# Statistical Analysis Plan

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

**Protocol Number:** APD371-004

**Product Name:** APD371

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APPROVAL SIGNATURES

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

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Date

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AAPS | average abdominal pain score |
| AE | adverse event |
| ANCOVA | analysis of covariance |
| APS | abdominal pain score |
| $AUC_{0-8}$ | area under the plasma concentration-time curve from time zero to 8 hours post-dose |
| BP | blood pressure |
| BMI | body mass index |
| bpm | beats per minute |
| [redacted] | [redacted] |
| CI | confidence interval |
| $C_{max}$ | maximum plasma concentration |
| CRP | C-reactive protein |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DBL | database lock |
| DBP | diastolic blood pressure |
| [redacted] | [redacted] |
| ET | early termination |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EOT | end-of-treatment |
| HR | heart rate |
| ICH | International Conference on Harmonization |
| IFN-g | interferon gamma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mmHg | millimeters of mercury |
| NRS | numerical rating scale |
| [redacted] | [redacted] |
| PK | pharmacokinetic(s) |
| PR | PR interval |
| PRN | as needed |
| PRO | patient-reported outcome |
| PT | preferred term |
| QTc | corrected QT interval |
| RR | inter-beat interval |
| SAE | serious adverse event |

| | |
|---|---|
| SAP | statistical analysis plan |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SES-CD | simple endoscopic score Crohn's disease |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| TID | 3 times a day |
| $t_{max}$ | time of maximum plasma concentration |
| TNF | tumor necrosis factor |
| WHO | World Health Organization |
| Wk | week |

**Statistical Analysis Plan Amendment 1: Summary of Changes**

The original statistical analysis plan (SAP) was approved on 12 September 2018, prior to the database lock (DBL) on 14 September 2018. This SAP amendment reflects the following changes, which are being incorporated after the DBL (original 14 September 2018, relock 19 November 2018):

- Correct minor typographical errors and inconsistencies regarding the footnotes on the tables, figures, and listings.
- The evaluation of the pharmacokinetics of APD371 is outlined in a standalone pharmacokinetics SAP (dated 23 January 2019).
- [redacted]
- The definitions of orthostatic hypotension and postural tachycardia (Section 9.2.2) have been clarified and impacted table and listing footnotes have been updated.
- The analysis populations have been added to titles of listings in Section 13.
- All tables, figures, and listings have been renumbered per ICH E3 "Structure and Content of Clinical Study Reports."
- Nine new tables, 4 new listings, and 5 new figures have been added:
  - Table 14.1.6.2. Crohn's Disease Medical History (Safety Population)
  - Table 14.2.4. Summary of Daily Abdominal Pain Scores (Efficacy Population)
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- [redacted]
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- [redacted]

# 1. INTRODUCTION

This statistical analysis plan (SAP) provides the statistical rationale and methods to be implemented during the analysis of data collected within the scope of clinical trial protocol APD371-004 to assess the tolerability and efficacy of APD371 in subjects with Crohn's disease (CD) experiencing abdominal pain.

The evaluation of the pharmacokinetics (PK) of APD371 is outlined in a standalone PK SAP (dated
23 January 2019)

This SAP has been written according to protocol APD371-004 Amendment 2, dated 10 August 2017.

# 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 (Wks).

## 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 three times a day (TID)
- To assess change in abdominal pain score (APS) from pre-dose (trough) to 1.5 hours 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 (EOT) responders
- To determine the number of pain-free days per week in each treatment cohort, based on responses to the APS

[redacted]

- To assess pain medication use in each treatment cohort
- To assess the effect of APD371 treatment on reduction in C-Reactive Protein (CRP) and other biomarkers at Wk 4 and Wk 8
- To assess the effect of APD371 treatment on reduction in fecal calprotectin at Wk 4 and Wk 8

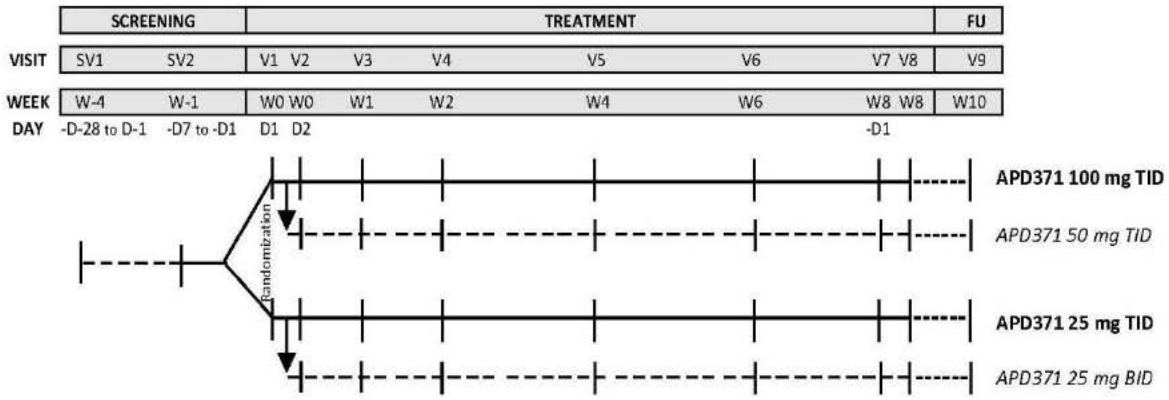
[redacted]

# 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, parallel group comparison consisting of two cohorts dosed with APD371 in up to a total of 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**




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). If subjects on APD371 100 mg TID experience hypotensive symptoms (systolic blood pressure [SBP] <90 or diastolic blood pressure [DBP] <50 mmHg) at any stage during study treatment, they will be titrated down to 50 mg TID.

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, adverse event (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.

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

## 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.

## 3.3. Study Endpoints

### 3.3.1. Primary Endpoints

There is no primary endpoint in this study.

### 3.3.2. Exploratory Endpoints

#### 3.3.2.1. Abdominal Pain Score (APS) and Average Abdominal Pain Score (AAPS)

The APS is a PRO using a numerical rating scale (NRS) which is recorded in a subject diary. The 11-point NRS 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 Period**

APS is recorded twice daily for at least 7 consecutive days within the 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

To establish a baseline for AAPS the following procedure will be adopted:

The last diary entry prior to treatment will be identified. The 7 consecutive days that terminate with this last data point constitute the Screening reference period. Baseline for AAPS is the mean of non-missing pain scores within the Screening reference period.

**During Treatment Period**

APS is recorded 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 (i.e., at trough APD371 concentration)
2. Approximately 1.5 hours after the morning dose (i.e., at peak APD371 concentration)
3. Before the evening dose (i.e., at evening trough ADP371 concentration)

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

It should be noted that:

- The AAPS is derived for each assessment period (Wks 1, 2, 4, 6, 8). For Wks 4, 6, and 8 scores are collected from the previous 7 days of diary entries prior to the visit day. 'Peak AAPS' is the mean of non-missing APS recorded at the time of peak concentration for those 7 days. Likewise, 'Trough APS' is the mean of non-missing APS recorded at the time of trough concentration for those 7 days. Similarly, 'Evening Trough APS' is the mean of non-missing APS recorded at the time of evening trough concentration for those 7 days. Wk 1 and Wk 2 peak, trough, evening trough, and overall AAPS are derived in a similar manner but note that:
    - For Wk 1, as Day 1 is neither peak nor trough, and APS scores cannot be accurately identified as pre-dose or post-dose, scores on Day 1 are disregarded. Hence, AAPS scores may be obtained from fewer than 7 days.
    - No APS score will contribute to more than 1 visit. Therefore, Wk 2 scores may be derived from fewer than 7 days (if the Wk 1 and Wk 2 Visits are less than 7 days apart).
    - Summary pain scores were auto-calculated and entered in the database. However, AAPS has been programmatically derived directly from the raw diary data using the above rules.

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

#### 3.3.2.2. Pain Relief Responders

Pain relief responders are defined as follows:

- A weekly pain relief responder at peak is defined as a subject who, in each week, has ≥30% reduction in peak AAPS from their Baseline AAPS.
- A weekly pain relief responder at trough is defined as a subject who, in each week, has ≥30% reduction in trough AAPS from their Baseline AAPS.
- A weekly pain relief responder at evening trough is defined as a subject who, in each week, has ≥30% reduction in evening trough AAPS from their Baseline AAPS.
- A weekly pain relief responder for average daily pain is defined as a subject who, in each week, has ≥30% reduction in average daily AAPS (averaged over peak, trough and evening trough diary entries) from their Baseline AAPS.
- An EOT pain relief responder at peak, trough, evening trough, and daily average is

defined as ≥30% reduction in peak, trough and average daily AAPS respectively from Baseline at EOT.

[redacted]

### 3.3.2.5. C-Reactive Protein (CRP)

CRP is measured at Baseline, Wk 4, and Wk 8.

### 3.3.2.6. Fecal Calprotectin

A stool sample is collected at Screening, Wk 4, and Wk 8. Fecal calprotectin level is recorded.

[redacted]

### 3.3.2.8. Number of Pain-Free Days

The number of pain-free days per week is recorded by visit (Screening, Wks 1, 2, 4, 6, 8). The screening score will be derived from the last 7 days of the Screening period.

### 3.3.2.9. Pain Rescue Medication

Pain rescue medication use during Screening or the Treatment period is defined as prednisone at a dose of 40 mg orally daily or hyoscyamine at a dose of 0.25 mg TID or as needed (PRN).

# 4. GENERAL STATISTICAL CONSIDERATIONS

This SAP was developed based on International Council on Harmonization (ICH) E3 and E9 Guidelines. This SAP should be read in conjunction with the study protocol and electronic case report forms.

Unless otherwise noted, the summary of continuous variables will include the number of non-missing observations (n), arithmetic mean, median, standard deviation (SD), minimum, and maximum. Percentages will be calculated using the number of subjects within group and overall as the denominator.

All statistical analyses will be conducted using SAS® software (Version 9.4 or higher, SAS Institute Inc., Cary, NC).

## 4.1. Determination of Sample Size

No formal sample size or power calculations were performed. For this initial study in subjects, it is planned to treat and complete safety and tolerability assessments in approximately16 subjects, which is reasonable to assess the primary and exploratory study endpoints. Since subjects may be 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.

## 4.2. Methods of Assigning Study Participants to Treatment Groups

Subjects who meet all the entry criteria and are eligible for the study will report to the investigator to be randomized on Day 1. Eligible subjects will be randomly assigned to receive 1 of 2 study treatments, either APD371 100 mg TID or APD371 25 mg TID in a 1:1 ratio. The investigator will randomize up to 20 subjects for entry from a sealed envelope held by the Sponsor clinical trial manager.

If a subject in the APD371 100 mg TID group experiences hypotensive symptoms (SBP <90 or DBP <50 mmHg) during the course of study drug treatment, the investigator can instruct the pharmacy to dispense an APD371 50 mg dose. In this situation all other study medication should be returned to the pharmacy.

The analyses for all safety outcomes will use the Safety population which consists of all randomized subjects who received at least 1 dose of study drug; in addition, if a subject is found to have taken a study therapy for the entire duration of the study different from that to which they was randomized, then the subject is counted in the treatment group of the drug they actually received.

## 4.3. Randomization and Stratification

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

Randomization will take place across all study sites using a centralized master list held by the Sponsor clinical trial manger, in consultation with the Medical Monitor. 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 electronic case report forms (eCRF). 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.

## 4.4. Blinding

This is an open-label study. For each dose cohort, the Sponsor, contract research organization (CRO), study safety medical monitors, subjects, and personnel involved with the conduct of the study will be unblinded to the identity of study medication.

## 4.5. Analysis Populations

The following analysis sets are defined in this study:

- The Randomized population will include all randomized subjects**.**
- The Efficacy population will include all randomized subjects who received at least 1 dose of study medication and have completed at least 7 days of assessments of APS on treatment up to Wk 4. The analyses of all efficacy variables will use the Efficacy population.
- The Per Protocol population will comprise all members of the Efficacy population without a major protocol violation that could affect the validity of efficacy assessments. The Per Protocol population will be used for the analysis of selected endpoints indicated in Section 8. The Per Protocol population will be identified prior to database lock.
- The Safety population will include all randomized subjects who received at least one dose of study medication. The analyses of all safety variables will use Safety population.

## 4.6. Multiple Comparisons/Multiplicity

Since this is an exploratory proof of concept study, no formal testing strategy or adjustments of p-values will be employed. Estimates and confidence intervals (CIs) for treatment groups and from pairwise comparisons will be used in an exploratory manner.

## 4.7. Data Handling

### 4.7.1. Baseline Definitions or Conventions

Unless, as specified in Section 3.3.2.1, the Screening period is used to derive a Baseline value, then Baseline value is defined as the Day 1 (randomization) measurement. If the Day 1 measurement is not available, the last non-missing pre-randomization measurement will be used as the Baseline value. For vital signs, where the time of the assessment is available, the last pre-treatment assessment on Day 1 will be the Baseline value.

### 4.7.2. Time Points and Day Ranges

Since it is not always possible for all study participants to come in for their clinic visits on the exact day specified in the protocol schedule, the "Week" of a subject's visit will be defined by the relative day ranges described in Tables 1 to 3.

**Table 1. Mapping for Endpoints Measured at Day 1, Wk 4, and Wk 8**

| Time Point | Target | Study Days |
|---|---|---|
| **Baseline** | **Day 1** | **≤ Day 1** |
| Wk 4 | Day 29 | 2 ≤ Day ≤ 42 |
| Wk 8 | Day 56 | > Day 42 |

**Table 2. Mapping for Endpoints Measured at Day 1 and Wk 8 or Wk 8 EOT**

| Time Point | Target | Study Days |
|---|---|---|
| **Baseline** | **Day 1** | **≤ Day 1** |
| Wk 8 | Day 56 | > Day 1 |
| Wk 8 EOT | Day 57 | > Day 1 |

**Table 3. Mapping for Endpoints Measured at Day 1 and Wk 1 to Wk 8**

| Time Point | Target | Study Days |
|---|---|---|
| **Baseline** | **Day 1** | **≤ Day 1** |
| Wk 1 | Day 8 | 2 ≤ Day ≤ 11 |
| Wk 2 | Day 15 | 12 ≤ Day ≤ 18 |
| Wk 3 | Day 22 | 19 ≤ Day ≤ 25 |
| Wk 4 | Day 29 | 26 ≤ Day ≤ 32 |
| Wk 5 | Day 36 | 33 ≤ Day ≤ 39 |
| Wk 6 | Day 43 | 40 ≤ Day ≤ 46 |
| Wk 7 | Day 50 | 47 ≤ Day ≤ 53 |
| Wk 8 | Day 56 | > Day 53 |

If a subject has more than one assessment in a window, the assessment date closest to the target date will be selected. If a subject has 2 assessments that are equidistant from the target date, the later assessment will be selected.

### 4.7.3. Missing Data

As described in Section 8.3, in responder analyses, subjects with missing data will be classified as non-responders. Otherwise, there will be no imputation of missing data.

# 5. SUBJECT DISPOSITION

## 5.1. Study Populations

The number and percentage of subjects in each analysis population will be summarized by treatment group. Subject inclusion in each analysis population will be presented in a subject listing.

Reasons for exclusion from the Per Protocol population will be listed.

## 5.2. Disposition

The number of subjects enrolled in the study by investigator and treatment group will be tabulated. Subject disposition will be summarized by treatment group and will include the number of subjects who were randomized into the study, the number of subjects who completed the study, and the number of subjects who discontinued prematurely (ET) for any of the following reasons:

- Deviation/noncompliance with the protocol or study drug
- Adverse event(s)
- Investigator decision
- Sponsor decision
- Subject withdrawal of consent
- Subject lost to follow up
- Death
- Other

## 5.3. Protocol Violations

Significant protocol violations will be tabulated displaying frequencies and percentages of the Efficacy population falling into the following categories:

- Treated despite violating inclusion criterion 8 (i.e., screening AAPS of $\geq 4$)
- Treated with dose other than the dose the subject was randomized to receive
- Developed withdrawal criterion but was not discontinued from treatment
- Less than 80% compliance

# 6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

## 6.1. Demographics

Demographic and baseline characteristics data (age, height, weight, BMI), social history (smoking, caffeine, alcohol use), medical history (abnormalities only), physical examination (abnormalities only), and concomitant medications at study entry will be listed for all subjects. Demographic and Baseline Characteristics of the Safety and Efficacy populations will be summarized by treatment group and for the overall population.

Baseline for the demographic and baseline characteristic variables will be the last pre-randomization value.

Continuous variables will be summarized using number of observations (n), mean, SD, median, minimum, and maximum. Frequencies and percentages will be reported for all categorical data. No formal statistical testing comparing treatment groups will be performed.

The following variables will be summarized by treatment group and overall:

Continuous demographic and Baseline characteristic variables: age (years), height (cm), weight (kg), body mass index (BMI; $kg/m^2$), and simple endoscopic score Crohn's disease (SES-CD).

Categorical demographic and Baseline characteristic variables: sex (female or male), ethnicity (Hispanic/Latino or Not Hispanic/Not Latino) and race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Other, specify) nicotine consumption (never, former, current), and alcohol consumption (never, former, current).

Baseline SES-CD, an optional assessment by colonoscopy, will be presented in subject listing.

## 6.2. Medical History

During the Screening Visit, a complete medical history 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 subject's screening medical history will be performed at the time of presentation on Day 1 (pre-treatment) to update findings including the requirement for an AAPS ≥4 (from a subject diary) and to document any pre-treatment AEs. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 21.0).

A summary of medical history, which includes the number (%) of subjects in each treatment group classified according to MedDRA system organ class (SOC) and preferred term (PT) will be provided, as well as a subject listing.

# 7. TREATMENT AND MEDICATIONS

## 7.1. Prior and Concomitant Medications

Medications administered prior to but not during study treatment were considered as prior medications. Medications initiated prior to start of study treatment and maintained during the study, or taken during the course of the study, were considered as concomitant medications. Medications with partial or missing start dates were assumed to be concomitant medications, unless there was clear evidence) to suggest that the medications were not taken during study. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2018).

## 7.2. Study Treatments

The duration of treatment for each subject will be assessed by descriptively summarizing the number of weeks on drug, both as a continuous and categorical variable (e.g., <1 week). In addition, the average daily dose (mg), total exposure (mg), and total duration of treatment in subject-weeks will be summarized by treatment group and overall.

## 7.3. Study Treatment Compliance

Compliance will be assessed using subject data recorded in the drug accountability form of the eCRFs. On each day, a subject should take their assigned treatment. The compliance rate for each subject will be computed as 100% × (actual number of tablets taken over the study period)/ (designated total number of tablets that should have been taken over the study period). Study period is defined as the number of days that the subject has been in the active treatment phase of the trial. Compliance rates will be summarized for each treatment group and overall.

# 8. EFFICACY ANALYSES

Complete specifications given below assume that the final sample size will allow for inferential statistical analysis. If the number of subjects analyzed is very low some, or all, inferential procedures will no longer be appropriate.

## 8.1. Abdominal Pain Score (APS)

For each subject, APS score measured at peak will be averaged over the entire treatment period. Likewise, the APS score measured at trough will be averaged for each subject. The difference (peak - trough) will be calculated, per subject, as mean (peak) - mean (trough).

Mean peak, trough, and peak - trough will be summarized by treatment and overall. The peak - trough differences will be analyzed between treatments using an analysis of covariance (ANCOVA) model with treatment as a factor and Baseline score as a covariate. The 95% CI for the adjusted treatment difference will be presented together with the p-value. For the pooled data, a 1-sample t-test will be conducted testing against the hypothesis of zero difference between peak and trough. The 95% CI for the overall difference between peak and trough assessments will be presented.

Additionally, the APS score measured prior to evening dose (evening trough) will be averaged for each subject. The difference (peak - evening trough) will be calculated, per subject, as mean (peak) - mean (evening trough). The analysis will be repeated using mean peak, evening trough, and peak - evening trough and will be summarized by treatment and overall.

## 8.2. Average Abdominal Pain Score (AAPS)

AAPS is the average of the APS score over each weekly assessment period (Wks 1, 2, 4, 6, 8). The Baseline value of AAPS will be derived as the average of the last (most recent) non-missing 7 days of morning and evening diary records within the Screening period prior to Day 1 of treatment. During the treatment period, summaries for a nominal week will be derived from the last 7 days within that period that contain a non-missing assessment. Summaries may be derived from fewer than 7 days (e.g., if the Wk 1 and Wk 2 Visits are less than 7 days apart). AAPS will be summarized for the Screening period and for each assessment week of treatment before morning dose (trough) assessments and 1.5 hours post-treatment first daily dose (peak) assessments, by treatment group and overall. Statistical comparisons of AAPS will be made between Screening and Wk 4 and Wk 8, trough and peak assessments, by treatment and overall. Change scores from Baseline for peak and trough at Wk 4 and Wk 8 will be derived. Treatment comparisons of the change scores will be analyzed using ANCOVA as for AAPS. The adjusted

treatment effect, 95% CI, and p-value will be presented. Overall changes from Baseline at Wk 4 and Wk 8 will be assessed using 1-sample t-tests as for AAPS. These analyses will be repeated for the Per Protocol population.

Peak and trough AAPS by treatment and visit will be plotted displaying treatment means and 95% CIs for the efficacy population only.

These analyses will be repeated where AAPS will be summarized for the Screening period and for each assessment week of treatment before evening dose (evening trough) assessments and 1.5 hours post first daily dose (peak) assessments, by treatment group and overall.

## 8.3. Pain Relief Responders

For each of Wks 1, 2, 4, 6, 8 a subject with a missing AAPS will be coded to non-responder. The number and proportion of responders for Wks 1 to 8 and at EOT will be tabulated by treatment group and overall. The difference in proportions of peak, trough, evening trough, and average daily pain weekly responders between the treatment groups at Wk 8 and EOT will be tested by Fisher's exact test and the p-value presented.

These analyses will be repeated for the Per Protocol population.

The percentage of peak, trough, evening trough, and average daily pain weekly responders will be plotted by treatment and visit for the Efficacy population only.

[redacted]

## 8.6. C-reactive protein (CRP)

CRP will be summarized by visit (Baseline, Wk 4, Wk 8). Within subject changes from Baseline at Wk 4 and Wk 8 will be analyzed by treatment and overall using dependent means t-tests. Mean change, 95% CIs and p-values will be presented. Changes from Baseline at Wk 4 and Wk 8/EOT will be analyzed using an ANCOVA model with treatment as a factor and Baseline value as a covariate. Adjusted treatment effects with p-values and 95% CIs will be presented. CRP by treatment and visit will be plotted for the Efficacy population displaying treatment means and 95% CIs. A scatterplot will be produced of change from Baseline in CRP and change from Baseline in peak AAPS at Wk 8 for all subjects (irrespective of treatment) in the Efficacy population. A regression line will be fitted.

## 8.7. Fecal Calprotectin

Fecal calprotectin will be summarized by visit (Baseline, Wk 4, Wk 8). Within subject changes from Baseline at Wk 4 and Wk 8 will be analyzed by treatment and overall using dependent means t-tests. Mean change, 95% CIs and p-values will be presented. Changes from Baseline at Wk 4 and Wk 8 EOT will be analyzed using an ANCOVA model with treatment as a factor and Baseline value as a covariate. Adjusted treatment effects with p-values and 95% CIs will be presented. Fecal calprotectin by treatment and visit will be plotted for the efficacy population displaying treatment means and 95% CIs. A scatterplot will be produced of change from Baseline in fecal calprotectin and change from Baseline in peak AAPS at Wk 8 for all subjects (irrespective of treatment) in the Efficacy population. A regression line will be fitted.

[redacted]

## 8.9. Number of Pain-Free Days

The number of pain-free days per week will be summarized by visit (Screening, Wks 1 to 8). The Screening score will be derived from the screening reference period as defined in Section 3.3.2.1. Because few subjects had pain-free days either at Screening or post-baseline, no inferential analyses will be conducted.

## 8.10. Use of Rescue Medication

The number of subjects using rescue medication during the Screening period and at any time during active treatment will be tabulated by treatment group and overall by shift table. Because of the paucity of data with respect to changes, no inferential analyses will be conducted.

# 9. SAFETY ANALYSES

Safety and tolerability will be assessed by a review of all safety parameters including AEs, laboratory safety parameters, vital signs, and ECG. Only summary tabulations (N, n, mean [or median], SD, mean [or median] change/percent change, percentage) and 95% CIs for between-group differences will be obtained. AEs will be presented as summary tabulations and listed.

## 9.1. Adverse Events

AEs will be coded using MedDRA (Version 21.0) 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. AEs will be regarded as 'pre-treatment' if they occur between Screening and the time of administration of the first dose of APD371 and will be recorded as medical history. All other AEs that occur after the first dose of study medication will be considered to be 'treatment-emergent'.

Treatment-emergent AEs (TEAE) will be listed by subject and by treatment. They will be summarized per treatment and expressed in terms of maximum severity and relationship to study medication. The incidence of TEAEs classified according to system organ class will be summarized by treatment group. TEAEs will also be summarized by maximum intensity (assessed according to the Common Terminology Criteria for Adverse Events v4.032 definitions) and relatedness to study medication.

Summaries of the number (%) of subjects in each treatment group with at least one TEAE, classified according to MedDRA system organ class (SOC) and preferred term (PT), will also be provided for:

- Drug-related TEAE
- TEAEs leading to permanent discontinuation of study medication (study medication discontinued or withdrawal from study).
- Serious adverse events (SAEs)

SAEs will be listed by subject and by treatment. If there are no SAEs at the end of the study, the tables or listings will state that there are no SAEs in the study.

## 9.2. Physical Examinations

Physical examination results (abnormalities only) will be listed and summarized by treatment group.

### 9.2.1. Vital Signs

Supine vital sign measurements (blood pressure, pulse rate, respiratory rate, and oral body temperature) are taken at the following timepoints:

- Initial and final Screenings
- Wk 0 (Day 1) prior to and 0.5, 1, 2, 4, 6 and 8 hours after the first daily dose (prior to second daily dose) and 9 and 10 hours (1 and 2 hours after the second daily dose).
- Once a day on Wk 0 (Day 2), at the end of Wk 1 (Day 8), 2, 4, 6 and 8 and at the Follow-up Visit at Wk 10
- Wk 8 (Day -1) prior to and 0.5, 1, 2, 4, 6 and 8 hours after the first daily dose (prior to second daily dose) and 9 and 10 hours (1 and 2 hours after the second daily dose).

All vital sign measurements will be listed by treatment. Assessments and changes from Baseline will be summarized for blood pressure (BP), pulse rate, respiratory rate, and temperature by treatment at all timepoints. Baseline is defined as the last pre-treatment measurement.

### 9.2.2. Active-Standing Test

The Active Standing Test measures BP and heart rate (HR) before and after changing the position from supine to standing. The test will be performed by the bedside by measuring BP and HR 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
- Wks 1, 2, 4, 6 and 8: 2 hours after the first dose

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

At each time point, differences between active-standing and supine assessments will be derived for SBP, DBP, and HR:

- Active Standing (1 minute) - Supine [redacted]
- Active Standing (3 minute) - Supine [redacted]

These derived variables and their changes from baseline will be summarized by treatment at all timepoints throughout the trial.

[redacted]

Individual subject profiles will be produced presenting the following data points on a single plot per subject at all timepoints:

- Supine DBP (mmHg)

- Active Standing DBP (1 minute) (mmHg)
- Active Standing DBP (3 minutes) (mmHg)
- Supine SBP (mmHg)
- Active Standing SBP (1 minute) (mmHg)
- Active Standing SBP (3 minutes) (mmHg)
- Supine HR (bpm)
- Active Standing HR (1 minute) (bpm)
- Active Standing HR (3 minutes) (bpm)

In addition, a summary of orthostatic hypotension and postural tachycardia will be presented. Specifically, the number of subjects (%) that have orthostatic hypotension (defined as a decrease in SBP of 20 mmHg or greater relative to supine or a decrease in DBP of 10 mmHg or greater relative to supine), postural tachycardia (defined as an increase in heart rate of 30 bpm or greater relative to supine or a maximum of 120 bpm), or both will be presented by treatment at all timepoints and summarized by treatment group and overall.

## 9.3. Clinical Laboratory Values

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

## 9.4. 12-lead ECGs

Individual safety ECG values will be listed by treatment and visit and summarized using descriptive statistics. Intervals to be provided for each ECG are: RR, PR, QRS, QT, QTc, QTcB, and QTcF. Summary statistics will be provided for change from Baseline in ECG values.

# 10. OTHER ANALYSES

## 10.1. Interim Analyses

No interim analyses are planned for this study.

## 10.2. Subgroup Analyses

Subgroup analyses based upon sex (and other subgroups) may be conducted on an exploratory basis.

# 11. CHANGES IN PLANNED ANALYSES

Following the database lock, additional analyses were conducted, and the Summary of changes is provided at the beginning of the SAP.

# 12. REFERENCES

1. Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Publish Date: June 14, 2010. Accessed October 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

2. Guideline on Structure and Content of Clinical Study Reports, International Conference on Harmonisation, Section ICH E3, 1996.

3. Guideline on Statistical Principles for Clinical Trials, International Conference on Harmonisation, Section ICH E9, 1998.

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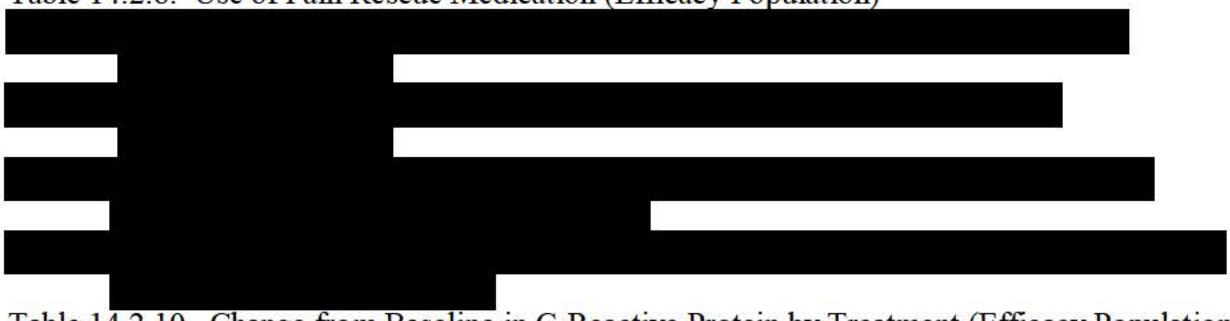

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