# Clinical Trial Protocol: APD334-005

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| **Study Title:** | An Extension Study of APD334-003 in Patients with Moderately to Severely Active Ulcerative Colitis |
| **Study Number:** | APD334-005 |
| **Study Phase:** | 2 |
| **Product Name:** | APD334 |
| **IND Number:** | 125,154 |
| **EudraCT Number:** | 2015-002109-12 |
| **Indication:** | Ulcerative Colitis |
| **Investigators:** | Multicenter |

**Sponsor:** Arena Pharmaceuticals, Inc.
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| | Date |
|---|---|
| **Original Protocol:** | 09 July 2015 |
| **Amendment 01:** | 20 August 2015 |
| **Amendment 02:** | 28 September 2015 |
| **Amendment 03:** | 20 October 2016 |
| **Amendment 04:** | 27 March 2017 |



NCT Number: NCT02536404
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

# PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD334-005 Protocol dated 20 October 2016. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 04 dated 27 March 2017.

| Section(s) Amended | Description of Changes Made |
|---|---|
| Header/Footer, Title Page, and TOC | Added "Amendment 04", updated date to reflect finalization of amended protocol, updated sponsor contact, pagination and TOC |
| Protocol Amendment Summary | Updated table to include summary of major changes to the protocol |
| Synopsis | Updated Sponsor and medical monitor contact details |
| Synopsis | Updated Secondary Outcome to add proportion of patients who achieve clinical response |
| Study Definitions | Updated to reflect APD334-003 completers to be eligible for APD334-005 study |
| 3.1 Overall Study Design and Plan | Updated to reflect APD334-003 completers to be eligible for APD334-005 study |
| 4.2 Inclusion Criteria #6 | Updated to reflect APD334-003 completers to be eligible for APD334-005 study |
| 5.3 Selection and Timing of Dose for Each Patient | Updated to reflect APD334-003 completers to be eligible for APD334-005 study |
| 5.4 Method of Assigning Patients to Treatment Groups | Updated to reflect APD334-003 completers to be eligible for APD334-005 study |
| 6.9.6 3-Component Mayo Score | Updated to reflect APD334-003 completers to be eligible for APD334-005 study |
| 6.15 Study and Site Discontinuation | Added section on reasons to terminate the study |
| 7.1 Extension Study Enrollment Activities | Updated to reflect APD334-003 completers to be eligible for APD334-005 study |
| 7.2 Study Activities | Updated to reflect APD334-003 completers to be eligible for APD334-005 study |
| 9.2 Sample Size and Power Calculation | Updated to reflect APD334-003 completers to be eligible for APD334-005 study |
| 9.5 Efficacy Endpoints | Updated Secondary Outcome to add proportion of patients who achieve clinical response |

| Section(s) Amended | Description of Changes Made |
|---|---|
| 9.6 Statistical Methods | Modified according to amended study design. |

# SYNOPSIS

| | |
|---|---|
| **Name of Active Ingredient:** | APD334 |
| **Study Title:** | An Extension Study of APD334-003 in Patients with Moderately to Severely Active Ulcerative Colitis |
| **Study Number:** | APD334-005 |
| **Indication:** | Ulcerative Colitis |
| **Study Phase** | 2 |
| **Sponsor:** | Arena Pharmaceuticals, Inc.<br>6154 Nancy Ridge Drive<br>San Diego, California 92121 |
| **Name of Sponsor Contact:** | [redacted], Research and Development & CMO<br>Arena Pharmaceuticals, Inc<br>6154 Nancy Ridge Drive<br>San Diego, California 92121<br>Phone [redacted] |
| **Name of Principal Investigator(s):** | Multi-center |
| **Medical Monitor:** | [redacted], MD<br>[redacted], Clinical Development<br>Arena Pharmaceuticals, Inc.<br>Phone: [redacted]<br>Mobile: [redacted] |
| **Objectives:** | **Primary:**<br>To evaluate the long-term safety and tolerability of APD334 in patients with ulcerative colitis who have completed the APD334-003 study.<br><br>**Secondary:**<br>To evaluate the effect of APD334 on achieving and maintaining clinical response and/or remission in patients with ulcerative colitis after 46 weeks of treatment.<br><br>**Exploratory:**<br>[redacted] |

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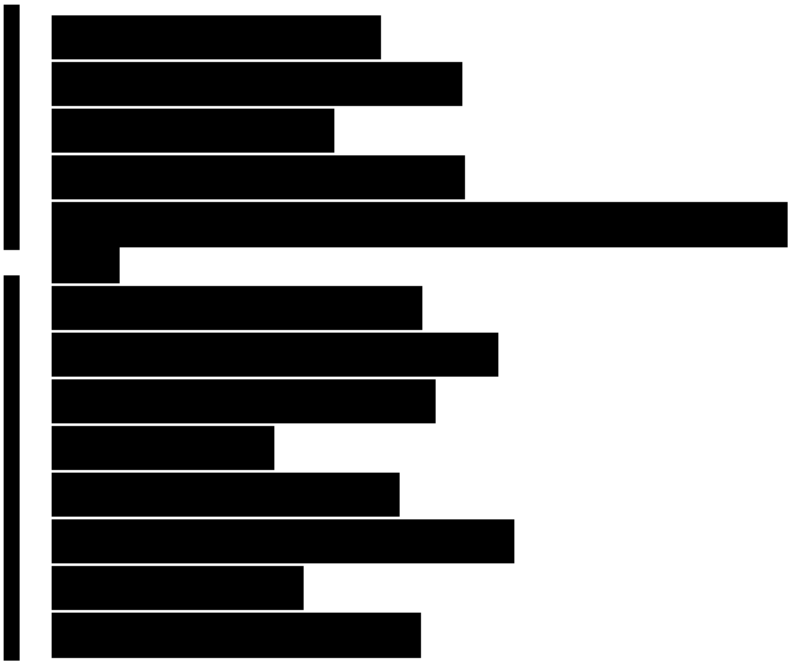
| |  |
| **Study Design:** | This protocol has been designed as an open-label extension study to help determine the long-term safety and tolerability of APD334 in patients with ulcerative colitis who have completed the 12-week phase 2 study, APD334-003. To be eligible, patients must have completed the APD334-003 study and must meet eligibility criteria for APD334-005 at time of entry.<br><br>All patients who have completed the APD334-003 induction study and who meet the eligibility criteria for the APD334-005 extension study will have the option to enroll and receive open-label 2 mg q.d. treatment with APD334. For this purpose, all patients shall be consented for APD334-005 prior to the final procedures being performed for APD334-003.<br><br>Selected procedures from the Week 12 visit in study APD334-003 will be carried over to the APD334-005 study to be included as baseline information for certain analyses. [redacted]<br><br>Following the Day 1 visit, there will be regular visits to monitor for safety and perform efficacy assessments throughout the treatment period. Final efficacy assessments will be conducted at |

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| | Week 46 from baseline of Study APD334-003 (Week 34 of this study) or upon early termination from the study. A 2 week follow-up visit will be conducted to ensure appropriate patient safety [redacted] |
| **Study Site(s):** | This study will be conducted in approximately 100 clinical centers worldwide. |
| **Patient Population:** | Patients with ulcerative colitis who have completed the APD334-003 study as planned, and who meet the eligibility criteria for APD334-005. |
| **Test Product, Dose, and Mode of Administration:** | 2 mg APD334 q.d. for up to 34 weeks of treatment; oral, tablets |
| **Concurrent Control:** | Not applicable |
| **Duration of Study Participation** | Up to 36 weeks (34 weeks of treatment and a 2-week follow-up visit after final visit). |
| **Patient Assignment:** | All patients will receive open-label 2 mg q.d. APD334. |
| **Sample Size:** | Limited by the total number of patients who completed the study APD334-003, and are fulfilling the eligibility criteria. |
| **Primary Outcome Measures:** | The primary endpoint for the study is long-term safety. The safety of APD334 will be monitored throughout the study with safety endpoints being as follows:<br>• Treatment-emergent adverse events (AEs) up to 30 days following discontinuation of the study drug.<br>• Treatment-emergent serious adverse events (SAEs) up to 30 days following discontinuation of the study drug. |
| **Secondary Outcome Measures** | The main secondary efficacy measure is maintenance of clinical response:<br>• The proportion of patients who achieve or maintain clinical response [defined as a decrease in 3-component Mayo Clinic score of $\geq$ 2 points and at least 30% with either a decrease of rectal bleeding of $\geq$ 1 or rectal bleeding score of 0 or 1] at Week 46 compared to APD334-003 baseline<br>• The proportion of patients who achieve or maintain clinical remission [defined as individual subscores of the 3-component Mayo Clinic score as follows: an endoscopy score (using |

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|---|---|
| | flexible proctosigmoidoscopy) of 0 or 1, a rectal bleeding score of 0, and a stool frequency score of 0 or 1 with a decrease of ≥ 1 point from baseline at Week 46 compared to APD334-003 baseline |
| **Exploratory:** |  |
| **Safety Assessments:** | • Physical & neurological examinations including ophthalmoscopy (and optical coherence tomography [OCT], where available)<br>• PML checklist<br>• Clinical laboratory tests to include hematology, serum chemistry, coagulation, and urinalysis<br>• Vital sign measurements<br>• Pulmonary Function Tests (PFTs)<br>• 12-lead electrocardiograms (ECGs)<br>• Adverse event reporting |

| | |
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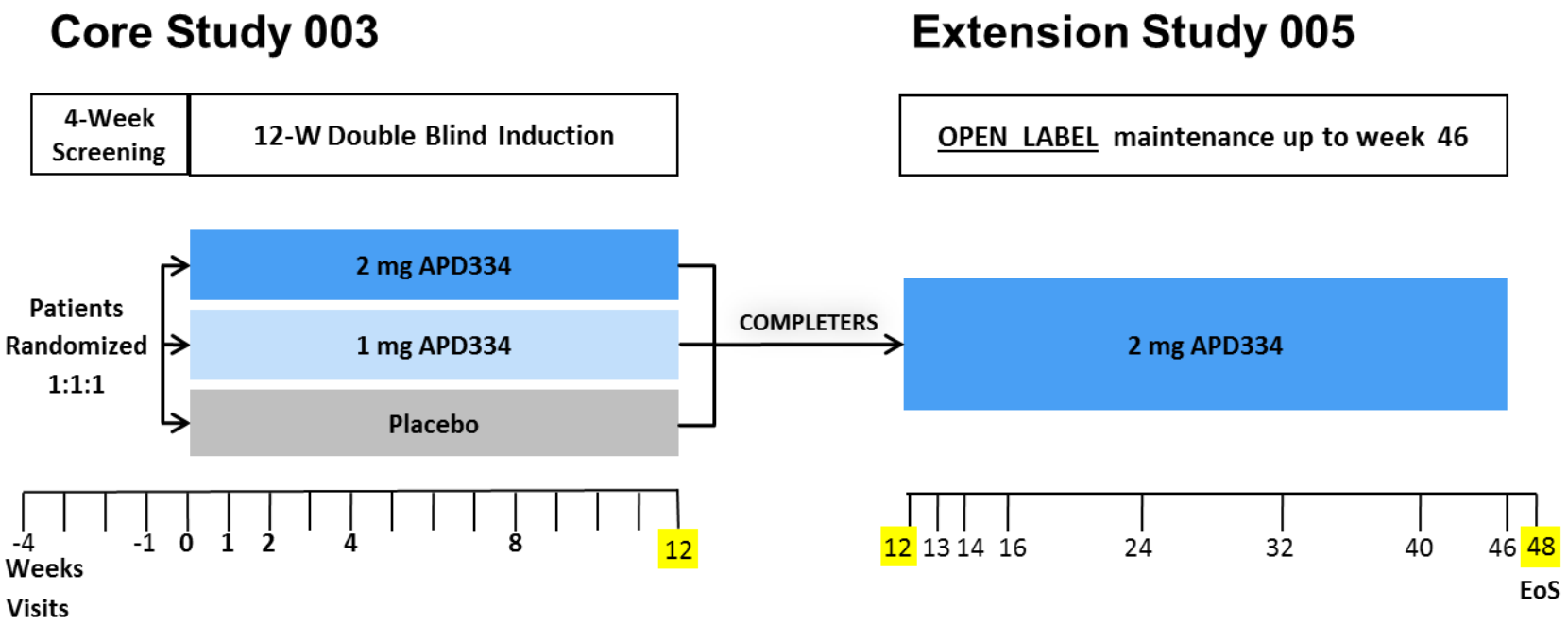
| [redacted] | [redacted] |
| **Data Analyses:** | There is no formal between group inferential comparison for study endpoints. Summary statistics will be provided for primary, secondary, exploratory measures, and additional safety measures. For proportion-based measures, N, frequencies, proportion and its 95% confidence interval (CI) will be produced. For continuous measure, N, mean, median, range, and SD will be produced for observed values, and additional 95% CI for change or percent change from baseline will be produced.<br><br>Additional analyses may be performed in some subgroups of medical interest, such as sex, age, race, presence or absence of current oral corticosteroid use, previous exposure to TNFα antagonists, baseline fecal calprotectin level, baseline CRP level, and previous treatment received in APD334-003. |

**Study Design: APD334-003 and -005 (extension)**



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# LIST OF ABBREVIATIONS

| | |
|---|---|
| µg | microgram |
| ABPM | ambulatory blood pressure monitor |
| ADL | Activities of Daily Living |
| ALB | albumin |
| ALK-P | alkaline phosphatase |
| ALT | alanine aminotransferase (SGPT) |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase (SGOT) |
| bpm | beats per minute |
| BUN | blood urea nitrogen |
| Ca | calcium |
| CBC | complete blood count (test) |
| CFR | Code of Federal Regulations |
| CGMP | Current Good Manufacturing Practice |
| CI | confidence interval |
| CIA | collagen-induced arthritis |
| Cl | chloride |
| CL/F | apparent oral clearance |
| CLr | renal clearance |
| CRF | case report form |
| CRO | contract research organization |
| DSMB | Data Safety Monitoring Board |
| EAE | experimental autoimmune encephalomyelitis |
| ECG | electrocardiogram |
| eCRF | electronic CRF |
| $ED_{50}$ | median effective dose |
| ELISA | enzyme-linked immunosorbent assay |
| FDA | Food and Drug Administration |
| $FEF_{25-75\%}$ | mean forced expiratory flow between 25 and to 75% of FVC |
| $FEV_1$ | forced expiratory volume in the first second |
| FVC | forced vital capacity |
| GCP | Good Clinical Practice |
| GGT | gamma glutamyl transferase |
| Hb | hemoglobin |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |

| | |
|---|---|
| Hct | hematocrit |
| HCV | hepatitis C virus |
| HDPE | High-density polyethylene |
| HIV | human immunodeficiency virus |
| h | hour |
| HR | heart rate |
| [redacted] | [redacted] |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| INR | International Normalized Ratio |
| kg | kilogram |
| LDH | lactate dehydrogenase |
| MCH | mean corpuscular hemoglobin |
| MCS | Mayo Clinic Score |
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram |
| mL | milliliter |
| mm | millimeter |
| mmHg | millimeters of mercury |
| MMRM | mixed-effect model repeated measures |
| MRSD | maximum recommended starting dose |
| Na | sodium |
| NOAEL | no observed adverse effect level |
| OCT | optical coherence tomography |
| OTC | over-the-counter |
| PA | posteroanterior |
| PD | pharmacodynamic |
| PBL | peripheral blood lymphocyte |
| PFT | pulmonary function test |
| PI | Principal Investigator |
| [redacted] | [redacted] |
| PML | progressive multifocal leukoencephalopathy |
| PRO | patient reported outcome |
| PT | prothrombin time |
| PTT | partial thromboplastin time |

| | |
|---|---|
| RBC | red blood cell (count) |
| RIBA | recombinant immunoblot assay |
| S1P(1-5) | sphingosine 1-phosphate (1-5) receptor |
| SAE | serious adverse event |
| SAS | statistical analysis software |
| SBP | systolic blood pressure |
| SD | standard deviation |
| sec | second |
| SOP(s) | standard operating procedure(s) |
| $T_{EM}$ | T effector memory cells |
| VICF | Voluntary Informed Consent Form |
| VS | vital signs |
| WBC | white blood cell (count) |
| WHO | World Health Organization |
| WHODRUG | World Health Organization Drug Dictionary |

## STUDY DEFINITIONS

| Term | Definition |
|---|---|
| [redacted] | [redacted] |
| 3-component Mayo Clinic score (9-point Mayo) | Consists of 3 of the 4 subscores found in the complete Mayo Clinic score as follows: stool frequency, rectal bleeding, findings of flexible proctosigmoidoscopy. Total score range: 0 to 9, each component ranging from 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe). |
| [redacted] | [redacted] |
| Day -1 or Day 1 | Refers to the corresponding initial visit days after enrollment in the APD334-005 study as a completer from the APD334-003 study. |
| [redacted] | [redacted] |
| Clinical Response | Decrease in the 3-component Mayo Clinic score of ≥ 2 points and at least 30% with either a decrease of rectal bleeding of ≥ 1 or rectal bleeding score of 0 or 1 at Week 46. |
| Clinical Remission | Individual subscores of the 3-component Mayo Clinic score as follows: an endoscopy score (using flexible proctosigmoidoscopy) of 0 or 1, a rectal bleeding score of 0, and a stool frequency score of 0 or 1 with a decrease of ≥ 1 point from baseline at Week 46. |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| Endoscopic Improvement | Mayo endoscopic subscore (using findings of flexible proctosigmoidoscopy) of ≤ 1 point at Week 46. |
| Endoscopic Remission | Mayo endoscopic subscore (using findings of flexible proctosigmoidoscopy) = 0 at Week 46. |
| Intolerable AE | Adverse event leading to study drug discontinuation. |

# 1 INTRODUCTION

APD334 is an orally available, selective, sphingosine 1-phosphate 1 receptor ($S1P_1$) agonist. The $S1P_1$ receptor is a physiological mediator which has been shown to regulate lymphocyte recirculation between lymphoid tissue and blood. Binding and internalization of the $S1P_1$ receptor may result in lymphocyte retention within lymphoid tissue, with subsequent reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. $S1P_1$ receptor surface expression is required for S1P gradient-mediated lymphocyte migration out of lymphoid tissue into the circulation.[1]

APD334 is being developed to treat autoimmune diseases. Initial investigations will focus on Inflammatory Bowel Disease (IBD), which is a broad term that describes conditions with chronic or recurring immune response and inflammation of the gastrointestinal tract.[2] There are two major types of IBD: Crohn's disease (CD) and ulcerative colitis (UC). These are chronic remittent or progressive inflammatory conditions that may affect the entire gastrointestinal tract (CD) and the colonic mucosa (UC), and are associated with an increased risk for colon cancer.[3] Collectively, patients with IBD suffer from a multitude of GI symptoms, including diarrhea, rectal bleeding and abdominal pain.[4]

The causes of these IBDs are not completely understood, but 3 characteristics define their etiology: (1) genetic predisposition; (2) an altered, dysregulated immune response; and (3) an altered response to gut microorganisms.[2] The triggering event for the activation of the immune response in IBD has yet to be identified, but possible factors include a pathogenic organism (as yet unidentified) or an inappropriate response to a normally innocuous microbial or other antigen (perhaps due to failure to downgrade the inflammatory response, and/or to repeated exposure to such antigen from an alteration in barrier function).[2] Once the inflammation has been triggered, it may be difficult for the IBD patient's immune system to turn off the response.[5]

The number of patients diagnosed with IBD has dramatically increased worldwide over the past 50 years.[6] In 2014, The Crohn's and Colitis Foundation of American estimated that approximately 1.6 million people are affected by IBD in the United States (US) alone[7], with as many as 70,000 new cases diagnosed in the US each year[8]. In Europe, an estimated 2.5 – 3 million people are affected by IBD[9] and as many as 5 million may be affected worldwide.[10] Universally, incidence rates for both Crohn's disease and ulcerative colitis were highest among individuals between 20 and 40 years old. Thus, IBD affects individuals in the most healthy and productive years of life, resulting in long-term cost to the patient, health-care system and society.[11]

Treatment for patients with IBD is generally for symptomatic care (relief of symptoms) and muscosal healing and includes 5 major classes of medications: aminosalicylates (5-ASA), antibiotics, corticosteroids, immunomodulators, and biologic therapies. These drugs are generally prescribed in a "step-up" approach, with escalation of the medical regimen until a response is achieved.[12]

[redacted]

[redacted] Lymphocyte trafficking agents such as the anti-integrins natalizumab and vedolizumab, both administered intravenously, have demonstrated proof-of-concept in IBD indications and are approved for treatment of CD and both CD and UC, respectively. And more recently, RCP1063, an $S1P_1$ oral receptor modulator showed promising results in a Phase 2 study for ulcerative colitis. The availability of oral lymphocyte trafficking agents such as APD334 would offer patients an additional, more convenient treatment for IBD.

## 1.1 Background Information

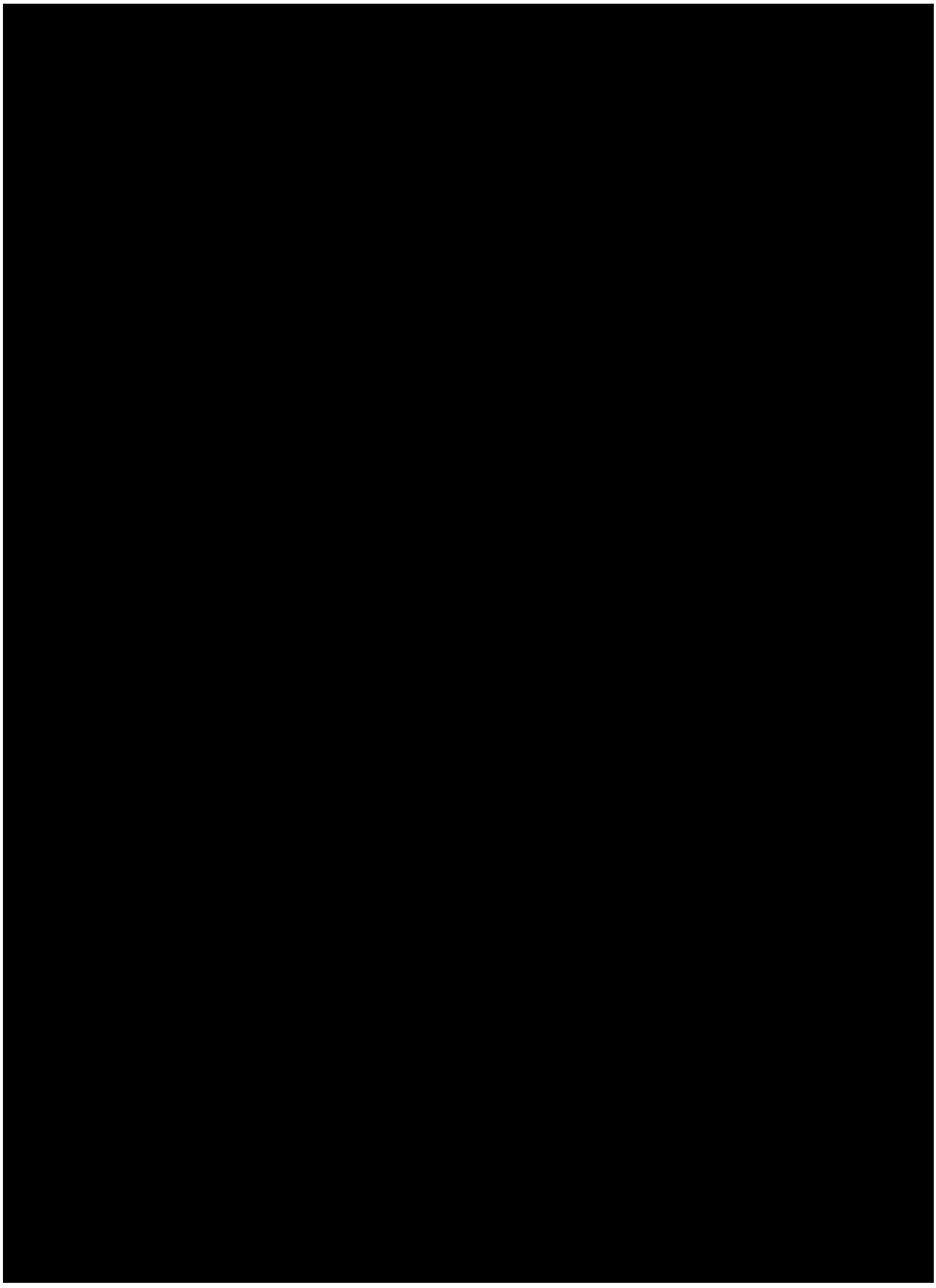
### 1.1.1 Rationale for Proposed Clinical Study

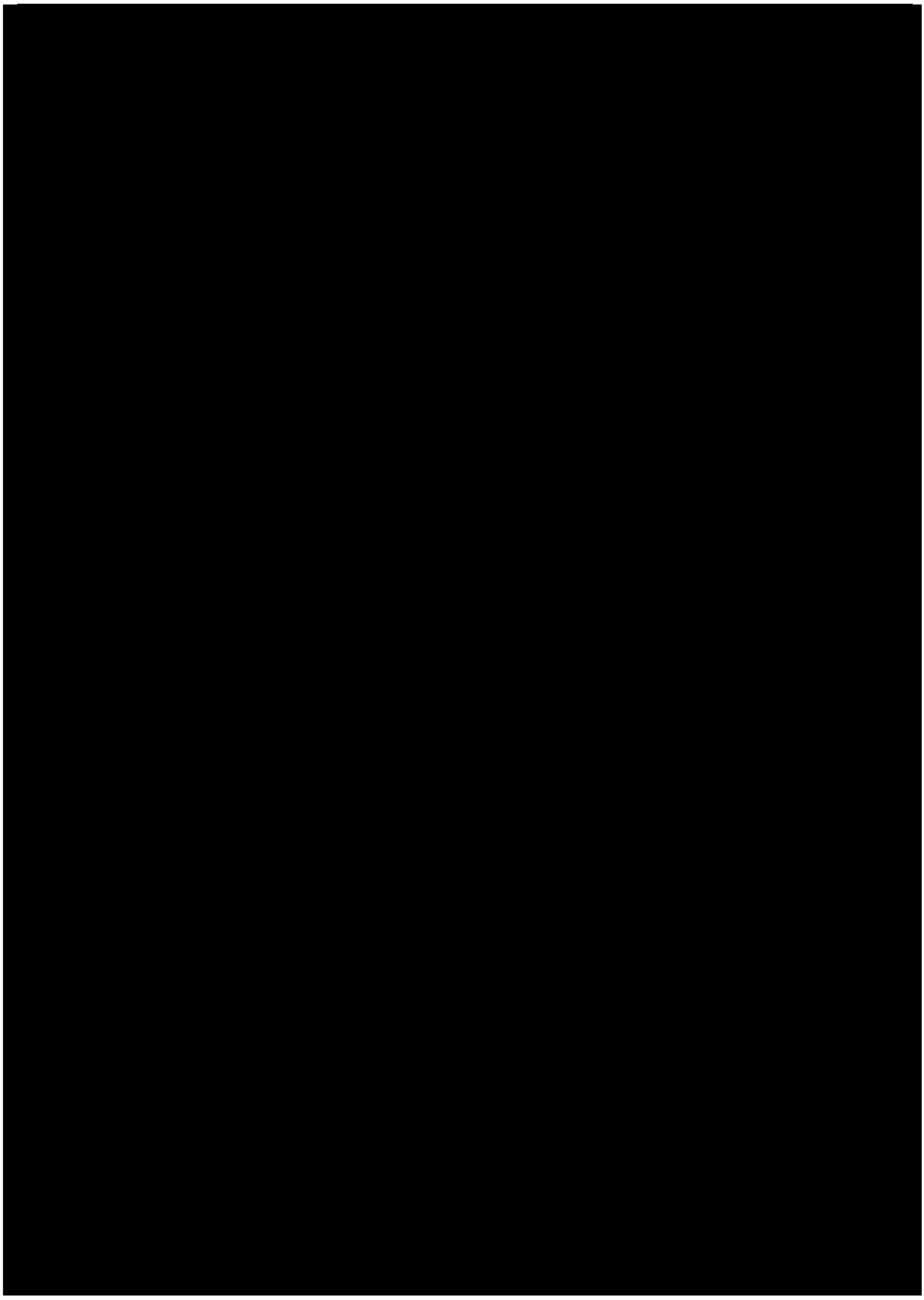
UC is characterized by diffuse mucosal inflammation limited to the colon which involves the rectum in about 95% of cases and may extend proximally, typically in a symmetrical, circumferential, and uninterrupted pattern, to involve parts or all of the large intestine.[13] Symptoms for UC can vary, depending on the location and severity of inflammation, but some of the most common are diarrhea, abdominal cramps and rectal bleeding. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus.[13]

$S1P_1$ receptor signaling on lymphocytes allows their exit from lymph nodes along a S1P gradient. Functional antagonism of these S1P1 receptors through agonist-mediated cellular internalization results in retention of certain lymphocyte subpopulations in lymph nodes and prevents their egress to the periphery. It is through this mechanism that APD334 may potentially reduce inflammation in inflammatory bowel disease. Lymphocyte lowering has been correlated with clinical efficacy for S1P functional antagonists in multiple sclerosis, psoriasis, and ulcerative colitis. This same mechanism may also be useful in treating a variety of other inflammatory and autoimmune diseases.

This study is designed to evaluate the long-term safety, tolerability and efficacy of APD334 in UC patients who have completed the APD334-003 induction study.

[redacted]





## 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 21 of the United States (US) Code of Federal Regulations (CFR) Part 50 (21CFR §50 (Protection of Human Subjects), 21 CFR §56 (Institutional Review Boards [IRB]), and 21 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/IEC 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/IEC must be notified promptly by the investigator of the following:

- Deviations from, or changes in, 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 AEs that meet the definition of a 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/IEC approval before implementation except when changes to the protocol are required immediately to eliminate hazards to the volunteer.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of APD334 in patients with ulcerative colitis who have completed the APD334-003 study.

## 2.2 Secondary Objective

The secondary objective of this study is to evaluate the effect of APD334 on achieving and maintaining clinical response and/or remission in patients with ulcerative colitis after 46 weeks of treatment.

# 3 INVESTIGATIONAL PLAN

## 3.1 Overall Study Design and Plan

APD334-005 is a phase 2, open-label extension study to determine the long-term safety and tolerability of APD334 as well as its ability to achieve and maintain clinical remission and response after 34 weeks of additional treatment in patients with ulcerative colitis who have completed the APD334-003 induction study.

To be eligible, patients must have completed the APD334-003 induction study and must meet the eligibility criteria for the APD334-005 at time of entry. All eligible patients will have the option to enroll and receive open-label 2 mg q.d. treatment with APD334. For this purpose, all patients shall be consented for APD334-005 prior to the final procedures being performed for APD334-003 (as some procedure results will be used for the extension study baseline).

Selected procedures from the Week 12 visit in study APD334-003 will be carried over to the APD334-005 study to be included as baseline information and assist in determining eligibility for the APD334-005 study.

[redacted] Following the Day 1 visit, there will be regular visits to monitor for safety and perform efficacy assessments throughout the treatment period. Final assessments will be conducted at Week 46 from baseline of study APD334-003 (Week 34 of this study), or upon early termination from the study. A 2-week follow-up visit will be conducted to ensure appropriate patient safety [redacted].

[redacted]

## 3.2 Study Duration and Dates

The total study participation/duration is up to 36 weeks (34 weeks of treatment and a 2-week follow-up visit after final visit). The schedule of procedures and visits for the study are provided in Appendix 1.

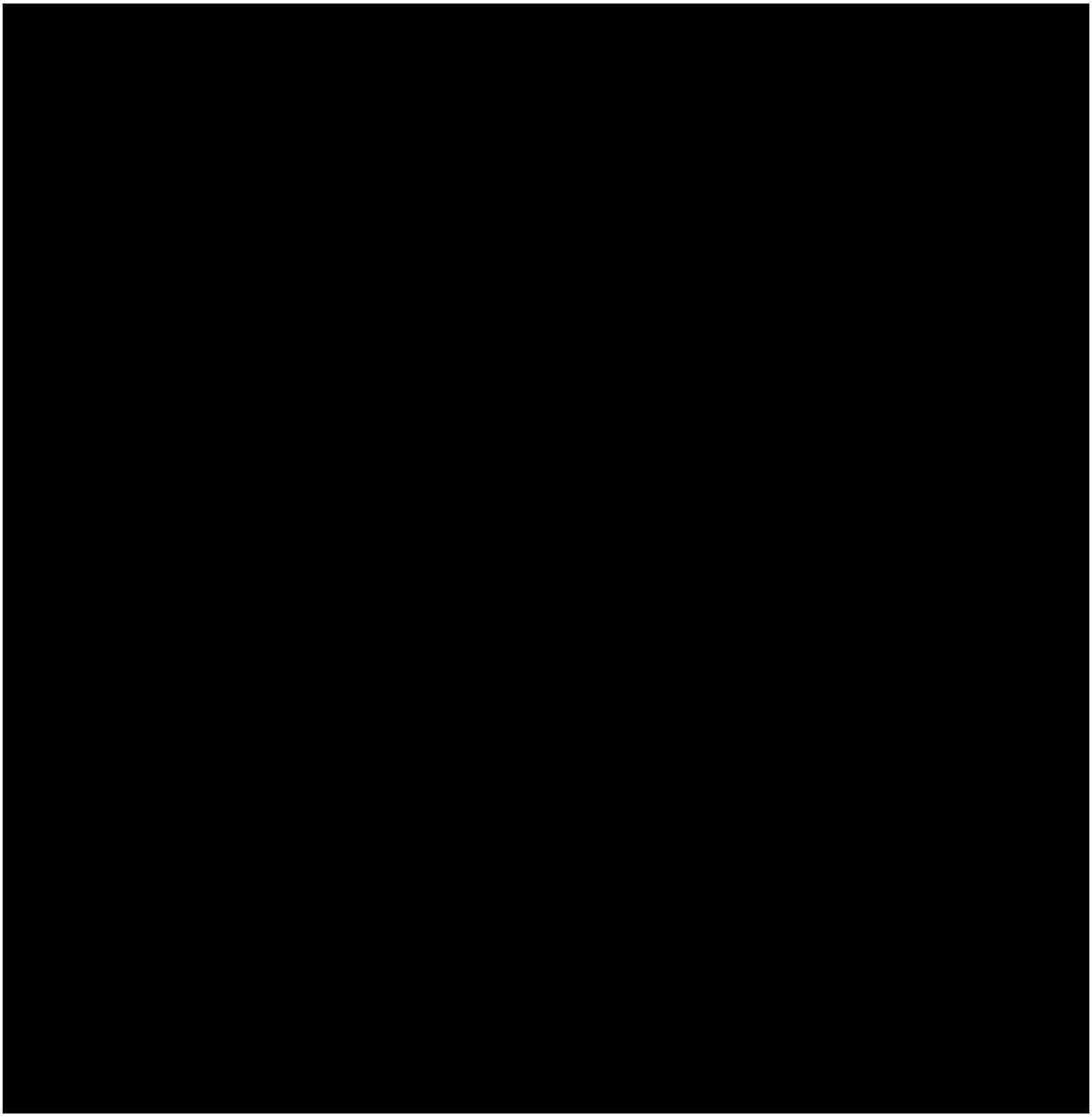
# 4 STUDY POPULATION SELECTION

## 4.1 Study Population

Patients with ulcerative colitis, who have completed the APD334-003 study as planned and who meet the eligibility criteria for APD334-005.

## 4.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:



6. Completion of the APD334-003 study

## 4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

[redacted]

patients who did not complete the APD334-003 study

[redacted]

# 5 STUDY TREATMENT(S)

[redacted]

## 5.3 Selection and Timing of Dose for Each Patient

Investigational product will be dispensed to eligible patients under the supervision of the investigator or his/her designee at the week 12 visit of the APD334-003 study.

[redacted]

## 5.4 Method of Assigning Patients to Treatment

After completing study APD334-003 and signing a voluntary informed consent form (VICF), eligible patients from study ADP334-003 will be assigned to receive 2 mg APD334 q.d. Treatment assignment and duration are as follows:

- Open-label 2 mg APD334 x 34 weeks

## 5.5 Randomization and Blinding

### 5.5.1 Randomization

Not applicable for this open-label extension study.

### 5.5.2 Blinding

The extension study is an open-label study.

In order to keep the blind of the induction study intact, the sponsor, patients, and personnel involved with the conduct of the APD334-005 study will continue to be blinded to the total WBC and lymphocyte counts, as access to this information may lead to unintentional unblinding of a patient (due to Investigational Product's mechanism of action). A central CRO physician(s) unblinded to the leucocyte count will continue to review and monitor the total WBC and lymphocyte counts for safety purposes in the trial. The study site personnel will not receive laboratory results for the total WBC or lymphocyte counts.

### 5.5.3 Maintenance of Randomization Codes and Code-break Procedures

Not applicable.

## 5.6 Concomitant Therapy

[redacted]

## 5.7 Restrictions

[redacted]

## 5.9 Storage and 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 patient in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Study medication will be reconciled by the Arena

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.

## 5.10 Investigational Product Retention at Study Site

At completion of the study, all study medication will be reconciled by the Arena monitor or contracted designee and then returned at the direction of Arena to be retained or destroyed according to applicable country regulations. Prior to any action being taken with study medication after the study is completed, the investigator will contact Arena (or contracted CRO) for approval of such action.

## 5.11 Data Safety Monitoring Board

Not applicable.

# 6 STUDY PROCEDURES

## 6.1 Informed Consent

The investigator will obtain and document VICF for each patient screened for this study. All patients will be informed in writing of the nature of the protocol and investigational therapy, their 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 patient's medical record should contain written documentation indicating that informed consent was obtained. The VICF must be reviewed and approved by the investigator's designated IRB/IEC and by the sponsor. The VICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

## 6.2 Medical and Social History

At baseline, evaluations will include a medical and social history update, to include tobacco, alcohol and caffeine use. Concomitant medications, recent blood donations, illnesses, and participation in other investigational drug studies will also be recorded.

## 6.3 Physical and Neurological Examination

The physical examination, which includes assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, thyroid, lungs, heart, abdomen, back, lymph nodes, extremities, height and body weight; and the neurological examination, which includes assessments of the neurological system (cranial nerves, motor and sensory function, coordination, and mental status) will be performed by the principal investigator or sub-investigator. The physical and neurological exams performed at the [redacted] visit of study APD334-003 will serve as baselines for the APD334-005 study.

The physical examination will also include visual acuity and dilated ophthalmoscopy (by an ophthalmologist) and with OCT (where available) [redacted] (to rule out and monitor for any significant retinal disease, including macular edema). Retinal photos will be taken during the baseline visit [redacted] and any subsequent unscheduled ophthalmoscopy.

## 6.4 Progressive Multifocal Leukoencephalopathy (PML) Checklist

Monitoring for progressive multifocal leukoencephalopathy (PML), a potential adverse effect of $S1P_1$ agonists, will be performed at each site visit [redacted] using a subjective PML checklist. The investigator or subinvestigator will administer the subjective PML checklist. The subjective PML checklist will also be administered to probe for symptoms suggestive of PML. Any patients reporting signs and/or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation. Additional information on PML is provided in Section 6.11.1.1 and a copy of the PML checklist is provided in Appendix 2.

## 6.5 Vital Signs

Supine (laying face upward) blood pressure, heart rate, temperature, and respiratory rate will be measured after the patient has been resting for 5 minutes. Vitals signs will be measured prior to any blood draw that occurs at the same time point. Vital signs will be measured according to the time points in the schedules of procedures and visits (Appendix 1).

[redacted]

## 6.6 Electrocardiography

### 6.6.1 ECG Equipment and Procedures

Safety ECGs will be recorded from an ECG machine (12-lead). Safety ECGs will be printed and reviewed on site by the PI or designee. Typically, all safety ECGs will be obtained as single tracings, with the exception of the pretreatment ECG obtained on Day 1, which is a triplicate recording. [redacted]

### 6.6.2 ECG Acquisition

The safety ECG equipment will be set according to the Centralized ECG Procedure Manual.

### 6.6.3 ECG Assessment

Safety ECGs will be performed as outlined in Appendix 1, schedules of procedures and events. Post-screening ECGs will be compared with screening ECG.

The PI or sub-investigator (physician) will be responsible for review and interpretation of safety ECG on site and determining if the ECG is normal, abnormal "not clinically significant" or abnormal "clinically significant". Findings will be documented in the CRF. This information will be used in the continuous safety review during the conduct of the trial. The ECGs will also be read and interpreted by the central ECG laboratory.

[redacted]

## 6.7 Pulmonary Function Testing

Pulmonary function testing (PFT) will be conducted using spirometry at time points listed in the schedules of procedures and events (Appendix 1). [redacted]

## 6.8 Clinical Laboratory Tests

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

In the event of abnormal clinical laboratory values, the physician will make a judgment whether or not the abnormality is clinically significant and is deemed an adverse event.

### 6.8.1 Laboratory Parameters

Clinical safety laboratory tests will be conducted as outlined in Appendix 1. Laboratory tests will include the following. Results of the total white blood cell and lymphocyte counts will be reviewed and monitored per Section 5.5.2.

**Serum Chemistry**
Albumin (ALB)
Alkaline phosphatase (ALK-P)
Alanine aminotransferase (ALT; SGPT)
Amylase
Aspartate aminotransferase (AST; SGOT)
Bicarbonate
Blood urea nitrogen (BUN)
Calcium (Ca)
Chloride (Cl)
Creatinine
Creatine kinase and MB subtype (if elevated) (% and total MB)
Gamma-glutamyl transferase (GGT)
Glucose
Lactate dehydrogenase (LDH)
Lipase
Magnesium
Phosphate
Potassium (K)
Sodium (Na)

**Serum Chemistry (cont.)**
Total bilirubin
Total cholesterol
Total protein
Triglycerides

**Hematology**
Hematocrit (Hct)
Hemoglobin (Hb)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular volume (MCV)
Platelet count
Red blood cell count (RBC)
White blood cell count (WBC) with differential (% and absolute counts)

**Coagulation**
Prothrombin time (PT)
Activated partial thromboplastin time (PTT)
International Normalized Ratio (INR)

### 6.8.2 Urinalysis

Urinalysis parameters for clinical laboratory tests include the following:

- appearance
- bilirubin
- color
- glucose
- ketones
- leukocyte esterase
- occult blood
- pH
- protein
- specific gravity
- urobilinogen

Microscopic urinalysis will be performed when there is a positive or abnormal macroscopic urinalysis result.

### 6.8.3 Sample Collection, Storage, and Shipping

Blood samples for hematology, coagulation parameters, serum chemistry, will be collected according to the laboratory manual provided by the local or central laboratory and according to the schedules of procedures and visits (Appendix 1).

### 6.8.4 Blood Volume

Total blood volume for clinical laboratory tests during study conduct is less than 150 mL.

## 6.9 Efficacy Assessments

### 6.9.1 Flexible Proctosigmoidoscopy

A flexible proctosigmoidoscopy, performed with a videoendoscope following a cleansing prep (oral or rectal cathartic) will be performed at Baseline [redacted] and [redacted] EOT.

A repeat flexible proctosigmoidoscopy may be permitted by the Sponsor when the central reader indicates that the videoendoscope data was acquired incorrectly, or did not meet the minimal required quality standards.

### 6.9.2 Stool Sample

A stool sample will be collected at time points listed in the schedule of procedures and visits (Appendix 1) for the analysis of fecal calprotectin [redacted].

### 6.9.3 C-reactive Protein (CRP)

Blood samples for analysis of C-reactive protein (CRP) will be collected at time points listed in the schedule of procedures and visits (Appendix 1).

### 6.9.4 Electronic Clinical Outcomes Assessments (eCOA)

Patient reported outcomes (stool frequency and rectal bleeding) will be captured daily using a handheld electronic device from CRF Health [redacted]. Diary entries will be reviewed by site personnel during scheduled visits and at any unscheduled visit(s) due to disease exacerbation.

The CRF Health eDiary software runs on the device and includes all the security features required of an eCOA solution for 21 CFR Part 11 compliance.

[redacted]

### 6.9.6 [redacted] 3-component Mayo Clinic [redacted]

[redacted]

[redacted]

### 3-COMPONENT MAYO CLINIC SCORE (9-POINT MAYO): SECONDARY OUTCOME MEASURES

The 3-component Mayo Clinic score consists of 3 of the 4 subscores found in the MCS as follows: stool frequency, rectal bleeding, and findings of flexible proctosigmoidoscopy. Total score range: 0 to 9, each component ranging from 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe).

The 3-component Mayo Clinic score [redacted] will determine if the patient achieves clinical response. The 3-component Mayo Clinic score will also be evaluated [redacted]

[redacted]

## 6.10 [redacted] Hematologic Assessments

[redacted]

[redacted]

### 6.10.2 Hematologic Sampling

Blood samples for CBC with differential and platelet count will be assessed [redacted].

If the [redacted] value at the 2-week follow-up, patients should return for weekly CBCs until the absolute peripheral lymphocyte count has returned to at least this value.

All details regarding collection of blood samples for CBC with differential analysis will be collected and prepared according to that specified in the laboratory manual provided separately by the central laboratory. The samples should be packed and shipped to the central laboratory, according to the directions in their laboratory manual, which will send them on to the bioanalytical laboratory for analysis.

### 6.10.3 Total Blood Volume

Total blood volume collected for [redacted]/hematologic samples is less than 120 mL during the study.

## 6.11 Adverse Events Assessments

Patients will be monitored from ICF signature to 30 days after the last dose of study drug for adverse reactions to the study drug and/or procedures.

AEs will be recorded and reported in accordance with ICH GCP and 21 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." The outcome of an AE will be defined according to ICH Topic E2B, ICH Guideline "Note for Guidance on Clinical Safety Data Management: Data Elements for

Transmission of Individual Case Safety Reports." The relationship to investigational product will be classified using the World Health Organization (WHO) criteria.

### 6.11.1 Adverse Event Reporting

Patients will be instructed that they may report AEs at any time. All events reported following study medication administration will be recorded as treatment emergent AEs (TEAEs).

Monitoring of ongoing AEs will be continued up to 30 days after 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 patient administered any dose of the study medication APD334 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 accidents
- Clinically relevant adverse changes in laboratory parameters observed in a patient 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 will be elicited at the time indicated in the schedule 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 Adverse Event Form including details of intensity, onset, duration, outcome and relationship to the drug as determined by the PI. 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). AEs may also be reported at any time. The type and duration of follow-up of patients after AEs will be documented.

#### 6.11.1.1 Progressive Multifocal Leukoencephalopathy (PML) Checklist

A patient with multiple sclerosis developed progressive multifocal leukoencephalopathy (PML) after nearly 8 months of treatment with another $S1P_1$ agonist[21], and enablement of the John Cunningham (JC) virus is therefore a potential adverse effect of this therapeutic class. Patients in this trial should therefore be monitored for any new onset or worsening of

neurological signs and symptoms. Signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing and refer to a neurologist; if confirmed, discontinue dosing permanently.

The investigator or subinvestigator will administer the subjective PML checklist. The subjective PML checklist will be administered at each site visit to probe for symptoms suggestive of PML. Any patients reporting signs and/or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation.

A copy of the PML checklist is provided in Appendix 2.

### 6.11.2 Serious Adverse Events and Expedited Reporting of Adverse Events

A Serious Adverse Event (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

SAEs will be captured from the time of ICF signature to 30 days after the last 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 a SAE when, based upon appropriate medical judgment, it may jeopardize the patient 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-patient 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 patient's entry into the study) will not be reported as a 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) using 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:

**PPD Medical Affairs/Pharmacovigilance**
**PPD PVG Hotline EMEA and APAC:** [redacted]
**PPD PVG Hotline NA:** [redacted]
**PPD PVG Fax line:** [redacted]

In the event that 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 safety issues as defined in ICH Topic E2A, 21 code of federal regulations (CFR) §312.32, and EU Volume 10 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 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.

#### 6.11.2.1 Patient and Patient-partner Pregnancy

Patients 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 until 30 days after the last dose of study drug should be reported to the sponsor contact and IRB/IEC in the same manner as an SAE.

Pregnancies will be followed every trimester through the first well baby visit. For female partners whom become pregnant by male study patients 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 patient.

### 6.11.3 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 CTCAE v4.03[22] 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.

**Activities of Daily Living (ADL):**

*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.

### 6.11.4 Assessment of Adverse Event Relationship to Study Medication

The relationship of an AE to investigational product(s) will be classified using modified 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.

### 6.11.5 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

### 6.11.6 Action Taken for Adverse Event

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

- Concomitant medication or other treatment
- Withdrawal from the study

### 6.11.7 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 CRF according to the following:

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

### 6.11.8 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 patient 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 company may suggest special tests based on expert advice.

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

Adverse events present at the last study day [redacted] that require follow-up or a repeat laboratory test will be followed-up initially for 30 days according to the site's standard practice for AE follow-up. AEs that have not resolved or stabilized at 30 days after the last patient's last study dose, will be reviewed with the sponsor on an individual basis to determine whether the database will be locked and subsequently updated once the events of ongoing AEs are resolved or whether database lock will be held.

## 6.12 Concomitant Medications and Procedures

All medications (OTC and prescribed) that are taken by patients and all procedures that are performed during the screening period and during the study must be recorded in the electronic case report form (eCRF) with start date/time and stop date/time, if known. Concomitant medication for medical conditions other than UC are permitted as clinically indicated patient to specific protocol requirements outlined in Sections 4.2 and 4.3 of study protocol APD334-003.

The following should be taken into account with regard to concomitant procedures:

- Patients may not undergo major elective surgery while enrolled in this study.
- Patients may not donate sperm, or oocytes during the study and for 30 days after the last dose of study drug.

[redacted]

### 6.12.2 Excluded Medications

The following medications are excluded from the study:

- Treatments for UC other than those listed in Section 6.12.1 (either approved or investigational)
- All live vaccines, during study treatment and for at least 6 months after the last dose of study drug

## 6.13 Removal of Patients from the Trial or Study Drug

The study may be terminated early if, in the opinion of the sponsor, investigator, or IRB/IEC, an unacceptable risk to the safety and welfare of patients is posed by the continuation of the study in light of review of the key safety data.

Patients will be free to withdraw from the study at any time should they so wish. A patient may be withdrawn from the study for any of the following reasons (including but not limited to):

- Clinical investigator may remove a patient if, in his/her opinion, it is in the best interest of the patient [redacted]
- Withdrawal of consent - Any patient 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 was withdrawn.
- Deviation/noncompliance with the protocol or study drug
- An adverse event
- Lost to follow up

### 6.13.1 Handling of Withdrawals

Although a patient 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 patient's rights. If there is a medical reason for withdrawal, the patient will remain under the supervision of the study physician until in satisfactory health. Reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

If a patient is prematurely discontinued from this study, every attempt will be made to follow the [redacted] procedures described in Section 7.2.2.4.

### 6.13.2 Replacements

Patients who terminate early from the study will not be replaced.

## 6.14 Allowable Visit and Procedure Windows

There are no visit windows defined in the study protocol.

## 6.15 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.

- Patient enrollment is unsatisfactory.
- The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.
- The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:
- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guidelines for GCP

# 7 STUDY ACTIVITIES

## 7.1 Extension Study Enrollment Activities (Week 12 of Study APD334-003)

Eligible patients will have a detailed oral presentation of the nature, purpose, risks, and requirements of the extension study in addition to receiving detailed written information. They will have adequate opportunity to ask the appropriate person of the clinical staff (i.e., principal investigator or designee) presenting the study about any aspect of the study. Once the patient is satisfied that he/she is willing to participate in the study, he/she will be asked to sign the study VICF. The clinical personnel obtaining written consent from the patient will also sign the form to confirm consent has been obtained. Once signed, the investigator will retain the original for the patient's study records and provide the patient with a signed copy. The investigator will verify that informed consent has been obtained from each patient prior to admission into the study and prior to the patient undergoing any study-related procedures. If it is standard practice at the site to conduct a few general non-invasive study procedures (i.e., medical/social history, collection of concomitant medications, etc.) before a patient can be considered for a specific study, the study center must have a written SOP detailing the procedure, and also ensure that each patient signs a general consent prior to undergoing the general procedures.

The review of all inclusion and exclusion criteria will occur prior to a patient's transition from study APD334-003 into the extension study APD334-005, subsequent to obtaining informed consent.

### 7.1.1 Treatment Assignment

Treatment assignment for APD334-005 will occur on Day 1 of APD334-005. All patients who complete the APD334-003 study and meet all the entry criteria and are eligible for the study will be assigned to 2 mg APD334 treatment. Select Week 12 results of APD334-003 study assessments will be carried over to study APD334-005 to serve as baseline assessments as outlined in Appendix 1.

## 7.2 Study Activities

### 7.2.1 Baseline Activities – Day -1

[redacted] Selected Week 12 results of APD334-003 study assessments will be carried over to study APD334-005 to serve as baseline assessments as outlined in Appendix 1.

#### 7.2.1.1 Day -1 Activities

[redacted]

[redacted]

- Record adverse events
- Record concomitant medications/procedures

### 7.2.2 Treatment Period

#### 7.2.2.1 Day 1

Completers from the APD334-003 study who meet eligibility criteria for APD334-005 will have the following Day 1 procedures:

- Treatment assignment
- Diary review
- Vital signs

[redacted]

- 12-lead ECG (per Appendix 1)
- Drug administration
- Drug dispensation
- Record adverse events
- Record concomitant medications/procedures

[redacted]

#### 7.2.2.2 Week [redacted] Procedures

- PML checklist
- Urine pregnancy test (females only, not diagnosed as postmenopausal) [redacted]
- CBC with differential and platelets
- Clinical laboratory tests (serum chemistry, hematology, coagulation parameters, urinalysis and CRP) [redacted]

[redacted]

- Diary review
- Vital signs

- [redacted]
- 12-lead ECG (per Appendix 1)
- Drug administration
- Drug dispensation/accountability
- Record adverse events
- Record concomitant medications/procedures

#### 7.2.2.3 Weeks [redacted] Procedures

- PML checklist
- Pulmonary function test (spirometry) [redacted]
- Urine pregnancy test (females only, not diagnosed as postmenopausal) [redacted]
- CBC with differential and platelets [redacted]
- Clinical laboratory tests (serum chemistry, hematology, coagulation parameters, urinalysis and CRP) [redacted]
- Stool Sample [redacted]
- Fecal calprotectin [redacted]
- [redacted]
- Diary review
- Vital signs
- [redacted]
- 12-lead ECG (per Appendix 1) [redacted]
- Drug administration
- Drug dispensation/accountability
- Record adverse events
- Record concomitant medications/procedures

#### 7.2.2.4 Week 46/End-of-Treatment (EOT) or Early Termination Procedures

- Physical/ neurological exam
- PML checklist
- Urine pregnancy test (females only, not diagnosed as postmenopausal)
- CBC with differential and platelets
- Ophthalmoscopy with OCT (where available) and retinal photos
- Clinical laboratory tests (serum chemistry, hematology, coagulation parameters, urinalysis and CRP)
- Pulmonary function test (spirometry)
- Stool Sample

- Fecal calprotectin
- Flexible proctosigmoidoscopy
- [redacted]
- Diary review
- [redacted]
- Vital signs
- [redacted]
- 12-lead ECG
- Drug administration
- Drug accountability
- Record adverse events
- Record concomitant medications/procedures

#### 7.2.2.5 2-week Follow-up Procedures, End of Study (EoS)

A 2-week follow-up visit to include additional safety assessments will be completed for all patients as outlined in the schedule of procedures and visits (Appendix 1). Patients will not receive study medication during the follow-up period.

# 8 DATA MANAGEMENT

## 8.1 Data Collection

All data (ECGs, clinical laboratory data, and all other study-related data) will be collected according to the sponsor or CRO's SOPs.

Upon database lock, which occurs after resolution of all queries, the CRO, if applicable, will provide statistical analysis software (SAS) transfer datasets to the sponsor and to the biostatistician for analysis using secure electronic data transfer per the sponsor's specifications.

## 8.2 Data Coding

### 8.2.1 Adverse Events

Adverse events will be coded using the most current Medical Dictionary for Regulatory Actvities (MedDRA) 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). AEs that occur after the first dose of study medication will be considered to be 'treatment-emergent'.

### 8.2.2 Concomitant Medications and Non-drug Treatments

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 World Health Organization Drug Dictionary (WHODRUG).

### 8.2.3 Medical History

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

# 9 PLANNED STATISTICAL METHODS

The statistical analysis of the data obtained from this study will be the responsibility of the CRO. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP) which will be finalized prior to database lock. If after database lock changes are made to the pre-specified statistical analysis plan, the changes will be listed along with an explanation as to why they occurred in the Clinical Study Report.

## 9.1 Hypotheses and Objectives

### 9.1.1 Objectives

#### 9.1.1.1 Primary Objective

The primary objective of this extension study is to evaluate the long-term safety and tolerability of APD334 in patients with ulcerative colitis who have completed the APD334-003 study.

#### 9.1.1.2 Secondary Objective(s)

The secondary objectives of the study are to evaluate the effect of APD334 on achieving and maintaining clinical response and/or remission in patients with ulcerative colitis after 46 weeks of treatment.

#### 9.1.1.3 Exploratory Objectives

The exploratory objectives of the study are to examine the effect of APD334 treatment in patients with ulcerative colitis on:

### 9.1.2 Hypotheses

There are no formal hypothesis tests specified in this study due to the lack of control treatment group.

## 9.2 Sample Size and Power Calculations

Patient enrollment is limited by the number of patients who complete the APD334-003 study. Therefore sample size and power calculation is not needed.

## 9.3 Analysis Populations

The analyses of all proportion based efficacy variables will use the Intent-to-Treat (ITT) population as primary. For other continuous efficacy endpoints, the Modified Intent-to-Treat (MITT) population will be used as primary. A completer's population will be used as a secondary analysis population for the efficacy endpoints.

**INTENT-TO-TREAT POPULATION (ITT):**

This population consists of all enrolled patients, who received at least 1 dose of APD334 in the extension study.

**MODIFIED INTENT-TO-TREAT POPULATION (MITT):**

This population consists of all enrolled patients, who received at least 1 dose of APD334, have a baseline measurement, and have a post-enrollment measurement in the extension study for the specific efficacy endpoint being assessed. Note that MITT population can vary with endpoints since some patients may have the needed data for inclusion in the MITT population for some endpoints but not for others.

**COMPLETERS POPULATION (CP):**

This population consists of all patients who completed the extension study. No missing data will be imputed for this analysis. Any substantial differences between conclusions based on the ITT/MITT population and the completers' population will be investigated.

**SAFETY POPULATION (SP):**

The Safety Population will include all enrolled patients who received study medication in the extension study.

## 9.4 Demographics and Baseline Characteristics

All baseline patient characteristics of demographic data (age, height, weight, race), ulcerative colitis history, 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 patients.

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

## 9.5 Efficacy Endpoints

### 9.5.1 Efficacy Endpoints

Secondary outcome measures are achievement, durability and maintenance of clinical response and/or clinical improvement. They include the following:

- The proportion of patients who achieve or maintain clinical response [defined as a decrease in 3-component Mayo Clinic score of ≥ 2 points and at least 30% with either a decrease of rectal bleeding of ≥ 1 or rectal bleeding score of 0 or 1] at Week 46 compared to APD334-003 baseline
- The proportion of patients who achieve or maintain clinical remission [defined as individual subscores of the 3-component Mayo Clinic score as follows: an endoscopy score (using flexible proctosigmoidoscopy) of 0 or 1, a rectal bleeding score of 0, and a stool frequency score of 0 or 1 with a decrease of ≥ 1 point at Week 46 compared to APD334-003 baseline

### 9.5.2 Exploratory Efficacy Endpoints

[redacted]

## 9.6 Statistical Methods

There is no between group inferential comparison for study endpoints. Summary statistical analyses will be performed for all efficacy measures. For proportion based measures, N, frequencies, proportion and its 95% confidence interval (CI) will be produced. For continuous measure, N, mean, median, range, and SD will be produced for observed values, and additional 95% CI for change or percent change from baseline will be produced if applicable.

### 9.6.1 Data Analysis for Secondary Efficacy Endpoints

The secondary efficacy outcome of achievement or maintenance of clinical response will be based on the proportion of patients who achieve or maintain clinical response [defined as a decrease in 3-component Mayo Clinic score of $\geq 2$ points and at least 30% with either a decrease of rectal bleeding of $\geq 1$ or rectal bleeding score of 0 or 1] at Week 46 compared to APD334-003 baseline using the ITT population. All patients who prematurely discontinue for any reason will be considered failures (non-responders) for all the proportion based endpoints. Similar analyses will be performed in terms of the other Week 46 proportion based endpoints such as proportion of patients achieving clinical remission and proportion of patients with endoscopic improvement.

For each study visit during the study, stool frequency and rectal bleeding subscores will be derived [redacted]

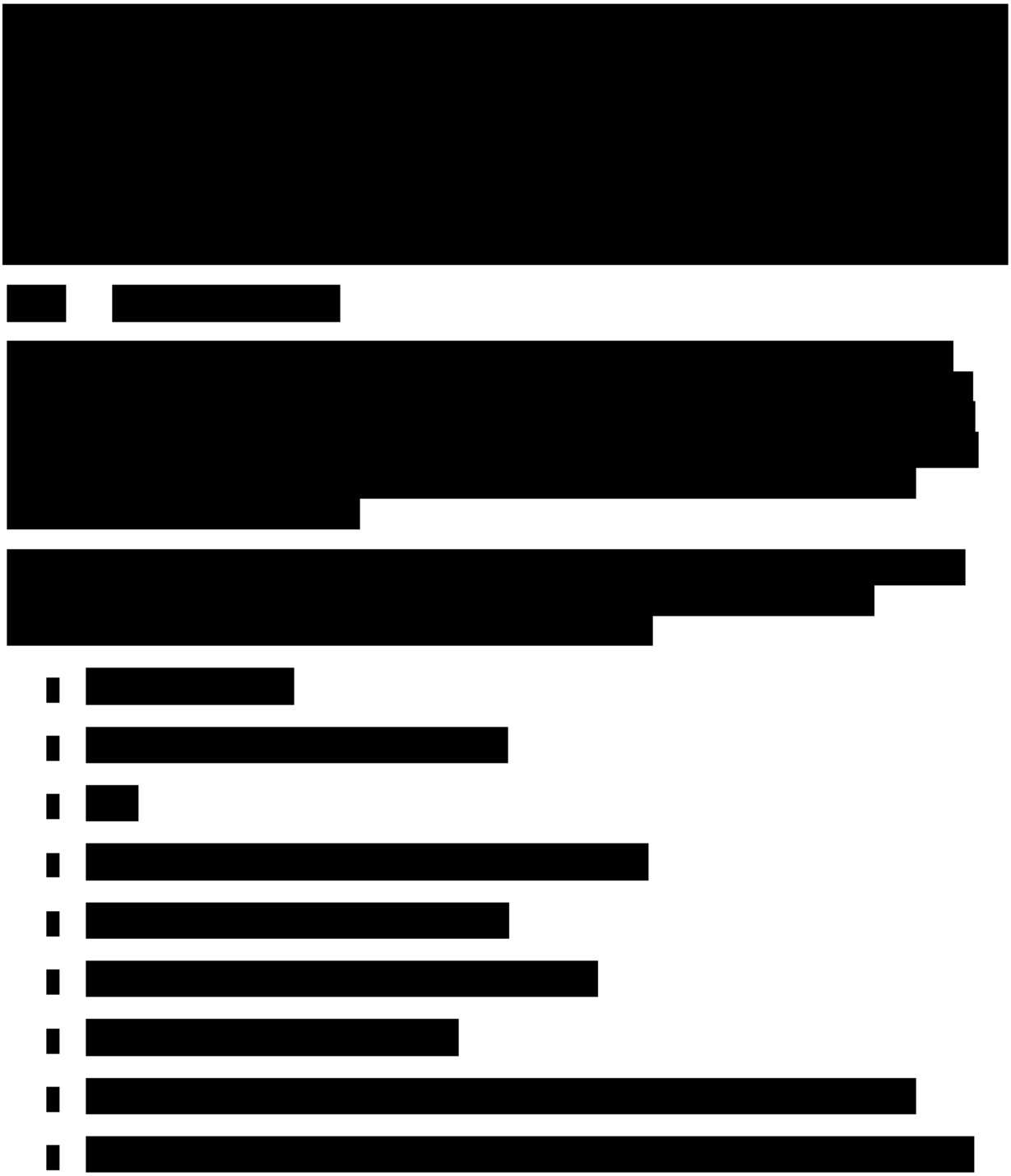
- [redacted]
- [redacted]
- [redacted]

[redacted]

All patients who prematurely discontinue for any reason will be considered failures (non-responders) for all the proportion based endpoints.

Descriptive statistics of N, mean or mean change, and standard deviation will be produced for continuous efficacy endpoints.

### 9.6.2 Data Analysis for Exploratory Efficacy Endpoints



[redacted]

- [redacted]
- [redacted]

### 9.6.4 Multiplicity

Not applicable.

### 9.6.5 Interim Analysis

No interim analyses are planned for this study.

### 9.6.6 Data Safety Monitoring Board

Not applicable.

[redacted]

## 9.8 Safety Analysis

Safety and tolerability will be assessed by a review of all safety parameters including adverse experiences (AEs), laboratory safety parameters, vital signs, and ECG. Only summary tabulations (N, mean [or median], SD, mean [or median] change/percent change) and 95% CIs will be obtained. Adverse experiences will only be presented as summary tabulations. The analyses for all safety outcomes (categorical or continuous measures) will use the safety population which consists of all enrolled patients who received at least 1 dose of study drug in the extension study.

For analysis based on laboratory measurements, at least 1 laboratory test post-enrollment measurement in the extension study is required for inclusion in the safety population. When assessing change from baseline, a baseline measurement is also required. Baseline for the safety analysis is defined as the last pre-enrollment measurement. No missing data will be imputed for the safety analysis.

### 9.8.1 Adverse Events

Adverse events will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA) 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 APD334. 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 patients. They will be summarized 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. TEAEs will also be summarized by maximum intensity (assessed according to the Common Terminology Criteria for Adverse Events v4.0313 definitions) and relatedness to study medication.

Summaries of the number (%) of patients with at least 1 TEAE, classified according to MedDRA system organ class and preferred term, will also be provided for:

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

Serious adverse events will be listed by patient. 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.

### 9.8.2 Physical Examinations

Physical examination results (abnormalities only) at each study visit will be listed.

### 9.8.3 Concomitant Medication

Pre-treatment and concomitant medication administered during the study will be listed. Concomitant medications will be coded using the WHODRUG Dictionary.

### 9.8.4 Vital Signs

Individual vital sign measurements will be listed and summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in vital sign measurements. Baseline is defined as the last pre-enrollment measurement.

### 9.8.5 Clinical Laboratory Values

Individual lab values will be listed by visit, and summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in lab values. Baseline is

defined as the last pre-enrollment measurement. Shift tables from baseline to last double-blind visit will also be produced for the laboratory assessments based on the categories of Low, Normal, and High. A clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor.

### 9.8.6 Safety ECG (12-lead ECG) [redacted]

Individual safety ECG (12-lead) 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. Post-screening ECGs will be compared with the baseline ECG. Any clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor.

[redacted]

### 9.8.7 Lymphocyte counts

Absolute lymphocyte counts at specified time points will be listed for each patient and will be summarized. The relationship between clinical efficacy and lymphocyte count lowering will be assessed.

# 10 REGULATORY REQUIREMENTS

## 10.1 Pre-Study Documentation

The sponsor must receive the following documentation prior to initiation of the trial:

- Protocol signature page signed and dated by the principal investigator (PI)
- FDA form 1572 signed and dated by the PI
- Curriculum vitae of the PI and subinvestigators, updated within 2 years
- Current medical licenses for the PI and all subinvestigators
- Financial disclosure form signed by the PI and all subinvestigators listed on the FDA Form 1572
- Copy of the IRB/IEC approval letter for the study and approved VICF
- IRB/IEC Membership List

Additional country specific documentation may be required per international regulatory authorities. Documents will be collected by the CRO per regulatory requirements.

## 10.2 Investigator Obligations

The PI is responsible for ensuring that all study site personnel, including subinvestigators and other study staff members, adhere to all FDA and other country specific 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 patient'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 ICH Guidelines E6, E2A, and E8.

## 10.3 Patient Confidentiality

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

## 10.4 Informed Consent

According to the ICH guideline for GCP (E6), the investigator will obtain and document informed consent for each patient screened for this study. All patients 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 patient's medical record should contain written documentation indicating that informed consent was obtained. The VICF must be reviewed and approved by the investigator's designated IRB/IEC and by the sponsor. The

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

## 10.5 Institutional Review Board

This protocol and relevant supporting data are to be submitted to the appropriate IRB/IEC for review and approval before the study can be initiated. Amendments to the protocol will also be submitted to the IRB/IEC prior to implementation of the change. The sponsor must receive a letter documenting the IRB/IEC approval prior to initiation of the study. The PI is also responsible for informing the IRB/IEC of the progress of the study and for obtaining annual IRB/IEC 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/IEC in writing of any SAE or any unexpected AE according to ICH guidelines.

# 11 PROTOCOL MANAGEMENT AND ADMINISTRATIVE CONSIDERATIONS

## 11.1 Study Documentation

The PI and study staff has 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/IEC, and regulatory authorities (i.e., FDA or international regulatory authorities) at any time, and should consist of the following elements:

Patient files, containing the completed case report forms (CRFs), supporting source documentation from the medical record including laboratory data and the VICF;

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/IEC 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 2 years after marketing application approval, or if the application is not approved or never submitted, 2 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.

## 11.2 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.

## 11.3 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 patients' complete medical records, laboratory data, and other source documentation as needed to monitor the trial appropriately.

# 12 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study as outlined in the protocol entitled, "An Extension Study of APD334-003 in Patients with Moderately to Severely Active Ulcerative Colitis" 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 country specific regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures patient 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/IEC 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/IEC.
- Submission of any proposed change in the protocol to the IRB/IEC 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/IEC.
- Documentation and explanation of individual protocol deviations.
- Submission of SAE reports within 24 hours after the investigator's initial receipt of the information.
- If required by local regulation, submission of reports of SAEs, as outlined in the protocol, to the IRB/IEC within 15 calendar days of their disclosure.
- Submission of timely progress reports to the IRB/IEC and sponsor at appropriate intervals on a schedule determined by the IRB/IEC.
- Maintenance of appropriate records: Federal regulations require an investigator to prepare and maintain adequate and accurate case histories 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 2 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 2 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 CRF in a manner to assure legibility and accuracy. To this end, I shall carefully follow the instructions for completing CRFs.

I also agree that all information provided to me by the sponsor, including protocols, CRFs, 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/IEC. 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/IEC or to the FDA or other legally constituted authority.

**Principal Investigator** **Date**

**Printed Name**

# 13 REFERENCE LIST

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# PROTOCOL SIGNATURE PAGE

**Protocol Title**: An Extension Study of APD334-003 in Patients with Moderately to Severely Active Ulcerative Colitis

This study will be conducted in accordance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) (E6) and applicable Food and Drug Administration (FDA) guidelines.

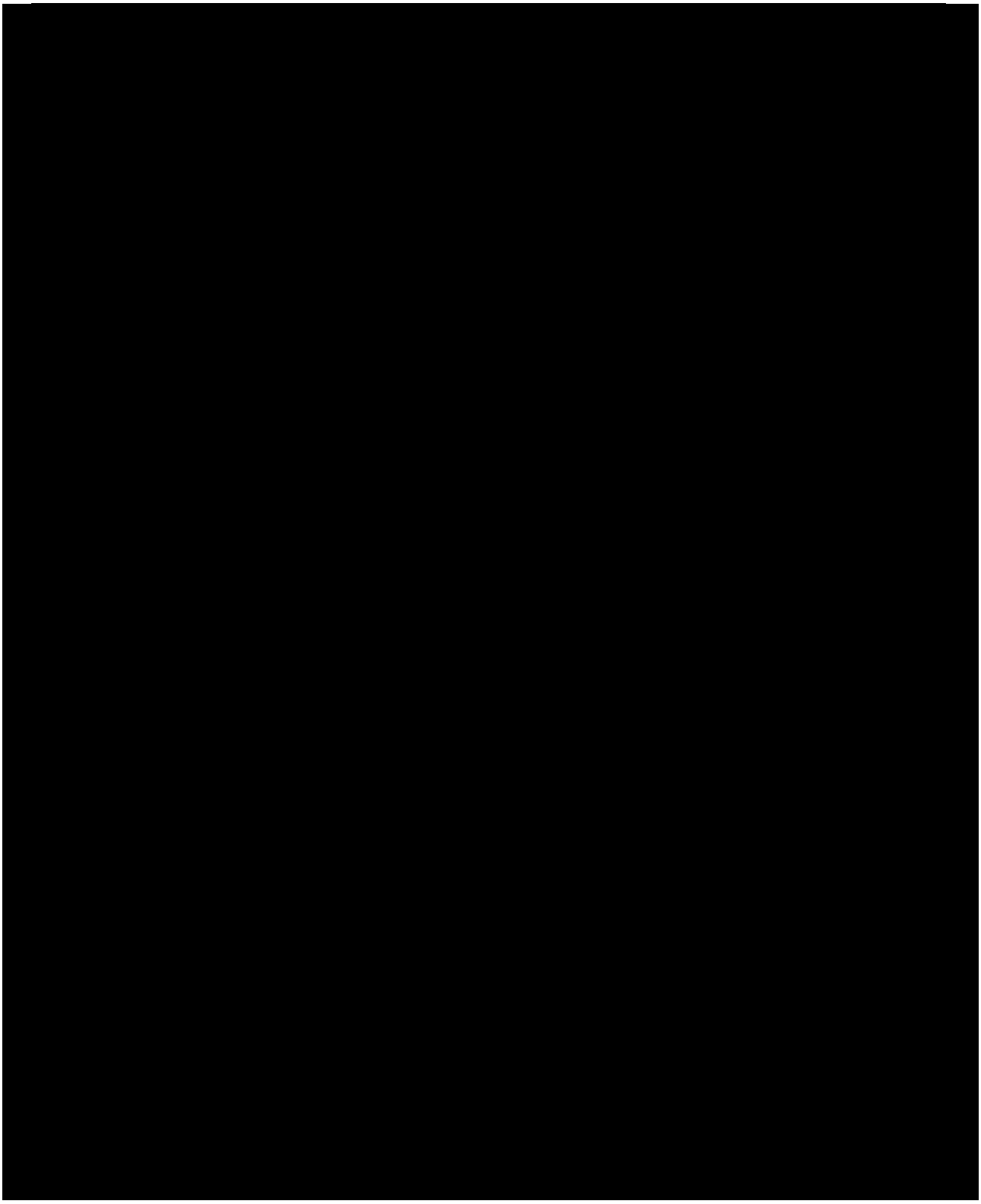
**Protocol Number: APD334-005**

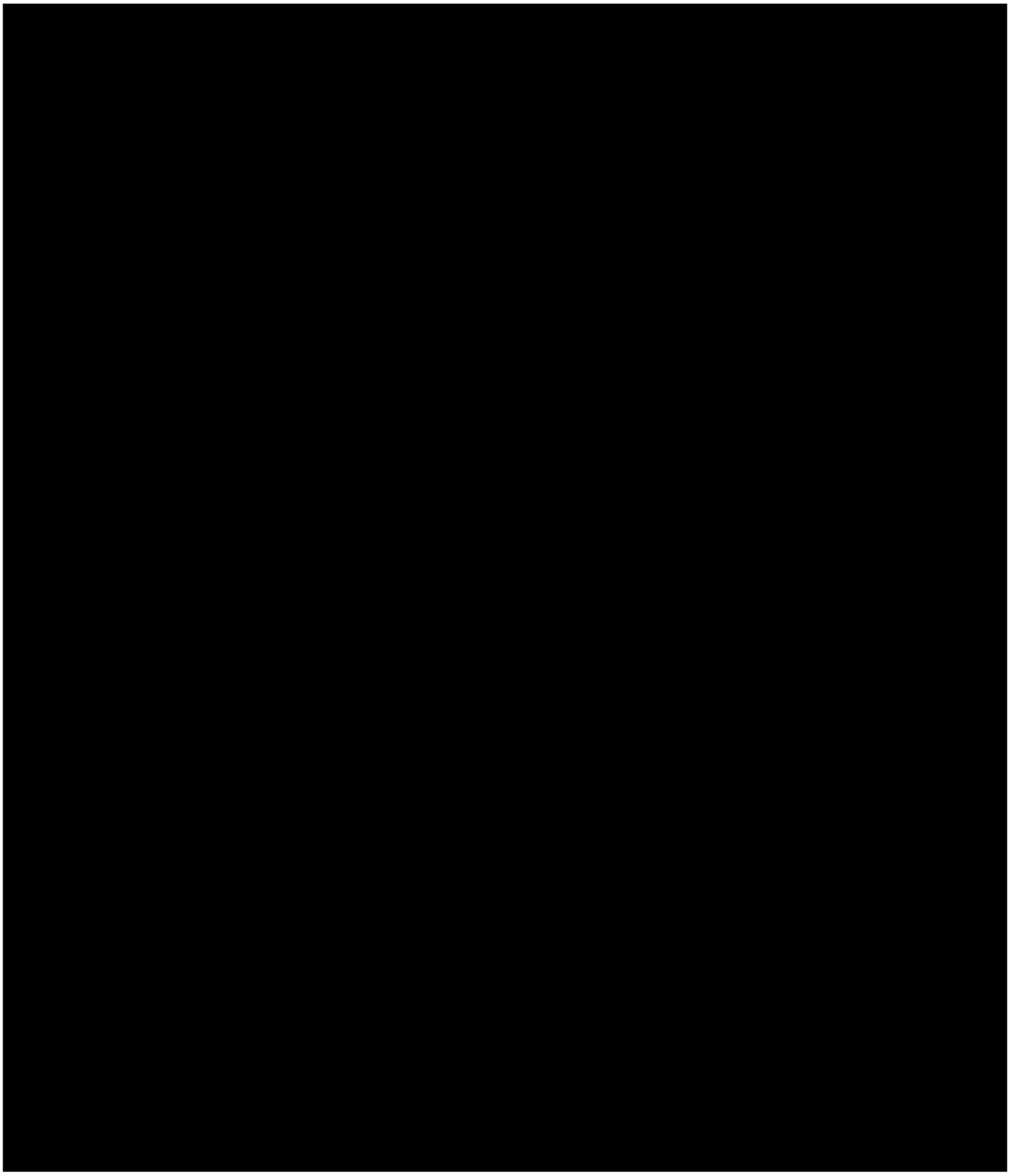
**Arena Pharmaceuticals, Inc. Signatures:**

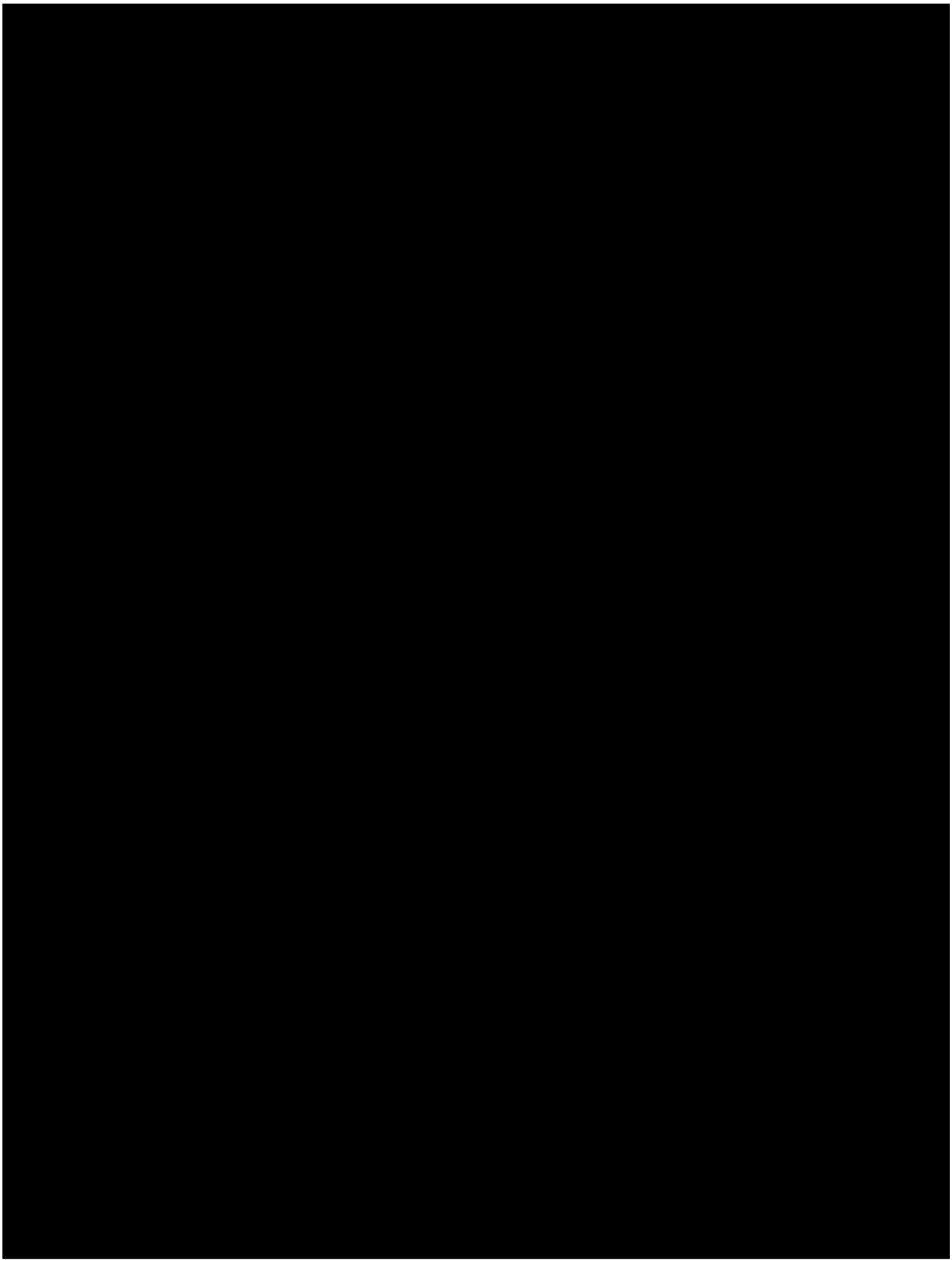
[redacted]

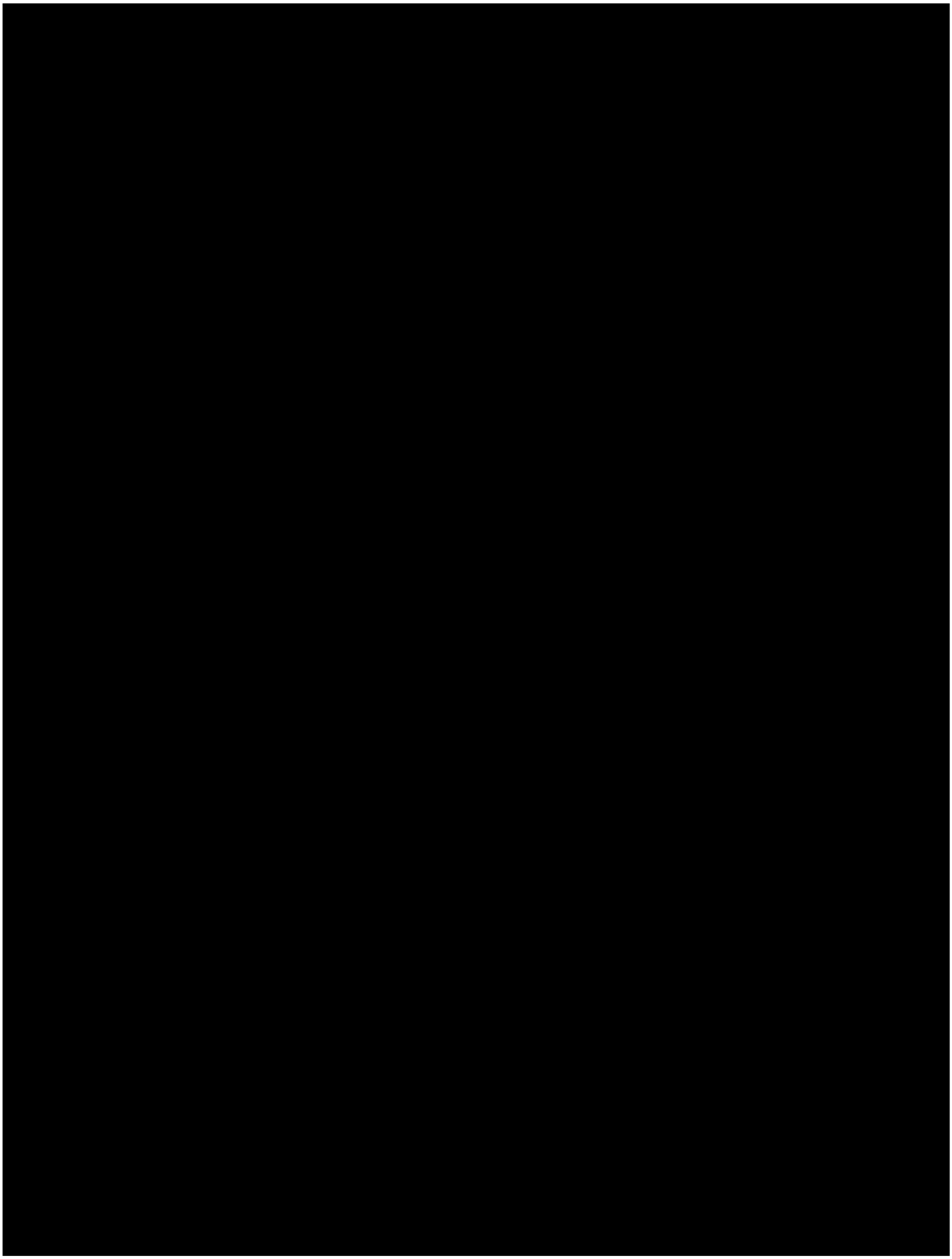
# Appendix 2 Progressive Multifocal Leukoencephalopathy (PML) Checklist

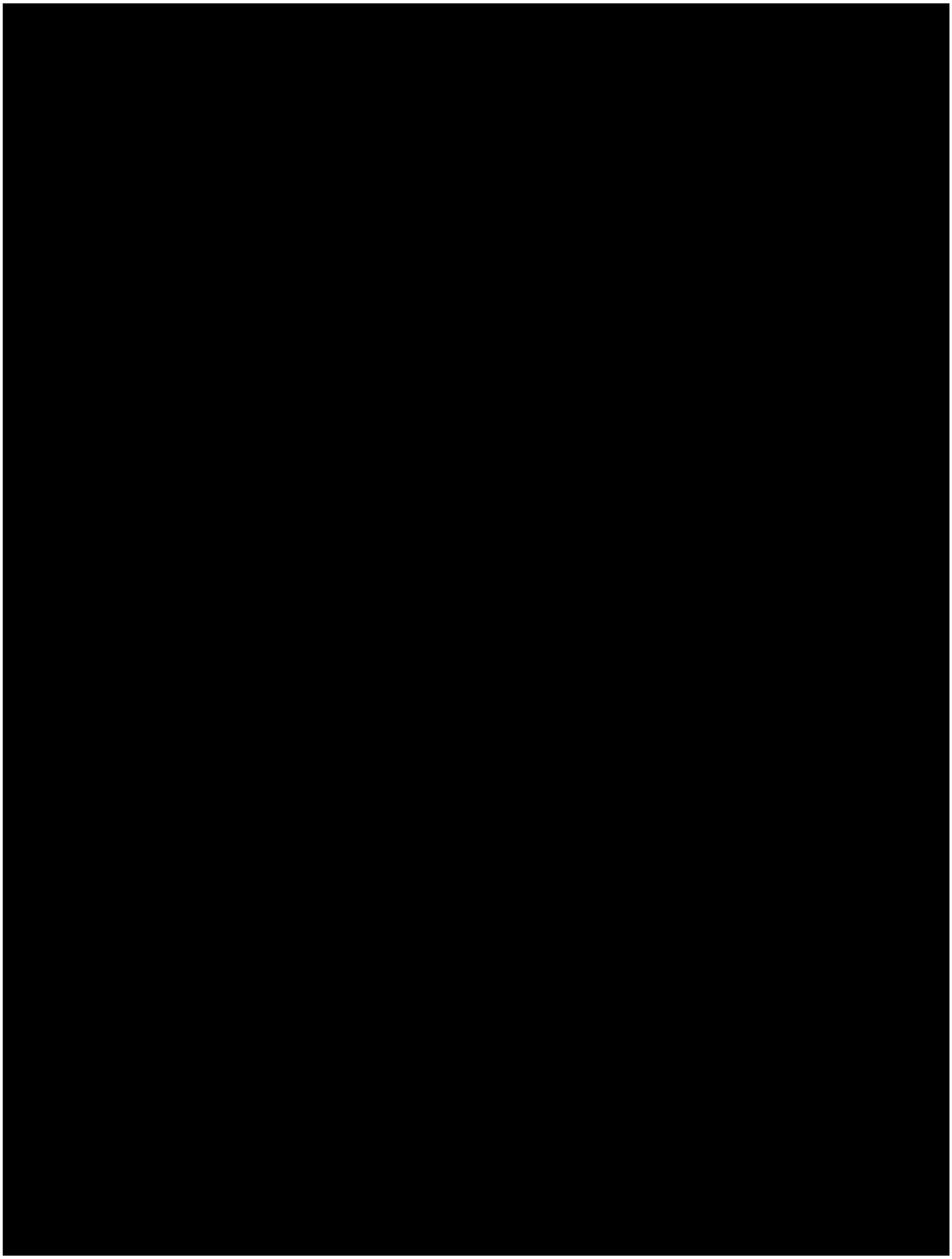
| Symptoms | "Compared to how you usually feel, have you had a significant change in any of the following?" | | If the answer is "yes", obtain a description of the symptom(s) with examples. | Applicable Objective Test(s): Document results on PML Object Checklist |
|---|---|---|---|---|
| | Yes | No | | |
| 1) Have you been experiencing any persistent difficulty with your vision such as loss of vision or double vision? Have you been having trouble reading? | | | | Test visual fields and ocular motility |
| 2) Have you been experiencing any persistent difficulty speaking or having your speech understood by others? | | | | Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase. |
| 3) Have you been experiencing any persistent weakness in an arm or leg? | | | | Test for pronator draft (Barre maneuver) and/or fixation on arm roll, Assess the ability to hop on either foot; foot and finger tapping. Test muscle strength. |
| 4) Have you noticed yourself regularly bumping into things or having difficulty writing? | | | | Ask for spontaneous writing sample and observe finger to nose, heel to shin, and tandem gait. |
| 5) Have you regularly been experiencing difficulty understanding others? | | | | Ability to follow serial commands |
| 6) Have you had persistent problems with your memory or thinking? | | | | Recall of 3 objects over 1 minute to distraction; ability to follow commands. |
| 7) Have you been experiencing any persistent numbness or other loss of sensation? | | | | Test sensation side to side with pinprick. |

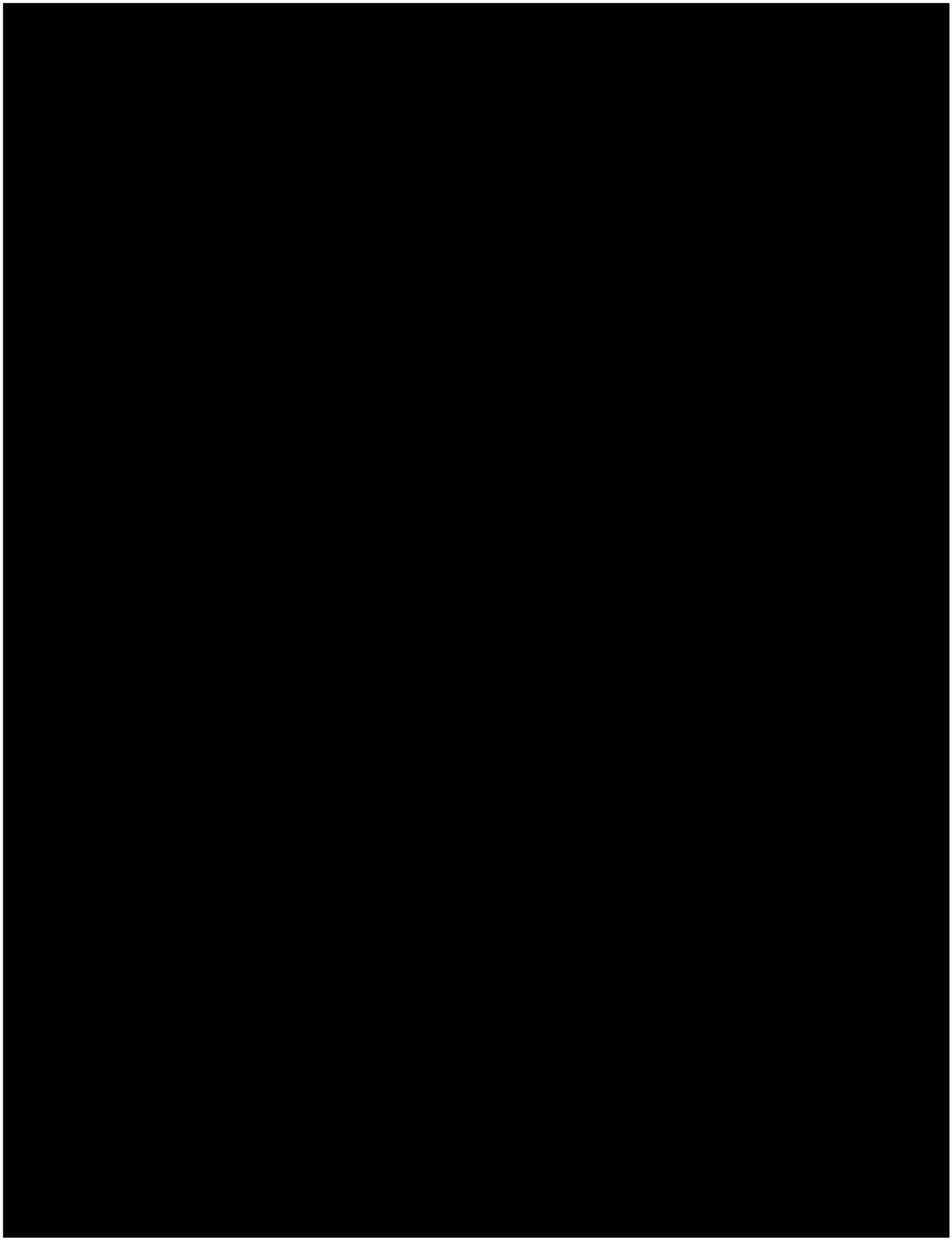


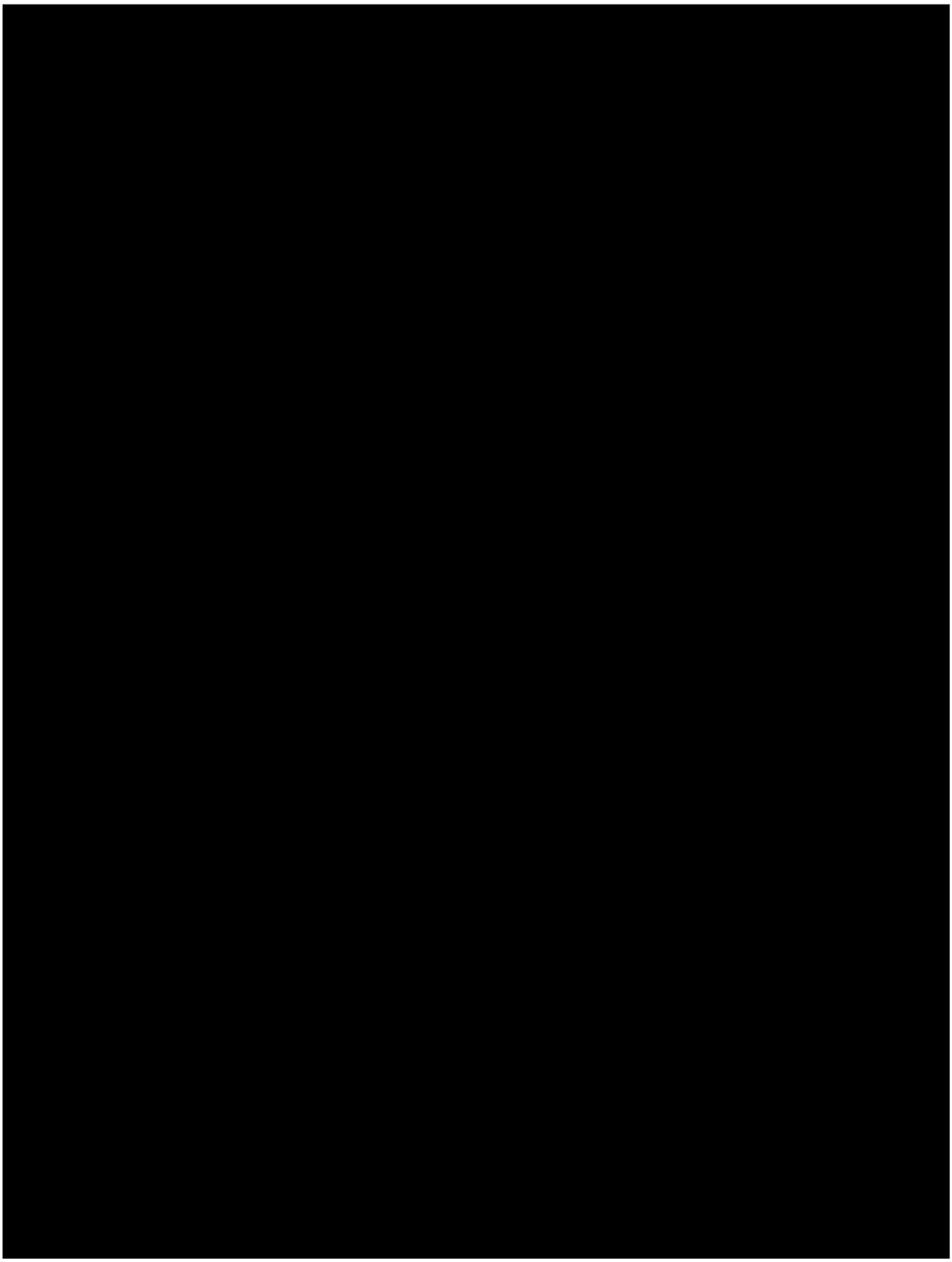


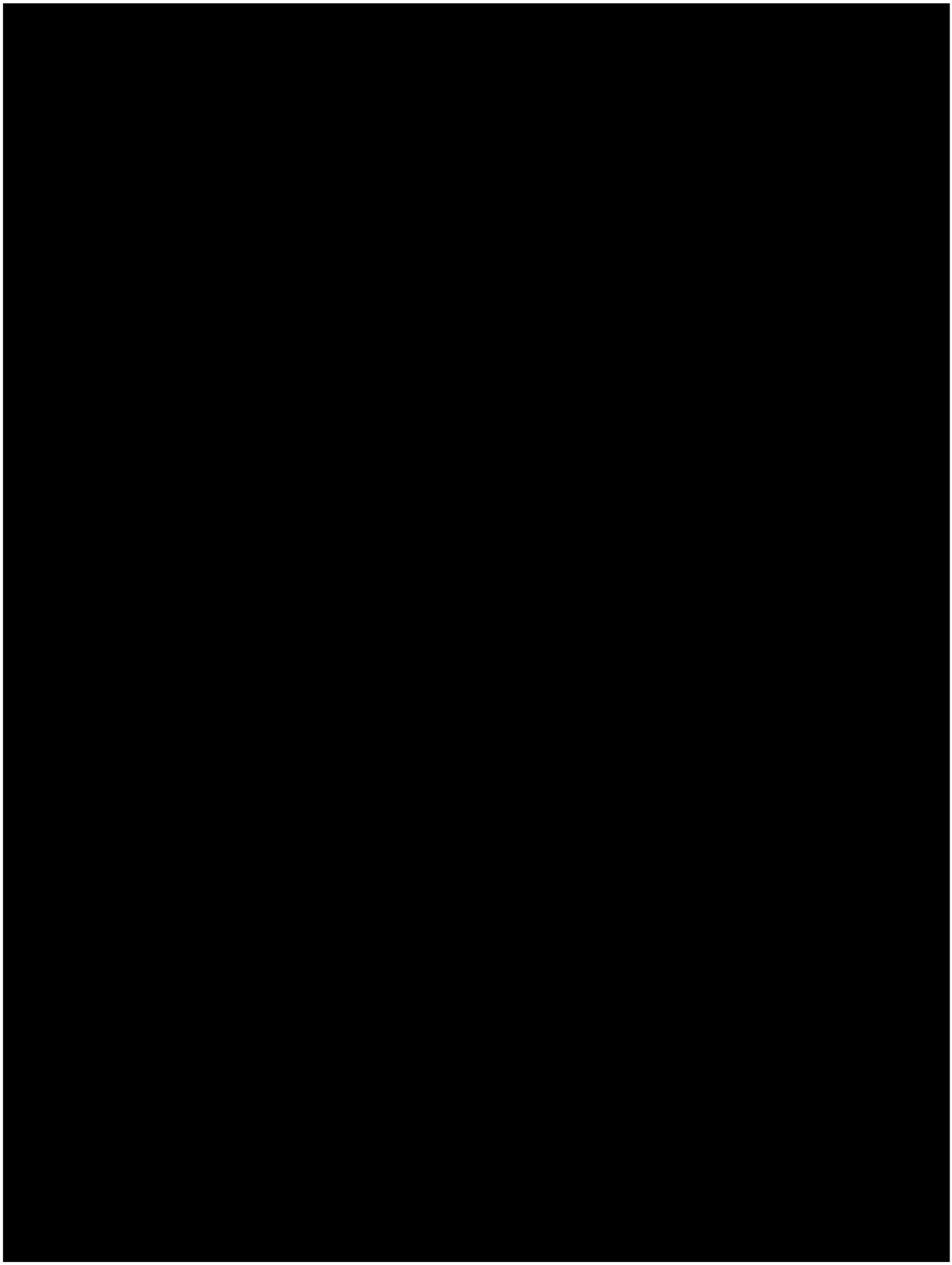


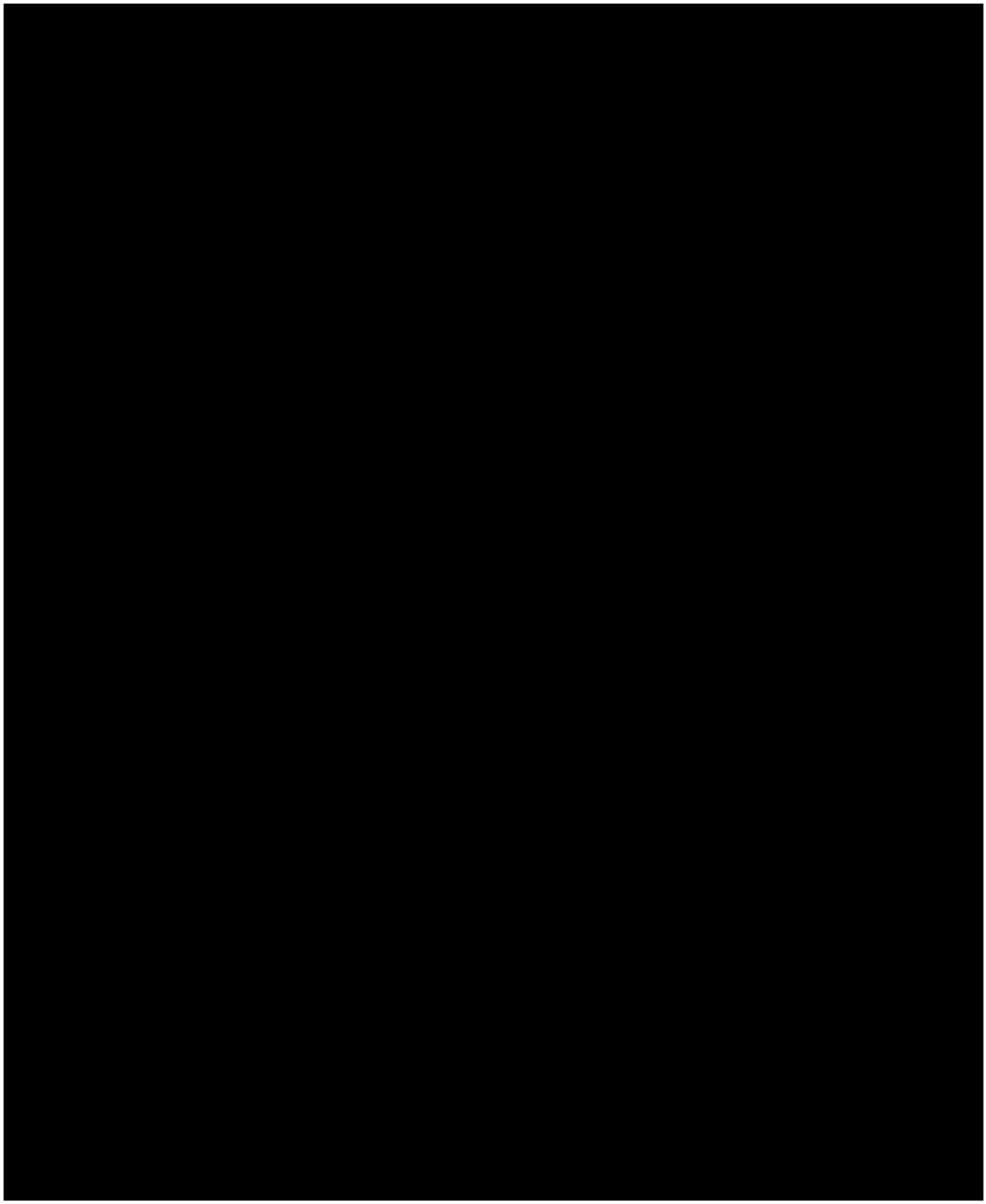












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UserName: [redacted]
Title: [redacted] Safety / Pharmacovigilance
Date: Wednesday, 29 March 2017, 11:43 AM Pacific Daylight Time
Meaning: Author Approval
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UserName: [redacted]
Title: Biostatistician/SAS Programmer
Date: Thursday, 30 March 2017, 07:40 AM Pacific Daylight Time
Meaning: Approval
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UserName: [redacted]
Title: [redacted], Regulatory Affairs and Quality
Date: Thursday, 30 March 2017, 02:20 PM Pacific Daylight Time
Meaning: Approval
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UserName: [redacted]
Title: [redacted], Research & Development
Date: Friday, 31 March 2017, 10:10 AM Pacific Daylight Time
Meaning: Approval
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UserName: [redacted]
Title: [redacted], Preclinical Development
Date: Monday, 03 April 2017, 08:34 AM Pacific Daylight Time
Meaning: Approval
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# PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD334-005 Protocol dated 28 September 2015. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 03 dated 20 October 2016.

| Section(s) Amended | Page No(s). | Description of Changes Made |
|---|---|---|
| Header/Footer, Title Page, and TOC | All | Added "Amendment 03", updated date to reflect finalization of amended protocol, updated pagination and TOC. |
| Protocol Amendment Summary | 2-5 | Updated table to include summary of changes to the protocol. |
| Synopsis | 6 | Updated sponsor contact and medical monitor. |
| Synopsis | 7-8 | Changed study duration from 52 weeks to 46 weeks total (including the APD334-003 study). |
| Synopsis | 7-8 | Changed study design to open label (2 mg) for APD334-003 responders only. |
| Synopsis | 7-8 | [redacted] |
| Synopsis | 8-9 | Updated secondary and exploratory outcome measures to reflect study duration of 46 weeks total (including the APD334-003 study). |
| Synopsis | 9-10 | [redacted] |
| Synopsis | 10 | Updated data analyses section to reflect changes in study design. |
| Synopsis | 11 | Updated figure "Study Design" according to the changes. |
| Study Definitions | 20 | Removed definitions of initial and new Day -1 or Day 1 to reflect amended study design (responders only). |
| 2.2 Secondary Objective | 27 | Updated to "46 weeks of treatment" |
| 3.1 Overall Study Design and Plan | 28 | Updated to reflect changes to single arm, open-label, 2 mg q.d. for responders in APD334-003 only. |

| | | |
|---|---|---|
| 3.1 Overall Study Design and Plan | 28 | [redacted] |
| 3.2 Study Duration and Dates | 28 | Changed study duration from approximately 42 weeks to up to 36 weeks. |
| 4.2 Inclusion Criteria 6 | 29-30 | Changed "completion of the study as planned" to "completion of the study as responder". Added definition of "responder". |
| 5.1.2 Placebo | 31 | Changed to "Not applicable". |
| 5.3 Selection and Timing of Dose for Each Patient | 31 | Updated to reflect eligibility for responders only. |
| 5.4 Method of Assigning Patients to Treatment Groups | 31-32 | Updated to reflect changes to single arm, open-label, 2 mg q.d. for responders in APD334-003 only. |
| 5.5.1 Randomization | 32 | Changed to "Not applicable". |
| 5.5.2 Blinding | 32 | Updated to reflect change to open-label. |
| 5.5.3 Maintenance of APD334-003 Randomization Codes and Code-break Procedures | 32 | Changed to "Not applicable". |
| 5.6 Concomitant Therapy | 32 | [redacted] |
| 5.11 Data Safety Monitoring Board | 33 | Changed to "Not applicable". |
| 6.5 Vital Signs | 35 | [redacted] |
| [redacted] | 35 | [redacted] |
| [redacted] | 38-39 | [redacted] |
| [redacted] | 39-40 | [redacted] |
| 6.10.2 Hematologic Sampling | 40 | [redacted] |
| 6.11.2 Serious Adverse Events and Expedited Reporting of Adverse Events | 42-43 | Changed SAE reporting contact information from Arena Pharmaceuticals to PPD Medical Affairs/Pharmacovigilance. |

| | | |
|---|---|---|
| [redacted] | 46 | [redacted] |
| 6.14 Allowable Visit and Procedure Windows | 47 | Removed all windows. |
| 7.1 Extension Study Enrollment Activities (Week 12 of Study APD334-003) | 48 | Removed "re-randomization or open-label treatment" according to amended study design. |
| 7.1.1 Treatment Assignment | 48 | Changed from re-randomization to assignment of 2 mg APD334 for responders. |
| 7.2.1 Baseline Activities | 48 | [redacted] |
| [redacted] | 49 | [redacted] |
| [redacted] | 49-50 | Added pregnancy test, CBC and clinical laboratory tests [redacted] |
| [redacted] | 50 | Added pregnancy test, CBC and clinical laboratory tests [redacted] Added pulmonary function test, fecal calprotectin, stool sample [redacted] |
| [redacted] | 50-51 | [redacted] |
| 9.1.2 Hypotheses | 54 | Removed Primary Safety and Secondary Efficacy hypotheses. |
| 9.2 Sample Size and Power Calculations | 54 | Removed sample size and power calculations. |
| 9.3 Analysis Populations | 54 | Changed "randomized" to "enrolled" for Intent-to-treat population and Modified Intent-to-Treat Population (MITT). |
| 9.4 Demographics and Baseline Characteristics | 54-55 | Removed treatment groups. |
| 9.5 Efficacy Endpoints | 55-56 | Modified Efficacy Endpoints according to amended study design. |
| 9.6 Statistical Methods | 56-58 | Modified according to amended study design. |

| | | |
|---|---|---|
| [redacted] | 58 | [redacted] |
| 9.8 Safety Analyses | 58-59 | Removed "between group differences", treatment groups, and provision for patients having taken the wrong medication.<br>Updated "randomization" to "enrollment". |
| Appendix 1 Schedule of Events | 69-71 | [redacted] |

# PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD334-005 Protocol dated 20 August 2015. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 02 dated 28 September 2015.

| Section(s) Amended | Page No(s). | Description of Changes Made |
|---|---|---|
| Header/Footer, Title Page, and TOC | All | Added "Amendment 02", updated date to reflect finalization of amended protocol, updated pagination and TOC. |
| Protocol Amendment Summary | 2-3 | Updated table to include summary of changes to the protocol. |
| Synopsis | 4 | Updated medical monitor. |
| Study definitions | 19 | Added definitions of *new* and *initial* Day -1 and Day 1. |
| 2.2 Secondary Objective | 27 | Corrected timeframe noted in secondary objective from 40 to 52 weeks. |
| 3.1 Overall Study Design and Plan | 29 | [redacted] |
| 6.3 Physical and Neurological Examination | 36 | Revised section to denote that retinal photos would be taken during each ophthalmoscopy. |
| [redacted] | 37 | [redacted] |
| 6.8 Clinical Laboratory Tests | 38-39 | Corrected numbering error in the section. |
| 6.13 Removal of Patients from the Trial or Study Drug | 49 | [redacted] |

| Section(s) Amended | Page No(s). | Description of Changes Made |
|---|---|---|
| [redacted] | 51-53 | [redacted] |
| [redacted] | 55 | Added retinal photos to be taken during each ophthalmoscopy. |
| Appendix 1 Schedule of Events | 75-77 | [redacted] |

# PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD334-005 Protocol dated 09 July 2015. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 01 dated 20 August 2015.

| Section(s) Amended | Page No(s). | Description of Changes Made |
|---|---|---|
| Header/Footer, Title Page, and TOC | All | Added "Amendment 01", updated date to reflect finalization of amended protocol, updated pagination and TOC. |
| Protocol Amendment Summary | 2 | Updated table to include summary of changes to the protocol. |
| Sections 3.1 Overall Study Design and Plan; 7.2.1 Baseline Activities [redacted] | 27 | Removed provision to allow [redacted] of study APD334-005 to be completed within 7 days after completion of study APD334-003, Week 12 procedures. |
| Sections 5.1 Description of Treatment(s) and 5.2 Treatments Administered | 31 | Removed reference to 1 mg strength of APD334. |
| [redacted] | 36 | [redacted] |
| Sections 6.8.2 Laboratory Parameters and 6.8.4 Sample collection, Storage, and Shipping | 37 | Removed references to serum human chorionic gonadotropin (hCG). |
| Section 6.9.2 Biopsy | 39 | Removed section pertaining to biopsy; there is no biopsy specified in the extension study.<br>Added new section "Stool Sample" to clarify that stool samples will be collected for analysis of fecal calprotectin. |
| Section 6.10.2 Hematologic Sampling and Table 1 Schedule of Procedures and Visits | 41, 74 | Updated section and Schedule of Procedures and Visits to reflect that a CBC is to be collected at the following [redacted] |

| Section(s) Amended | Page No(s). | Description of Changes Made |
|---|---|---|
| Section 7.2 Study Activities | 50-51 | Clarified which procedures take place [redacted] for the enrollees depending on response status. |
| [redacted] | 53-54, 75 | Added stool sample (for analysis of fecal calprotectin) [redacted] |
| [redacted] | 54 | Removed "dispensation" from drug dispensation/accountability procedure at [redacted] |
| Table 1 Schedule of Procedures and Visits | 74-76 | [redacted] |