Clinical Trial Protocol: APD334-006

Study Title:	A Phase 2a, Proof of Concept, Open-label Study Evaluating the Efficacy and Safety of Etrasimod (APD334) in Inflammatory Bowel Disease Patients with active Skin Extra-intestinal Manifestations
Study Number:	APD334-006
Study Phase:	2a
Product Name:	Etrasimod (APD334)
EudraCT Number:	2016-003797-40
Indication:	Inflammatory Bowel Disease with active skin extra-intestinal manifestations
Investigators:	Multicenter
Sponsor:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121
Sponsor Contact:	[redacted] MD CMO Research and Development Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Dr. San Diego, CA 92121 Phone: [redacted] email: [redacted]

	Date
Original Protocol:	20 October 2016
Amendment 01:	11 April 2017

Confidentiality Statement

NCT Number: NCT03139032
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 key changes of **no substantial** protocol clarifications to the APD334-006 Protocol Amendment 01 dated 11 April 2017.

Section(s) Amended	Description of Changes made
Synopsis	Deleted sentence "Diagnosis of active psoriasis, erythema nodosum or pyoderma gangrenosum by Investigator assessments. ~~After the enrollment of 10 patients with active EIM, patients with active psoriasis due to anti TNF-alpha therapy can also be included.~~"
4.1 Study Population	Deleted sentence "Adult men and women, ages 18-80 years, who have mild, moderate or severe UC or CD with active skin extra-intestinal manifestations including pyoderma gangrenosum, erythema nodosum or psoriasis. ~~After the enrollment of 10 patients with active EIM, also patients with psoriasis due to anti TNF-alpha treatment can be enrolled into the study~~".
Synopsis Sample Size	Changed "10-20 patients" to: ***current***: "Up to 20 patients (with up to 10 patients with anti TNF-alpha induced psoriasis)"
3.1 Overall Study Design and Plan	Study number corrected "APD334-003 is an open-label, …" to: ***current*** "APD334-006 is an open label, …."
3.1 Overall Study Design and Plan	Changed "Between 10 to 20 IBD patients with acute psoriasis, pyoderma gangrenosum or erythema nodosum will be included in the study. In these patients, psoriasis cannot be triggered by anti-TNF-alpha. However, after the enrollment of 10 patients, IBD patients with psoriasis due to anti-TNF-alpha treatment can be included to the study" to: ***current*** "Up to 20 IBD patients with acute psoriasis, pyoderma gangrenosum or erythema nodosum (with up to 10 patients with anti TNF-alpha induced psoriasis) will be included in the study".
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SYNOPSIS

Name of Drug:	Etrasimod (APD334)
Indication	Inflammatory Bowel Disease (IBD) with active skin extra-intestinal manifestations (EIM) including Psoriasis, Erythema Nodosum (EN), and Pyoderma Gangrenosum (PG)
Sponsor:	Arena Pharmaceuticals, Inc. 154 Nancy Ridge Drive San Diego, CA 92121
Name of Sponsor Contact	[redacted], MD CMO Research and Development Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Dr. San Diego, CA 92121 Phone: [redacted] email: [redacted]
Name of Principal Investigator(s):	Multi-center
Medical Monitor:	[redacted], MD Medical Monitor Arena Arena Pharmaceuticals, Inc. Gotthardstrasse 3 CH-6300 Zug Phone: [redacted] email: [redacted]
Test Product, Dose and Mode of Administration:	• [redacted] etrasimod once daily (q.d.) for 12 weeks • Patients should be instructed to take their tablet on an empty stomach (after overnight fast) and to avoid eating for 1 hour after dosing. Patients should be advised not to crush, break, chew, or dissolve the tablet and to take study medication with an adequate amount of water.
Concurrent Control:	None. This is an open-label study.
Objectives:	The efficacy objective is to determine the treatment effect of etrasimod in Inflammatory Bowel Disease patients on the clinical improvement of active skin extra-intestinal manifestations. The safety objective is to determine the safety profile and tolerability of etrasimod.
Study Design	This is a phase 2a, proof-of-concept, multicenter, open-label, single-arm study in 10-20 IBD patients with active skin extra-intestinal manifestations. All visits in the study are ambulatory visits. The screening period

will last up to 4 weeks and is followed by a 12-week treatment period. During this treatment period patients will take one tablet of study medication once per day. The last dose is planned to be taken one day before the last treatment visit at week 12. A follow-up visit will take place 2 weeks after the end of treatment.

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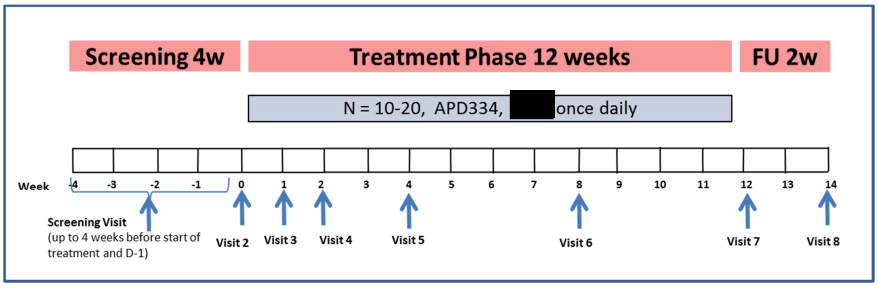


Study Site(s)	This study will be conducted in approximately 3 clinical centers.
Patient Population:	Inclusion Criteria 1. Men or women of age 18 to 80 years, inclusive. 2. Able to give signed informed consent and willing and able to comply with the study requirements. 3. Considered to be in stable health in the opinion of the investigator as determined by: a.) A pre-study physical examination with no clinically significant abnormalities unrelated to IBD. b.) Vital signs (VS) at screening: pulse rate ≥ 55 bpm, systolic blood pressure (SBP) ≥ 90, and diastolic blood pressure (DBP) ≥ 55 mmHg. c.) Liver function tests (ALT/AST, bilirubin and alkaline phosphatase) < 2x the upper limit of normal [ULN]. d.) All other pre-study clinical laboratory findings within normal range, or if outside of the normal range are not deemed clinically significant in the opinion of the investigator. e.) 12-lead electrocardiogram (ECG) showing no clinically significant abnormalities in the opinion of the investigator (for confirmation please refer to exclusion criteria # 22). f.) A chest x- ray showing no evidence of active pulmonary disease (a chest x-ray taken within the previous 12 months from the screening visit may also be used). g.) Ophthalmology evaluation (by an ophthalmologist) without evidence of macular edema, supported with OCT where available (dependent on site capability) no later than 3 months prior to screening. 4. Patients receiving stable treatment for IBD and EIM as defined in section 6.12. 5. Diagnosis of active psoriasis, erythema nodosum or pyoderma gangrenosum by Investigator assessments. 6. Diagnosis of ulcerative colitis (UC) or Crohn's disease (CD) established prior to screening by clinical and endoscopic evidence. 7. Eligible female patients must be: a.) non-pregnant, evidenced by a negative serum human chorionic gonadotropin (hCG) pregnancy test at screening and a urine dipstick pregnancy test at Day 1.

b.) non-lactating.
c.) sexually abstinent (if this is the preferred and usual lifestyle of the individual). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), and lactational amenorrhoea method are not acceptable methods of contraception.
d.) surgically sterile or postmenopausal or agree to continue to use an accepted method of birth control during and for at least 30 days after last study medication administration. Acceptable methods of birth control are:
- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation)
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)

patients should be consistently taking the hormonal contraceptive for at least 3 months [90 days] prior to screening);
- surgical sterility for at least 6 months prior to screening for tubal ligation performed laparoscopically, hysterectomy and/or bilateral oophorectomy; and/or postmenopausal (defined as at least 2 years without menses).

Contraceptive measures, such as Plan B (used after unprotected sex), are not acceptable methods of contraception for this study.

8. Eligible male patients will either be:
- surgically sterile (i.e., vasectomy), for at least 3 months (90 days) prior to screening

or
- when sexually active with a female partner, the partner must be either surgically sterile, postmenopausal, or agree to continue to use an accepted method of birth control during and for at

	least 30 days after last study medication administration as defined in 7 above. Please note that the use of condoms is an acceptable method of contraception for this study. 9. Eligible male and female patients must agree not to participate in a conception process (i.e. active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization) for **30 days** after the last dose of study drug. <u>Exclusion Criteria:</u> 1. Evidence of abdominal abscess or toxic megacolon at the screening visit. 2. Patients with history of extensive colitis or pancolitis of > 8 years duration or left-sided colitis of > 12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit (if not, the patient should undergo a colonoscopy in lieu of a flexible proctosigmoidoscopy during screening). 3. Previous extensive colonic resection (subtotal or total colectomy). 4. Current evidence of adenomatous colonic polyps that have not been removed. 5. Current evidence of colonic mucosal dysplasia. 6. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine or stoma. 7. Clinical significant infection as judged by the investigator in the previous 6 weeks before enrollment. 8. Evidence of or treatment for *C. difficile* infection within 60 days or other intestinal pathogen within 30 days prior to randomization. 9. Within 5 half-lives prior to randomization exposure to natalizumab or rituximab. 10. Within 30 days prior to randomization, treatment of underlying disease other than those specifically listed in Section 6.12. 11. Within 30 days or 5 half-lives (whichever is longer) prior to randomization receipt of any investigational agent. 12. Currently require or are anticipated to require surgical intervention for IBD during the study. 13. FEV_1 or FVC < 80% of predicted values (i.e., abnormal). 14. Infection with the Hepatitis B or C virus. 15. Active or latent tuberculosis, regardless of treatment history, as evidenced by any of the following:

	a. History of tuberculosis (that has not been successfully treated) b. A positive diagnostic tuberculosis (TB) test within one month of randomization defined as a positive QuantiFERON® test or 2 successive indeterminate QuantiFERON tests c. Chest X-ray within 12 months of randomization in which active or latent pulmonary tuberculosis cannot be excluded. 16. Any known history of congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection [ELISA and Western blot] test result, organ transplantation). 17. Clinically significant extra-intestinal infection (e.g., pneumonia, pyelonephritis) within 30 days prior to randomization. 18. Recent history (within 6 months of screening visit) of cardio or cerebrovascular disease, ACS, MI, unstable angina, CVA, TIA at screening. 19. Any surgical procedure requiring general anesthesia within 30 days prior to randomization or plans to undergo major surgery during the study period. 20. History of retinal macular edema. 21. History of or signs and symptoms of progressive multifocal leukoencephalopathy (PML) as assessed by the PML checklist. 22. History of cardiac arrhythmia, conduction system disease (including AV node dysfunction, 2nd or 3rd degree heart block, and sick sinus syndrome), or use of Class Ia and Class III anti-arrhythmic agents, or baseline QTc ≥ 500 msec. 23. Infection requiring hospitalization or intravenous antimicrobial therapy, or opportunistic infection within 4 weeks of screening. 24. History of more than one episode of herpes zoster or any episode of disseminated zoster. 25. Without documented positive varicella zoster virus (VZV) IgG antibody status or who have completed VZV vaccination within 30 days prior to randomization. 26. Receipt of live vaccine within 4 weeks prior to screening. 27. History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma. 28. History of malignancy except for adequately treated basal cell skin cancer. 29. History of severe allergic or anaphylactic reactions requiring medical attention. 30. Current or recent history (within one year prior to randomization) of alcohol dependence or illicit drug use. 31. History of clinically significant leukopenia or lymphopenia at screening. 32. Active psychiatric problems that, in the investigator's opinion,

	may interfere with compliance with the study procedures. 33. History of any clinically significant medical condition that, in the investigator's opinion, would preclude participation in the study. 34. Use of moderate to strong inhibitors of CYP2C9. 35. History of severe renal or hepatic impairment. 36. Inability to attend all the study visits or comply with study procedures. 37. Prior exposure of etrasimod.
Duration per Patient:	Up to 18 weeks total: up to 4 weeks for screening, followed by a 12-week treatment period and a follow-up visit 2 weeks after the end of treatment.
Sample Size:	Up to 20 patients (with up to 10 patients with anti TNF-alpha induced psoriasis).
Efficacy Endpoints:	<u>As this is a proof-of-concept study, all endpoints are exploratory.</u> - <u>UC endpoint:</u> Change from baseline in stool frequency, rectal bleeding, PGA (Physicians Global Assessments) at weeks 1, 2, 4, 8 and 12. - <u>CD endpoint:</u> Change from baseline in disease activity score at week 1, 2, 4, 8 and 12. - Change from baseline in endoscopic improvement/histologic healing using endoscopy or flexible proctosigmoidoscopy. (Only if there are signs of inflammation at screening another evaluation will be performed at week 12). - Change from baseline in level of fecal calprotectin at week 4, 8 and 12. - Change from baseline in Physician Global Assessments for active skin extra-intestinal manifestations (PG, EN and psoriasis) at week 1, 2, 4, 8 and 12. - Change from baseline in Patients Global Assessments for active skin extra-intestinal manifestations (PG, EN and psoriasis) at week 1, 2, 4, 8 and 12. - Change from baseline in the Dermatology Life Quality Index (DLQI) score at week 1, 2, 4, 8 and 12. - <u>Psoriasis endpoint only (all other endpoints are for all skin manifestations):</u> Change from baseline in Psoriasis

	Area and Severity Index (PASI) score at week 1, 2, 4, 8 and 12. - Change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score at week 2, 4, 8 and 12. - Skin punch biopsies (from healthy skin and from target lesion) will be collected before treatment and at week 8 or 12. Immunohistochemistry and other analyzing methods such as RT-PCR will be performed to evaluate immune cell infiltration, cytokine expression in the skin and other inflammatory parameters. - Change from baseline in C - reactive protein (CRP) at Weeks 1, 2, 4, 8 and 12. - Chang from baseline in leucocyte characterization. - Change from baseline in lymphocyte counts at Weeks 1, 2, 4, 8 and 12.
Safety Assessments:	- Clinical laboratory tests (chemistry, hematology and urinalysis) - Vital sign measurements - Physical examination - 12-lead electrocardiograms (ECGs) - Adverse event reporting - Concomitant medication - Lymphocyte counts
Statistical Analyses:	There is no formal sample size estimation for this proof-of-concept open label study. Sample size of 10 - 20 subjects is reasonable to assess proof-of-concept of the efficacy of etrasimod in the target population. Summary statistics will be provided to describe efficacy and safety measures. Confidence interval of key efficacy measures will be also produced for non-inferential comparisons with historical data.
Date	11 April 2017

LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
ADL	Activities of Daily Living
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
bpm	beats per minute
BUN	blood urea nitrogen
Ca	calcium
CBC	complete blood count (test)
CD	Crohn's disease
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CI	confidence interval
CIA	collagen-induced arthritis
Cl	chloride
CL/F	apparent oral clearance
CMO	contract manufacturing organization
CRF	case report form
CRP	C-reactive protein
CRO	contract research organization
D	day
DLQI	Dermatology Life Quality Index
EAE	experimental autoimmune encephalomyelitis
ECG	electrocardiogram
ED50	median effective dose
EIM	Extra-intestinal Manifestation
ELISA	enzyme-linked immunosorbent assay
EN	Erythema Nodosum
EOS	End of Study
EOT	End of Treatment
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
FU	follow-up
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
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
INR	International Normalized Ratio
IUD	intrauterine device
IUS	hormone-releasing system
kg	kilogram
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	Myocardial Infarction
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
MRSD	maximum recommended starting dose
Na	sodium
NOAEL	no observed adverse effect level
OCT	optical coherence tomography
OTC	over-the-counter
PA	Posteroanterior

PASI	Psoriasis Area and Severity Index
PBL	peripheral blood lymphocyte
PFT	pulmonary function test
PG	Pyoderma Gangrenosum
PGA	Physicians Global Assessments
PI	Principal Investigator
PRO	patient reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PV	Pharmacovigilance
RBC	red blood cell (count)
RT-PCR	real-time polymerase chain reaction
S1P(1-5)	sphingosine 1-phosphate (1-5) receptor
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
sec	second
SOP(s)	standard operating procedure(s)
TEM	T effector memory cells
TIA	Transient Ischemic Attack
UC	Ulcerative Colitis
ULN	upper limit of normal
VAS	visual analogue scale
VS	vital signs
VZV	varicella zoster virus
WBC	white blood cell (count)
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

Etrasimod (APD334) is an orally available, selective, sphingosine 1-phosphate receptor (S1P) 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]

Etrasimod 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]

A single ascending dose study (APD334-001) and a multiple ascending dose study (APD334-002), conducted in healthy subjects, have demonstrated the lymphocyte lowering capabilities of etrasimod (see Section 1.1.3). Lymphocyte trafficking agents such as natalizumab and vedolizumab, both injectable or infused therapies, have demonstrated efficacy in IBD indications. More recently, ozanimod, an $S1P_1$ oral receptor modulator showed promising results in a Phase 2 study for UC. The availability of oral lymphocyte trafficking agents such as etrasimod would offer patients an additional, more convenient treatment for IBD.

1.1 Background Information

1.1.1 Rationale for Proposed Clinical Study

Inflammatory bowel diseases are associated with various extra-intestinal manifestations (EIMs). The prevalence of IBD patients with EIMs as co-morbidities varies from 25% to 40% depending on the clinical presentation.[15]. Specifically, IBD patients with EIMs could have a negative impact on disease prognosis and quality of life, and in most cases their clinical course becomes independent of gut disease activity.

IBD patients with skin EIMs are common, occurring in 2% to 34% of the IBD population.[15] Specifically, erythema nodosum and pyoderma gangrenosum are the most common skin manifestations of IBD, while psoriasis is the active dermatological comorbidity disease observed most often, affecting 7%-11% of the IBD population.[16] IBD and these major skin EIMs in IBD share some common pathogenic mechanisms including neutrophil and lymphocyte infiltration.[17] To this point, targeted immunosuppressive therapies have demonstrated efficacy in IBD patients with skin EIMs. For example, TNF-alpha inhibitors are known to reduce intestinal inflammation and induce clinical remission in IBD patients, and are also known to reduce EIMs of IBD. However a small percentage of IBD patients taking TNF-alpha inhibitors experience de novo paradoxical psoriasis (reporting a rate ranging from 1.6 to 8.8%) despite beneficial intestinal effects while on treatment.[18] The pathophysiology of the paradoxical disease is not understood, but the leading hypothesis is that decreased TNF-alpha induces the activation of autoreactive T cells and an increased interferon activity as well as other pro-inflammatory cytokines, such as IL-12, IL-17, IL-23. Recently, interferon-alpha (IFN-alpha) production by dermal plasmacytoid dendritic cells (DCs) has been identified as a key element in the early phase of psoriatic skin lesion induction. Plasmacytoid DCs, the natural IFN-alpha producing cells, have recently been shown to infiltrate the skin of patients with psoriasis and to produce IFN-alpha. IFN-alpha induces the expression of CXCR3 on T cells, facilitating homing to the skin.[19]

It is clear that existing treatments for IBD, and IBD skin EIMs, including TNF-alpha inhibitors, have limitations and a need remains for therapies with sustained efficacy, improved safety, and convenient administration.[20]

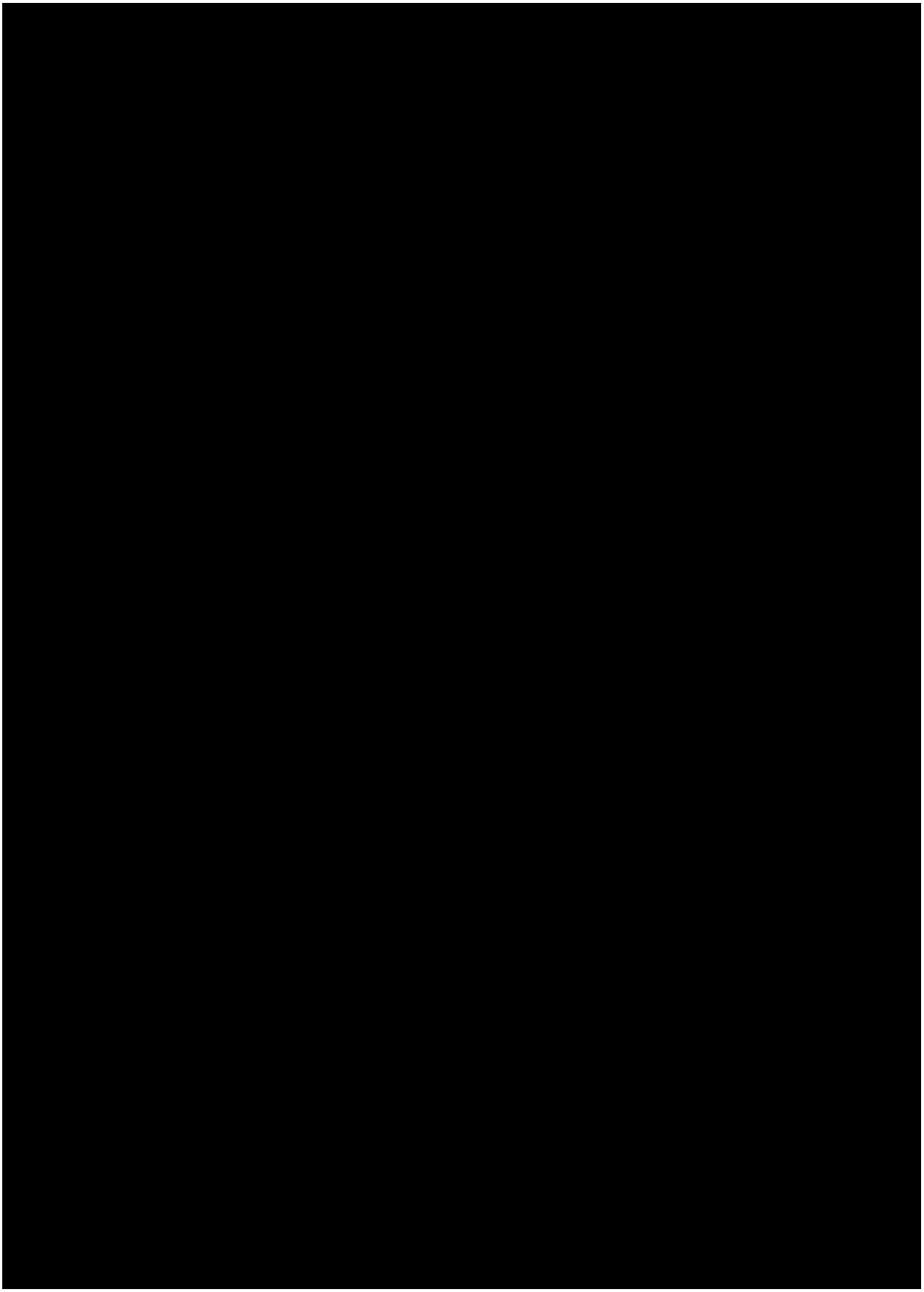
Spingosine-1-phosphate (S1P) is a spingolipid required by lymphocytes to exit the lymphoid tissue and enter the bloodstream via a chemotactic gradient. Agonists of the S1P receptor-1 ($S1P_1$) block lymphocyte migration out of the lymph tissue through internalization of the receptor, resulting in a sequestration of lymphocytes.[21] Recent clinical development of $S1P_1$

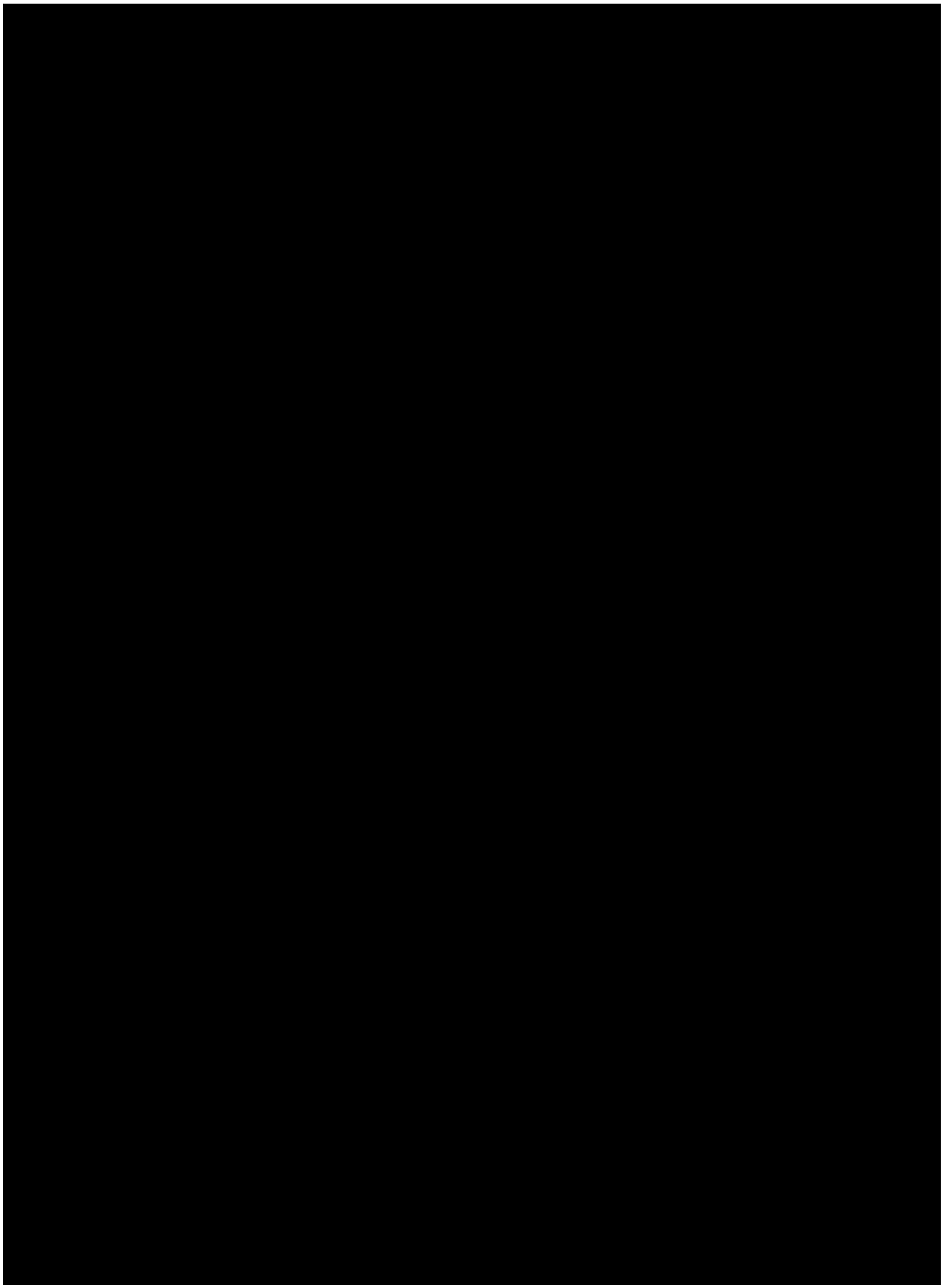
agonists and the resulting lymphocyte sequestration have potential for treating multiple autoimmune and chronic inflammatory diseases including multiple sclerosis, IBD and psoriasis. Fingolimod was the first drug in this class to be approved the treatment of multiple sclerosis.[22] More recently the $S1P_1$ receptor agonist ponesimod was observed to reduce the severity of chronic plaque psoriasis after chronic oral administration in a phase 2 randomized clinical trial.[23] In this study, ponesimod was associated with dyspnea, elevated liver enzymes, bradycardia, headache and dizziness. Furthermore, $S1P_1$ agonists (FTY720, SEW2871) have been observed to have an anti-inflammatory impact on the production of IL-12 family cytokines, indicating therapeutic potential for S1P treatment of several inflammatory diseases like psoriasis.[24] Importantly, a recent report demonstrating $S1P_4$ agonists inhibit plasmacytoid dendritic cell activation and interferon-alpha production suggest a potential therapeutic role for $S1P_1$/$S1P_4$ agonists like etrasimod in paradoxical psoriasis.[25]

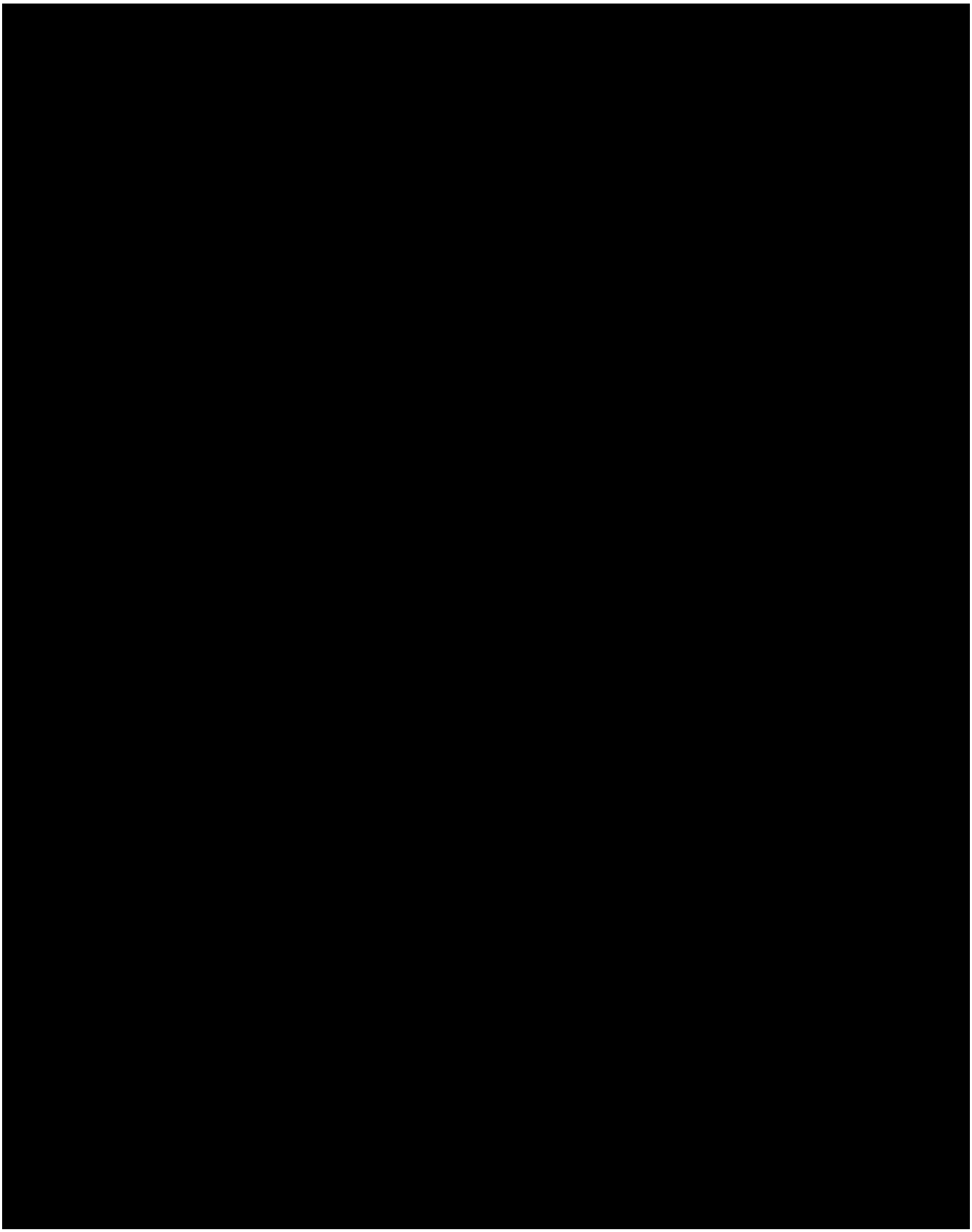
In addition to the potential anti-inflammatory benefits of systemic lymphocyte immunomodulation, S1P is known to exert anti-proliferative effects in human keratinocytes,[26] and inhibits dendritic cell migration.[27] Thus, the potential role of S1P receptor modulation in skin EIMs of IBD might involve both systemic and local epidermal mechanisms.

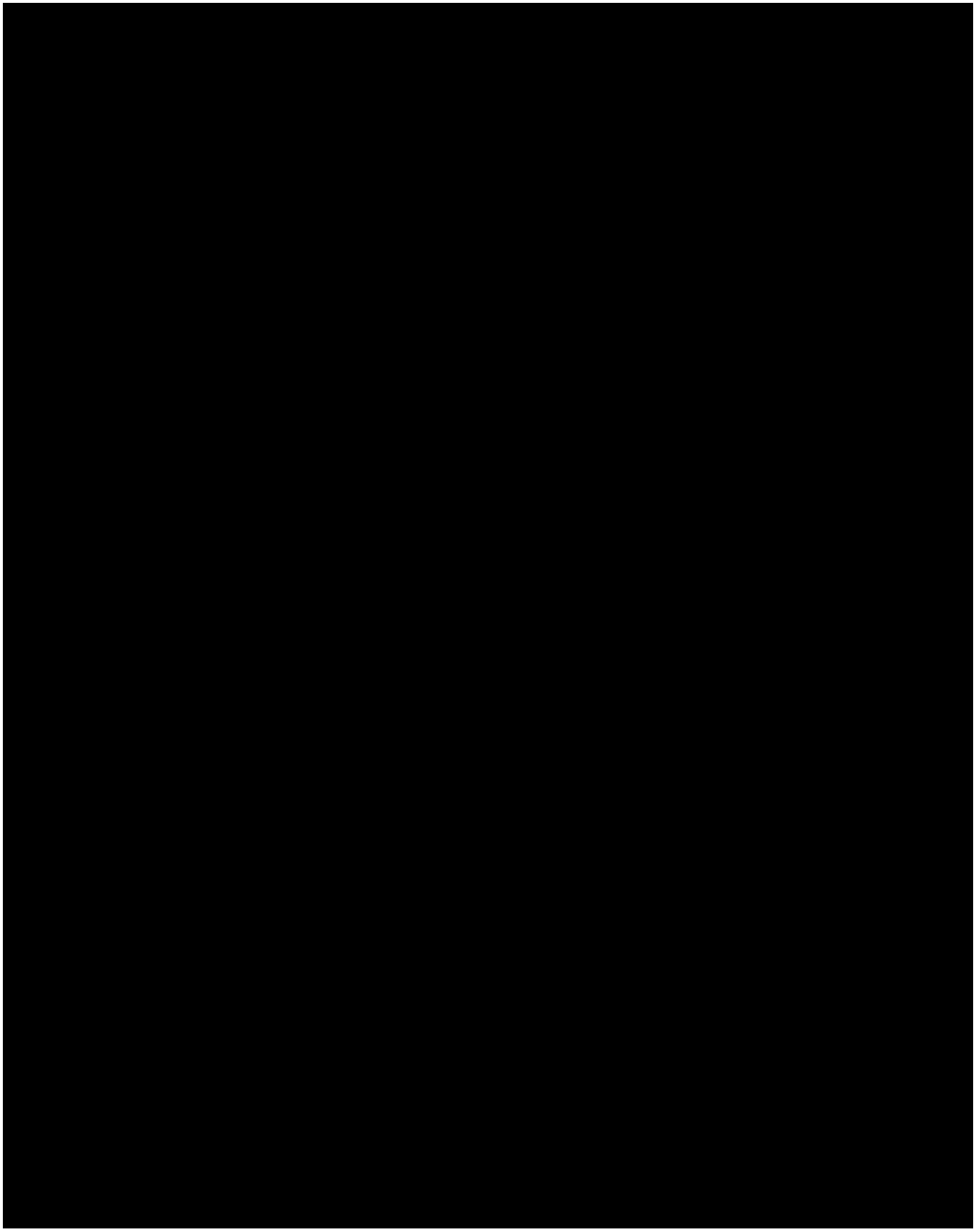
The aim of the proposed clinical studies is to evaluate the role of S1P modulation in the setting of IBD with skin EIMs. Next generation S1P modulators such as etrasimod with improved side effect profiles may represent a novel therapy for IBD patients with skin EIMs.

1.1.2 Summary of Preclinical Data









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 if according to the local law and regulation
- 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 Objectives

The efficacy objectives will be to determine the effect of etrasimod in Inflammatory Bowel Disease patients on the clinical improvement of active skin extra-intestinal manifestations. The safety objective will be to determine the safety and tolerability of etrasimod.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

APD334-006 is an open-label, phase 2, proof-of-concept single-arm study designed to evaluate the efficacy and safety of etrasimod in IBD patients with active skin extra-intestinal manifestations.

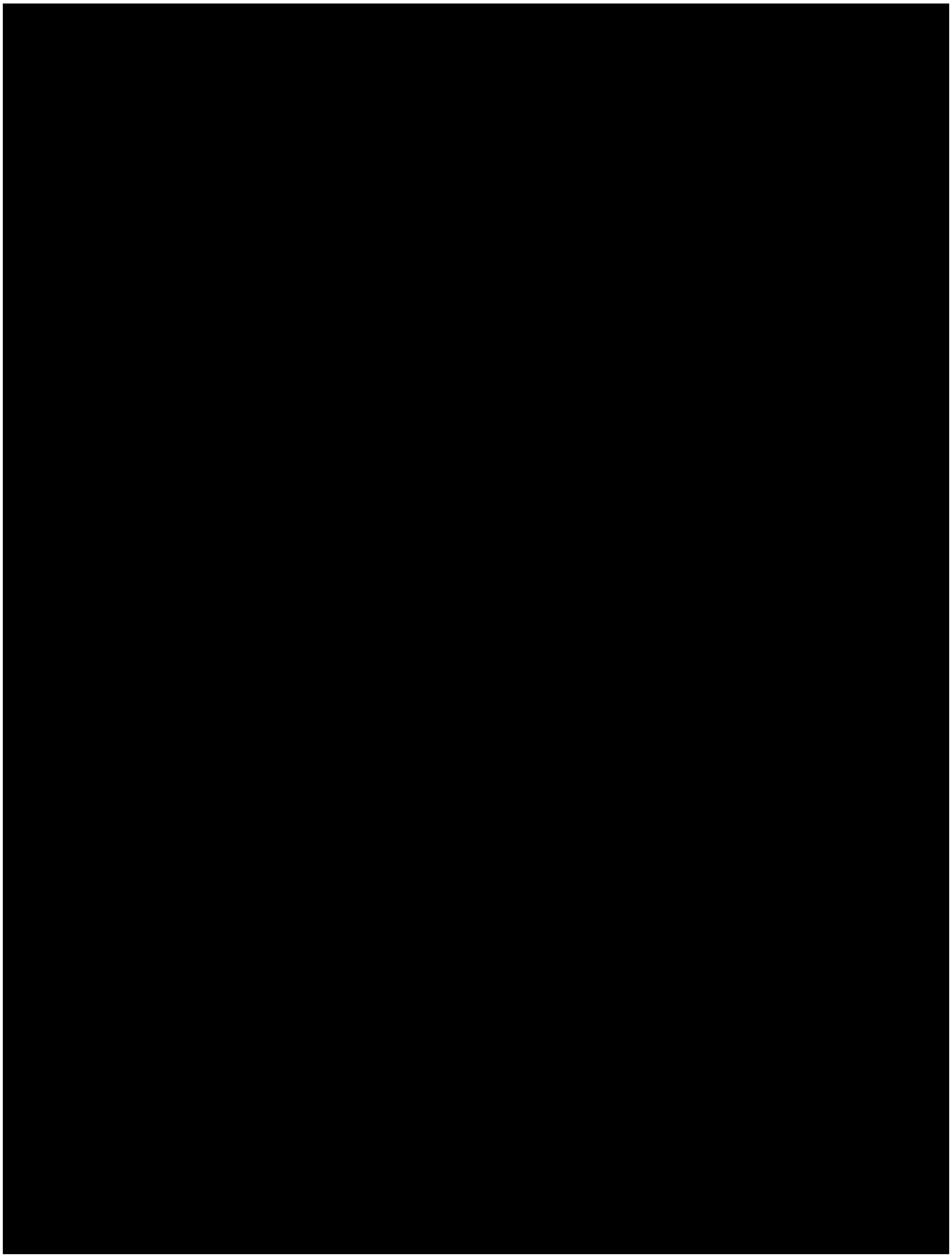
Up to 20 IBD patients with acute psoriasis, pyoderma gangrenosum or erythema nodosum (with up to 10 patients with anti TNF-alpha induced psoriasis) will be included in the study.

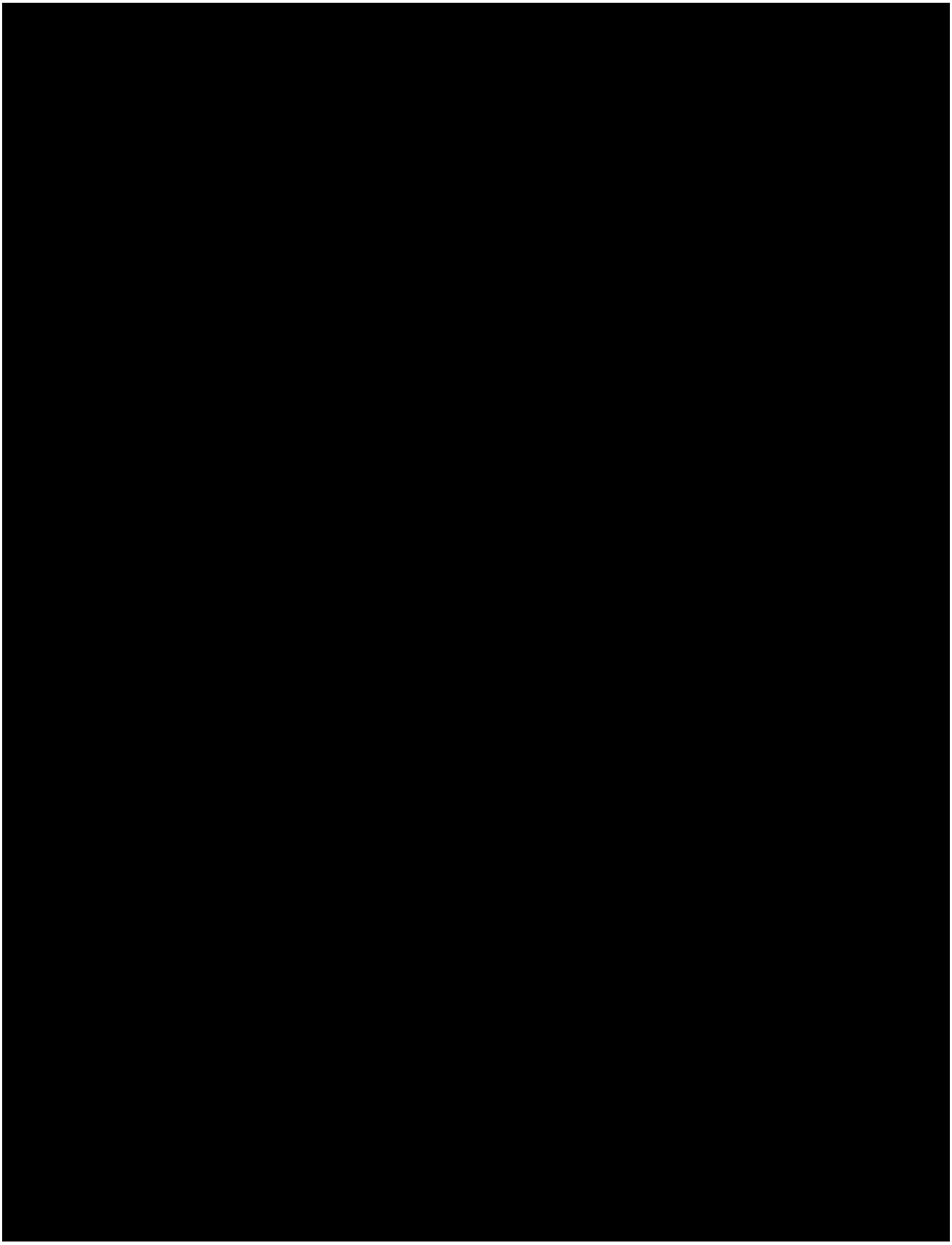
Patients will receive once daily (q.d.) [redacted] doses of etrasimod for 12 weeks.

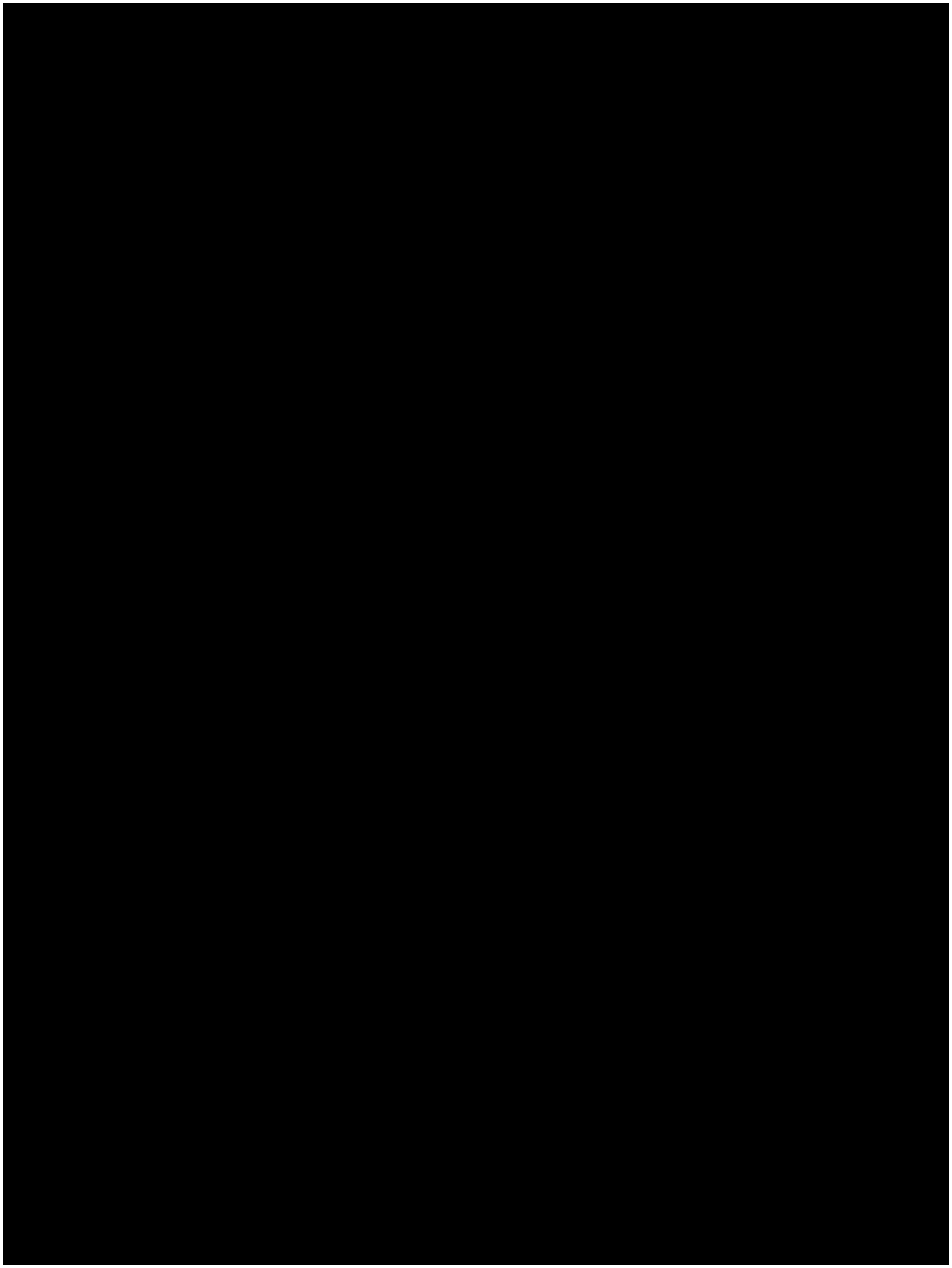
3.2 Study Duration and Dates

The total study participation/duration is approximately 18 weeks; up to 4 weeks for screening, followed by 12 weeks of dosing, and a follow-up visit 2 weeks after end of treatment.

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







4 STUDY POPULATION SELECTION

4.1 Study Population

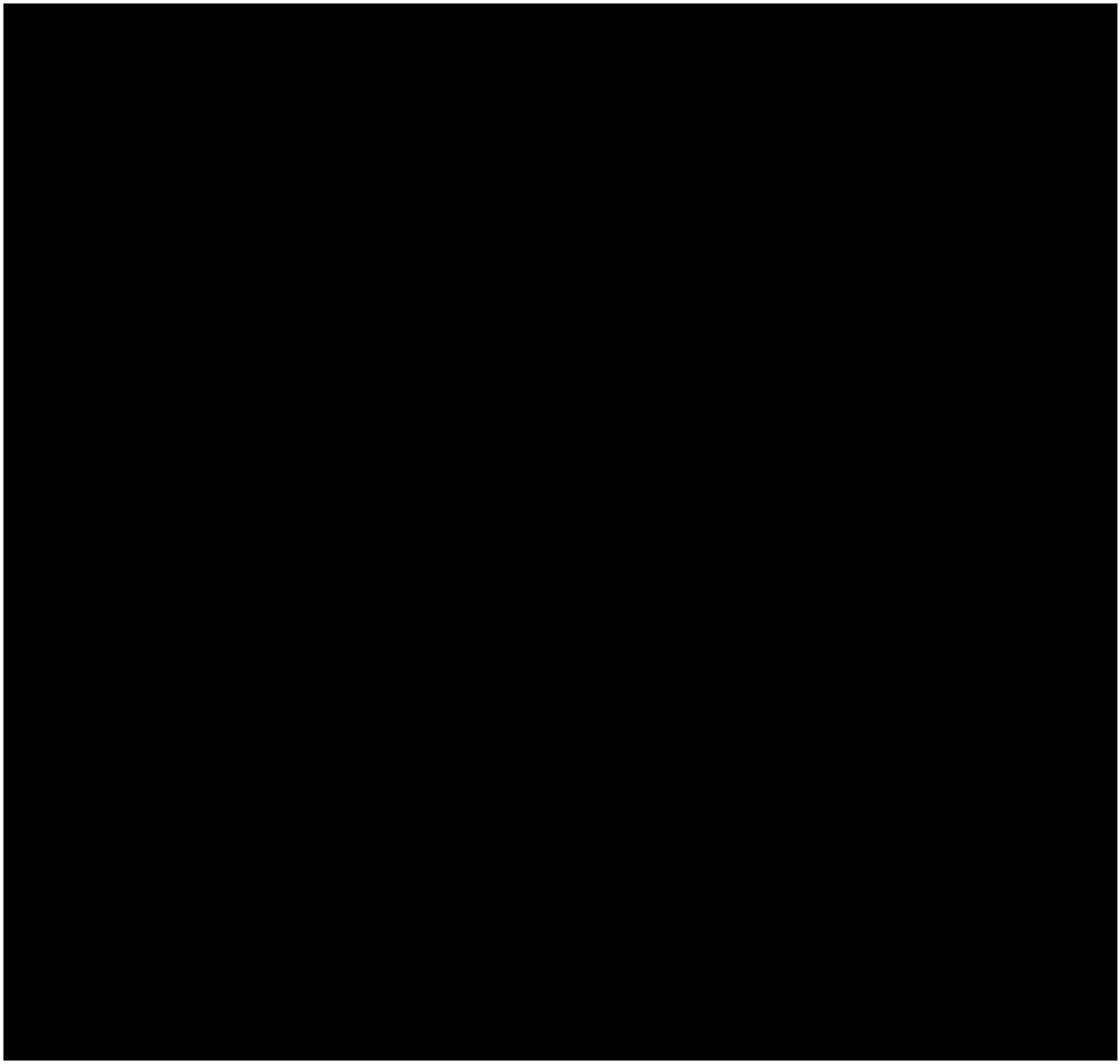
Adult men and women, ages 18-80 years, who have mild, moderate or severe UC or CD with active skin extra-intestinal manifestations including pyoderma gangrenosum, erythema nodosum or psoriasis.

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

4.2 Inclusion and Exclusion Criteria

Each patient must meet the inclusion and exclusion criteria described in the synopsis to be enrolled in the study.

5 STUDY TREATMENT(S)



5.4 Study Restrictions of Fluid and Food Intake prior drug screening

Consumption of foods and beverages containing the substances listed below will be prohibited as indicated. Exceptions may be permitted upon the joint agreement of 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.

5.5 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.

5.6 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.

6 STUDY PROCEDURES

6.1 Informed Consent

The investigator will obtain and document ICF 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 ICF must be reviewed and approved by the investigator's designated IRB/IEC and by the sponsor. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

6.2 Medical History

At screening, a complete medical history, as well as a full history of IBD 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 IBD and skin manifestations will be collected during screening.

6.2.2 History of IBD

A detailed history of IBD, including date of diagnosis, disease severity, hospitalizations, and extra-intestinal 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 screening and Week 12 by the investigator. A limited examination to assess clinically significant changes from the examination performed at screening will be completed during the Week 0/Day 1 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 Week 12 to rule out and monitor for any significant retinal disease, including macular edema. Retinal photos will be taken during the screening visit, Week 12 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

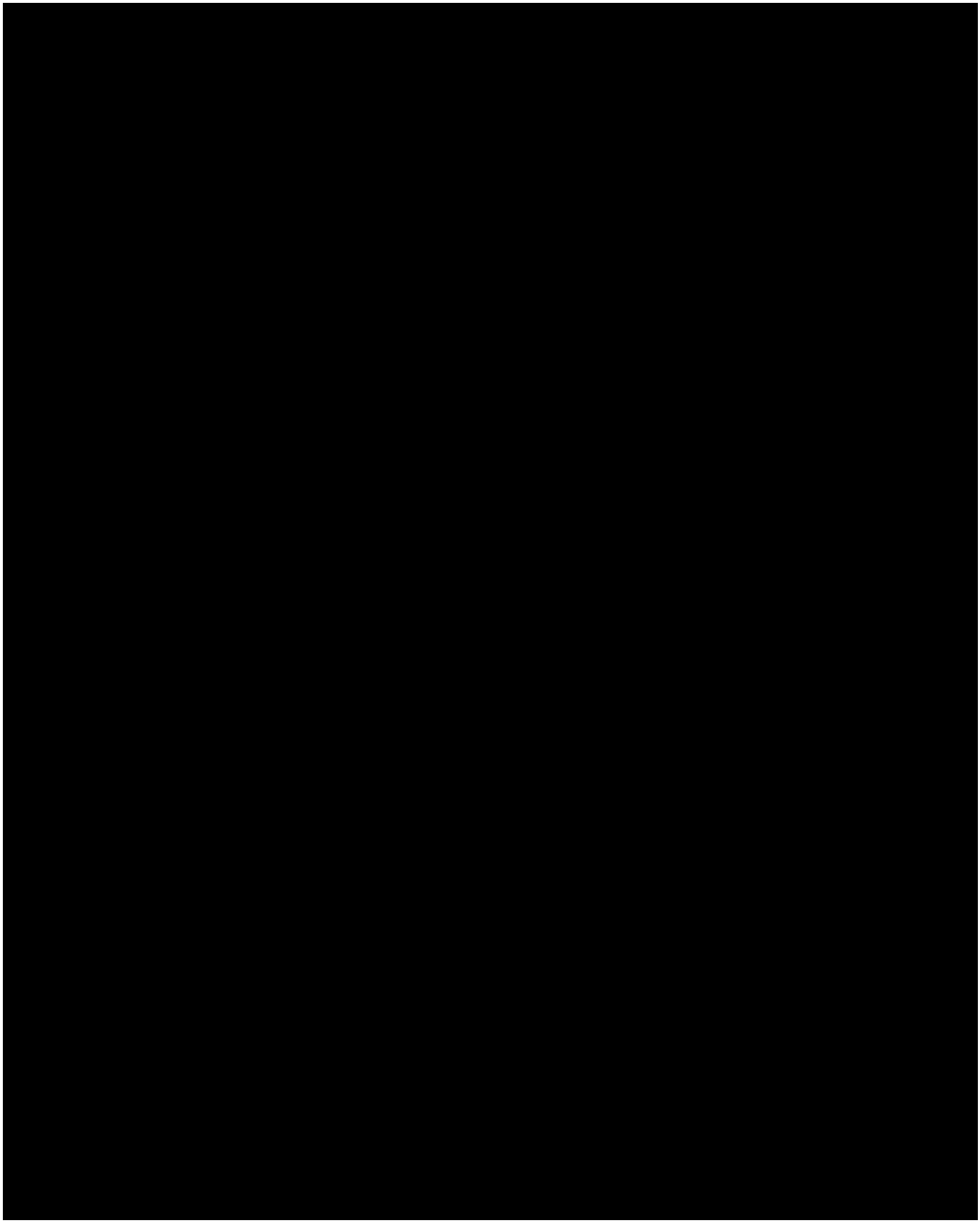
The neurological examination includes assessments of the neurological system (cranial nerves, motor and sensory function, coordination, and mental status), and will be performed during screening, Week 0/Day 1 (limited examination to assess clinically significant changes from the screening), and at Week 12 by the principal investigator or sub-investigator. 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 Day -1 [redacted]) using a subjective PML checklist.

The investigator or sub-investigator 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 -1) 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]



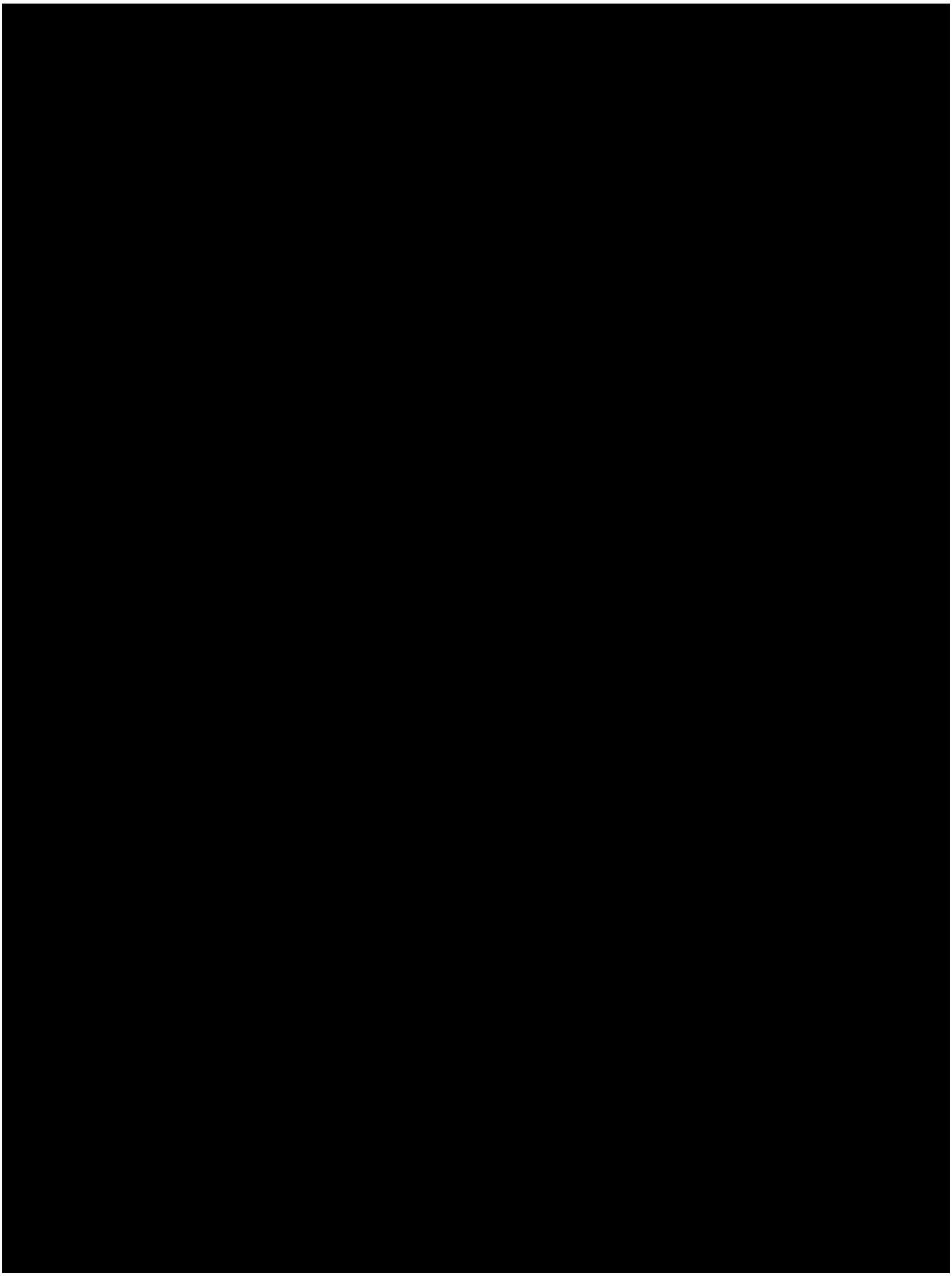
6.6 Tuberculosis Screening and Chest X- ray

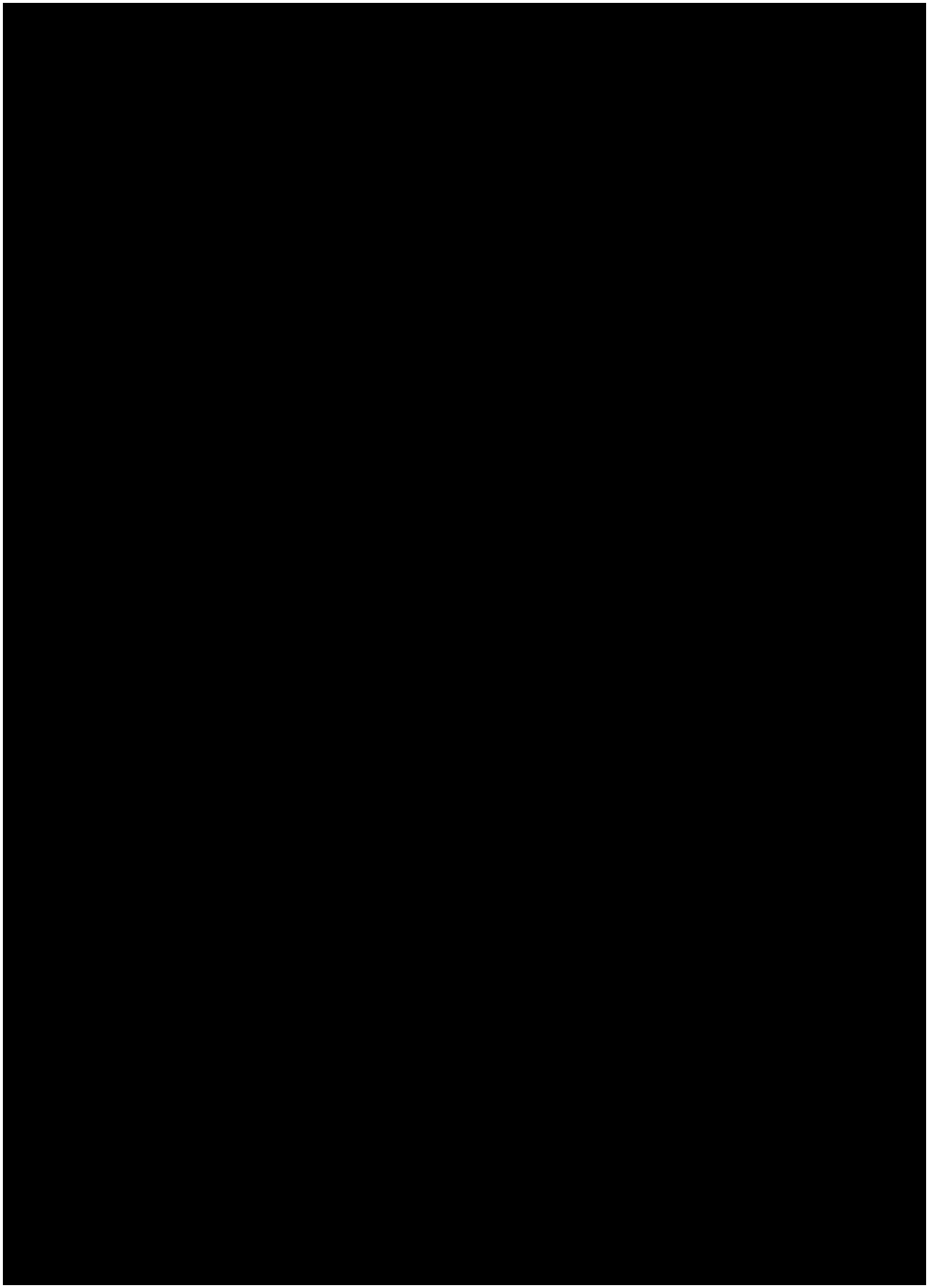
All patients will complete tuberculosis (TB) screening to determine eligibility. All patients who do not report a history of TB must complete a diagnostic TB test within 1 month prior to randomization and a chest X-ray within 12 months prior to randomization.
Patients will be excluded from the study if they have active or latent TB, regardless of treatment history, as evidenced by any of the following:

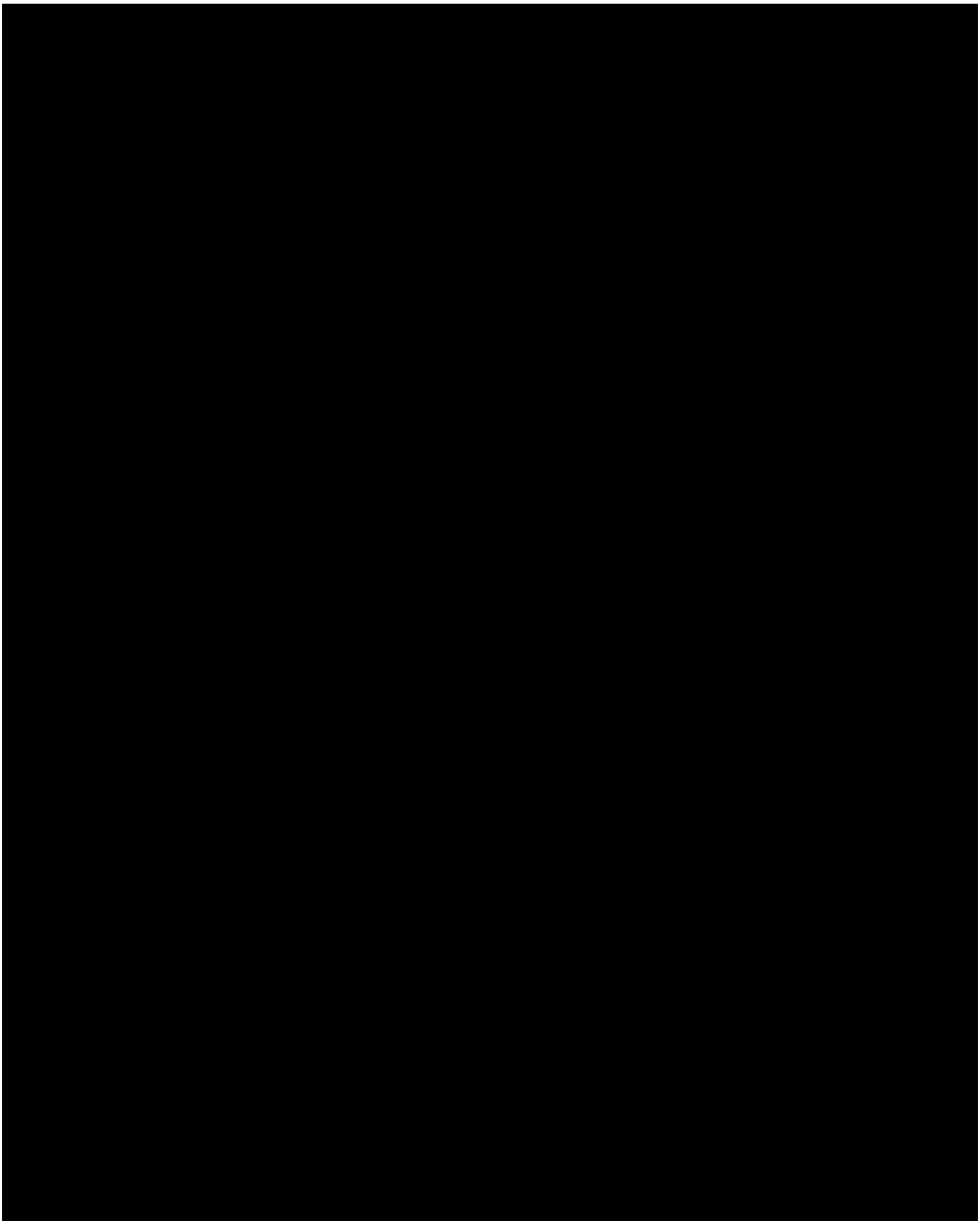
- History of TB (that has not been acceptably treated and the treatment was successfully completed)
- A positive diagnostic TB test within 1 month of randomization defined as:
  - A positive QuantiFERON® test or 2 successive indeterminate QuantiFERON® tests
  - Chest X-ray within 12 months of randomization in which active or latent pulmonary TB cannot be excluded

6.7 Pulmonary Function Testing

Pulmonary function testing (PFT) will be conducted using spirometry during screening and at Week 12 (and at the 2-week follow-up visit for patients not continuing on to the extension study). Spirometry will include measures of forced vital capacity (FVC), forced expiratory volume in the first second ($FEV_{1)}$ and mean forced expiratory flow between 25 and 75% of FVC ($FEF_{25-75\%}$). Since FVC and FEV are highly effort dependent, abnormal values or significant changes from baseline or the previous measurement should be verified with a repeat assessment.







6.11 Adverse Events Assessments

Patients will be monitored from ICF signature to 2 weeks after the last dose of study drug for adverse reactions (AEs) 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 serious AEs (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 etrasimod 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 ongoing AEs will be continued up to 2 weeks 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 etrasimod 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 AE because it is an expected pharmacologic effect of the drug.

AEs 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)

A patient with multiple sclerosis developed progressive multifocal leukoencephalopathy (PML) after nearly 8 months of treatment with another $S1P_1$ agonist[38], 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 each site visit (except Day -1) 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: [redacted]
PPD PVG Fax line:

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 SAE 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 (Day 1 to Week 12) until 30 days after the last dose of study drug should be reported to the sponsor contact and IRB/IEC in the same manner as an SAE.

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

6.11.3 Assessment of Adverse Event Severity

The severity of each AE will be assessed at onset by a nurse and/or physician. When recording the outcome of the AE the maximum severity of the AE experienced will also be recorded. The severity of the AE will be graded according to the CTCAE v4.03[35] 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

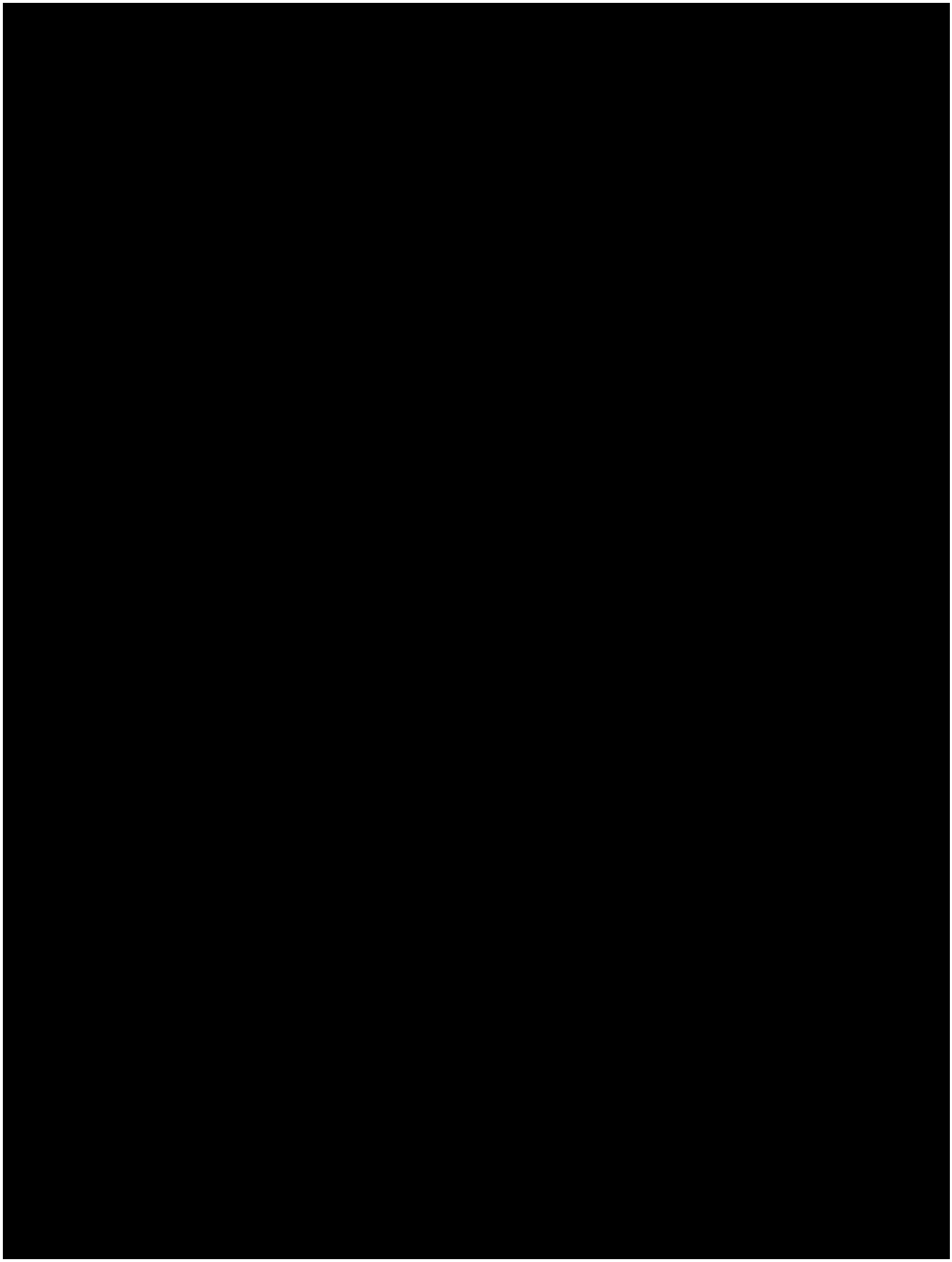
Any action taken with study drug will be defined according to ICH Topic E2B, ICH

Guideline and documented in the CRF according to the following:

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

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

Adverse events present at the last study day (Week 12) that require follow-up or a repeat laboratory test will be followed-up according to the site's standard practice for AE follow-up.



6.13 Removal of Patients from the Trial or Study Drug

Patients experiencing a significant infection as judged by the investigator will be discontinued from the 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

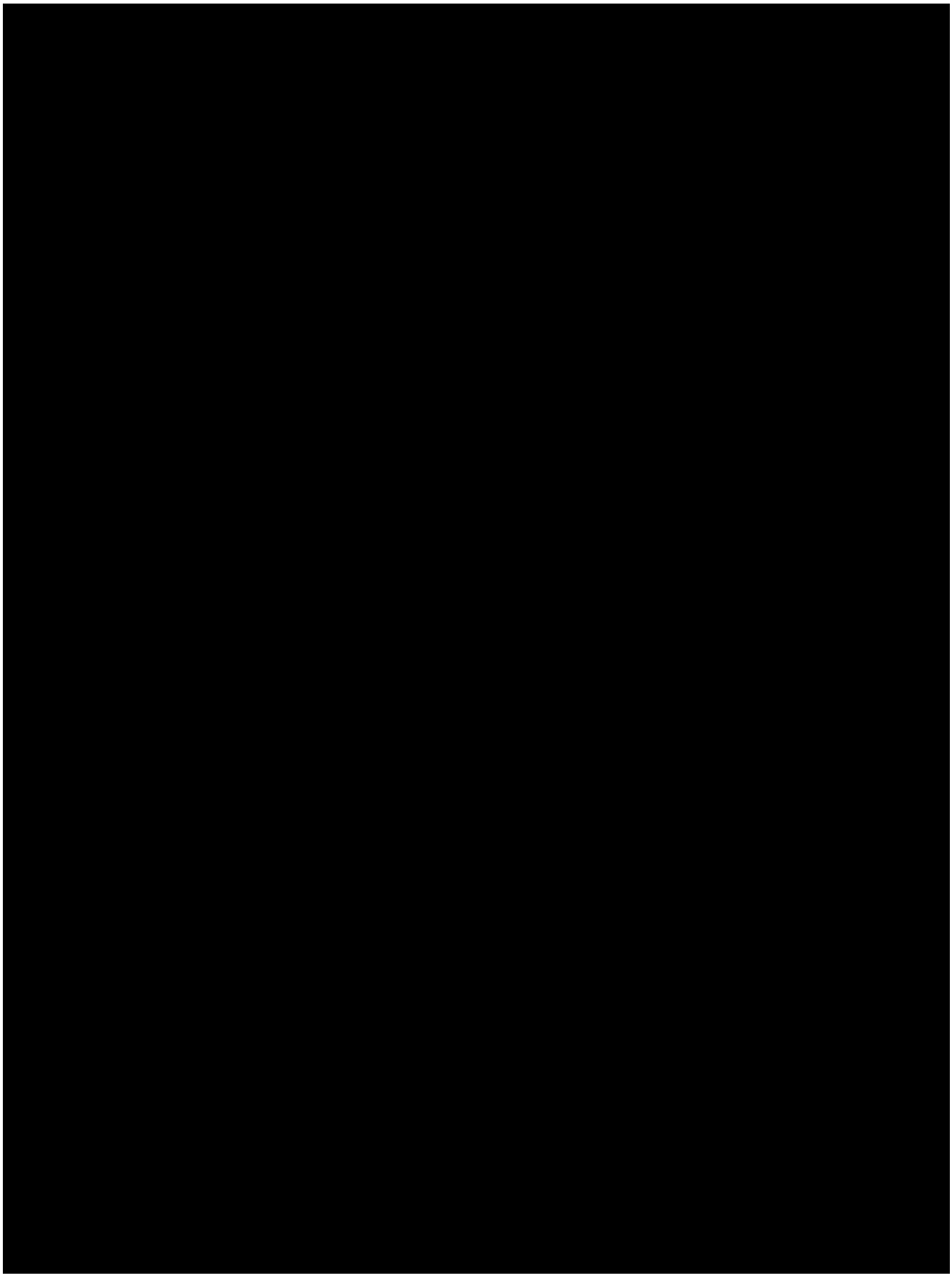
6.13.1 Handling of Withdrawals

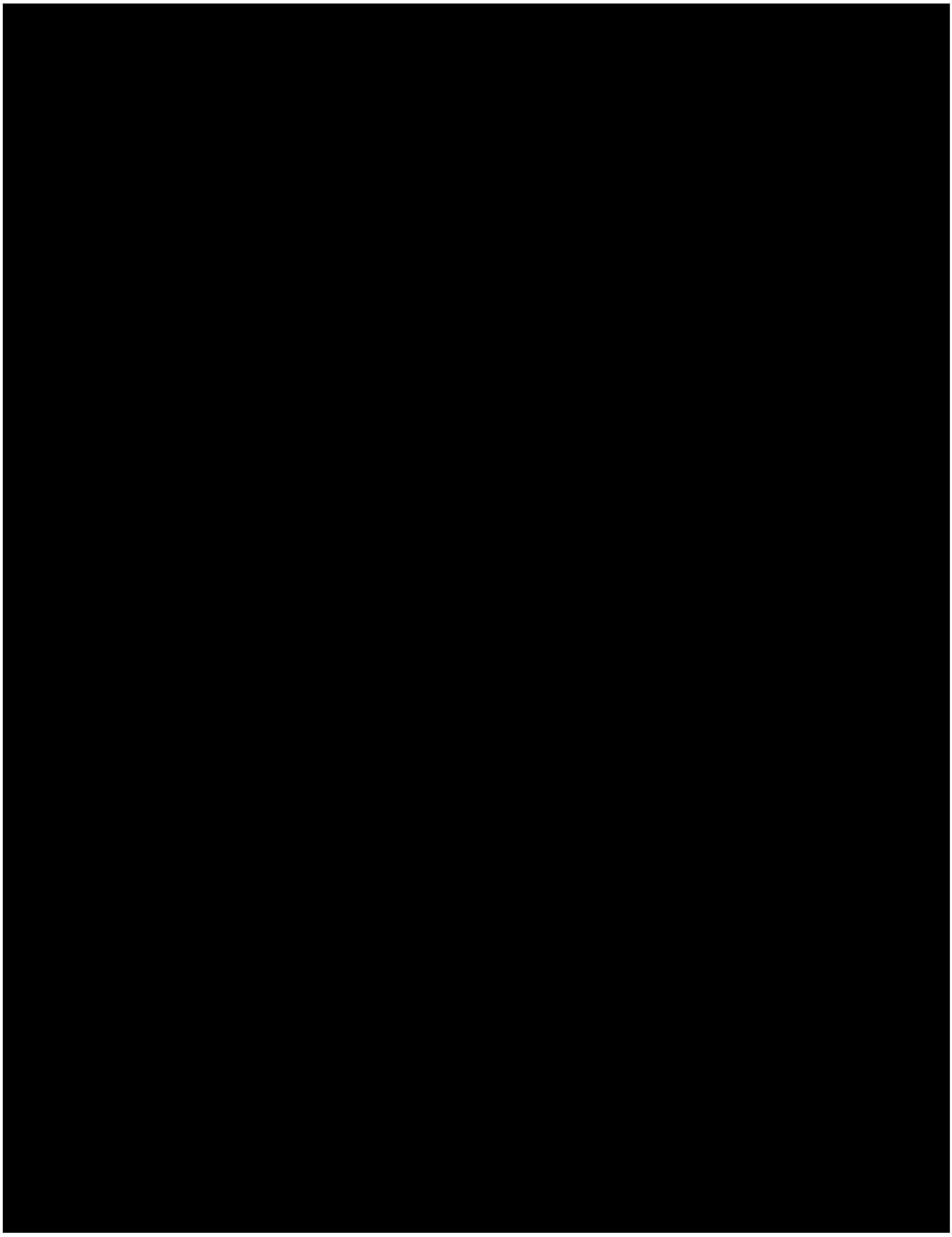
Although a patient is not obliged to give his/her reason for withdrawing prematurely, the investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. If there is a medical reason for withdrawal, the patient will remain under the supervision of the study 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.

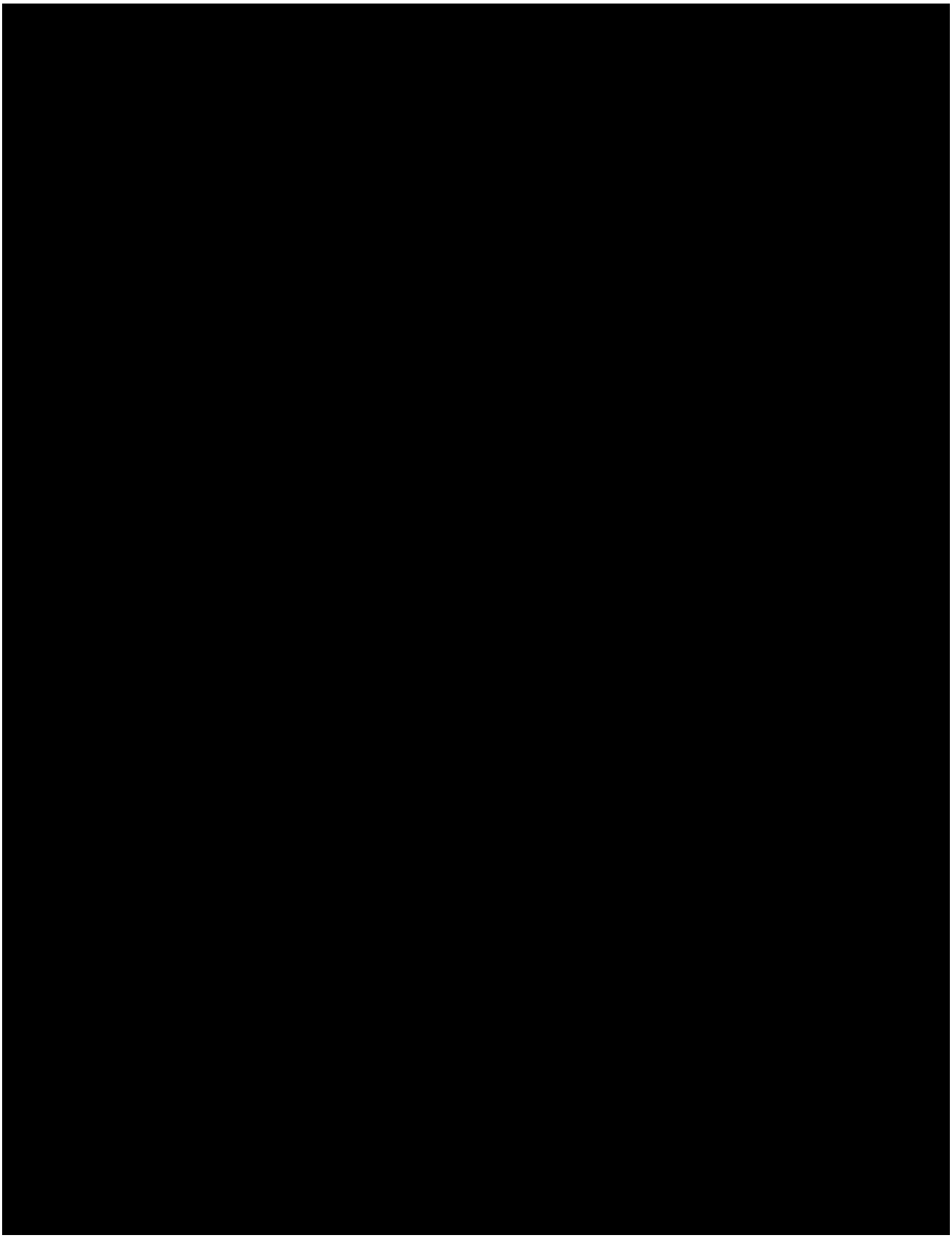
If a patient is prematurely discontinued from this study, every attempt will be made to follow the Week 12 procedures.

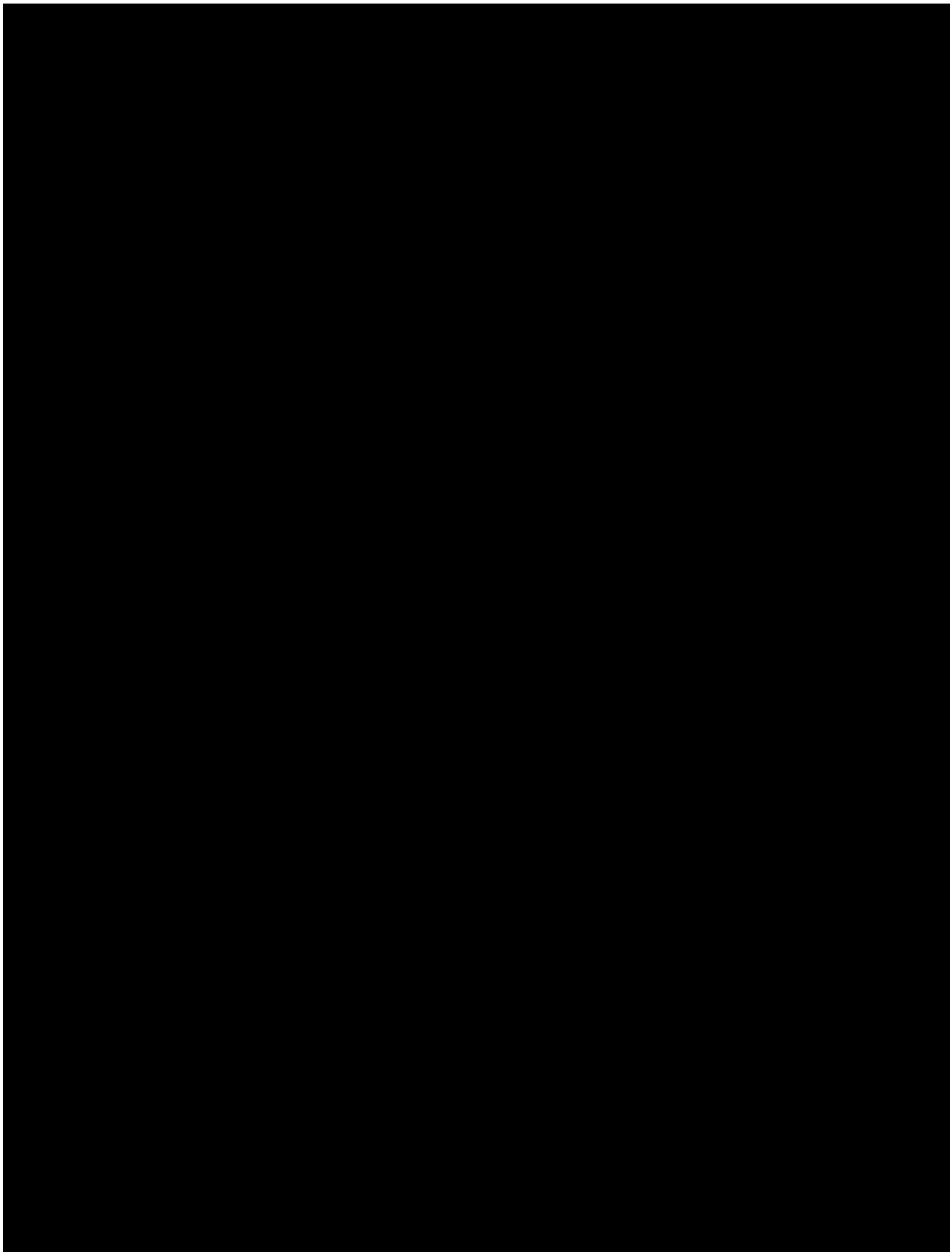
6.13.2 Replacements

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









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 / CRO's SOPs or according to study site standard if applicable.

8.2 Data Coding

8.2.1 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. 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 etrasimod. 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 (WHO DD), Format C.

8.2.3 Medical History

Medical history will be coded using the most current MedDRA-version.

9 PLANNED STATISTICAL METHODS

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

9.1 Hypotheses and Objectives

9.1.1 Objectives

9.1.1.1 Efficacy Objectives

The objectives will be to determine the effect of etrasimod in Inflammatory Bowel Disease patients on the clinical improvement of active skin extra-intestinal manifestations.

9.1.1.2 Safety Objective

The safety objective will be to determine the safety profile and tolerability of etrasimod

9.1.2 Hypotheses

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

9.2 Sample Size and Power Calculations

There is no formal sample size estimation for this proof-of-concept open-label study. Sample size of 10 - 20 subjects is reasonable to assess proof-of-concept of the efficacy of etrasimod in the target population.

9.3 Analysis Populations

Efficacy endpoints will be analyzed in enrolled patients who have baseline and at least one post-baseline measure.
Safety endpoints will be analyzed in enrolled patients who received at least one dose of study drug.

9.4 Demographics and Baseline Characteristics

All baseline patient characteristics of demographic data (age, height, weight, race), disease history, 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

Efficacy endpoints are outlined in the synopsis.

9.6 Statistical Methods

9.6.1 Efficacy Analysis

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

9.6.2 Subgroup Analyses

Efficacy endpoints will be analyzed on following patient populations. Certain subgroups may be combined when deemed clinically necessary.

- PG EIM
- EN EIM
- psoriasis EIM
- psoriasis due to anti TNF-alpha treatment

Other subgroup analyses based on demographics (such as sex, age, race, etc.) may be performed when deemed appropriate.

9.6.3 Interim Analysis

No interim analyses are planned for this study.

9.7 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. Adverse experiences will only be presented as summary tabulations. When assessing change from baseline, a baseline measurement is also required. Baseline for the safety analysis is defined as the last pre-dose measurement. No missing data will be imputed for the safety analysis. For continuous variables, summary statistics (N, mean [or median], SD, mean [or median] change/percent change) and 95% CI will be produced if applicable; for proportion based measures, N, frequencies, proportion and its 95% CI will be produced.

9.7.1 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 etrasimod. All other AEs that occur after the first dose of study medication will be considered to be 'treatment-emergent'.

Pre-treatment and Treatment-emergent AEs will be listed by patients, in terms of seriousness, severity and Intensity (assessed according to the Common Terminology Criteria for Adverse Events v4.0313 definitions). TEAEs will be classified according to system organ class.

9.7.2 Physical Examinations

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

9.7.3 Concomitant Medication

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

9.7.4 Vital Signs

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

9.7.5 Clinical Laboratory Values

Individual lab values will be listed by visit, and summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in lab values. Baseline is defined as the last pre-dose measurement. A clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor.

[redacted]

9.7.7 Lymphocyte counts

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

10 REGULATORY REQUIREMENTS

10.1 Pre-Study Documentation:

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

- Protocol signature page signed and dated by the principal investigator (PI)
- FDA form 1572 signed and dated by all PIs
- 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 (USA only)
- Copy of the IRB/IEC approval letter for the study and approved ICF
- IRB/IEC Membership List

Additional country specific documentation may be required per international regulatory authorities.

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 country regulatory requirements 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 ICF 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 ICF must be reviewed and approved by the investigator's designated IRB/IEC and by the sponsor. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

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 ICF; Regulatory files, containing the protocol with all amendments and investigator signature pages, copies of all other regulatory documentation, and all correspondence between the site and the IRB/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 2a, Proof of Concept, Open-label Study Evaluating the Efficacy and Safety of Etrasimod (APD334) in Inflammatory Bowel Disease Patients with active Skin Extra-intestinal Manifestations" 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, or 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 on the appropriate CRF page or in letters to the sponsor.
- Submission of written reports of SAEs to Arena Pharmaceuticals, Inc. or designated CRO within 24 hours after the investigator's initial receipt of the information.
- 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

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PROTOCOL SIGNATURE PAGE

Protocol Title: A Phase 2a, Proof of Concept, Open-label Study Evaluating the Efficacy and Safety of Etrasimod (APD334) in Inflammatory Bowel Disease Patients with active Skin Extra-intestinal Manifestations

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: APD334-006

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.