Clinical Trial Protocol: APD334-003

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study to Investigate the Safety and Efficacy of APD334 in Patients with Moderately to Severely Active Ulcerative Colitis
Study Number:	APD334-003
Study Phase:	2
Product Name:	APD334
IND Number:	125,154
EudraCT Number:	2015-001942-28
Indication:	Ulcerative Colitis
Investigators:	Multicenter
Sponsor:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121

	Date
Original Protocol:	08 April 2015
Amendment 01:	01 May 2015
Amendment 02:	17 June 2015
Amendment 03:	30 June 2015
Amendment 04:	21 September 2015
Amendment 05:	10 October 2016
Amendment 06:	27 March 2017

NCT Number: NCT02447302
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 APD334-003 Protocol Amendment 05 dated 10 October 2016. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 06 dated 27 March 2017.

Section(s) Amended	Description of Changes Made
Header/Footer, Title Page, and TOC	Added "Amendment 06", updated date to reflect finalization of amended protocol, updated pagination and TOC.
Protocol Amendment Summary	Updated table to include summary of changes to the protocol.
Synopsis	Updated sponsor contact details
Synopsis	Changed Primary Objective "The primary objective will be to determine the effect of treatment with APD334 in inducing clinical remission at 12 weeks" to: ***Current*** "The primary objective of this proof-of-concept study is to determine the effect of treatment with APD334 in improving 3-component Mayo Clinic Score (score ranging from 0 to 9, including stool frequency, rectal bleeding and findings on endoscopy) at Week 12"
Synopsis	Added the following Secondary Objectives: • To determine the effect of treatment with APD334 on a combination of clinical remission and clinical response reflected by a composite endpoint at 12 weeks • To determine the effect of treatment with APD334 in inducing clinical remission at 12 weeks
Synopsis	Added the following Exploratory Objectives: • to determine the effect of APD334 treatment on Total Mayo Clinic Score at 12 weeks. [redacted]

Synopsis	Study Design: Changed the study description: "phase 2, dose-ranging, placebo-controlled clinical study" to: ***Current*** "phase 2, proof-of-concept and dose-ranging, placebo-controlled clinical study" Changed patients with the option to enroll in an extension study APD334-005: "responder patients" to: ***Current*** "all patients"
Synopsis	Changed Primary Efficacy Endpoints "The proportion of patients achieving 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 from baseline subscore at Week 12" to: ***Current*** " • The improvement of 3-component Mayo Clinic Score (score ranging from 0 to 9, including stool frequency, rectal bleeding and findings on endoscopy) at Week 12."
Synopsis	Added the following Secondary Efficacy Endpoints: • The trichotomous composite endpoint of clinical remission and clinical response (score ranging 0 to 2: score 2 for achieving both clinical remission and clinical response; 1 for achieving only clinical response, and 0 for achieving neither) at Week 12 • The proportion of patients achieving 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 from baseline subscore at Week 12
Synopsis	Added the following Exploratory Objectives: • Improvement in Total Mayo Clinic Score (score ranging from 0 to 12, including stool frequency, rectal bleeding and findings on endoscopy, and physician's global assessment) at Week 12

	
Synopsis	Data Analysis section updated to reflect new primary, secondary and exploratory Endpoints.
Study Definition	Added "Trichotomous composite endpoint" definition
2. Study Objectives	Updated Primary and Secondary Objectives according to changes highlighted in the Synopsis.
3.1 Overall Study Design and Plan	Study Design: Changed the study description: "phase 2, dose-ranging, placebo-controlled clinical study" to: ***Current*** "phase 2, proof-of-concept and dose-ranging, placebo-controlled clinical study" Changed patients with the option to enroll in an extension study APD334-005: "responder patients" to: ***Current*** "all patients (responders and non-responders)"

4.2 Inclusion Criteria	[redacted]
4.3 Exclusion Criteria	[redacted]
6.12.1 Permitted Medications for the Treatment of UC	Changed "for the 4 weeks immediately prior to screening" to: ***Current*** "for the 4 weeks immediately prior to screening **endoscopy assessment**"
6.15 Study and Site Discontinuation	Added section 6.15 to provide reasons to terminate the study or replace a site.
9 Planned Statistical Methods	Added specifications related to the intention of Section 9.
9.1.1 Hypotheses and Objectives	Primary, Secondary and Exploratory Objectives and Hypothesis were updated to reflect the updated Primary, Secondary and Exploratory Endpoints.

9.5 Efficacy Endpoints	Primary, Secondary and Exploratory Efficacy Endpoints were updated reflecting the changes highlighted in the Synopsis amendment summary section.
9.6.1 Primary, Secondary and Exploratory Efficacy Analysis	Primary, Secondary and Exploratory Efficacy Analysis were updated reflecting the changes highlighted in the Primary, Secondary and Exploratory Endpoints section.
9.6.3 Multiplicity	Updated to reflect the new Primary, Secondary and Exploratory Endpoints. Removal of Figure 1 – Statistical testing procedure in the UC Trial
9.6.4 Interim Analysis	Changed "No interim analyses are planned for this study", to: ***Current*** "Sponsor may plan an unblinded interim analysis at time when sufficient number of patients have finished 12 weeks of treatment. If Sponsor decides to perform an interim analysis, it will be operated by an independent Data Review Committee (DMC). The revision of statistical analysis plan (SAP) with detailed interim analysis specifications and a DMC charter will be provided to regulatory agency in timely manner and will be finalized prior to the interim analysis."

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

SYNOPSIS

Name of Drug:	APD334
Indication:	Ulcerative Colitis
Sponsor:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121
Name of Sponsor Contact:	[redacted] Arena Pharmaceuticals, Inc 6154 Nancy Ridge Drive San Diego, California 92121 Phone [redacted]
Name of Principal Investigator(s):	Multi-center
Medical Monitor:	[redacted] Arena Pharmaceuticals, Inc. Phone: [redacted] Mobile: [redacted]
Test Product, Dose and Mode of Administration:	• 1 mg APD334 once daily (q.d.) for 12 weeks • 2 mg APD334 once daily (q.d.) for 12 weeks • Placebo once daily (q.d.) x 12 weeks The route and mode of administration of APD334 and placebo capsules will be oral with an adequate amount of water (240 mL).
Concurrent Control:	Placebo; microcrystalline cellulose in hard gelatin capsules
Objectives:	**Primary Objective:** The primary objective of this proof-of-concept study is to determine the effect of treatment with APD334 in improving 3-component Mayo Clinic Score (score ranging from 0 to 9, including stool frequency, rectal bleeding and findings on endoscopy) at Week 12

	Secondary Objectives: The secondary objectives of this study are: • To determine the effect of treatment with APD334 on a combination of clinical remission and clinical response reflected by a composite endpoint at 12 weeks • To determine the effect of treatment with APD334 in inducing clinical remission at 12 weeks • To determine the effect of treatment with APD334 in inducing clinical response at 12 weeks • To determine the effect of treatment with APD334 on endoscopic improvement at 12 weeks **Safety Objective:** The safety objective of this study is to determine the safety profile and tolerability of APD334 induction treatment. **Exploratory Objectives:** The exploratory objectives of the study are: • to determine the effect of APD334 treatment on Total Mayo Clinic Score at 12 weeks. [redacted]

	[redacted]
Study Design:	This phase 2, proof-of-concept and dose-ranging, placebo-controlled clinical study will test 2 doses of APD334 or placebo in up to 240 patients with moderately to severely active ulcerative colitis. [redacted] will be randomized into a double-blind, placebo-controlled study, receiving one of 2 doses of APD334 or matching placebo for 12 weeks. Treatment arms will consist of once daily (q.d.) doses of 1 mg APD334, 2 mg APD334, or matching placebo. Patients will be randomized in a 1:1:1 ratio and will be stratified by presence or absence of current oral corticosteroid usage and previous exposure to TNFα antagonists. Entry criteria will be based on confirmation of moderately to severely active UC, as defined by a 3-component Mayo Clinic [redacted]

	At the end of the study all patients will have the option to enroll in an extension of the study (APD334-005) following completion of all study procedures and providing they meet all inclusion criteria for the extension study. Patients who do not participate in the extension study (APD334-005) will have a 2-week follow-up visit after the last clinical visit.
Study Site(s):	This study will be conducted in approximately 100 clinical centers worldwide.
Patient Population:	[redacted]
Duration per Patient:	~18 weeks: ~28 days of screening, followed by a 12-week induction period. Patients who do not participate in the APD334-005 extension study will have a 2-week follow-up visit after the last clinical visit. Clinic visits will occur during the screening period (to be completed up to ~28 days before first dose of study medication) and approximately every 2-4 weeks during the study. Additional visits may occur at the discretion of the investigator.
Patient Assignment:	Eligible patients will be randomized in a 1:1:1 ratio to receive once daily (q.d.) doses of 1 mg APD334, 2 mg APD334, or matching placebo.
Sample Size:	Up to 240 patients total.
Efficacy Endpoints	**Primary:** • The improvement of 3-component Mayo Clinic Score (score ranging from 0 to 9, including stool frequency, rectal bleeding and findings on endoscopy) at Week 12. **Secondary:** • The trichotomous composite endpoint of clinical remission and clinical response (score ranging 0 to 2: score 2 for achieving both clinical remission and clinical response; 1 for achieving only clinical response, and 0 for achieving neither) at Week 12

	• The proportion of patients achieving 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 from baseline subscore at Week 12 • The proportion of patients who achieve clinical response [defined as a decrease in the 3-component Mayo Clinic score of ≥ 2 points and a decrease of ≥ 30% with either a decrease of rectal bleeding of ≥ 1 or rectal bleeding score of 0 or 1] at Week 12 • The proportion of patients who achieve endoscopic improvement [defined as Mayo endoscopic subscore (using findings of flexible proctosigmoidoscopy) of ≤ 1 point] at Week 12 **Exploratory:** • Improvement in Total Mayo Clinic Score (score ranging from 0 to 12, including stool frequency, rectal bleeding and findings on endoscopy, and physician's global assessment) at Week 12 

	[redacted]
Safety Assessments:	• Physical examinations including ophthalmoscopy (and optical coherence tomography [OCT], where available) • Clinical laboratory tests to include hematology, serum chemistry, coagulation, and urinalysis • Vital sign measurements • Pulmonary Function Tests (PFTs) • 12-lead electrocardiograms (ECGs) • Adverse event reporting
[redacted]	[redacted]

	[redacted]
Data Analyses:	The primary analysis will be based on the change of 3-component Mayo Clinic Score at Week 12 from baseline using an analysis of covariate (ANCOVA) model with terms for treatment, current oral corticosteroid use, prior exposure to TNFα antagonists and baseline value as covariate. Least-squares mean (LSM) by treatment group and its 95% confidence interval (CI), and least-squares mean difference between treatment group and its 95% CI will be reported. The secondary analyses include following: • Trichotomous composite endpoint of clinical remission and clinical response at Week 12 is an ordinal categorical endpoint with 3 categories (2, 1, 0). It will be analyzed using Cochran-Mantel-Haenszel method adjusted for the stratification factors of presence or absence of current oral corticosteroid therapy at baseline and previous exposure to TNFα antagonists. The testing statistic will be computed using modified ridit score for between-treatment comparison. • The proportion of patients who achieve clinical remission, clinical response, or endoscopic improvement will be analyzed individually using Cochran-Mantel-Haenszel (CMH) test adjusted for the stratification factors of presence or absence of current oral corticosteroid therapy at baseline and previous exposure to TNFα antagonists, to compare the difference of proportions between treatment group. The CMH stratified risk difference and its 95% confidence interval will be provided Mayo Clinic Score data handling: for each visit during the study (excluding the screening/baseline visit which uses 10 prior days), stool frequency and rectal bleeding subscores will be derived from electronic patient diaries completed over the 7 days prior to a study visit. Note that the day prior, day of and day after proctosigmoidoscopy will not be used for patient diary entry because of the required bowel prep for the procedure. These subscores will be calculated using the following rules:

	1. The scores from the 3 most recent days prior to the actual day of the study visit will be averaged and rounded to the nearest integer. 2. If patient diary entries from 3 days are not available, the scores from the 2 most recent entries will be averaged and rounded to the nearest integer. 3. If less than 2 days of diary data are available, the subscore will be considered missing. All patients who prematurely discontinue for any reason will be considered failures (non-responders) for all the proportion based endpoints. <u>Exploratory efficacy analyses</u>: [redacted] Dose response analyses will be performed using ANCOVA model for continuous variables, or logistic regression model for categorical variables, as appropriate. Treatment group and appropriate baseline covariates will be included in the analysis model. Statistical testing of dose response trend will be based on appropriate contrast statement assuming monotonic dose response profile in placebo, APD334 low dose and APD334 high dose. A statistical testing procedure will be constructed to manage multiplicity issues concerning primary and secondary efficacy analyses in order to control overall Type I error rate for efficacy testing not exceeding 0.05. The details of testing procedure will be specified in a separate Statistical Analysis Plan. For the comparison of the proportion of patients who achieve clinical remission between APD334 versus placebo, a sample of ~80 patients per group will provide 80% power to detect a difference of 18% (from 10% to 28%) at α=5% (2-sided test). This calculation is based upon an assumed placebo rate of 10%. Safety information after administration of multiple doses of APD334 in patients with moderately to severely active ulcerative colitis will be evaluated by tabulating adverse experiences and clinical assessment of clinical laboratory data.
Date:	27 March 2017

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
ED50	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
[redacted]	[redacted]
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
Mayo Clinic score (Complete Mayo or MCS)	Instrument designed to measure disease activity of ulcerative colitis consisting of 4 subscores: stool frequency, rectal bleeding, findings of flexible proctosigmoidoscopy, and physician global assessment with each component ranging from 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe). Total score therefore ranges from 0 to 12, with a higher score indicating more severe disease.
3-component Mayo Clinic score	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]	
Physician's global assessment	The physician's global assessment acknowledges the three other criteria findings of the Mayo Clinic score; the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance. Total score range: 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe).
Clinical Response	Decrease in the 3-component Mayo Clinic score of ≥ 2 points and a decrease of ≥ 30% with either a decrease of rectal bleeding of ≥ 1 or rectal bleeding score of 0 or 1 at Week 12.
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 12.
Trichotomous composite endpoint	An ordinal categorical endpoint with 3 scores: score 2 for achieving both clinical remission and clinical response, 1 for achieving only clinical response, 0 for achieving neither.

Term	Definition
Endoscopic Improvement	Mayo endoscopic subscore (using findings of flexible proctosigmoidoscopy) of ≤ 1 point at Week 12.
[redacted]	
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.[11] Collectively, patients with IBD suffer from a multitude of GI symptoms, including diarrhea, rectal bleeding and abdominal pain.

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 related to this event 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.[3]

The number of patients diagnosed with IBD has dramatically increased worldwide over the past 50 years.[5] 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[6], with as many as 70,000 new cases diagnosed in the US each year[7]. In Europe, an estimated 2.5 – 3 million people are affected by IBD[8] and as many as 5 million may be affected worldwide[9]. 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.[10]

Treatment for patients with IBD is generally for symptomatic care (relief of symptoms) and mucosal 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[14].

[redacted] Lymphocyte trafficking agents such as natalizumab and vedolizumab, both injectable or infused therapies, have demonstrated proof-of-concept in IBD indications. 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 in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine.[12] 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.[12]

The $S1P_1$ receptor signaling on lymphocytes allows their exit from lymph nodes along a S1P gradient. Functional antagonism of these S1P1 receptors results in retention of lymphocytes 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 different inflammatory and autoimmune diseases.

This study is designed to test the safety and efficacy of APD334 as a means to reduce the inflammation in the GI tract and induce a clinical response or remission in patients with severely to moderately active ulcerative colitis.

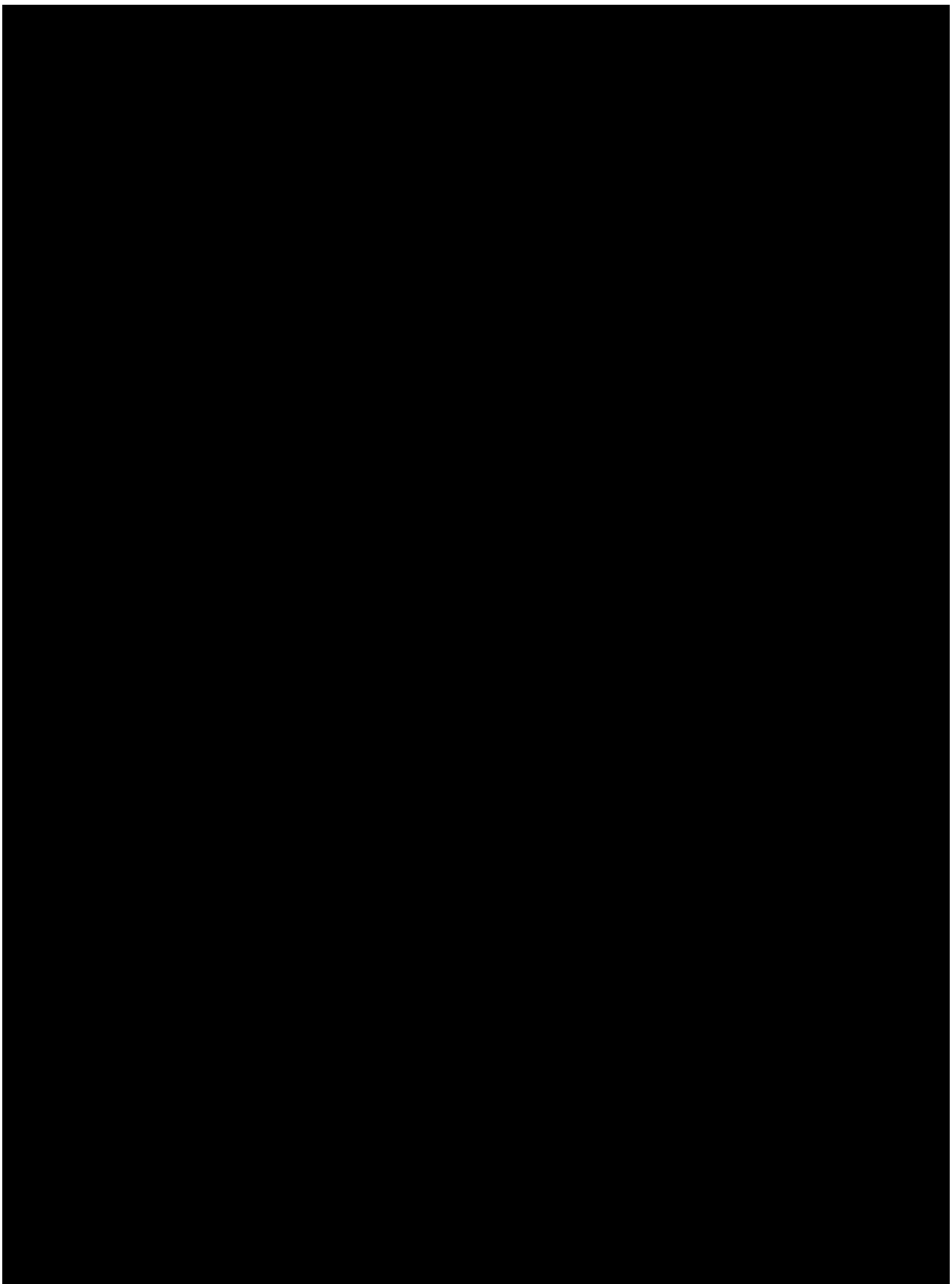
1.1.2 Summary of Preclinical Data

[redacted]

[redacted]

1.1.3 Summary of Clinical Data

[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 proof-of-concept study will be to determine the effect of treatment with APD334 in improving 3-component Mayo Clinic score (score ranging from 0 to 9, including stool frequency, rectal bleeding and findings on endoscopy) at 12 weeks.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To determine the effect of treatment with APD334 on a combination of clinical remission and clinical response reflected by a composite endpoint at 12 weeks
- To determine the effect of treatment with APD334 in inducing clinical remission at 12 weeks
- To determine the effect of treatment with APD334 in inducing clinical response at 12 weeks
- To determine the effect of treatment with APD334 on endoscopic improvement at 12 weeks

This amendment clarifies that the primary endpoint is being changed to a 3-component Mayo Clinic Score (stool frequency, rectal bleeding, and findings on endoscopy) derived from the Total Mayo Clinic Score. Thus, the primary endpoint is a continuous variable ranging from 0 to 9. The rationale for this change is that the endpoint should be more sensitive to detecting clinically important differences between two doses of APD334 and placebo compared to a dichotomous complete remission endpoint. Because the trial is considered a proof-of-concept trial and dose ranging study, the primary endpoint will reflect a broad examination of potential clinical improvement across three domains (stool frequency, rectal bleeding, and and findings on endoscopy). The secondary endpoints reflect clinical endpoints that are well recognized in the clinical community (complete remission, clinical response, and endoscopic score) and a combination of both clinical remission and clinical response reflected by a trichotmous endpoint.

3 INVESTIGATIONAL PLAN

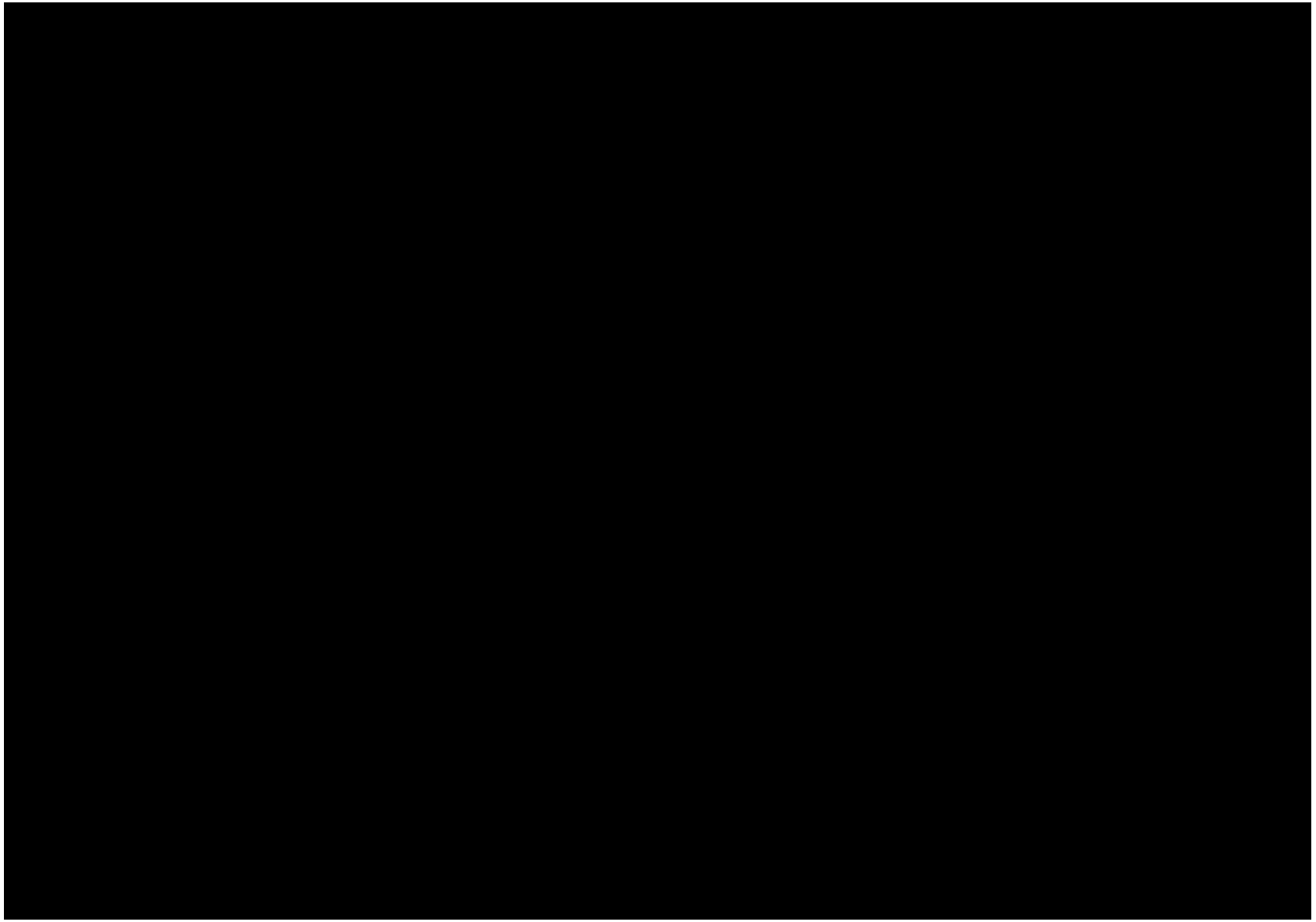
3.1 Overall Study Design and Plan

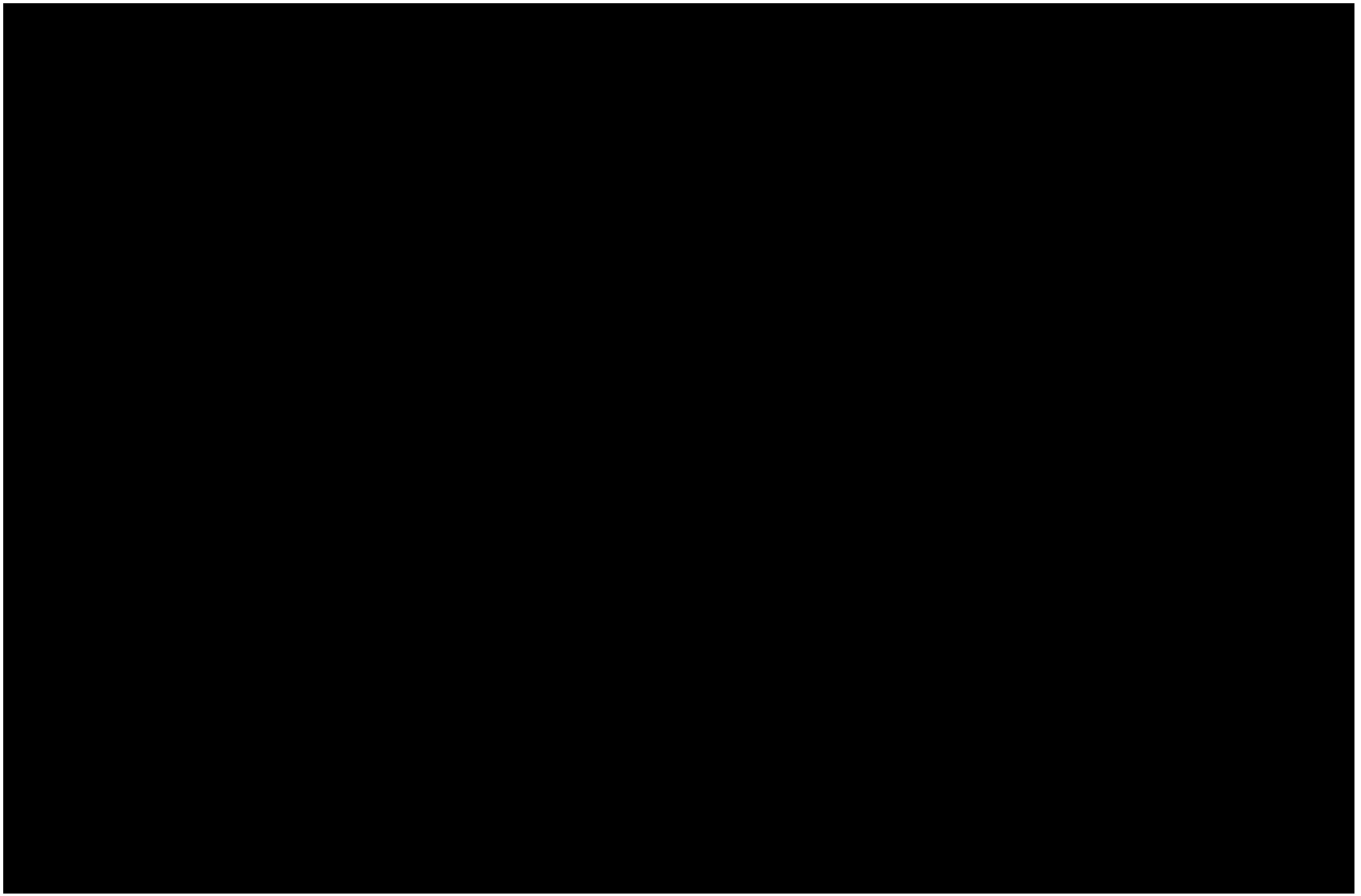
APD334-003 is a phase 2, proof-of-concept and dose ranging clinical study designed to test the ability of APD334 to induce clinical response and/or remission in patients with moderately to severely active ulcerative colitis. Up to 240 eligible patients will be randomized into a double-blind, placebo-controlled study to receive once daily (q.d.) doses of APD334 (1 mg or 2 mg) or matching placebo in a 1:1:1 ratio for 12 weeks. The screening period for the study is up to ~28 days which includes several assessments that must be completed within 10 days prior to randomization to ensure eligibility for the study. Patient's vital signs will be monitored using a Holter monitor for up to 24 hours pre-dose through 24 hours post dose. Patients will report daily stool frequency and rectal bleeding using an electronic device throughout the study and will be scheduled at regular intervals for safety, [redacted], and efficacy assessments. A 34-week extension study (APD334-005) is offered to all patients (responders and non-responders) who complete the study and will meet the relevant eligibility criteria. Patients who do not participate in the extension study or who have discontinued prematurely from the study will have a 2-week follow-up visit after the last clinical visit.

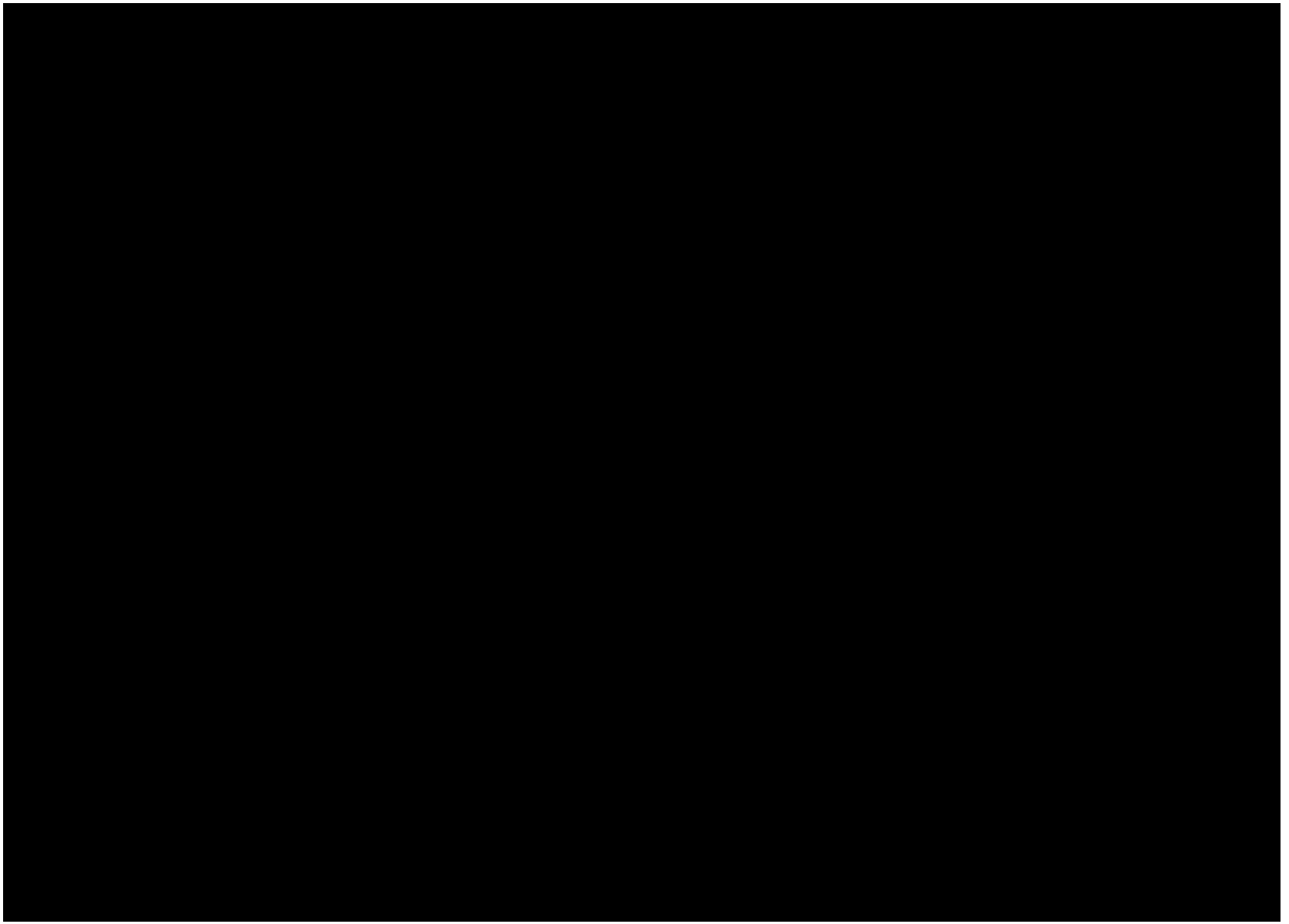
3.2 Study Duration and Dates

The total study participation/duration is approximately 18 weeks; ~4 weeks for screening procedures, followed by 12 weeks of dosing, and a possible follow-up visit at Week 14.

The schedule of procedures and visits for the study is provided in [redacted]







4 STUDY POPULATION SELECTION

4.1 Study Population

Adult men and women, ages 18-80 years, who have moderately to severely active ulcerative colitis [redacted]

Eligible patients must meet all entry criteria prior to being randomized to receive study medication as outlined below. Any patient-specific concerns or questions regarding these criteria must be discussed with the medical monitor or Arena Pharmaceuticals, Inc. prior to the patient being randomized.

4.2 Inclusion Criteria

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

[redacted]

6. Moderately to severely active ulcerative colitis defined as a 3-component Mayo Clinic [redacted]

[redacted]

7. Evidence of colonic ulcerative colitis activity on endoscopy [redacted]

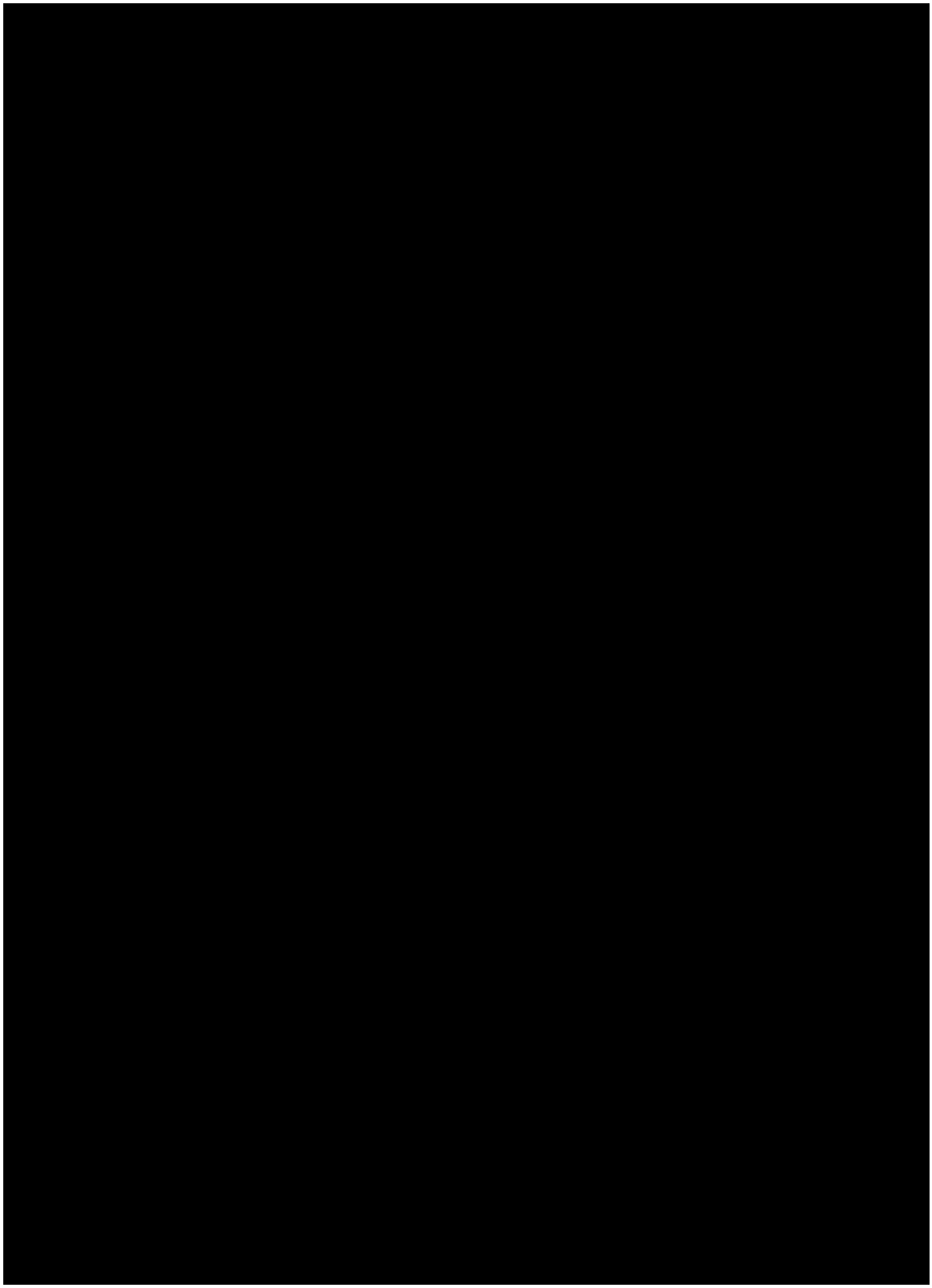
[redacted]

[redacted]

4.3 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

4. Within 30 days prior to randomization, receipt of any of the following for the treatment of underlying disease:
   a. Non-biologic therapies (e.g., cyclosporine, tacrolimus, tofacitinib, thalidomide) other than those specifically listed in Section 6.12.1.
   b. A non-biologic investigational therapy
   c. An approved non-biologic therapy in an investigational protocol
5. Within 60 days prior to randomization, receipt of any of the following:
   a. Infliximab, adalimumab, golimumab, certolizumab, vedolizumab
   b. Any other investigational or approved biologic agent
6. Any prior exposure to natalizumab, efalizumab, or rituximab



5 STUDY TREATMENT(S)

5.4 Test Article Accountability

The investigator will maintain accurate records of the receipt of all study medication. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each 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.

5.5 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 the 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.

5.6 Dosage and Administration

Investigational product will be dispensed in a double-blind fashion to the patients under the supervision of the investigator or his/her designee as determined by the randomization schedule. All enrolled patients will receive 1 oral dose per day of 1 mg APD334, 2 mg

APD334, or matching placebo for 12 weeks. [redacted]

On days with scheduled study visits, patients should **not** take their dose of study medication at home in order to complete pre-dose study procedures. [redacted]

[redacted]

5.7 Method of Assigning Patients to Treatment Groups

After signing the voluntary informed consent form (VICF) and completing all screening procedures, eligible patients will be randomly assigned in a 1:1:1 ratio to receive 1 of 3 study treatments:

- 1 mg APD334 x 12 weeks
- 2 mg APD334 x 12 weeks
- Placebo x 12 weeks

5.8 Randomization and Blinding

5.8.1 Randomization

Sites will randomize approximately 240 patients for entry into the study in a 1:1:1 ratio to receive once daily doses of 1 mg APD334, 2 mg APD334, or matching placebo and will be stratified by presence or absence of current oral corticosteroid usage and previous exposure to TNFα antagonists. The number of patients with previous exposure to TNFα antagonists will be capped at 50% (or at most 120 with previous exposure to TNFα antagonists will be randomized).

5.8.2 Blinding

The sponsor, patients, and personnel involved with the conduct of the study, with the exception of the clinical supply staff, safety staff, and the unblinded statistician supporting the Data Safety Monitoring Board (DSMB), will be blinded to the identity of study medication.

In addition, the sponsor, patients, and personnel involved with the conduct of the study will also be blinded to the total WBC and [redacted], 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 [redacted] and leucocyte counts, but blinded to the study medication, will review and monitor the total WBC and [redacted] counts for safety purposes in the trial. The study site personnel will not receive laboratory results for the total WBC or [redacted].

5.8.3 Maintenance of Randomization Codes and Code-break Procedures

The randomization code will be generated by a CRO statistician not directly involved with the study. All other personnel directly related to this study (i.e., investigators, site personnel, monitors, CRO personnel, Arena personnel) with the exception the individuals stipulated in Section 5.8.2, will remain blinded for the duration of the study. After APD334-003 has been completed, the study will be unblinded to selected individuals (which may or may not include: CRO statistician, Sponsor designate[s], DMPK representative[s]) in order to conduct the analyses and reporting for the study. As these activities will occur while APD334-005 is ongoing, patients, investigators and site will remain blinded to patient-level data of the APD334-003 study until the completion of APD334-005. The CRO will obtain written consent from Arena prior to breaking the code.

Breaking of the randomization code without Arena's permission is expressly forbidden except in the event of a medical emergency where the identity of the study medication must be known in order to properly treat the patient. In the event of a medical emergency, it is requested that the investigator make every effort to contact the study monitor or designee prior to breaking the code. If the blind is broken, the individual responsible should document the date, time, and reason for breaking the blind. A written communication should be sent to Arena within 1 working day.

5.9 Study Restrictions

5.9.1 Fluid and Food Intake

Consumption of foods and beverages containing the substances listed below will be prohibited as indicated. Exceptions may be permitted upon the joint agreement of the Arena and the investigator provided the safety of the patient and integrity of the study are not compromised.

- Poppy seeds: Consumption of poppy seeds within 48 hours prior to drug screen may cause a positive drug screen. Patients who report that they have consumed poppy seeds within 48 hours of the screening visit should not be screened. They may return 48 hours after the last poppy seed consumption for screening. Poppy seeds should not be eaten between screening and Week 0/Day 1 and throughout the inpatient period.

5.10 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB), independent from Arena, will be established to review safety data from this study including, but not limited to, AEs of special interest (e.g., bradycardia, infections, PML) at regular intervals and make recommendations. The roles and responsibilities of the DSMB will be outlined in a separate charter.

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 screening, a complete medical history and a social history, including tobacco, alcohol and caffeine use, as well as a full history of UC, will be collected by patient interview. Concomitant medications, recent blood donations, illnesses, and participation in other investigational drug studies will also be recorded. A partial examination will be performed at check-in to update findings from screening and document any pre-treatment AEs.

6.2.1 Prior Therapies

Prior therapies related to UC will be collected during screening.

6.2.2 History of UC

A detailed history of UC, including date of diagnosis, disease severity, hospitalizations, and extraintestinal manifestations will be collected during screening.

6.3 Physical and Neurological Examinations

6.3.1 Physical Examination

The physical examination include assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, thyroid, lungs, heart, abdomen, back, lymph nodes, and extremities, and body weight will be performed during [redacted] by the principal investigator or subinvestigator. A limited examination to assess clinically significant changes from the examination performed at screening will be completed during the [redacted] visit. Height will only be obtained at screening.

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

Safety ECGs will also be performed as outlined in the schedule of procedures and visits ([redacted]).

Clinically significant findings from the physical/neurological examination performed at screening will be recorded as medical history. Any new clinically significant findings from the time of screening through the first dose of study drug will be recorded as pre-treatment AEs. After the administration of the first dose of study drug, clinically significant findings will be recorded as AEs.

6.3.2 Neurological Examination

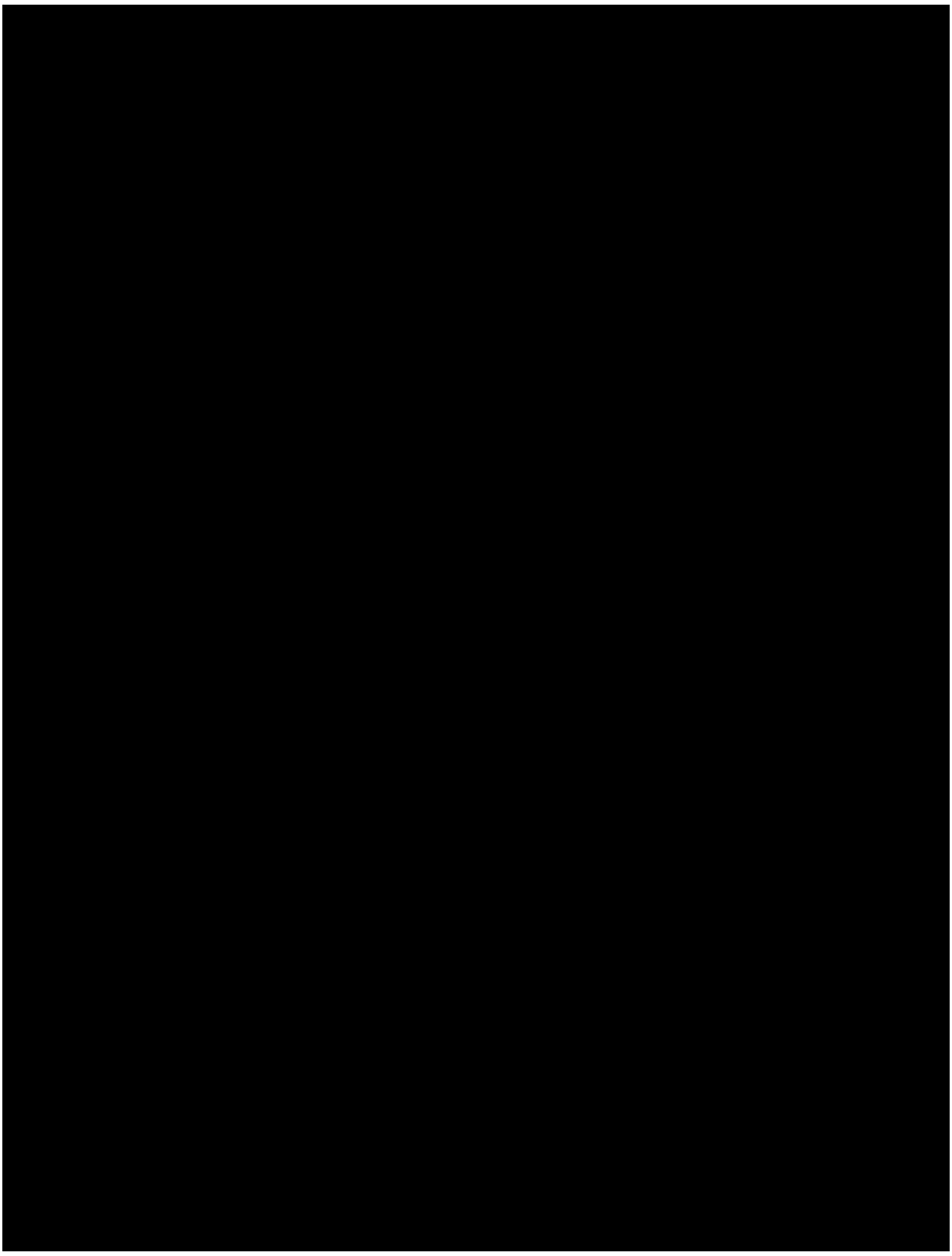
The neurological examination includes assessments of the neurological system (cranial nerves, motor and sensory function, coordination, and mental status), and will be performed during screening, [redacted] (limited examination to assess clinically significant changes from the screening), and at [redacted] by the principal investigator or subinvestigator. In addition, monitoring for progressive multifocal leukoencephalopathy (PML), a potential adverse effect of $S1P_1$ agonists, will be performed at each site visit (except for the [redacted]) using a subjective PML checklist.

The investigator or subinvestigator will administer the subjective PML checklist during screening to exclude patients with positive responses from enrolling into the study. The subjective PML checklist will also be administered at each site visit (except Day [redacted] 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 1.

6.4 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 schedule of procedures and visits ([redacted]).

[redacted]



[redacted]

6.6 Tuberculosis Screening and Chest X- ray

All patients will complete tuberculosis (TB) screening to determine eligibility. All patients who do not report a history of TB must complete a diagnostic TB test within [redacted] prior to randomization and a chest X-ray within [redacted] prior to randomization. (In most countries where the BCG vaccine is standard, the TB skin test will likely be positive and a Quantiferon test will be needed.) Patients will be excluded from the study if they have active or latent TB, regardless of treatment history, as evidenced by any of the following:

- History of TB (that has not been acceptably treated)
- A positive diagnostic TB test within 1 month of randomization defined as:
  - A positive QuantiFERON® test or 2 successive indeterminate QuantiFERON® tests ***OR***
  - A tuberculin skin test reaction ≥ 10 mm (≥ 5 mm in patients receiving the equivalent of > 15 mg/day prednisone)
- Chest X-ray within 12 months of randomization in which active or latent pulmonary TB cannot be excluded

[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 and the [redacted] manual provided by Arena.

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 [redacted] and should be completed pre-dose. Laboratory tests will include the following. Complete blood count (CBC) will be obtained prior to dosing. Results of the total white blood cell and [redacted] will be reviewed and monitored per Section 5.8.2.

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)
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)

Additional tests
Serum human chorionic gonadotropin (hCG)
HIV test
HBsAg
Anti- HCV
VZV IgG

6.8.2 Virology

Human immunodeficiency virus (HIV antibody), hepatitis B (HBsAg), hepatitis C virus (RIBA 2 or 3), and varicella zoster virus (VZV) IgG antibody will be performed at [redacted]

6.8.3 Drugs of Abuse Screen

Urine samples for the drugs of abuse screen will be collected according to the laboratory manual provided by the local or central laboratory and according to the schedule of procedures and events ([redacted]).

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

6.8.4 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.

[redacted]

6.8.6 Sample Collection, Storage, and Shipping

Blood samples for hematology, coagulation parameters, serum chemistry, HIV and hepatitis screens, serum hCG, will be collected according to the laboratory manual provided by the local or central laboratory and according to the schedule of procedures and visits ([redacted]).

6.8.7 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 during screening [redacted] and at Week 12/Exit visit.

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.

[redacted]

6.9.3 Stool Sample

A stool sample will be obtained for culture, ova and parasite evaluation for *C. difficile* assay. A sample will be collected and cultured during screening and at any point in the study when a patient becomes symptomatic, including worsening or return of disease activity.

[redacted]

6.9.6 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 called a TrialMax Touch Android (HTC Desire 310).

During screening, patients will be instructed on how to appropriately complete the electronic diary. The symptoms of UC must be recorded throughout the study, including the screening period. Diary entries will be reviewed by site personnel during screening and (prior to dosing, if applicable) at [redacted]

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.

6.9.7 Complete Mayo Clinic Score, 3-component Mayo Clinic Score, [redacted]

COMPLETE MAYO CLINIC SCORE (MCS): SCREENING AND WEEK 12/EXIT ASSESSMENT

The complete Mayo Clinic Score (MCS) is an instrument designed to measure disease activity of ulcerative colitis and consists of 4 subscores: stool frequency, rectal bleeding, findings of flexible proctosigmoidoscopy, and physician global assessment with each component ranging from 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe). Total score therefore ranges from 0 to 12, with a higher score indicating more severe disease.

The MCS will be evaluated during screening using patient diary entries within the 10 days prior to randomization and flexible proctosigmoidoscopy results within 10 days prior to randomization. The subscores for stool frequency and rectal bleeding are derived from the patient diaries. The scores from the 3 most recent days prior to the actual day of the study visit will be averaged and rounded to the nearest integer. Note that the day prior, day of and day after proctosigmoidoscopy cannot be used for patient diary entry because of the required bowel prep for the procedure. Patients who have less than 3 days of diary data during screening are not eligible for randomization. Examples of the subscore entries for eligibility and subscore derivation are provided in Table 2. The rounding will be applied to each subscore prior to the creation of the total score. The MCS will also be evaluated at Week 12/Exit using the Week 12/Exit proctocsigmoidoscopy and stool frequency and rectal bleeding scores completed by the patients up to seven days prior to the visit.

Table 2. Examples of eDiary Subscore Entries for Study Eligibility and Corresponding Subscore Derivation

Example	Diary Day											Valid Days for Calculation of Subscore	Average Subscore	Final Subscore
	-10	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**			
Diary #1	1	2	3	X	P	X	2	**1**	**3**	**1**	E	-1, -2, -3	1.66	2
Diary #2	2	2	2	**3**	X	P	X	M	**1**	**3**	E	-1, -2, -7	2.33	2
Diary #3	3	2	3	**3**	**3**	X	P	X	**3**	M	E	-2, -6, -7	3.00	3
Diary #4	**3**	**0**	**1**	X	P	X	M	M	M	M	E	-8, -9, -10	1.33	1
Diary #5	1	2	X	P	X	M	M	M	M	M	E	Missing	N/A	Missing

Abbreviations: E = eligibility; M = missing; P = proctosigmoidoscopy; X = non-scoring day before and after proctosigmoidoscopy

3-COMPONENT MAYO CLINIC SCORE: STUDY ENTRY CRITERIA AND PRIMARY ENDPOINT

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).

Entry criteria will be based on a 3-component Mayo Clinic score (as defined in the inclusion criteria).

[redacted]

Physician's Global Assessment (PGA)

The physician's global assessment acknowledges the three other criteria findings of the MCS, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance. The PGA will be used in calculation of the MCS at screening and Week 12/Exit.

A sample of the complete Mayo Clinic score is provided in [redacted]

6.10 [redacted] and Hematologic Assessments

[redacted]

6.10.2 Hematologic Sampling

Blood samples for CBC with differential and platelet count will be assessed during screening, and at [redacted] for those not continuing on to the extension study and with abnormal CBC results at exit.

If the absolute peripheral [redacted] has not recovered to at least 80% of the baseline value at th [redacted] patients should return for weekly CBCs until the absolute peripheral [redacted] 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. AEs that occur from ICF signature until the time of administration of the first dose of APD334 will be regarded as 'pre-treatment' and recorded as an AE. All events reported following study medication administration up to 30 days after the last medication intake will be presented as treatment emergent AEs (TEAEs)

Monitoring of 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 study medication (APD334 or placebo) 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

Lymphopenia will not be captured as an adverse event both to maintain the study blind, and also because it is an expected pharmacologic effect of the drug. In order to ensure safe conduct of the study and minimize the risk of study personnel or sponsor becoming unblinded to treatment assignment, total WBC and [redacted] will be monitored by a central CRO physician(s) unblinded to the [redacted] and leucocyte counts. This person will remain blinded to the study medication

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[25], 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 during screening to exclude patients with positive responses from enrolling into the study. The subjective PML checklist will be administered at [redacted] 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 1.

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 [redacted] 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 according to 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 according to 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 (Week 12/Exit) 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 Section 4.2 and Section 4.3.

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.

6.12.1 Permitted Medications for the Treatment of UC

Oral 5-ASA treatment is permitted for the treatment of UC, provided that the patient was receiving the medication(s) at baseline, and that the dose(s) has been stable as specified in Section 4.2. These medications should remain stable throughout the study.

Oral corticosteroids that the patient is receiving at baseline may be continued, provided that the dose has been stable for the 4 weeks immediately prior to screening endoscopy assessment if corticosteroids have just been initiated as specified in Section 4.2. These medications should remain stable throughout the study (tapering may be initiated after participation in this study or during extension study APD334-005).

Azathioprine or 6-mercaptopurine, provided that the dose has been stable for the 8 weeks immediately prior to screening. (**These immunosuppressive agents must be discontinued at the time of randomization**.)

Probiotics (e.g., Culturelle, *Saccharomyces boulardii*) provided that the dose has been stable for the 2 weeks immediately prior to randomization.

Antidiarrheals are allowed throughout the study as necessary for control of chronic diarrhea; stable doses are encouraged.

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
- Moderate to strong inhibitors of CYP2C9

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

- 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 Week 12/Exit visit procedures described in Section 7.4.4.

6.13.2 Replacements

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

6.14 Allowable Visit and Procedure Windows

- [redacted]

  If screening process is interrupted due to technical issues (timing, medical devices functioning etc.), patient can continue the screening after the [redacted] have passed, but time extension must not exceed [redacted] In this case, all medical evaluations performed previously are considered still valid, except for the following procedures, which have to be performed within [redacted] to randomization:

  - Flexible proctosigmoidoscopy with [redacted]
  - Diary review
  - Complete Mayo score (MCS)
  - Record adverse events
  - Record concomitant medications/procedures
  - [redacted]

- There are no visit windows after randomization.

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

[redacted]

At the initial screening visit, potential patients will have a detailed oral presentation of the nature, purpose, risks, and requirements of the 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.

A unique patient screening number will be assigned upon completion of the VICF.

Within 28 days before administration of the study medication, or sooner, all screening activities subsequent to obtaining informed consent will be conducted and consist of the following**:**

- Review of all inclusion and exclusion criteria
- Collection of demographic data (sex, age, race/ethnicity)
- Completion of medical and social history (to include tobacco, alcohol, and caffeine use)
- UC medical history
- Physical/neurological examination, including height, weight, vital signs (i.e., supine blood pressure, heart rate, respirations, and temperature after a 5 minute rest) and ophthalmoscopy with OCT (where available) and retinal photos
- [redacted]
- PML checklist
- Safety ECG (12-lead)
- Pulmonary function test (spirometry)
- Stool sample

- [redacted]
- TB screening
- Chest X-ray, Posteroanterior (PA) and Lateral (per [redacted])
- Clinical laboratory tests (hematology, serum chemistry, coagulation parameters, urinalysis, [redacted], and drugs of abuse screen), and virology screen (HBsAg, HIV antibodies, and HCV antibodies).
- CBC with differential and platelet count
- Serum hCG pregnancy test (non-postmenopausal females only)
- Diary instruction
- Record adverse events
- Record concomitant medications/procedures

The following activities must occur within 10 days prior to randomization:

- Flexible proctosigmoidoscopy with [redacted]
- Diary review
- Complete Mayo Clinic score (MCS)
- Record adverse events
- Record concomitant medications/procedures

Extension of screening time-window (up to 35 days) might be allowed, and performed as per Section 6.14.

7.2 Screening Failures

A screening failure is defined as a patient who has signed the VICF, does not meet all the entry criteria as outlined in this protocol and has not been randomized or received study medication.

7.2.1 Re-screening

In case of screening failure (e.g. due to low ulcerative colitis severity, temporary intestinal infection, concomitant medication etc.), a patient can be re-screened. During re-screening, if not feasible for the patient, ophthalmology and pulmonary function tests do not have to be repeated if the last assessment was not done longer than three months before. All other assessments have to be repeated.

7.3 [redacted] Holter Fitting and Monitoring

Patients who meet all the entry criteria and are eligible for the study will report to the site on the morning of [redacted] to receive their Holter monitor for the [redacted] monitoring period. Patients will be monitored on site to confirm the monitor is working correctly before being released to return on [redacted]

7.4 Treatment Period

[redacted]

- Medical history (partial history, to update findings from screening and document any pre-treatment AEs)
- Physical and neurological exam (limited examination to assess clinically significant changes from screening)
- [redacted]
- Holter monitoring (per [redacted])
- PML checklist
- Clinical laboratory tests (serum chemistry, hematology, coagulation parameters, urinalysis and [redacted]) (per [redacted])
- CBC with differential and platelets (per [redacted])
- [redacted]
- Drugs of abuse screen (to include amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines and cannabinoids).
- Urine pregnancy test (women only)
- [redacted].
- Diary review
- [redacted]
- Vital signs (per [redacted])
- Drug dispensation
- Record adverse events
- Record concomitant medications/ procedures
- Randomization

- Study drug administration (per [redacted])

7.4.2 At-home Holter Removal

Patients will remove their Holter monitors after the [redacted] monitoring periods have completed (on [redacted]. Removal time and instructions will be provided to the patient by the site. For convenience, the patients may return the Holter monitor at the next visit.

[redacted]

- Safety ECG (12-lead) (per [redacted])
- PML checklist
- Clinical laboratory tests (serum chemistry, hematology, coagulation parameters, urinalysis and [redacted]) (per [redacted])
- CBC with differential and platelets (per [redacted])
- Urine pregnancy test (women only) (per [redacted])
- [redacted]
- Diary review
- [redacted]
- Stool sample [redacted] per [redacted])
- [redacted]
- Vital signs (per [redacted])
- Study drug dispensation/administration (per [redacted])
- Drug accountability
- Record adverse events
- Record concomitant medications/ procedures

[redacted]

- Physical/ neurological exam and ophthalmoscopy with OCT and retinal photos (per [redacted])
- Safety ECG (per [redacted])
- PML checklist

- [redacted]
- Pulmonary function test (spirometry) (per [redacted])
- Clinical laboratory tests (serum chemistry, hematology, coagulation parameters, urinalysis and [redacted])
- CBC with differential and platelets (per [redacted])
- Serum pregnancy test (women only)
- [redacted]
- Diary review
- Flexible proctosigmoidoscopy with [redacted]
- Complete Mayo Clinic score (MCS)
- Determine clinical responder/non-responder status of patient based on the following criteria: a decrease (from baseline) in 3-component Mayo Clinic score of ≥ 2 points and a decrease of ≥ 30% with either a decrease of rectal bleeding of ≥ 1 or rectal bleeding score of 0 or 1 at Week 12.
- Stool sample
- [redacted]
- Vital signs
- Study drug administration (per [redacted])
- Drug accountability
- Record adverse events
- Record concomitant medications/ procedures

[redacted]

Patients who do not wish to continue into the extension study will have a [redacted] visit after their final visit to have additional safety assessments performed as outlined in the schedule of procedures and visits ([redacted]).

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 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'.

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), Format C.

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. The intention of Section 9 is to provide overview of statistical analyses. Details of the statistical analyses and statistical testing procedure will be included in a separate statistical analysis plan (SAP) which will be finalized before database lock. If, after the study has been unblinded, 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 proof-of-concept study will be to determine the effect of treatment with APD334 in improving 3-component Mayo Clinic Score (score ranging from 0 to 9, including stool frequency, rectal bleeding and findings on endoscopy) at Week 12.

9.1.1.2 Secondary Objective(s)

The secondary objectives of the study are:

- To determine the effect of treatment with APD334 on a combination of clinical remission and clinical response reflected by a composite endpoint at 12 weeks
- To determine the effect of treatment with APD334 in inducing clinical remission at 12 weeks
- To determine the effect of treatment with APD334 in inducing clinical response at 12 weeks
- To determine the effect of treatment with APD334 on endoscopic improvement at 12 weeks

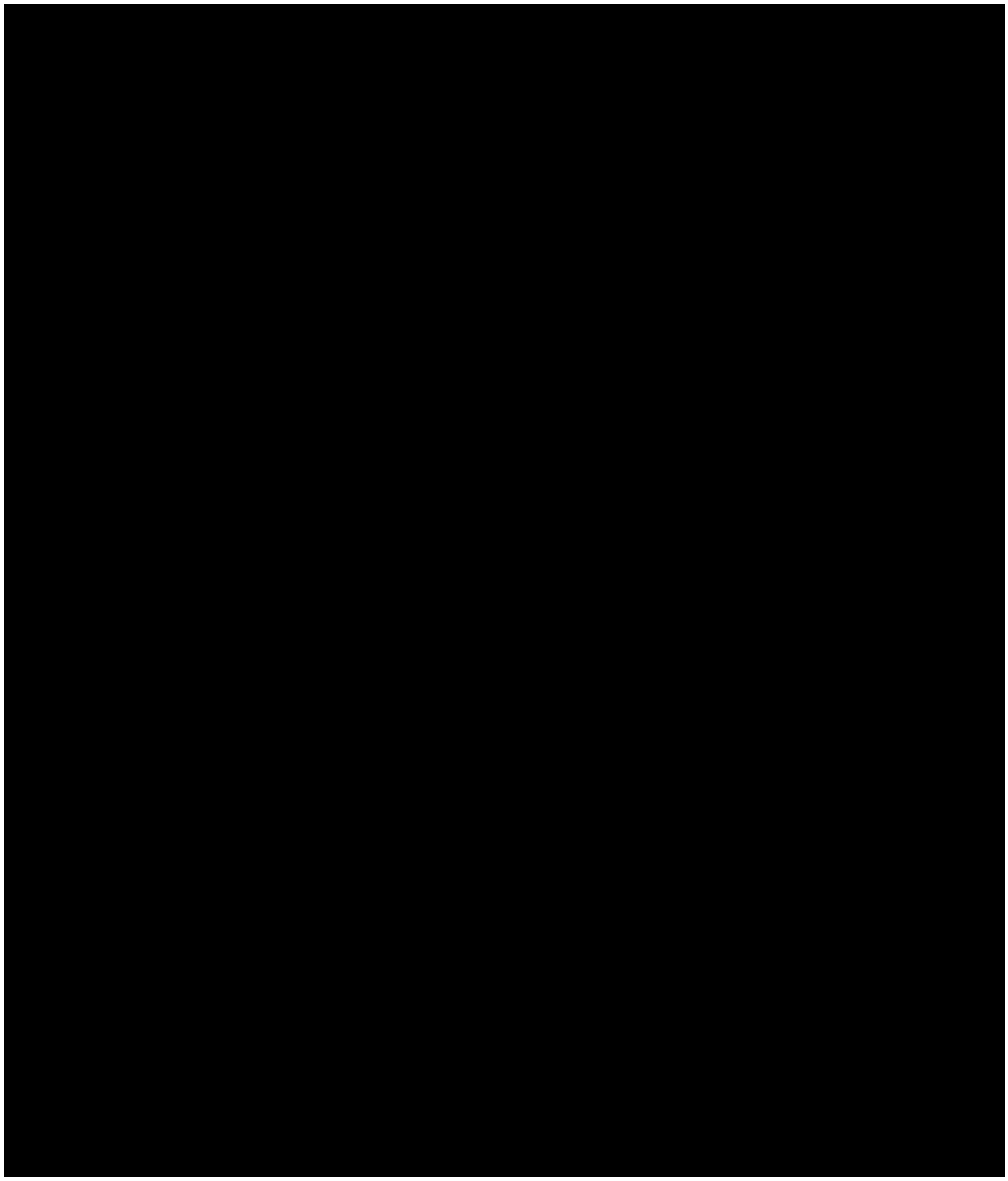
9.1.1.3 Safety Objective

The safety objective of this study is to determine the safety profile and tolerability of APD334 induction treatment.

9.1.1.4 Exploratory Objective(s)

The exploratory objectives of the study are:

- To determine the effect of APD334 treatment on Total Mayo Score at 12 weeks.



9.1.2 Hypotheses

9.1.2.1 Primary Hypothesis

In patients with moderately to severely active ulcerative colitis, treatment with APD334 compared with placebo will provide greater improvement in 3-component Mayo Clinic Score at 12 weeks.

9.1.2.2 Secondary Hypotheses

- In patients with moderately to severely active ulcerative colitis, treatment with APD334 compared with placebo will provide better combination of clinical remission and clinical response reflected by a composite endpoint at 12 weeks.
- In patients with moderately to severely active ulcerative colitis, treatment with APD334 compared with placebo will provide more patients that achieve clinical remission at 12 weeks.
- In patients with moderately to severely active ulcerative colitis, treatment with APD334 compared with placebo will provide more patients that achieve clinical response at 12 weeks.
- In patients with moderately to severely active ulcerative colitis, treatment with APD334 compared with placebo will provide more patients that achieve endoscopic improvement at 12 weeks.

9.2 Sample Size and Power Calculations

For the comparison of the proportion of patients who achieve clinical remission between APD334 versus placebo, a sample of ~80 patients per group will provide 80% power to detect a difference of 18% (from 10% to 28%) at α=5% (2-sided test). This calculation is based upon an assumed placebo rate of 10%.

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 primary endpoint, secondary endpoints and other efficacy endpoints.

INTENT-TO-TREAT POPULATION (ITT):

This population consists of all randomized patients, who received at least 1 dose of study medication. Under this approach, patients are counted in the treatment group to which they were randomized, regardless of the treatment received during the course of the trial.

MODIFIED INTENT-TO-TREAT POPULATION (MITT):

This population consists of all randomized patients, who received at least 1 dose of study medication, have a baseline measurement, and have at least one post-randomization measurement. Under this approach, patients are counted in the treatment group to which they were randomized, regardless of the treatment received during the course of the trial. 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 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 randomized patients who received study medication.

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. 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

Primary:

- The improvement of 3-component Mayo Clinic Score (score ranging from 0 to 9, including stool frequency, rectal bleeding and findings on endoscopy) at Week 12.

Secondary:

- The trichotomous composite score of clinical remission and clinical response (score ranging 0 to 2: score 2 for achieving both clinical remission and clinical response; 1 for only achieving clinical response, and 0 for achieving neither) at Week 12.
- The proportion of patients achieving 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 from baseline subscore at Week 12
- The proportion of patients who achieve clinical response [defined as a decrease in 3-component Mayo Clinic score of ≥ 2 points and a decrease of ≥ 30% with either a decrease of rectal bleeding of ≥ 1 or rectal bleeding score of 0 or 1] at Week 12

- The proportion of patients who achieve endoscopic improvement [defined as Mayo endoscopic subscore (using findings of flexible proctosigmoidoscopy) of ≤ 1 point] at Week 12

Exploratory:

- Improvement in Total Mayo Clinic Score (score ranging from 0 to 12, including stool frequency, rectal bleeding and findings on endoscopy, and physician's global assessment) at Week 12

9.6 Statistical Methods

9.6.1 Primary Efficacy Analysis

The primary analysis will be based on the change from baseline in 3-component Mayo Clinic Score at Week 12 using an analysis of covariate (ANCOVA) model with terms for treatment,

current oral corticosteroid use, prior exposure to TNFα antagonists and baseline value as covariate. Least-squares mean (LSM) by treatment group and its 95% confidence interval (CI), and least-squares mean difference between treatment group and its 95% CI will be reported.

Mayo Clinic Score data handling: for each study visit during the study (excluding the screening/baseline visit which uses 10 prior days), stool frequency and rectal bleeding subscores will be derived from electronic patient diaries completed over the 7 days prior to a study visit. Note that the day prior, day of and day after proctosigmoidoscopy will not be used for patient diary entry because of the required bowel prep for the procedure. These subscores will be calculated using the following rules:

1. The scores from the 3 most recent days prior to the actual day of the study visit will be averaged and rounded to the nearest integer.
2. If patient diary entries from 3 days are not available, the scores from the 2 most recent entries will be averaged and rounded to the nearest integer.
3. If less than 2 days of diary data are available, the subscore will be considered missing.

The rounding will be applied to each subscore prior to the creation of the total score.

9.6.1.1 Secondary and Exploratory Efficacy Analyses

The secondary analyses include following:

- Trichotomous composite score of clinical remission and clinical response at Week 12 is an ordinal categorical endpoint with 3 scores (2, 1, 0). It will be analyzed using Cochran-Mantel-Haenszel method adjusted for the stratification factors of presence or absence of current oral corticosteroid therapy at baseline and previous exposure to TNFα antagonists, and using modified ridit score to compute testing statistic and p-value for between-treatment comparison.

- The proportion of patients who achieve clinical remission, clinical response, and endoscopic improvement will be analyzed individually using Cochran-Mantel-Haenszel (CMH) test adjusted for the stratification factors of presence or absence of current oral corticosteroid therapy at baseline and previous exposure to TNFα antagonists, to compare the difference of proportions between treatment group. The CMH stratified risk difference and its 95% confidence interval will be provided.

All patients who prematurely discontinue for any reason will be considered failures (non-responders) for all the proportion based endpoints. To assess the robustness of the results,

several imputation/sensitivity analyses will be performed (i.e. completers population; more details will be specified in the SAP).

Exploratory efficacy analyses

Dose response analyses will be performed using ANCOVA model for continuous variables, or logistic regression model for categorical variables, as appropriate. Treatment group and appropriate baseline covariates will be included in the analysis model. Statistical testing of dose response trend will be based on appropriate contrast statement assuming monotonic dose response profile in placebo, APD334 low dose and APD334 high dose.

For the repeated measures analysis, no explicit imputations will be made for this approach. Missing data are assumed to be missing at random (that is, ignorable missingness), which means that the missingness of the data does not depend on the value that is missing after adjusting for the effect of the data that are observed.

An analysis of covariance (ANCOVA) with LOCF imputation for missing data will be performed for Week 12 change from baseline in the complete Mayo Clinic Score, [redacted] The ANCOVA model will include terms for treatment, current oral corticosteroid use, previous exposure to TNFα antagonists and baseline value as a covariate.

9.6.2 Subgroup Analyses

Subgroup analyses for the primary efficacy endpoint will be performed in order to explore whether the treatment effects are consistent across different subgroups. The baseline patient characteristics below are the subgroup factors to be explored.

- Sex (Male, Female)
- Age: > or ≤ median age, ≥ or < 65 years
- Race
- Presence or absence of current oral corticosteroid use

- Previous exposure to TNFα antagonists
- [redacted]
- [redacted]

In addition to the subgroup analyses for the primary endpoint, the following analyses will be performed:

- [redacted]
- [redacted]

9.6.3 Multiplicity

A statistical testing procedure will be constructed to manage multiplicity issues concerning primary and secondary efficacy analyses in order to control overall Type I error rate for efficacy testing not exceeding 0.05. The details of testing procedure will be specified in a separate SAP.

9.6.4 Interim Analysis

Sponsor may plan an unblinded interim analysis at time when sufficient number of patients have finished 12 weeks of treatment. If Sponsor decides to perform an interim analysis, it will be operated by an independent Data Review Committee (DMC). The revision of statistical analysis plan (SAP) with detailed interim analysis specifications and a DMC charter will be provided to regulatory agency in timely manner and will be finalized prior to the interim analysis.

9.6.5 Data Safety Monitoring Board

The DSMB will monitor emerging study safety data and has the responsibility to review specific safety data reports, and to request additional reports as needed. Unblinded data reports generated by the unblinded statistician will be reviewed for adverse treatment effects and patient safety. The DSMB must keep results from blinded and unblinded data reports confidential. The roles and responsibilities of the DSMB will be outlined in a separate charter.

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 for between-group differences 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 randomized patients who received at least 1 dose of study drug; in addition, if a patient is found to have taken a study therapy for the entire duration of the study different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received.

For analysis based on laboratory measurements, at least 1 laboratory test post-randomization 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-randomization 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 and by treatment. They will be summarized per treatment and expressed in terms of maximum severity and relationship to study medication. The incidence of TEAEs classified according to system organ class will be summarized by treatment group. TEAEs will also be summarized by maximum intensity (assessed according to the Common Terminology Criteria for Adverse Events v4.0313 definitions) and relatedness to study medication.

Summaries of the number (%) of patients in each treatment group 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 and by treatment. If there are no SAEs at the end of the study, the tables or listings will state that there are no SAEs in the study.

9.8.2 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 by treatment summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in vital sign measurements by treatment. Baseline is defined as the last pre-randomization measurement.

9.8.5 Clinical Laboratory Values

Individual lab values will be listed by treatment and visit, and summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in lab values. Baseline is defined as the last pre-randomization 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.

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 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, "A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study to Investigate the Safety and Efficacy of APD334 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 REFERENCES

1. Brinkmann V, Billich A, Baumruker T, et al. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. *Nat Rev Drug Discov* 2010 November;9(11):883-97.

2. Centers for Disease Control and Prevention. Inflammatory bowel disease (IBD). http://www.cdc.gov/ibd/. Accessed January 8, 2015.

3. Danese S and Fiocchi C. Ulcerative Colitis. *N Engl J Med.* 2011 Nov;365;18:1713-1725.

4. IBD Insights. IBD etiology and pathophysiology: Understanding the process. https://www.ibdinsights.com/about/etiology-pathophysiology/. Accessed January 8, 2015.

5. Gasparetto M and Guariso G. Highlights in IBD Epidemiology and Its Natural History in the Paediatric Age. Gastroenterology Research and Practice, Volume 2013 (2013), Article ID 829040, 12 pages.

6. Crohn's and Colitis Foundation of America. The Facts About Inflammatory Bowel Diseases. November 2014, New York, NY 10017. http://www.ccfa.org/assets/pdfs/ibdfactbook.pdf. Accessed January 7, 2015.

7. Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology*. 2004; 126:1504-17.

8. Burisch J, Jess T, Martinato M, Lakatos PL; ECCO -EpiCom. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis.* 2013 May;7(4):322-37.

9. World IBD Day. http://www.worldibdday.org/index.html. Accessed January 7, 2015.

10. American Gastroenterological Association. Inflammatory bowel disease emerges as a global disease. (2012, January 5). *ScienceDaily*. www.sciencedaily.com/releases/2012/01/120104135402.htm. Accessed January 7, 2015.

11. Kaser A, Zeissig S, Blumberg RS. Inflammatory Bowel Disease. *Annu Rev Immunol.* 2010;28:573-621.

12. Kornbluth A, Sachar D, MACG and The Practice Parameters Committee of the American College of Gastroenterology. Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; 105:501–523; doi: 10.1038/ajg.2009.727; published online 12 January 2010.

13. Lichtenstein GR, Hanauer SB, Sandborn WJ, and The Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's Disease in Adults.

Am J Gastroenterol advance online publication, 6 January 2009; doi: 10.1038/ajg.2008.168.

14. Medscape. Inflammatory Bowel Disease: Practice Essentials. http://emedicine.medscape.com/article/179037-overview#aw2aab6b2b4. Accessed January 8, 2015.

15. World Health Organization Atlas, "Multiple Sclerosis Resources in the World," 2008.

16. Lutton JD, Winston R, Rodman TC. Multiple sclerosis: etiological mechanisms and future directions. *Exp Biol Med (Maywood)* 2004 January;229(1):12-20.

17. Wipfler P, Harrer A, Pilz G, et al. Recent developments in approved and oral multiple sclerosis treatment and an update on future treatment options. *Drug Discov. Today* 2011 January; 16: 8-21.

22. Gergely P, Nuesslein-Hildesheim B, Guerini D et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. *Br J Pharmacol* 2012 Nov;167(5):1035-1047.

23. Brossard P, Derendorf H, Xu J et al. Pharmacokinetics and pharmacodynamics of ponesimod, a selective S1P(1) receptor modulator, in the first-in-human study. *Br J Clin Pharmacol* 2013 Apr 18. doi:10.1111/bcp.12129. [Epub ahead of print] PubMed PMID: 23594176.

24. Kovarik JM, Schmouder R, Barilla D et al. Multiple-dose FTY720: tolerability, pharmacokinetics, and lymphocyte responses in healthy subjects. *J Clin Pharmacol* 2004 May;44(5):532-537.

25. http://www.fda.gov/drugs/drugsafety/ucm366529.htm. Accessed 27-April-2015.

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

27. Rutgeerts P, Sandborn WJ, Feagan BG et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005 Dec 8;353(23):2462-2476.

28. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis: a randomized study. *N Engl J Med.* 1987;317:1625-1629.

PROTOCOL SIGNATURE PAGE

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study to Investigate the Safety and Efficacy of APD334 in Patients with Moderately to Severely Active Ulcerative Colitis

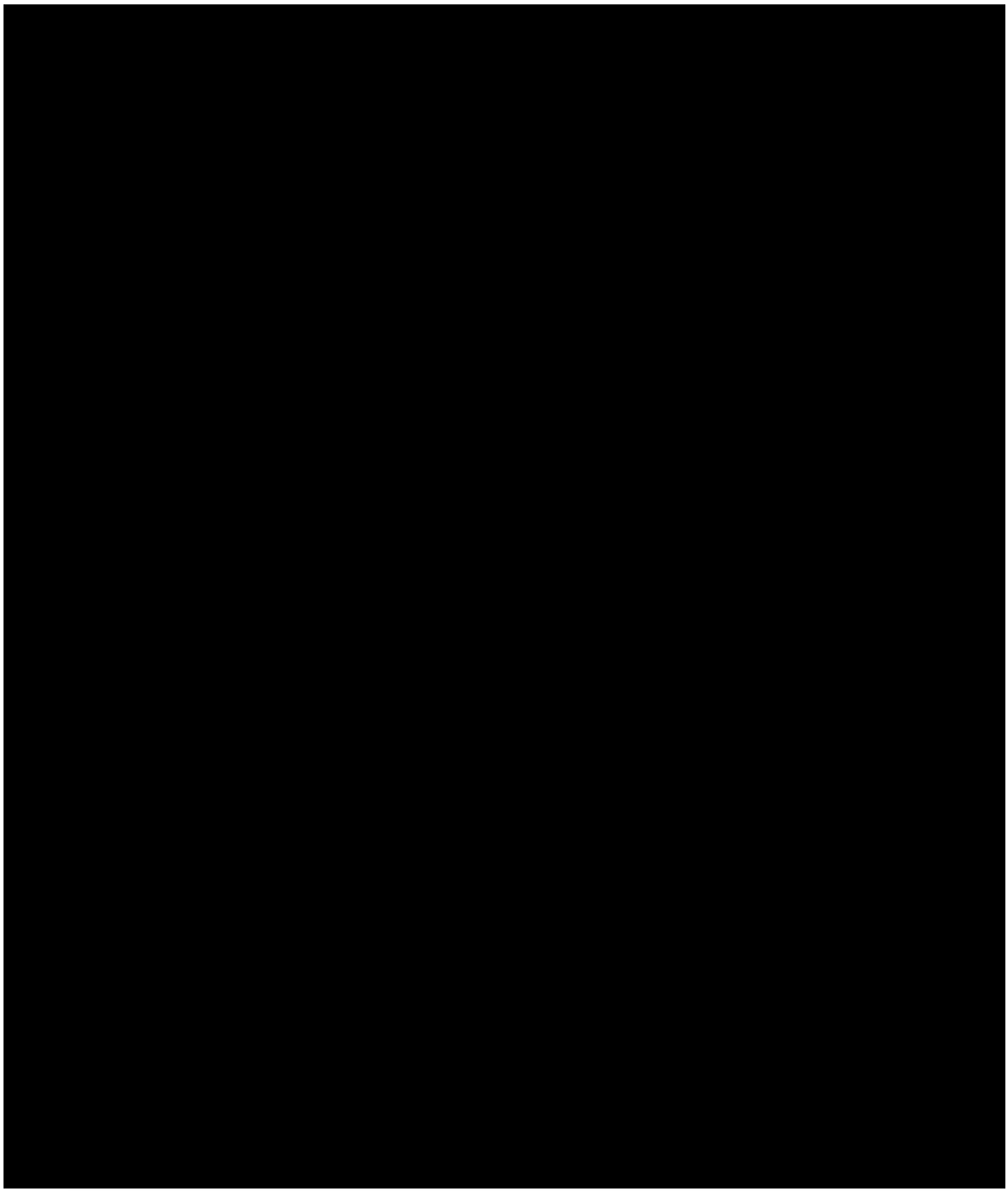
This study will be conducted in accordance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) (E6) and applicable Food and Drug Administration (FDA) guidelines.

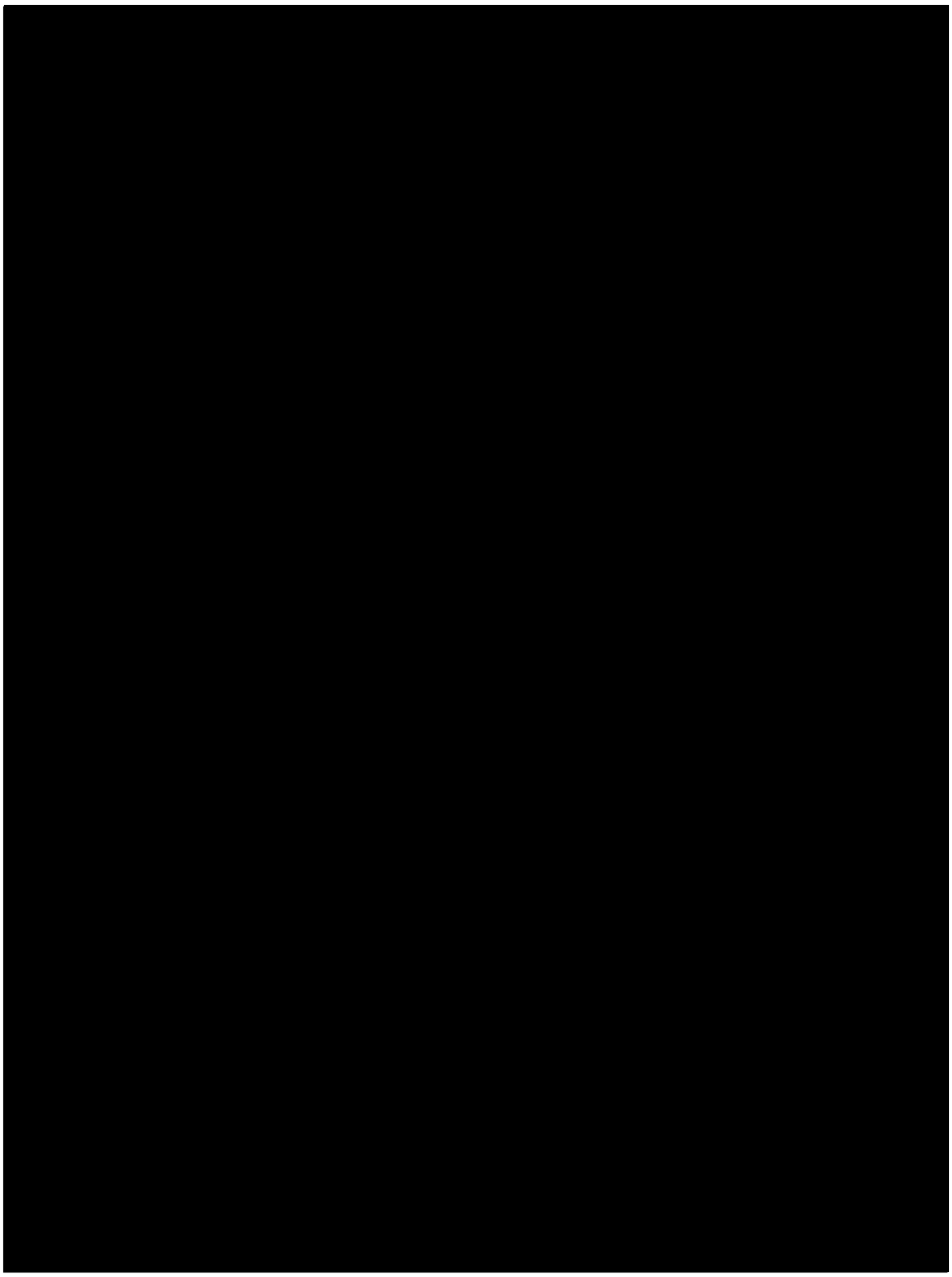
Protocol Number: APD334-003

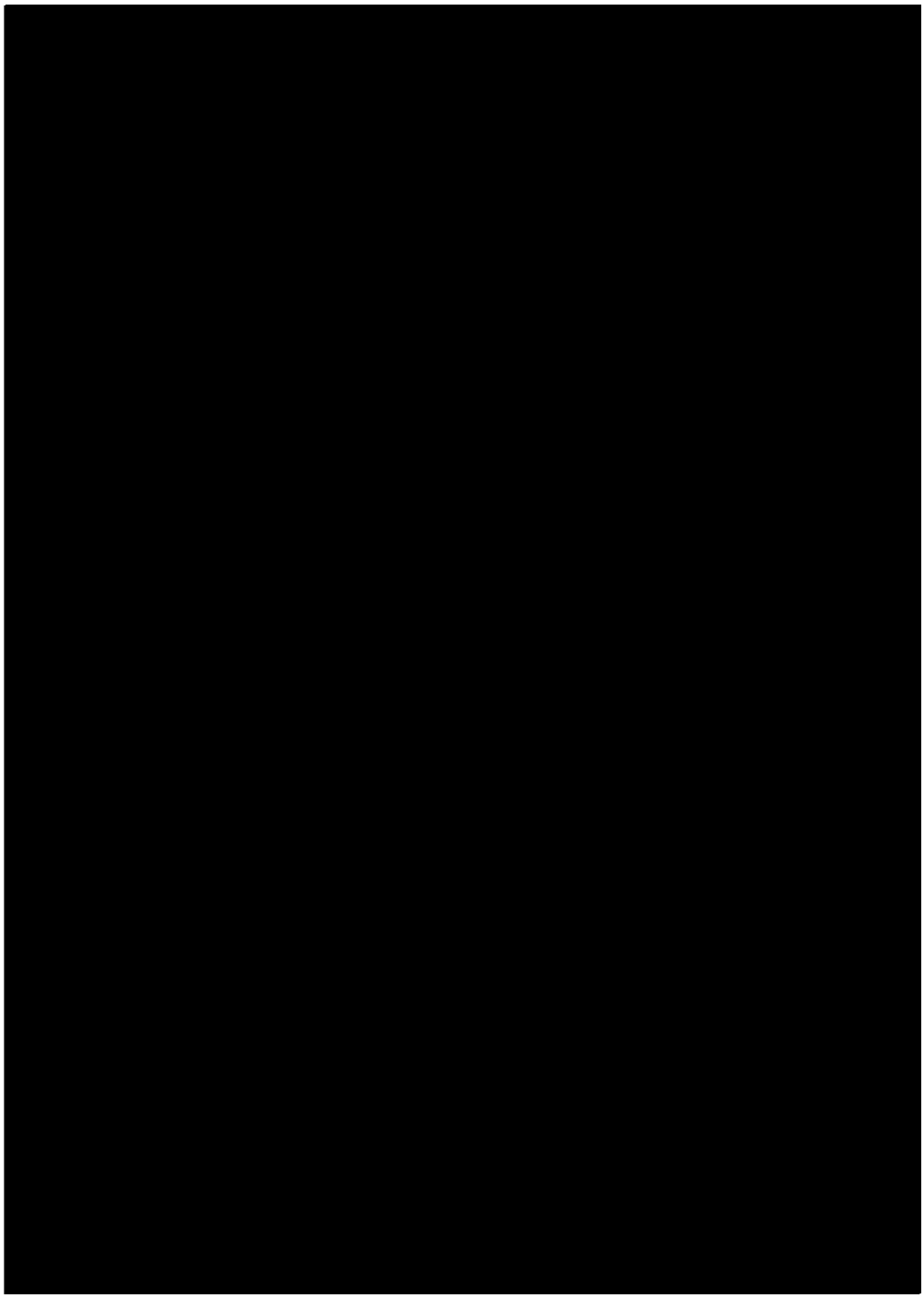
Arena Pharmaceuticals, Inc. Signatures:

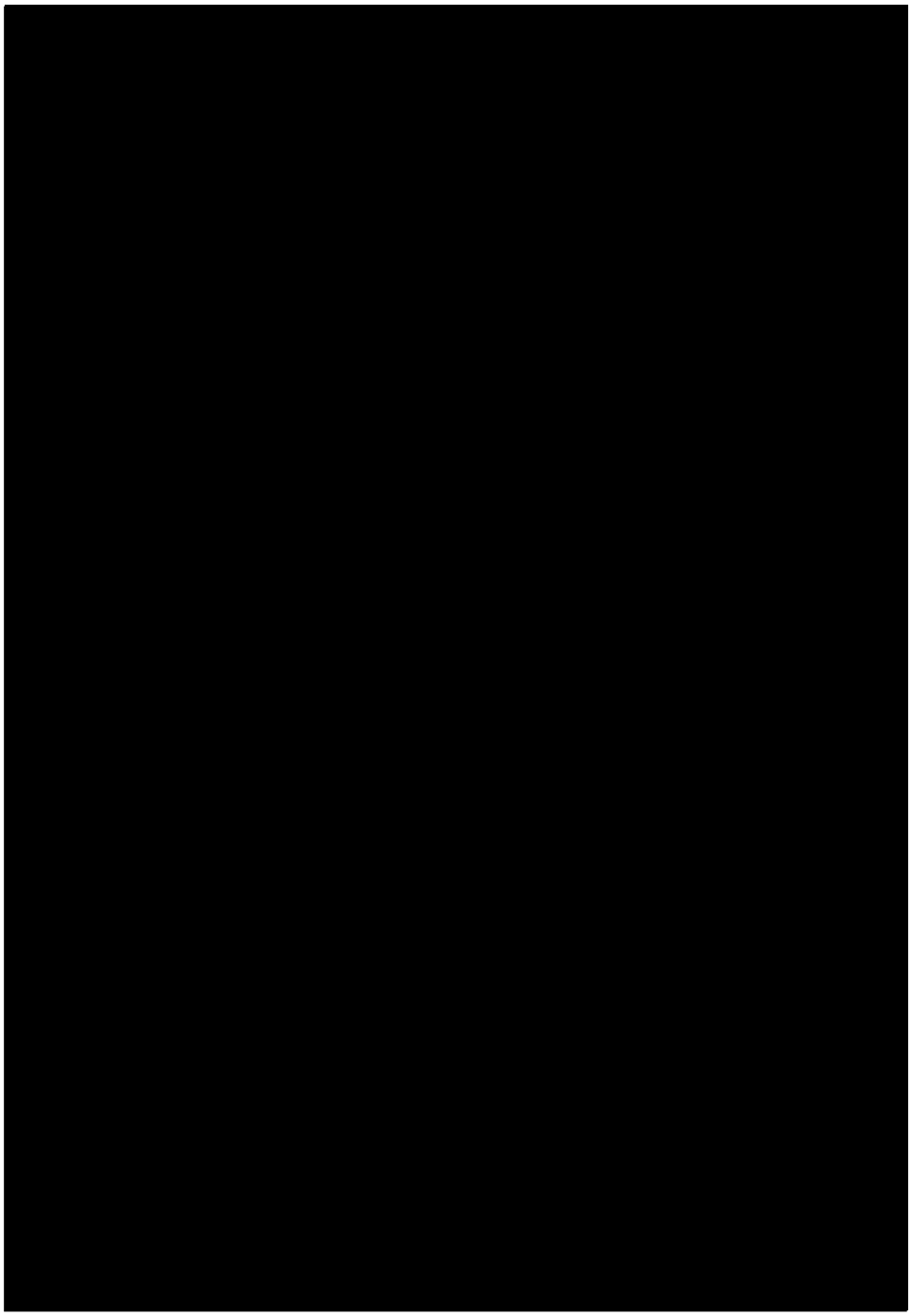
Appendix 1 Progressive Multifocal Leukoencephalopathy (PML) Checklist

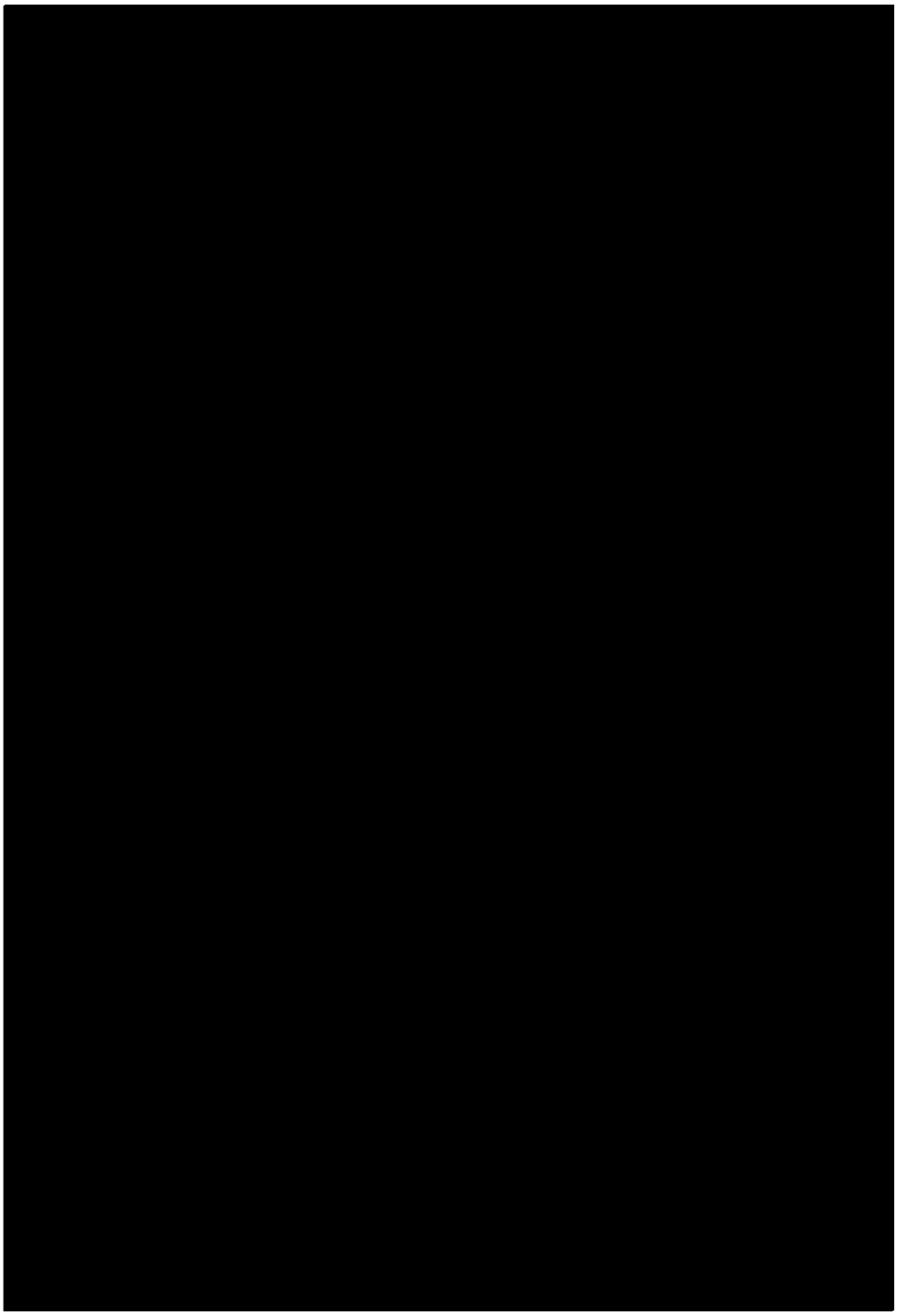
Symptoms	"Compared to how you usually feel, have you had a significant change in any of the following?"		If the answer is "yes", obtain a description of the symptom(s) with examples.	Applicable Objective Test(s): Document results on PML Object Checklist
	Yes	No		
1) Have you been experiencing any persistent 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 pinprock.

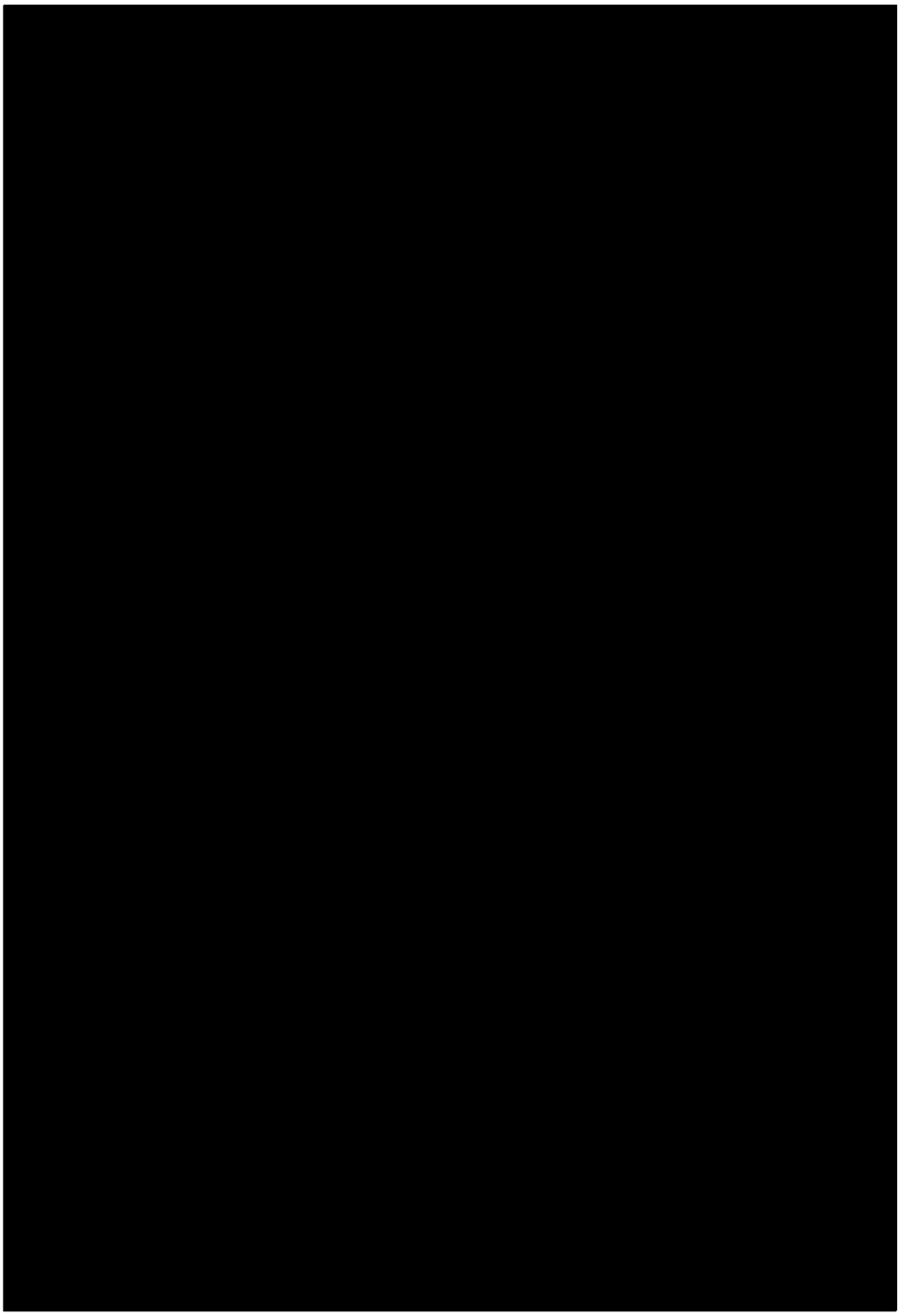


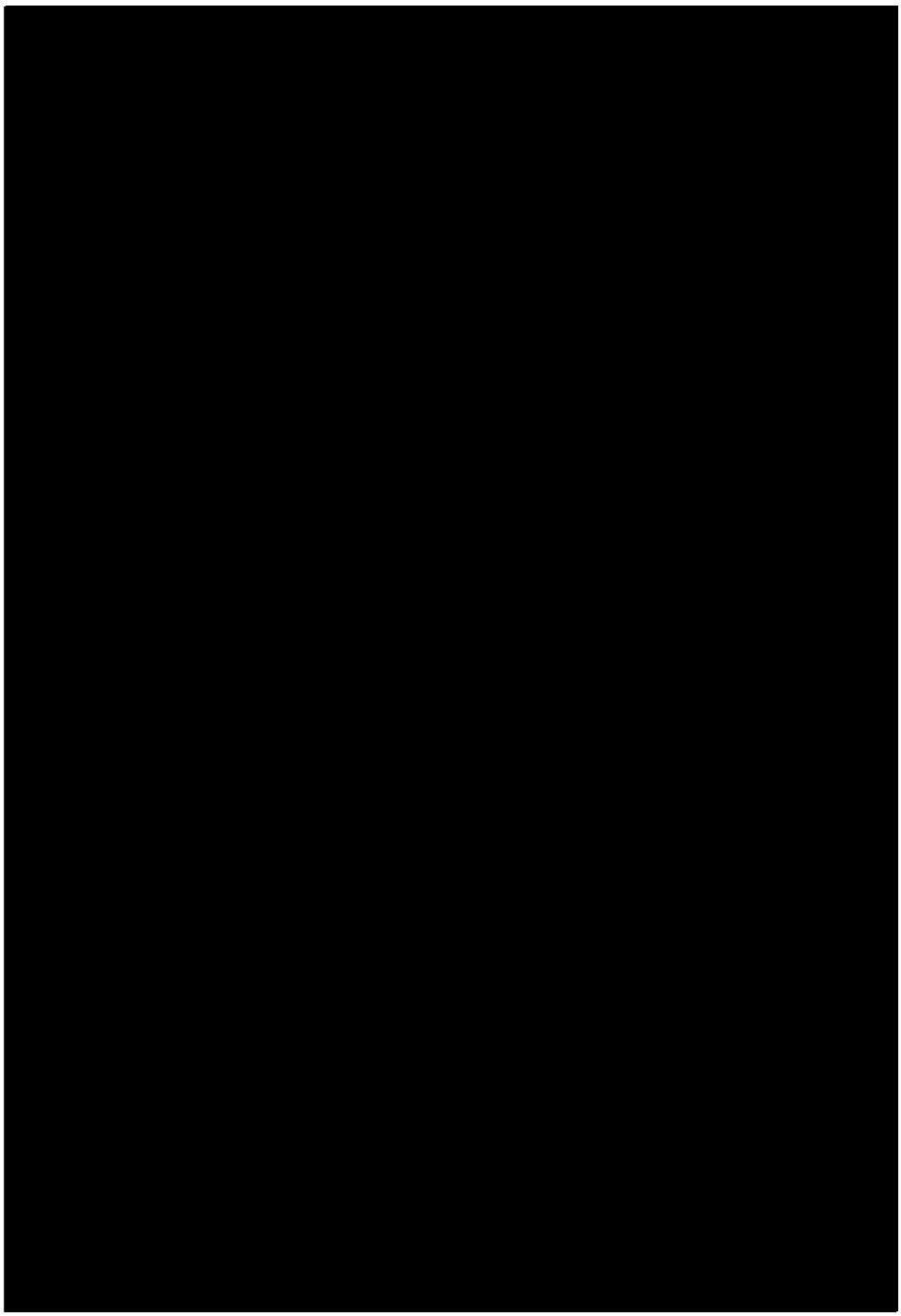


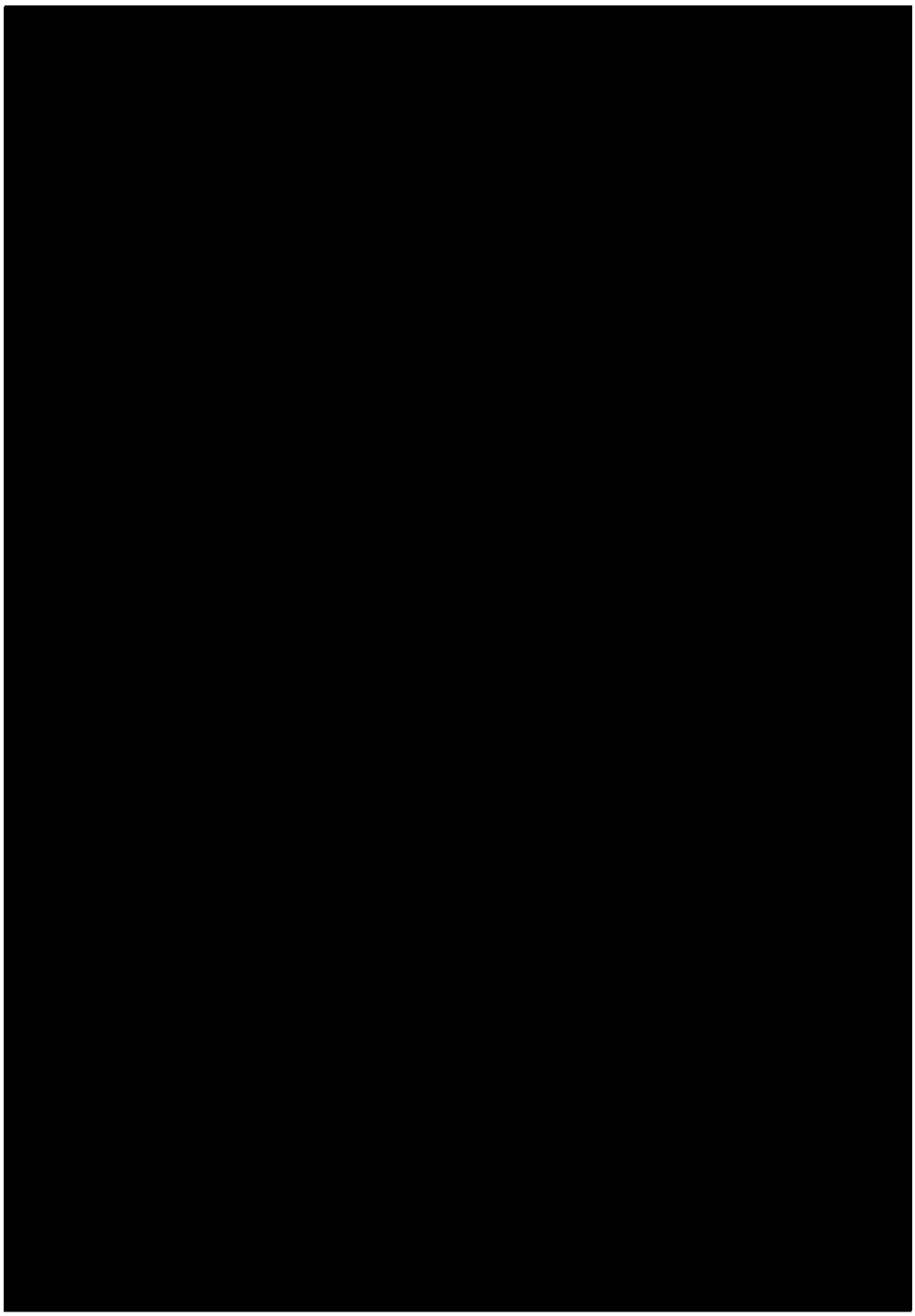


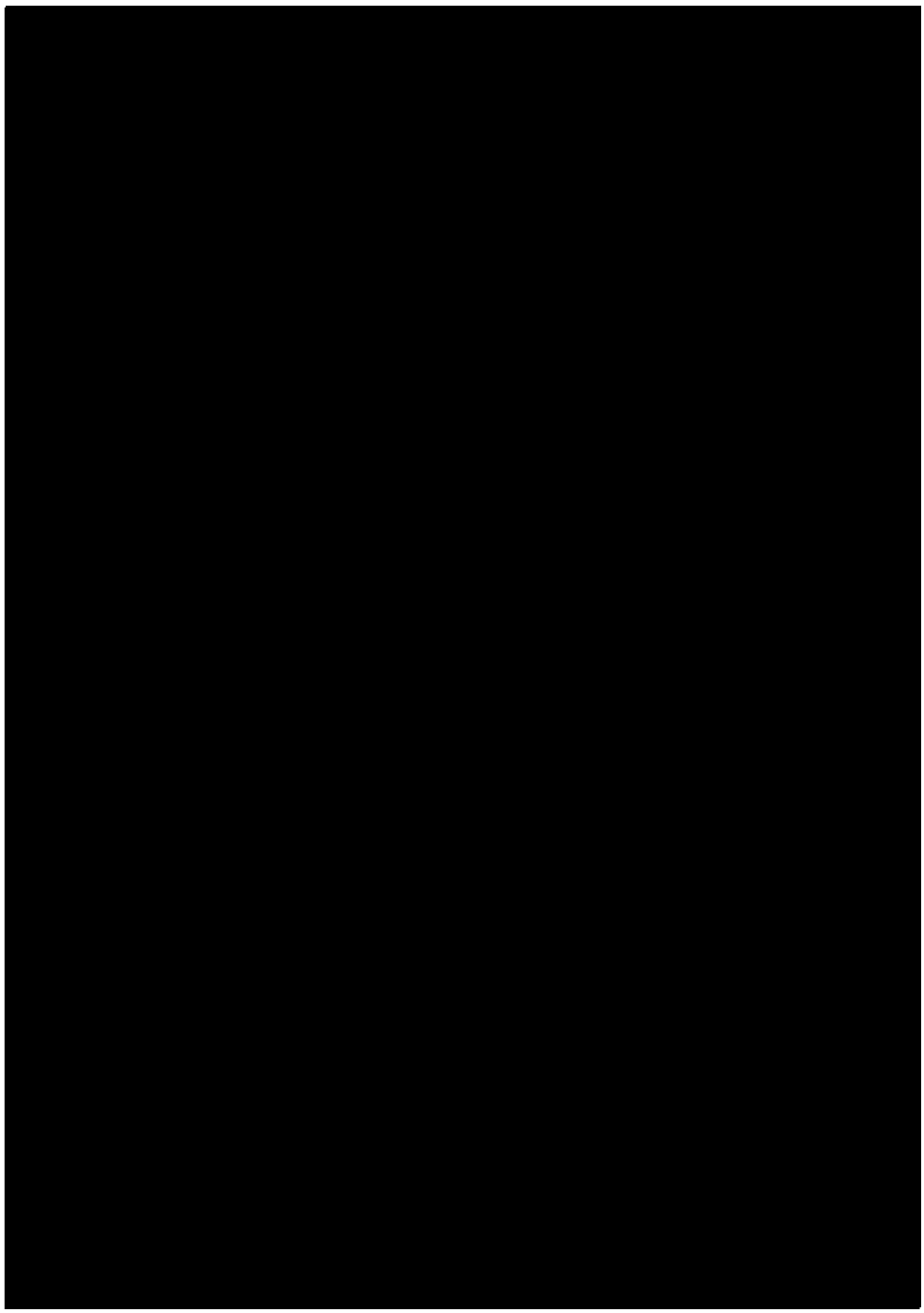


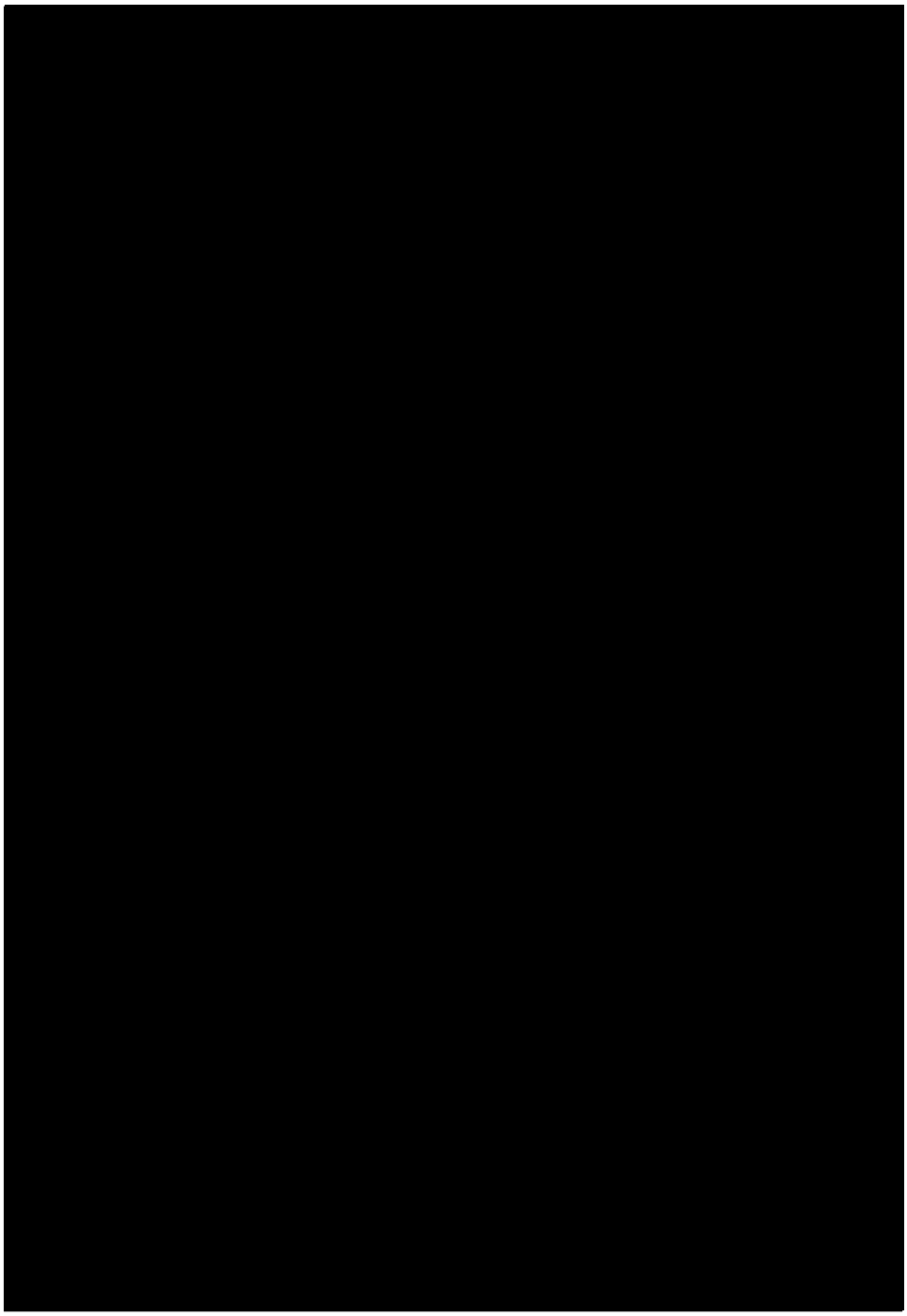












Appendix 3 Mayo Clinic Score – SAMPLE

Mayo Scoring System for Assessment of Ulcerative Colitis Activity[27,]*

Stool Frequency†

0 = Normal number of stools for this patient
1 = 1–2 stools more than normal
2 = 3–4 stools more than normal
3 = 5 or more stools more than normal
Subscore, 0 to 3

Rectal bleeding‡

0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passes
Subscore, 0 to 3

Findings on endoscopy†

0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern)
2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Subscore, 0 to 3

Physician's Global Assessment§

0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Subscore, 0 to 3

---

* The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.[28]
† Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
† The daily bleeding score represents the most severe bleeding of the day.
§ The physician's global assessment acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

This is a representation of an electronic record that was signed electronically, and this page is the manifestation of the electronic signature.

UserName: [redacted]
Title: [redacted]
Date: Monday, 03 April 2017, 10:36 AM Pacific Daylight Time
Meaning: Author Approval
==========

UserName: [redacted]
Title: [redacted]
Date: Monday, 03 April 2017, 12:39 PM Pacific Daylight Time
Meaning: Approval
==========

UserName: [redacted]
Title: [redacted]
Date: Monday, 03 April 2017, 01:05 PM Pacific Daylight Time
Meaning: Approval
==========

UserName: [redacted]
Title: [redacted]
Date: Monday, 03 April 2017, 01:07 PM Pacific Daylight Time
Meaning: Approval
==========

UserName: [redacted]
Title: [redacted]
Date: Monday, 03 April 2017, 01:10 PM Pacific Daylight Time
Meaning: Approval
==========

PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD334-003 Protocol Amendment 04 dated 21 September 2015. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 05 dated 10 October 2016.

Section(s) Amended	Page No(s).	Description of Changes Made
Header/Footer, Title Page, and TOC	All	Added "Amendment 05", updated date to reflect finalization of amended protocol, updated pagination and TOC.
Title Page	1	Removed "Sponsor Contact"
Protocol Amendment Summary	2-5	Updated table to include summary of changes to the protocol.
Synopsis	11	Updated sponsor contact and medical monitor.
Synopsis	13, 15	• Study Design: Changed patients with the option to enroll in the APD334-005 extension study: "all patients (responders and non-responders)", to: ***Current*** "responder patients" • [redacted]
3.1 Overall Study Design and Plan	29	Reviewed extension study: "A 40-week extension study (APD334-005) is offered to all patients (responders and non-responders)", to: ***Current*** "A 34-week extension study (APD334-005) is offered to responder patients".
[redacted]	30-32	• [redacted]

Section(s) Amended	Page No(s).	Description of Changes Made
		• [redacted] • [redacted] • [redacted] • [redacted]
4.2 Inclusion Criteria #6	33	[redacted]
4.3 Exclusion Criteria, #7	36	Revised exclusion of patients that, within 60 days prior to randomization, received treatment with more than 2 biologic agents

Section(s) Amended	Page No(s).	Description of Changes Made
		Current exclusion of patients that, within 60 days prior to randomization, received treatment with more than 3 biologics
5.6 Dosage and Administration	40	Changed "Patients will be observed at the clinic site for 8 hours post-dose on Day 1", to: ***Current*** Patients will be observed at the clinic site for 6 hours post-dose on Day 1
5.8.3 Maintenance of Randomization Codes and Code-break Procedures	41	Added specification that APD334-003 study will remain blinded until completion of the APD334-005 study.
6.4 Vital Signs	44	Updated to highlight need for extended monitoring if heart rate at 6 hours is the lowest since the first dose was administered.
[redacted]		
6.8.1 Laboratory Parameters	47	Added the following procedure information: • clinical safety laboratory tests should be completed pre-dose • Complete blood count (CBC) will be obtained prior to dosing.
6.9.1 Flexible Proctosigmoidoscopy	48	Revised assessment window from "will be performed during screening (within 7 days prior to the administration of the first dose of study drug)" to ***Current:*** "will be performed during screening (within 10 days prior to the administration of the first dose of study drug)".
6.9.7 Complete Mayo Clinic Score, 3-component Mayo Clinic Score, and [redacted]	50	Revised MCS from "using … flexible proctosigmoidoscopy results within 7 days prior to randomization" to ***Current***: "within 10 days prior to randomization".

Section(s) Amended	Page No(s).	Description of Changes Made
[redacted]	51	[redacted]
6.11.2 Serious Adverse Events and Expedited Reporting of Adverse Events	54, 55	Changed recipient of notification of serious adverse event from sponsor to PPD
6.14 Allowable Visit and Procedure Windows	59, 60	Added possibility to prolong time window for screening to 35 days. Extended window for specified procedures (proctosigmoidoscopy) to 10 days. Removed all other visit and procedure windows.
7.1 [redacted]	62	Extended window for specified procedures to [redacted] days. Added possibility to prolong time window for screening to [redacted] days.
7.2.1 Re-screening	62	Added clarification of re-screening procedures.
7.4.1 [redacted]	63	Changed "Safety ECG (12-lead) pre-dose and hourly through [redacted] hours post-dose", to: ***Current*** "Safety ECG (12-lead) pre-dose and hourly through [redacted] hours post-dose"
7.4.3 [redacted]	64	[redacted]
7.4.4 Week 12/Exit or Early Termination Procedures	65	Changed "Determine responder/non-responder status of patient for treatment assignment in extension study (APD334-005)", to: ***Current*** "Determine clinical responder/non-responder status of patient based on the following criteria…".

PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD334-003 Protocol Amendment 03 dated 30 June 2015. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 04 dated 21 September 2015.

Section(s) Amended	Page No(s).	Description of Changes Made
Header/Footer, Title Page, and TOC	All	Added "Amendment 04", 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	9	Updated medical monitor for the study.
[redacted]	28-30	• [redacted] • [redacted]
4.2 Inclusion Criteria, #10b 6.12.1 Permitted Medications for the Treatment of UC	33, 55	[redacted]
4.3 Exclusion Criteria	35	[redacted]

Section(s) Amended	Page No(s).	Description of Changes Made
		[redacted]
6.3.1 Physical Examination	41	Revised section to denote that an ophthalmoscopy would be performed as part of the physical examination at [redacted] visits and that retinal photos will be taken during each ophthalmoscopy.
Table 2. Examples of eDiary Subscore Entries for Study Eligibility and Corresponding Subscore Derivation	47	Minor corrections to example table.
7.1 [redacted] and 7.4.4 [redacted]	58, 61	Added retinal photos to physical/neurological examination section.

PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD334-003 Protocol Amendment 02 dated 17 June 2015. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 03 dated 30 June 2015.

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	Updated table to include summary of changes to the protocol.
Section 4.3 Exclusion Criteria	33	[redacted]
Section 6.9.1 Flexible Proctosigmoidoscopy	45	The following provision is added to this section: "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."

PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD334-003 Protocol Amendment 01 dated 01 May 2015. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 02 dated 17 June 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.
Title page	1	Updated medical monitor for study.
Protocol Amendment Summary	2-4	Updated table to include summary of changes to the original protocol.
Synopsis Section 9.1.1.4 Exploratory Objective(s) Section 9.5 Efficacy Endpoints	11, 13-14, 63-64	[redacted]
Synopsis Section 9.6.1 Primary Efficacy analysis	14, 67	Added the following secondary analysis: • a logistic regression analysis with terms for treatment, presence or absence of current oral corticosteroid therapy at baseline and previous exposure to TNFα antagonists and the interaction between the 2 stratification factors (if appropriate)

Section(s) Amended	Page No(s).	Description of Changes Made
[redacted] Section 7.1 [redacted] Section 7.4.4 [redacted]	29, 59 and 61	[redacted]
[redacted]	30	[redacted]
Section 4.2 Inclusion Criteria #8	32	[redacted]
Section 4.3 Exclusion Criteria #27 Section 6.8.1 Laboratory Parameters Section 6.8.2 Virology	35, 44-45	[redacted]
Section 4.3 Exclusion Criteria	36	[redacted]
Section 5.6 Dosage and Administration	38	Added the following clarification: On days with scheduled study visits, patients should **not** take their dose of study medication at home in order to complete pre-dose study procedures. Patients **must be fasting** on the days of their scheduled study visits.
Section 6.9.7 Complete Mayo Clinic Score, 3-component Mayo Clinic Score, and [redacted]	47, 67	Clarified the rounding procedure for the primary endpoint.

Section(s) Amended	Page No(s).	Description of Changes Made
Section 9.6.1 Primary Efficacy Analysis		
Section 6.12.2 Excluded Medications	55	Added moderate to strong inhibitors of CYP2C9 to the excluded medications section.
Section 9.6.1.1 Secondary and Exploratory Efficacy Analyses	68	Updated the various analyses to be performed by ANCOVA.
Section 9.6.2 Subgroup Analyses	68	[redacted]

PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD334-003 Protocol dated 08 April 2015. Minor clarifications and corrections have been made throughout for consistency. These changes are incorporated in Protocol Amendment 01 dated 30 April 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.
Title page	1	Updated medical monitor for study.
Protocol Amendment Summary	2-3	Updated table to include summary of changes to the original protocol.
Throughout	--	Changed the term Partial Mayo Clinic score to 3-component Mayo Clinic score.
Synopsis, List of Abbreviations, Study Definition, [redacted] 7 Study Activities, 9.1.1.4 Exploratory Objectives, 9.5 Efficacy Endpoints, 9.6.1.1 Secondary and Exploratory Endpoints, [redacted]	11, 13, 17, 29, 44, 55, 58, 61, 64, 65, 82-92	[redacted]
Study Definitions	19	Added definition of intolerable AE
1 Introduction	20	Minor changes to text for clarification
1.2 Ethics and Regulatory Considerations, Protocol Signature Page	24, 80	Removed reference to Declaration of Helsinki
[redacted]	27-29	• [redacted] •

Section(s) Amended	Page No(s).	Description of Changes Made
		• [redacted]
[redacted] 7.4.4 Week 12/Exit or Early Termination Procedures	27, 58	• [redacted]
[redacted] 5.6 Dosage and Administration	27, 36-37	[redacted]
4.2 Inclusion Criteria, 6.12.1 Permitted Medications for the Treatment of UC	32, 53	[redacted]
4.2 Inclusion Criteria	31-32	[redacted]
4.3 Exclusion Criteria	33-35	Removed separate exclusion criteria categories.
5.8.1 Randomization	37	Added statement capping the number of patients with previous exposure to TNFα antagonists
5.8.2 Blinding, 6.8.1 Laboratory Parameters, 6.11.1 Adverse Event Reporting	37, 42, 48	Added blinding of [redacted] and White Blood Cell (WBC) counts from sponsor, patients and personnel involved in the conduct of the study. These values will not be sent to the sites, but reviewed by an unblinded CRO physician(s) for safety purposes.
[redacted]		

Section(s) Amended	Page No(s).	Description of Changes Made
6.8.1 Laboratory Parameters	42	Added (% and total MB) to creatinine kinase and MB subtype.
6.8.1 Laboratory Parameters, 7.1 Screening Visit	42, 56	Removed thyroid function tests.
6.8.3 Drugs of Abuse Screen, 7.4.1 Week 0/Day 1 Procedures	43, 57	Removed alcohol (breathalyzer).
6.8.4 Urinalysis	43	Added the following detail to section: "Microscopic urinalysis will be performed when there is a positive or abnormal macroscopic urinalysis result".
6.10 [redacted] and Hematologic Assessments	46-47	Replaced pharmacodynamic with "hematologic"
6.14 Allowable Visit and Procedure Windows	54	Revised window for 2-week follow-up visit to ± 3 days from last dose
7.4.1 Week 0/Day 1 Procedures, 7.4.4 Week 12/Exit or Early Termination Procedures	57, 58	Corrected list of laboratory tests to be administered to include hematology.
9.6.2 Subgroup Analyses	66	[redacted]