressure, pulse rate, temperature, and respiratory rate will be measured after the subject has been resting in the supine position for 5 minutes at the timepoints indicated in the Schedule of Events (Table 1). Vitals signs will be measured after any 12-lead ECG measurement but prior to any blood draw that is scheduled at the same timepoint. Pulse rate will be measured with a pulse oximeter. *Now reads:* Supine blood pressure, pulse rate, temperature, and respiratory rate will be measured after the subject has been resting in the supine position for 5 minutes at the timepoints indicated in the Schedule of Events (Table 1). All once daily vital sign assessments are to take place before morning dosing or equivalent times when not dosed at approximately 08:00. Vitals signs will be measured after any 12-lead ECG measurement but prior to any blood draw that is scheduled at the same timepoint. Pulse rate will be measured with a pulse oximeter. Active-Standing Test The Active-Standing Test that measures BP and heart rate before and after changing the position from supine to standing will also be performed. The test will be performed by the bedside by measuring blood pressure (BP) and heart rate after the subject has been resting in the supine position for 5 minutes and then after 1 and 3 minutes of standing.	Amended to include assessments of orthostatic parameters.

	The test will be performed at the following timepoints: • Day 1: pre-dose, 2, 4, 6, 8 and 10 hours after first dose • Day 2: 2, 4 and 6 hours after the first dose • Weeks 1, 2 4, 6 and 8 visits 2 hours after the first dose. The active-standing test will be performed if subjects discontinue the study (Early Termination).	
39	**5.5 Abdominal Pain Assessment – 5.5.1 Abdominal Pain Score and Average Abdominal Pain Score** *Previously read:* Note: Subjects will also be required to complete the diary before their first morning dose on Wk 0 (Day 1), and at the End-of-Treatment Visit at Wk 8 in the early morning (06:00 - 08:00). *Now reads:* Note: Subjects will also be required to complete the diary before their first morning dose on Wk 0 (Day 1), and at the End-of-Treatment Visit at Wk 8 in the early morning (06:00 - 08:00). If a subject discontinues the study, Early Termination, the APS score will be assessed.	Amended to include assessment at time of early termination.
40	[redacted]	[redacted]
41	**5.9 Clinical Laboratory Tests** *Added:* Protocol-required laboratory testing will be collected during screening to determine eligibility. Clinical laboratory tests will be repeated at pre-treatment on Wk 0 (Day 1), pre-treatment at the end of Wk 4 and 8 (Day -1), at the Follow-up visit (Wk 10) and in the event of early termination.	Clarification on laboratory assessments from screening through study conduct, including early termination.
41	**5.9 Clinical Laboratory Tests – 5.9.1 Laboratory Parameters** *Previously read:* **Other** Serum/urine pregnancy test (females only), Thyroid function tests (TSH, T4, and free T4), C-reactive Protein *Now reads:* **Other**	Clarifying collection period for Thyroid function tests.

<table>
<tr><td></td><td>Serum/urine pregnancy test (females only), Thyroid function tests [(TSH, T4, and free T4) - Screening only], C-reactive Protein</td><td></td></tr>
<tr><td>42</td><td>5.11 Pharmacokinetic sampling

Previously read:
Pharmacokinetic samples for the assay of APD371 and metabolites M1 [redacted], M2 [redacted], and M4 [redacted] will be collected will be collected at the visit time points indicated in the Schedule of Events (Table 1) and detailed in Pharmacokinetic sampling, Table 2.

Table 2. Pharmacokinetic sampling
<table><tr><th>Study Day</th><th>Blood sampling assessments*</th></tr><tr><td>Wk 0 (Day 1)</td><td>Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9 and 10 hours post first daily dose.</td></tr><tr><td>Wk 0 (Day 2)</td><td>24 hours post dose first daily dose on Day 1</td></tr><tr><td>Wk 2</td><td>Prior to first daily dose</td></tr><tr><td>Wk 4</td><td>Prior to first daily dose</td></tr><tr><td>Wk 6</td><td>Prior to first daily dose</td></tr><tr><td>Wk 8 (Day -1)</td><td>Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9, 10 post first daily dose.</td></tr><tr><td>Wk 8 (End-of-Treatment)</td><td>24 hours post dose first daily dose on Wk 8 (Day-1)</td></tr></table>
Now reads:
Pharmacokinetic samples for the assay of APD371 and metabolites M1 [redacted], M2 [redacted], and M4 [redacted] will be collected will be collected at the visit time points indicated in the Schedule of Events (Table 1) and detailed in Pharmacokinetic sampling, Table 3.

Table 1. Pharmacokinetic sampling
<table><tr><th>Study Day</th><th>Blood sampling assessments*</th></tr><tr><td>Wk 0 (Day 1)</td><td>Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9 and 10 hours post first daily dose.</td></tr><tr><td>Wk 0 (Day 2)</td><td>24 hours post dose first daily dose on Day 1</td></tr><tr><td>Wk 2</td><td>Prior to first daily dose</td></tr><tr><td>Wk 4</td><td>Prior to first daily dose</td></tr><tr><td>Wk 6</td><td>Prior to first daily dose</td></tr><tr><td>Wk 8 (Day -1)</td><td>Prior to and 0.5, 1, 2, 4, 6, 8 (prior to second daily dose), 9, 10 post first daily dose.</td></tr><tr><td>Wk 8 (End-of-Treatment)</td><td>24 hours post dose first daily dose on Wk 8 (Day-1)</td></tr></table>* Allowable windows for sample collection:</td><td>Correction of Table numbering and addition of collection windows.</td></tr>
</table>

	- time points up to 4 hours: ± 5 mins - time points after 4 hours: ± 15 mins	
49	**5.15 Allowable Visit and Procedure Windows** *Previously read:* All visit and procedure windows are detailed in Table 1 study schedule. *Now reads:* The following are allowable windows for study visits and procedures: • Study visits: - Wks 2, 4, 6, 8 and 10 (Follow-up): ± 2 days • Vital signs and Active-Standing Test: - Pre-dose timepoint: - 15 mins - Post-dose timepoints: ± 15 min	Amended to include visit and procedure windows.
50	**6 STUDY ACTIVITIES – 6.1 Screening Visits Wk -4 to Wk -1 (Days -28 to -1)** *Previously read:* • Physical examination (complete examination) *Now reads:* • Physical examination (complete examination) at initial screening visit	Amended to clarify timing for examination.
50	**6 STUDY ACTIVITIES – 6.1 Screening Visits Wk -4 to Wk -1 (Days -28 to -1)** *Added:* • Abbreviated physical exam (includes body weight and evaluation of changes to previously observed abnormal findings) at final screening visit	Amended to clarify type and timing for examination.
50	**6 STUDY ACTIVITIES – 6.1 Screening Visits Wk -4 to Wk -1 (Days -28 to -1)** *Previously read:* • Serum hCG pregnancy test (females only) *Now reads:* • Serum hCG pregnancy test (females only) at the initial screening visit	Amended to clarify timing for examination.
50	**6 STUDY ACTIVITIES – 6.1 Screening Visits Wk -4 to Wk -1 (Days -28 to -1)** *Added:* • Urine pregnancy test (females only) at the final screening visit	Amended to clarify type and timing for examination.
50	**6 STUDY ACTIVITIES – 6.1 Screening Visits Wk -4 to Wk -1 (Days -28 to -1)** *Previously read:* • Clinical laboratory tests (hematology, serum chemistry, coagulation, CRP, thyroid function tests [TSH, T4, and free T4] and urinalysis) *Now reads:*	Amended to clarify timing for assessment.

	• Clinical laboratory tests to include hematology, serum chemistry, coagulation, CRP, thyroid function tests (TSH, T4, and free T4 at initial Screening visit only) and urinalysis	
50	**6 STUDY ACTIVITIES – 6.1 Screening Visits Wk -4 to Wk -1 (Days -28 to -1)** *Previously read:* • total Simple Endoscopic Score (SES-CD) score < 6 or ileal SES-CD < 4 or FCP < 300. Endoscopy results obtained within 1 month prior to screening may be utilized *Now reads:* • Total Simple Endoscopic Score (SES-CD) score < 6 or ileal SES-CD < 4 or FCP < 300 mcg/g. Endoscopy results obtained within 1 month prior to screening may be utilized	Clarified units associated with FCP result.
51	**6 STUDY ACTIVITIES – 6.3.1 Wk 0 (Day 1) Pre-treatment** *Previously read:* • Vital signs *Now reads:* • Vital signs and Active-Standing Test	Addition of Active-Standing Test to scheduled procedures
51	**6 STUDY ACTIVITIES – 6.3.2 Wk 0 (Day 1) Post treatment** *Previously read:* • Vital signs • 12-lead ECG • Abdominal Pain Score before dosing and 1.5 hr after first morning dose *Now reads:* • Vital signs and Active-Standing Test • 12-lead ECG at 1.5 hours after initial Day 1 dose • Abdominal Pain Score at 1.5 hr after first morning dose	Clarification of assessments and times.
52	**6 STUDY ACTIVITIES – 6.3.3 Wk 0 (Day 2)** *Previously read:* • Vital signs *Now reads:* • Vital signs and Active-Standing Test	Addition of Active-Standing Test to scheduled procedures
52	**6 STUDY ACTIVITIES – 6.3.3 Wk 0 (Day 2)** *Deleted:* If there are no immediate safety concerns, the subject will be discharged from the CRU approximately 4 hours after the morning dose.	Deleted as protocol requires all subjects to stay overnight on Day 1.

	Following review of the safety and tolerability of first 6 subjects the Investigator may at their discretion, remove the Wk 0 (Day 1) CRU overnight stay and discharge subjects from the CRU following completion of the last 10 hr post first-dose PK sample. On Day 2 subjects will continue with their three times daily APS assessments, but an assessment visit will not be required.	
52	**6 STUDY ACTIVITIES – 6.3.4** *Previously read:* 6.3.4 Wk 0 to 8 (Day -1) (Days 3 to 56) *Now reads:* 6.3.4 Wk 0 to 8 (Day -1) (Days 1 to 56)	Clarification on start day.
52	**6 STUDY ACTIVITIES – 6.3.5 End of Wk 1, 2, 4, 6** *Previously read:* • Vital signs *Now reads:* • Vital signs and Active-Standing Test	Clarification for addition for active-standing assessment
52	**6 STUDY ACTIVITIES – 6.3.5 End of Wk 1, 2, 4, 6** *Added:* Compliance will be assessed based on all returned bottles and treatment duration at Wks 2, 4, 6 and 8	Inclusion of dose administration compliance to visit schedule.
53	**6 STUDY ACTIVITIES – 6.3.6 Wk 8 (Day -1)** *Previously read:* • Vital signs *Now reads:* • Vital signs and Active-Standing Test	Clarification for addition for active-standing assessment
53	**6 STUDY ACTIVITIES – 6.3.6 Wk 8 (Day -1)** *Added:* [redacted]	Inclusion of [redacted] to visit schedule.
53	**6 STUDY ACTIVITIES – 6.3.7 Wk 8 End of Treatment** *Previously read:* • Vital signs *Now reads:* • Vital signs and Active-Standing Test	Clarification for addition for active-standing assessment

53	**6 STUDY ACTIVITIES – 6.3.7 Wk 8 End of Treatment** *Previously read:* Following review of safety and tolerability of the first 6 subjects the Investigator may at their discretion remove Visit 8 (Wk 8); including all evaluations with the exception of APS and [redacted] detailed in diary cards by the subject at home. These evaluations should be collected at a later date up to the follow-up visit, together with the return of study drug for compliance assessment *Now reads:* Each subject will be evaluated continuously by the Investigator and Sponsor with regards to safety, and then the decision will be made on a case-by-case basis on whether the subject needs to stay overnight at Week 8 to be assessed for safety, including blood pressure and heart rate. If the decision to remove the Visit 8 (Wk 8) overnight stay has been determined, all scheduled evaluations still must be done, including serial PK collections vital signs, active-standing test, APS, [redacted] detailed in the diary cards.	Amended to clarify the safety review of each subject for determination of Visit 8 overnight stay and procedures to be performed if overnight stay is not required.
54	**6 STUDY ACTIVITIES – 6.4 Early Termination Procedures** *Previously read:* • Physical examination (abbreviated examination including body weight measurement) • Vital signs • 12-lead ECG • Serum hCG pregnancy test (females only) • Final PK blood sample • Clinical laboratory tests (to include hematology, serum chemistry, coagulation, and urinalysis) • Record AEs • Record concomitant medications *Now reads:* • Physical examination (abbreviated examination including body weight and evaluation of changes to previously observed abnormal findings) • Vital signs and Active-Standing Test • 12-lead ECG • Serum hCG pregnancy test (females only) • Final PK blood sample • Clinical laboratory tests (to include hematology, serum chemistry, coagulation, and urinalysis) • Abdominal Pain Score • [redacted] • Record AEs	Amended to include Active-Standing Test, Abdominal Pain Score, [redacted] for subject who terminate the study early.

	• Record concomitant medications	
54	**6 STUDY ACTIVITIES – 6.5 Wk 10 Follow-up Visit Procedures** *Previously read:* • Physical exam (abbreviated examination including body weight and evaluation of changes to previously observed abnormal findings) • Vital signs • 12-lead ECG • Serum hCG pregnancy test (females only) • Clinical laboratory tests (to include hematology, serum chemistry, coagulation, CRP and urinalysis) • Record AEs • Record concomitant medications *Now reads:* • Physical exam (abbreviated examination including body weight measurement) • Vital signs and Active-Standing Test • 12-lead ECG • Serum hCG pregnancy test (females only) • Clinical laboratory tests (to include hematology, serum chemistry, coagulation, CRP and urinalysis) • Record AEs • Record concomitant medications The Principal Investigator and study site staff should exert every effort to secure subject attendance to the Follow-Up visit. Three attempted telephone contacts should be documented by study personnel before a subject can be considered lost to follow-up. Furthermore, key research personnel should mail a certified letter to the subject's address if no response to 3 telephone contacts remain unanswered. If the subject or a family member does not respond, the certified letter receipt should be filed in the individual's research record with a copy of the letter sent.	Amended to clarify abbreviated physical examination, include Active-Standing Test and provide clarification on process to appropriately document subject lost to follow-up.
61	**9 REGULATORY REQUIREMENTS – 9.1 Pre-study Documentation** *Previously read:* The Sponsor must receive the following documentation prior to initiation of the study: *Now reads:* The Sponsor or designee must receive the following documentation prior to initiation of the study:	Clarify responsibility may be assigned to sponsor designee.
61	**9 REGULATORY REQUIREMENTS – 9.1 Pre-study Documentation** *Deleted:* Documents should be faxed or mailed to the Sponsor Contact at the following address: [redacted] Director, Clinical Operations	Not required for this study.

	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121 Phone: [redacted] ext. [redacted] Fax: email: [redacted]	
66	**12 REFERENCES** *Added:* 15. Shibao C, Lipsitz LA, Biaggioni I. ASH Position Paper: Evaluation and Treatment of Orthostatic Hypotension. The Journal of Clinical Hypotension 2013; (15):147-153. 16. Vilela EG, Gama Tores, HO, et. al. Evaluation of inflammatory activity in Crohn's disease and ulcerative colitis. World J Gastroenterol 2012; 18(9):872-881.	Additional references
77	**Appendix A** *Deleted*	Information clarified in main body of the protocol.