Clinical Trial Protocol: APD334-011

Study Title:	A Phase 2a, Open-label, Proof of Concept Study to Determine the Efficacy and Safety of Etrasimod (APD334) in Patients with Pyoderma Gangrenosum
Study Number:	APD334-011
Study Phase:	2a
Product Name:	Etrasimod (APD334)
EudraCT Number:	NA
Indication:	Pyoderma Gangrenosum
Investigators:	Multicenter
Sponsor:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121 United States

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	Date
Original Protocol:	08 Feb 2017

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

SYNOPSIS

Name of Drug:	Etrasimod (APD334)
Indication	Pyoderma Gangrenosum (PG)
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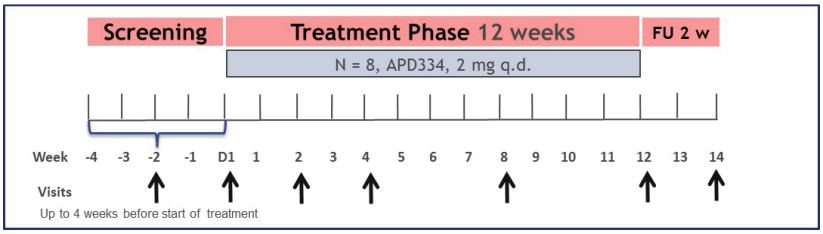
Test Product, Dose and Mode of Administration:	Etrasimod (APD334) 2mg tablets, once daily (q.d.) for 12 weeks. Patients should be instructed to take their tablet as a first thing in the morning on an empty stomach). Patients should be advised not to crush, break, chew, or dissolve the tablet and to take study medication with water.
Concurrent Control:	No concurrent control
Background	Etrasimod is an orally available, selective, sphingosine 1-phosphate (S1P) receptor agonist. S1P is a signaling sphingolipid required by lymphocytes to exit the lymphoid tissue and enter the bloodstream via a chemotactic gradient. 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]. Agonists of the $S1P_1$ receptor, such as etrasimod , block lymphocyte

	migration out of the lymph tissue through internalization of the receptor, resulting in a sequestration of lymphocytes [1]. Recent clinical development of $S1P_1$ receptor agonists has demonstrated their effect on resulting lymphocyte sequestration, have potential for treating multiple autoimmune and chronic inflammatory diseases including multiple sclerosis, IBD and psoriasis. *Rationale for use of etrasimod in Treatment of Pyoderma Gangrenosum* Histopathology of ulcerative Pyoderma Gangrenosum (PG) is characterized by a dense dermal infiltrate composed mainly of neutrophils in biopsy from the central area of ulceration, and a mainly lymphocytic infiltrate with thrombosis of vessels and extravasated erythrocytes in biopsy from the border of the ulcer [2]. In patients with ulcerative PG the number of T-lymphocytes are significantly higher at the wound edge compared to the wound bed. In contrast, neutrophils are significantly more numerous in the wound bed than the wound edge [3]. This suggests that activated T-lymphocytes at the wound edge could promote ulcer formation. Further support for T-cell involvement in the disease comes from observations in PG patients that are characterized by an over-expression in the blood of the CD4+CCR5+ and CD4+CCR6+ and a down-regulation of CD4+CCR4+ counts with respect to healthy subjects [4]. In addition, a differentiated profile for etrasimod compared to other S1P modulators for the treatment of PG could arise from the hypothesis that $S1P_4$ as well as $S1P_1$ receptor agonism could aid in neutrophil trafficking [5]. Together, this evidence suggests that T-lymphocytes can play a role in PG and that reduction of lymphocytes by $S1P_1$ modulators like etrasimod may represent a novel therapeutic approach in PG.
Objectives:	Efficacy • To evaluate the efficacy of etrasimod in patients with PG over a 12-week treatment period. Safety • To assess the safety and tolerability of etrasimod in patients with PG over a 12-week treatment period.
Study Design	This is a Phase 2a, open label, proof-of-concept clinical study to assess the efficacy and safety of etrasimod in patients with PG. The trial will include adult patients 18-80 years of age with active PG ulcers.



All visits in the study are ambulatory visits. The screening period will last up to 4 weeks and will be followed by a 12-week treatment period. During the treatment period, patients will need to take 1 tablet of study medication once per day. The last dose is planned to be taken one day before the end of the treatment period (Week 12). A follow-up visit will take place 2 weeks after the end of treatment.

Screening Period(up to 4 weeks):
Each patient will be asked to visit the study site for screening assessments within 4 weeks prior to the planned start of the treatment (Day 1). All patients must be consented before any study specific procedure is performed and written informed consent must be obtained. Patients will then undergo screening procedures to determine eligibility.

[redacted]

Treatment Visits:
Baseline Visit (Day 1): Patients will return to the study site to receive the first dose of the study medication. Patients should be instructed to take their tablet as a first thing in the morning on an empty stomach. Patients should be advised not to crush, break, chew, or dissolve the tablet and to take study medication with water. The patients will remain at the study site for at least 6 hours for safety evaluation (please refer to the [redacted]

Visits Week 2, Week 4, Week 8, and Week 12: Patients will return to the study site and all planned examinations as described in [redacted] will be conducted. Last dose of study medication is planned 1 day before the end of the treatment visit at Week 12.

Follow up Visit/End of Study Visit:
Visit Week 14, 2 weeks after end of treatment: Patients will return to the study site for the final visit, and final procedures will be performed per [redacted]

	Premature Discontinuation: All procedures planned for Week 12 visit should be performed for all patients who discontinue the study prematurely.
Study Site(s)	This study will be conducted in approximately 6 clinical centers.
Study population	Patients with PG who fulfill eligibility criteria.
Inclusion Criteria:	1. Male or female of age 18 to 80 years (inclusive) at the time of screening. 2. Able to provide a signed informed consent prior to any study related procedure being conducted and willing and able to comply with the study requirements. 3. Diagnosis of PG with active, non-healing ulcer. 4. Considered to be in stable health in the opinion of the investigator, as determined by: a.) A screening physical examination with no clinically significant abnormalities unrelated to PG. b.) Vital signs at screening: pulse rate ≥ 55 bpm, systolic blood pressure (SBP) ≥ 90 mmHg, and diastolic blood pressure (DBP) ≥ 55 mmHg. c.) Liver function tests (alanine aminotransferase [ALT]/aspartate aminotransferase [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 with exemption to leucopenia and lymphopenia – please refer to exclusion criterion #24. e.) No clinical abnormalities noted in the12-lead electrocardiogram (ECG) in the opinion of the investigator (Refer also to exclusion criterion #13. f.) No evidence of macular edema in an ophthalmology evaluation (performed by an ophthalmologist), supported with optical coherence tomography (OCT), where available (dependent on site capability) at screening. 5. Eligible male and female patients must agree not to participate in a conception process (i.e. active attempt to let female partner to become pregnant or to impregnate, sperm donation, oocyte donation, in vitro fertilization) for at least 30 days after the last dose of study drug. Female patients who are sexually active with non-sterile male partner 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.) one of the following: - either 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 methods are <u>not acceptable</u> - or surgically sterile (surgical sterility prior to screening for at least 6 months for tubal ligation performed laparoscopically, hysterectomy and/or bilateral oophorectomy) - or postmenopausal (at least 2 years without menses) - or agree to continue to use an accepted method of birth control. Patients should be consistently using the hormonal contraceptive for at least 1 month (30 days) prior to screening, during the study 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) Contraceptive measures, such as Plan B (used after unprotected sex), are <u>not acceptable</u> methods of contraception for this study. 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 above. Please note that the use of condoms alone or double barrier and use of spermicide are not an acceptable method of contraception for this study.
Exclusion criteria	1. Clinically significant infection (e.g., pneumonia, pyelonephritis) as judged by the investigator with an end date less than 6-weeks prior to treatment start (Day 1). In case of infection requiring hospitalization or intravenous antimicrobial therapy, or opportunistic infection, this infection must have ended at least 8 weeks prior to Day 1. 2. Infection with hepatitis C virus anytime in the past; confirmed active infection with hepatitis B virus at screening. 3. History of severe renal or severe hepatic impairment. 4. Current active or latent tuberculosis (TB), regardless of treatment history or history of TB that has not been successfully treated 5. A positive diagnostic TB test at screening defined as a positive QuantiFERON® test or 2 successive indeterminate QuantiFERON® tests 6. Exposure to B-cell or T-cell targeted therapies (such as natalizumab, rituximab, abatacept) within 5 half-lives prior to Day 1. 7. Other immunosuppressive, immunomodulating or antineoplastic agents not listed in Section 6.13.1 or not meeting the stability time period for concomitant medications indicated as permitted in Section 6.13. 8. Receipt of any investigational agent within 30 days or 5 half-lives (whichever is longer), prior to Day 1. 9. Use of moderate to strong inhibitors of CYP2C9 (e.g., amiodarone, felbamate, fluconazole, miconazole, piperine). 10. Abnormal forced expiratory volume (FEV_1) or forced vital capacity (FVC) i.e., < 80% of predicted values at screening 11. Any known history of congenital or acquired immuno-deficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection [ELISA and Western blot] test result, organ transplantation). 12. Recent history (within 6 months of screening assessments) of cardio- or cerebrovascular disease, acute coronary syndrome (ACS), myocardial infarction (MI), unstable angina, cerebro-vascular accident, including transient ischemic attack (TIA).

	13. History or presence 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 or Class III anti arrhythmic agents, or baseline QTc ≥ 500 msec. 14. Congestive heart failure (NYHA III or NYHA IV) 15. Any surgical procedure requiring general anesthesia within 30 days prior to Day 1 or plans to undergo major surgery during the study period. 16. History of retinal macular edema. 17. History of or signs and symptoms of progressive multifocal leukoencephalopathy (PML) as assessed by the PML checklist at screening. 18. History of more than one episode of herpes zoster or any episode of disseminated zoster. 19. Patients without documented positive varicella zoster virus (VZV) IgG-antibody status or patients who have not completed VZV vaccination within 6 weeks prior to Day 1. 20. Receipt of live vaccine within 6 weeks prior to Day 1. 21. History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma. 22. History of malignancy except for adequately treated basal cell skin cancer and in situ carcinoma of the cervix of the uterus that have been completely excised with documented, clear margins. 23. History of severe allergic or anaphylactic reactions requiring medical attention. 24. Leukopenia or lymphopenia at screening. 25. Current or recent history (within 1 year prior to Day 1) of alcohol dependence or illicit drug use. 26. Active psychiatric problems that, in the investigator's opinion, may interfere with compliance with the study procedures. 27. History of any other clinically significant medical condition that, in the investigator's opinion, would preclude patient from safe participation in the study. 28. Inability to attend all the study visits or comply with study procedures. 29. Prior exposure to etrasimod or prior participation in any study of etrasimod.
Duration of the	Up to 18 weeks total: up to 4 weeks for screening, followed by a

Study (per Patient):	12-week treatment period and a follow-up visit 2 weeks after the end of treatment.
Sample Size:	Eight (8) patients
Efficacy Endpoints:	As this is a proof-of-concept study, all endpoints will be exploratory. The efficacy endpoints will be as follows: - change from baseline (Day 1 pre-dose) to Week 12 in Physician Global Assessments for active skin manifestations. *Assessment of target lesion/ulceration* ***0**: Total resolution of target ulcer with no signs of active PG* ***1**: almost completely healed target ulcer with only minimal signs of active PG* ***2**: Evidence of target ulcer healing which involves at least 50% of ulcer/ulcer margin* ***3**: Evidence of target ulcer healing which involves less than 50% of ulcer/ulcer margin* ***4**: No evidence of target ulcer healing* - change from baseline (Day 1 pre-dose) to Week 12 in Patient Global Assessments for active skin manifestations: visual analog scale (VAS) for assessment of severity of the disease and severity of pain by patient. - change from baseline (Day 1 pre-dose) to Week 12 in Dermatology Life Quality Index (DLQI) - change from baseline (Day 1 pre-dose) to Week 12 in CRP levels In addition, the following measures will be assessed as per [redacted] - Imaging (digital photos) of the target lesion. - Evaluation of the changes in surface area of target lesion. - Punch Biopsy (Histology)
Safety Assessments:	The following will be captured to assess the safety endpoints: - Adverse event reporting - Clinical laboratory test (including hematology, serum chemistry, coagulation and urinalysis) - Physical and neurological examination - Vital sign measurement - 12-lead ECG
Pharmacokinetic Assessments	Not planned.
Statistical Analyses:	There is no formal sample size estimation for this proof-of-concept

	open label study. A sample size of 8 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	**08 February 2017**

LIST OF ABBREVIATIONS

ACS	acute coronary syndrome
ADL	activities of daily living
AE	adverse event
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
bpm	beats per minute
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CRP	C-reactive protein
CRO	contract research organization
D	day
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
EIM	extra-intestinal manifestation
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in the first second
FU	follow-up
FVC	forced vital capacity
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HREC	human research ethics committee (AUS)
HIV	human immunodeficiency virus
HR	heart rate
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
MI	myocardial infarction
NOAEL	no observed adverse effect level
OCT	optical coherence tomography
OTC	over-the-counter
PBL	peripheral blood lymphocyte
PFT	pulmonary function test
PG	pyoderma gangrenosum
PGA	Physicians Global Assessments
PI	Principal Investigator
PPD	A CRO responsible for SAE processing in this study
PPD PVG	A Pharmacovigilance department of PPD
PRO	patient reported outcome
PV	pharmacovigilance
q.d.	quaque die (once daily)
SAP	statistical analysis plan
S1P	sphingosine 1-phosphate receptor
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
sec	second
SOP(s)	standard operating procedure(s)
$t_{1/2}$	elimination half-life
t_{max}	the median time to reach maximum plasma concentration
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
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

Etrasimod (APD334) is an orally available, selective, sphingosine 1-phosphate (S1P) receptor agonist. S1P is a signaling sphingolipid required by lymphocytes to exit the lymphoid tissue and enter the bloodstream via a chemotactic gradient. 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].

PG is considered to be a rare disorder associated with inflammation, mainly characterized by large skin ulcers [2, 3]. The ulcers are known to break down at a rapid rate and are painful, often turning necrotic [6]. Other inflammatory diseases such as inflammatory bowel disorder (IBD), ulcerative colitis (UC) and Bechet's disease are indicated to share the same clinicopathophysiology [7]. PG was considered to have a parallel relationship with other underlying diseases (e.g., UC, IBD) with PG being the cutaneous manifestation [8], however this was refuted by Driesch [9] and published data support consideration of PG as an independent disease, irrespective of underlying disorders.

Based upon U.S. Department of Health and Human Services' National Institutes of Health's Office of Rare Disease Research, the incidence of PG has been estimated that each year in the United States, 1 person per 100,000 people is affected [10]. The incidence peak occurs between the ages of 20 to 50 years, with women being more often affected than men [11].

Diagnosis of PG is reliant on clinical signs, exclusion principle and supported by histopathology of the biopsy [11, 12]. The histopathology can differ dependent on the timing (early stage-mild to moderate perivascular lymphocytic infiltrate; late-stage necrosis with dense lymphocytic infiltration along with involvement of blood vessels) and site of biopsy[6]. The diagnosis using clinical signs alone has been shown historically to lead to misdiagnoses as PG for at least 6 categories including vascular occlusive or venous disease, vasculitis, cancer, infectious disease, exogenous tissue injury and drug reactions [12], and support of exclusion and histopathology is recommended for diagnosis.

Treatment options

The best documented treatments are systemic corticosteroids and cyclosporin A. Combinations of steroids with cytotoxic drugs are used in resistant cases. The combination of steroids with sulfa drugs or immunosuppressants has been used as steroid-sparing modalities. In some cases, anti-TNF therapy was reported to be beneficial which suggests that inhibition of TNF may help.

Gevokizumab is a potent IL-1 beta monoclonal antibody with unique allosteric modulating properties and has the potential to treat patients with a wide variety of inflammatory and other diseases. Gevokizumab binds strongly to interleukin-1 beta (IL-1 beta), a pro-inflammatory cytokine, and modulates the cellular signaling events that produce inflammation. This agent was being developed as a potential treatment for PG but development was discontinued in 2016.

In addition, results from studies for canakinumab, another anti IL-1β biologic, have been published for this drug [13].

[redacted] 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 [14].

The availability of lymphocyte trafficking agents such as etrasimod would offer patients an additional, oral treatment for PG.

1.1 Background Information

1.1.1 Rationale for Proposed Clinical Study

Agonists of the $S1P_1$ receptor block lymphocyte migration out of the lymph tissue through internalization of the receptor, resulting in a sequestration of lymphocytes [15]. Recent clinical development of $S1P_1$ receptor 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 for the treatment of multiple sclerosis [16]. 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 [17]. 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 [18]. Importantly, a recent report demonstrating $S1P_4$ agonists inhibition of plasmacytoid dendritic cell activation and interferon-alpha production suggest a potential therapeutic role for $S1P_1$/$S1P_4$ agonists like etrasimod in paradoxical psoriasis [19].

In addition to the potential anti-inflammatory benefits of systemic lymphocyte immunomodulation, S1P is known to exert anti-proliferative effects in human keratinocytes [20], and inhibits dendritic cell migration [21]. Thus, the potential role of S1P receptor modulation in skin–EIMs of IBD might involve both systemic and local epidermal mechanisms.

Histopathology of ulcerative PG is characterized by a dense dermal infiltrate composed mainly of neutrophils in biopsy from the central area of ulceration, and a mainly lymphocytic infiltrate with thrombosis of vessels and extravasated erythrocytes in biopsy from the border of the ulcer [2]. In patients with ulcerative PG the number of T-lymphocytes are significantly higher at the wound edge compared to the wound bed. In contrast, neutrophils were significantly more numerous in the wound bed than the wound edge [3]. This suggests that activated T-lymphocytes at the wound edge could promote ulcer formation. Further support for T-cell involvement in the disease comes from observations in PG patients that are characterized by an over-expression in the blood of

the CD4+CCR5+ and CD4+CCR6+ and a down-regulation of CD4+CCR4+ counts with respect to healthy subjects [4].

In addition, a differentiated profile for etrasimod compared to other S1P modulators for the treatment of PG could arise from the hypothesis that $S1P_4$ as well as $S1P_1$ receptor modulation could aid in neutrophil trafficking [5].

Together, this evidence suggests that T-lymphocytes can play a role in PG and that reduction of lymphocytes by $S1P_1$ receptor modulators like etrasimod may represent a novel therapeutic approach in PG.

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

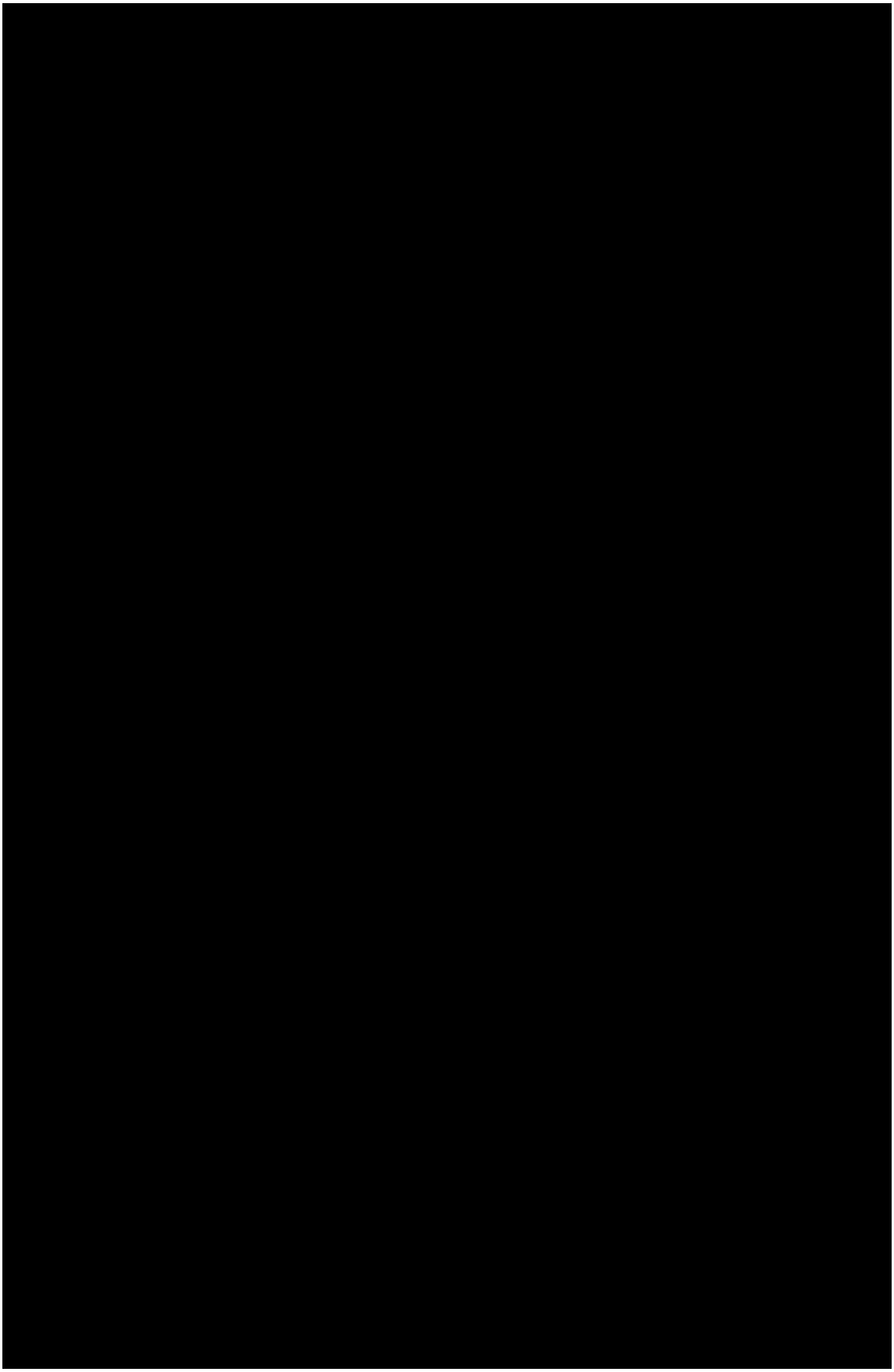
1.1.2 Summary of Preclinical Data

1.1.2.1 Pharmacology

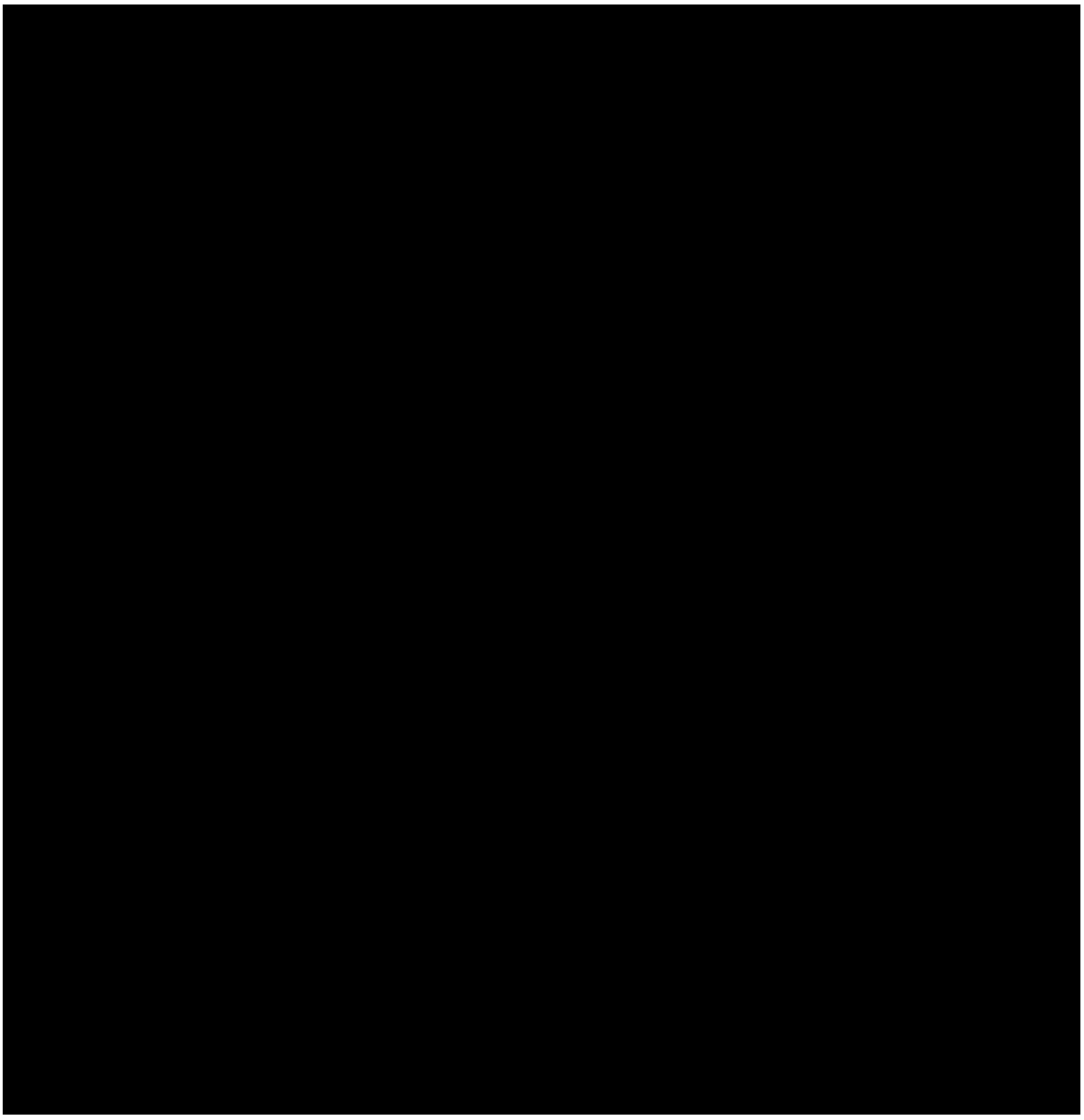
[redacted]

1.1.2.2 Nonclinical Safety

[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 Harmonization (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) 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 IEC and written approval from the Chair or designated deputy of the IEC is required before clinical activities of the study can commence.

The 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 participants
- Changes increasing the risk to participants 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 participants during 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 IEC approval before implementation except when changes to the protocol are required immediately to eliminate hazards to the volunteer or when the changes involve only logistical or administrative aspects of the trial (for example, change of medical monitor, change in telephone number, etc.).

2 STUDY OBJECTIVES

2.1 Objectives

Efficacy

- To evaluate the efficacy of etrasimod (APD334) in patients with PG over a 12-week treatment period.

Safety

- To assess the safety and tolerability of etrasimod (APD334) in patients with PG over a 12-week treatment period.

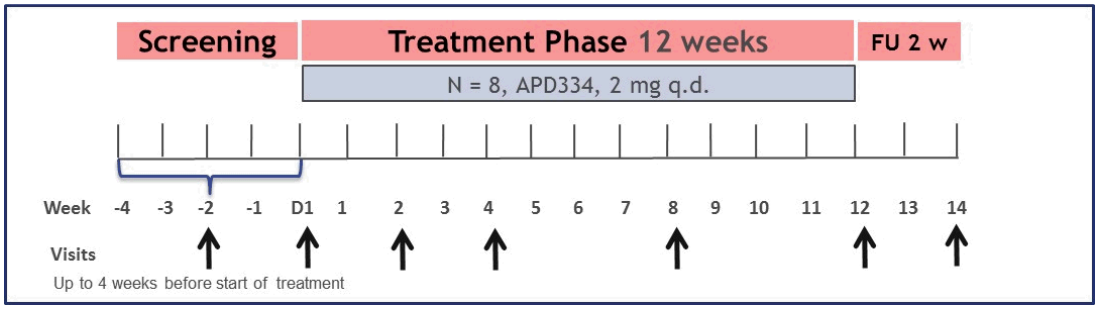
3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2a, open label, proof-of-concept clinical study to assess the efficacy and safety of etrasimod (APD334) in patients with PG. The trial will include adult patients, 18-80 years of age with active PG ulcers.

All visits in the study are ambulatory visits. The screening period will last up to 4 weeks and will be followed by a 12-week treatment period. During the treatment period, patients will need to take 1 tablet of study medication once per day. The last dose is planned to be taken one day before the end of the treatment period at Week 12. A follow-up visit will take place 2 weeks after the end of treatment.

Figure 1 Study Design



The study will consist of the following periods:

Screening Period (up to 4 weeks before baseline visit):

Each patient will be asked to visit the study site for screening assessments within 4 weeks prior to the planned start of the treatment (Day 1). All patients must be consented before any study specific procedure is performed and written informed consent must be obtained. Patients will then undergo screening procedures to determine eligibility.

[redacted]

Treatment Visits:

Baseline Visit (Day 1): Patients will return to the study site to receive the first dose of the study medication. Patients should be instructed to take their tablet as a first thing in the morning on an empty stomach. Patients should be advised not to crush, break, chew, or dissolve the tablet and to take study medication with water. The patients will remain at the study site for at least 6 hours for safety evaluation (please refer to the [redacted]

Visits Week 2, Week 4, Week 8, and Week 12: Patients will return to the study site and perform all planned examinations as described in [redacted] Last dose of study medication is planned 1 day before the end of the treatment visit at Week 12.

Follow up Visit/End of Study Visit:

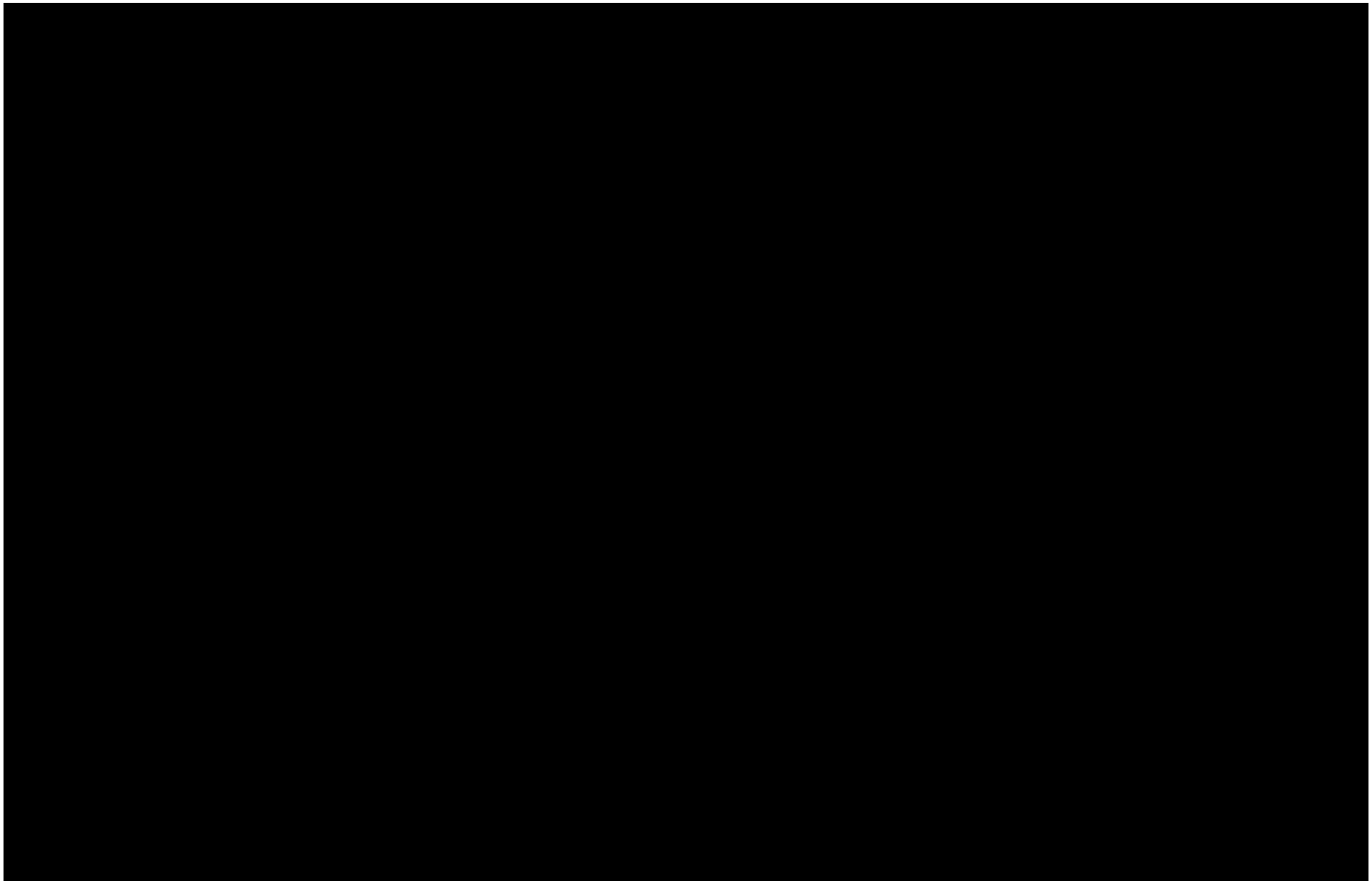
Visit Week 14, 2 weeks after end of treatment: Patients will return to the study site for the final visit, and final procedures will be performed per [redacted]

Premature Discontinuation: All procedures planned for Week 12 visit should be performed for all patients that discontinue the study prematurely.

3.2 Study Duration and Dates

The study duration will be up to 18 weeks per patient. This will include 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.

[redacted]



4 STUDY POPULATION

The study population will consist of eight (8) patients with PG who fulfill eligibility (inclusion & exclusion) criteria.

4.1 Inclusion and Exclusion Criteria

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

4.1.1 Inclusion Criteria

1. Male or female of age 18 to 80 years (inclusive) at the time of screening.
2. Able to provide a signed informed consent prior to any study related procedure being conducted and willing and able to comply with the study requirements.
3. Diagnosis of PG with active, non-healing ulcer.
4. Considered to be in stable health in the opinion of the investigator as determined by:

    a.) A screening physical examination with no clinically significant abnormalities unrelated to PG.

    b.) Vital signs at screening: pulse rate ≥ 55 bpm, systolic blood pressure (SBP) ≥ 90 mmHg, and diastolic blood pressure (DBP) ≥ 55 mmHg.

    c.) Liver function tests (alanine aminotransferase [ALT]/aspartate aminotransferase [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 with exemption to leucopenia and lymphopenia – please refer to exclusion criterion #24.

    e.) No clinical abnormalities noted in the12-lead ECG in the opinion of the investigator (Refer also to exclusion criterion #13).

    f.) No evidence of macular edema in an ophthalmology evaluation (performed by an ophthalmologist), supported with optical coherence tomography (OCT), where available (dependent on site capability) no later than 3 months prior to screening.

5. Eligible male and female patients must agree not to participate in a conception process (i.e. active attempt to let female partner to become pregnant or to impregnate, sperm donation, oocyte donation, in vitro fertilization) for at least 30 days after the last dose of study drug.

Female patients who are sexually active with non-sterile male partner 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.) one of the following:

- either 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 methods are <u>not acceptable</u>

- or surgically sterile (surgical sterility prior to screening for at least 6 months for tubal ligation performed laparoscopically, hysterectomy and/or bilateral oophorectomy)
- or postmenopausal (at least 2 years without menses)
- or agree to continue to use an accepted method of birth control. Patients should be consistently using the hormonal contraceptive for at least 1 month (30 days) prior to screening, during the study 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)

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

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 alone or double barrier and use of spermicide are not an acceptable method of contraception for this study.

4.1.2 Exclusion criteria

1. Clinically significant infection (e.g., pneumonia, pyelonephritis) as judged by the investigator with an end date less than 6-weeks prior to treatment start (Day 1). In case of infection requiring hospitalization or intravenous antimicrobial therapy, or opportunistic infection, this infection must have ended at least 8 weeks prior to Day 1.

2. Infection with hepatitis C virus anytime in the past; confirmed active infection with hepatitis B virus at screening.
3. History of severe renal or severe hepatic impairment.
4. Current active or latent tuberculosis (TB), regardless of treatment history or history of TB that has not been successfully treated
5. A positive diagnostic TB test at screening defined as a positive QuantiFERON® test or 2 successive indeterminate QuantiFERON® tests
6. Exposure to B-cell or T-cell targeted therapies (such as natalizumab, rituximab, abatacept) within 5 half-lives prior to Day 1.
7. Other immunosuppressive, immunomodulating or antineoplastic agents not listed in Section 6.13.1 or not meeting the stability time period for concomitant medications indicated as permitted in Section 6.13.
8. Receipt of any investigational agent within 30 days or 5 half-lives (whichever is longer), prior to Day 1.
9. Use of moderate to strong inhibitors of CYP2C9 (e.g., amiodarone, felbamate, fluconazole, miconazole, piperine).
10. Abnormal forced expiratory volume (FEV_1) or forced vital capacity (FVC) i.e., < 80% of predicted values at screening.
11. Any known history of congenital or acquired immuno-deficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection [ELISA and Western blot] test result, organ transplantation).
12. Recent history (within 6 months of screening assessments) of cardio- or cerebrovascular disease, acute coronary syndrome (ACS), myocardial infarction (MI), unstable angina, cerebro-vascular accident, including transient ischemic attack (TIA).
13. History or presence 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 or Class III anti arrhythmic agents, or baseline QTc ≥ 500 msec.
14. Congestive heart failure (NYHA III or NYHA IV).
15. Any surgical procedure requiring general anesthesia within 30 days prior to Day 1 or plans to undergo major surgery during the study period.
16. History of retinal macular edema.
17. History of or signs and symptoms of progressive multifocal leukoencephalopathy (PML) as assessed by the PML checklist at screening.
18. History of more than one episode of herpes zoster or any episode of disseminated zoster.
19. Patients without documented positive varicella zoster virus (VZV) IgG-antibody status or patients who have not completed VZV vaccination within 6 weeks prior to Day 1.
20. Receipt of live vaccine within 6 weeks prior to Day 1.

21. History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma.
22. History of malignancy except for adequately treated basal cell skin cancer and in situ carcinoma of the cervix of the uterus that have been completely excised with documented, clear margins.
23. History of severe allergic or anaphylactic reactions requiring medical attention.
24. Leukopenia or lymphopenia at screening;
25. Current or recent history (within 1 year prior to Day 1) of alcohol dependence or illicit drug use.
26. Active psychiatric problems that, in the investigator’s opinion, may interfere with compliance with the study procedures.
27. History of any other clinically significant medical condition that, in the investigator's opinion, would preclude patient from safe participation in the study.
28. Inability to attend all the study visits or comply with study procedures.
29. Prior exposure to etrasimod (APD334) or prior participation in any study of etrasimod (APD334).

5 STUDY TREATMENT(S)

5.1 Study Drug

Etrasimod is an investigational product and will be provided by the Sponsor for the study. Etrasimod will be supplied as 2 mg immediate release tablets, packaged in high-density polyethylene bottles with child-resistant screw caps. [redacted]

Bottles should be stored at [redacted] °C ([redacted] ºF); excursions are permitted from [redacted] °C to [redacted] °C, until medication is dispensed.

5.2 Dosage, Administration and Accountability

Investigational product will be dispensed to the patients under the supervision of the investigator or his/her designee. Patients should be instructed to take their tablet **as a first thing** in the morning on an empty stomach. Patients should be advised not to crush, break, chew, or dissolve the tablet and to take study medication with water.

Investigational product will be dispensed as follows:

- 1 bottle of 40 tablets at Day 1. Patient will be requested to bring the bottle back for drug accountability on Week 2; patient will return the bottle with all remaining tablets at Week 4.
- 1 bottle of 40 tablets at Week 4. Patient will return the bottle with all remaining tablets at Week 8.
- 1 bottle of 40 tablets at Week 8. Patient will return the bottle with all remaining tablets at Week 12.

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.

Investigational product accountability will be performed by the site at Week 2, Week 4, Week 8 and Week 12.

Reasons for deviation from the expected dispensing regimen must also be recorded. Study medication will be reconciled by the Arena Pharmaceuticals 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.

5.3 Investigational Product Retention at Study Site

At completion of the study, all study medication will be reconciled by the Arena Pharmaceuticals monitor or contracted designee, and then returned at the direction of the Arena Pharmaceuticals 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 Pharmaceuticals (or contracted CRO) for approval of such action.

6 STUDY PROCEDURES

6.1 Informed Consent

Prior to undergoing any study specific procedures, each subject must sign a written Informed Consent Form (ICF) that has been approved by the investigator's designated Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and by the Sponsor. All patients will be informed 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 signed ICF should be included in the patient's medical record, that should also contain written documentation indicating that informed consent was obtained. Study procedures will be conducted only after a written informed consent has been obtained and documented appropriately in the source data.

6.2 Medical History

A complete medical history will be collected at screening. Concomitant medications, recent illnesses, and participation in other investigational drug studies will also be recorded. The examinations will be performed as outlined in [redacted]

6.3 Physical, Ophthalmological and Neurological Examinations

6.3.1 Physical Examination

The examinations will be performed as outlined in [redacted] The physical examination will be performed by the investigator. It will 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. Height will only be obtained at screening.

6.3.2 Ophthalmological Examination

This examination will include visual acuity and dilated ophthalmoscopy (by an ophthalmologist) and with OCT (where available) to rule out and monitor for any significant retinal disease, including macular edema. Retinal photos will be taken. The examinations will be performed as outlined in [redacted]

6.3.3 Neurological Examination

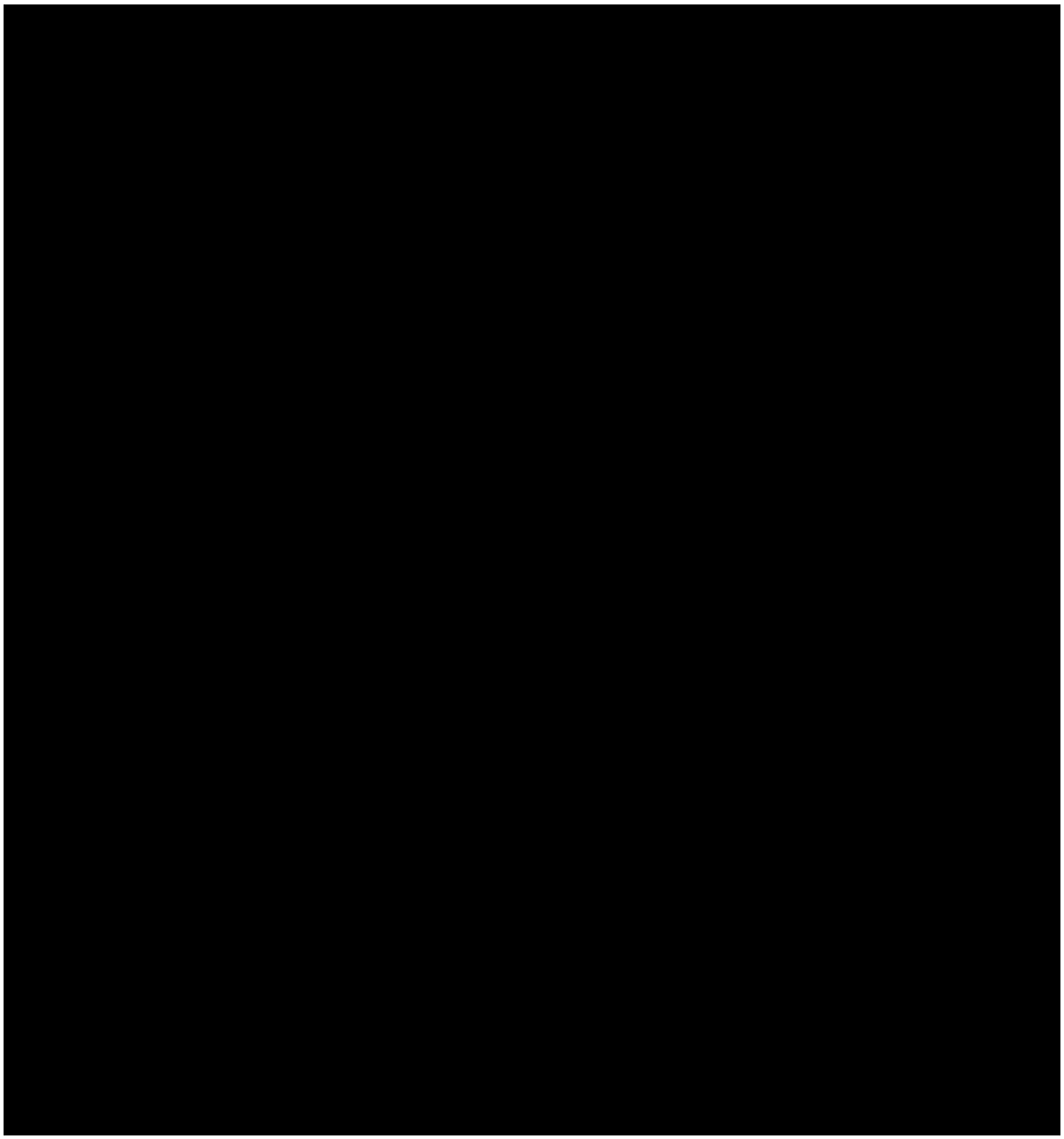
The neurological examination includes assessments of the neurological system (cranial nerves, motor and sensory function, coordination, and mental status). The examinations will be performed as outlined in [redacted] In addition, monitoring for PML, a potential AE of $S1P_1$ agonists, will be performed at each site visit [redacted] using a subjective PML checklist (refer Section 6.12.1.1).

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 must be referred to a neurologist for a full evaluation. Additional information on PML is provided in Section 6.12.1.1 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 or any other invasive procedure that occurs at the same visit or time point. Vital signs will be measured according to the time points in the



[redacted]

6.6 Tuberculosis Screening

All patients will complete TB screening to determine eligibility. All patients must complete QuantiFERON® Test at screening.

Patients will be excluded from the study participation if they have active or latent TB, regardless of treatment history or a history of TB that has not been successfully treated. Patients will be also excluded from the study participation if they had a positive QuantiFERON® test or 2 successive indeterminate QuantiFERON® tests at screening.

[redacted]

6.8 Clinical Laboratory Tests

The clinical laboratory tests will be performed as outlined in [redacted] Tests will be performed in the local laboratory as per study site standard. In the event of abnormal clinical laboratory values, the physician will make a judgment whether or not the abnormality is clinically significant. If clinically significant, it will be captured and recorded as an AE.

6.8.1 List of Laboratory Parameters

Laboratory tests will include the following:

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)
FSH
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)
Follicle stimulating hormone (FSH)
HIV test
HBsAg
Anti- HCV
VZV IgG
QuantiFERON®

6.8.2 Virology

Evaluation of human immunodeficiency virus (HIV), hepatitis B (hepatitis B surface antigen), hepatitis C virus, and VZV IgG antibody will be performed at screening only.

6.8.3 Urinalysis

Urinalysis will follow the local practice at the study site (as dip-stick). Tests will be performed as outlined in [redacted] Parameters for clinical laboratory tests include the following:

- appearance + color
- specific gravity
- pH
- leukocytes
- protein
- glucose
- nitrites
- ketones
- urobilinogen
- bilirubin
- blood/erythrocytes

Microscopic urinalysis will be performed when there is a positive or abnormal macroscopic urinalysis result as deemed necessary by the investigator.

6.8.4 Sample Collection

All blood and urine samples will be collected according to site standards. Tests will be performed as outlined in [redacted]

6.8.5 Blood Volume

Total blood volume collected for CBC is up to 200 mL during the study.

6.9 Efficacy Assessments

All efficacy assessments are treated as exploratory, this being a proof of concept study.

6.9.1 Patient Global Assessment for Active Skin Manifestation Visual Analog Scale (VAS)

The patient global assessment for active skin manifestation is a tool to capture the disease and pain severity using a visual analogue to mark the patient's score. The assessment sheet asks the patient to rate their disease severity from "not severe" to "extremely severe" and pain levels from "no pain at all' to "worst pain imaginable". This assessment sheet (Appendix 3) will be completed by the patient as per [redacted]

The assessment will be conducted at the study site during the patient's scheduled visits.

6.9.2 Physician Global Assessment for Active Skin Manifestations

The physician's global assessment for active skin manifestations will record the number of ulcers, target lesion noted for endpoint evaluation, diameters of each target lesion and score of evaluation at each visit. The scores range from 0 (total resolution) to 4 (no evidence of healing) (Appendix 2).

This assessment sheet will be completed by the investigator after evaluating the patient's disease as per [redacted]

6.9.3 Dermatology Life Quality Index (DLQI)

DLQI has been developed to use 10 simple questions to assess how much a patient's life is affected through their skin problems (Appendix 4). This assessment sheet will be completed by the patient as per [redacted]

6.9.4 C-reactive Protein (CRP)

Elevation of CRP concentration have been observed in active PG and during subsequent relapses. High CRP levels have been also associated with poor prognosis of PG. Therefore CRP will be measured during the study to monitor potential correlation between the response to therapy and disease activity [29, 30].

6.10 Other Exploratory Assessments

The following exploratory measures will also be assessed as per [redacted]

6.10.1 Skin Punch Biopsies

Histology data will be collected from the lesions via punch biopsies. Skin punch biopsies will be taken only if possible or necessary if deemed by investigator.

6.10.2 Imaging

Digital photos of the **target lesion** will be taken to document visual changes in the lesion.

6.10.3 Surface Area Evaluation

Evaluation of the changes in surface area of the target lesion will be done by the investigator.

6.11 Hematologic Assessments

6.11.1 Complete Blood Count

Blood samples for complete blood count (CBC) with differential and platelet count will be assessed. Tests will be performed as outlined in [redacted]

If the absolute peripheral lymphocyte count has not recovered to at least 80% of the baseline value at the 2-week follow-up (week 14), the patient must return for weekly CBCs until the absolute peripheral lymphocyte count has returned to at least this value.

6.12 Adverse Events Assessments

Patients will be monitored from ICF signature to 2 weeks after the last dose of study drug for 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.

6.12.1 Adverse Event Reporting

Patients will be instructed to report all AEs, which can be reported 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.

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 AE 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.

6.12.1.1 Progressive Multifocal Leukoencephalopathy (PML)

A patient with multiple sclerosis developed PML after nearly 8 months of treatment with another $S1P_1$ agonist [31], 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 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 be administered at each site visit (except D-1) to probe for symptoms suggestive of PML. Any patients reporting signs and/or symptoms of PML will undergo objective testing and must be referred to a neurologist for a full evaluation.

A copy of the PML checklist is provided in Appendix 1.

6.12.2 Serious Adverse Events and Expedited Reporting of Adverse Events

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

- Death
- Is Life-Threatening
- Required/Prolonged Hospitalization
- Disability/Incapacity
- Congenital Anomaly/Birth Defect
- Important Medical Event

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) 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:

EMEA ASIA Safety Central Mailbox: [redacted]

Or alternatively:

PPD Medical Affairs/Pharmacovigilance
PPD PVG Hotline: (United Kingdom number) [redacted]
PPD PVG Fax line: (United Kingdom number) [redacted]

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 Eudralex 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.

6.12.2.1 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 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.

6.12.3 Assessment of Adverse Event Severity

The severity of each AE will be assessed at onset by a nurse and/or physician. When recording the outcome of the AE the maximum severity of the AE experienced will also be recorded. The severity of the AE will be graded according to the CTCAE v4.03 [32] 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:

*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.

6.12.4 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, WHO 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. Re-challenge 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.

6.12.5 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

6.12.6 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

6.12.7 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

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

AEs 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 Concomitant Medications and Procedures

All medications (over the counter [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 case report form (CRF) with start date/time and stop date/time, if known.

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.

6.13.1 Permitted medications for the treatment of pyoderma gangrenosum and associated conditions

The following concomitant medication are allowed provided that the dose has been stable for at least 2 weeks prior to baseline and remain stable throughout the study:

- Oral corticosteroids (maximal allowed prednisone ≤20mg/day, or equivalent)
- TNF-alpha inhibitor (etanercept, infliximab, adalimumab or other)
- Oral 5-ASA medication (for patients with ulcerative colitis)
- Antidiarrheal treatment
- OTC analgesics (paracetamol / acetaminophen, NSAIDs)

In addition, topical medication (other than excluded medication) that the patient is receiving at baseline should be continued, provided that these are stable for 2 weeks prior to baseline and should remain stable throughout the study.

Only non-sticking dressing of the wounds (e.g., jelonet and compression bandages) could be used throughout the study period.

6.13.2 Excluded Medications

The following medications are excluded prior or during the study:

- Exposure to B-cell or T-cell targeted therapies (such as natalizumab, rituximab, abatacept) within 5 half-lives prior to Day 1
- Other immunosuppressive, immunomodulating or antineoplastic agents or other monoclonal antibody / biologic not listed in the Permitted Medications within 5-half-lives prior to Day 1 (small molecules) or 60 days prior to D1 (biologics).
- All live vaccines within 6 weeks prior to Day 1, during study treatment and for at least 6 months after the last dose of study drug
- Moderate to strong inhibitors of CYP2C9 (e.g., amiodarone, felbamate, fluconazole, miconazole, piperine). within 5-half-lives prior to Day 1, during the study and for 2 weeks after the last intake of study medication
- Other routes for systemic corticosteroids (IM and IV)
- Class Ia or Class III anti-arrhythmic agents
- Any other medication which in the opinion of the investigator would affect the suitability of the patient to continue in the study, interfere with interpretation of study results or affect compliance with the protocol requirements
- Receipt of any investigational agent within 30 days or 5 half-lives (whichever is longer), prior to Day 1.

6.14 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 <u>immediately</u>.

The study may be terminated early if, in the opinion of the sponsor, investigator, or 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 (<80%).
- An AE.
- Lost to follow up.

6.14.1 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. If consented by the patient, effort will be made to conduct a follow-up visit within 2 weeks of discontinuation [redacted] if the patient has received at least 1 dose of the study drug.

6.14.2 Replacements

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

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 DATA MANAGEMENT

7.1 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 standards, if applicable.

7.2 Data Coding

7.2.1 Adverse Events

AEs 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'.

7.2.2 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.

7.2.3 Medical History

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

8 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 SAP, the changes will be listed along with an explanation as to why they occurred in the Clinical Study Report.

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.

8.1 Hypotheses and Objectives

8.1.1 Objectives

8.1.1.1 Efficacy Objective

To evaluate the efficacy of etrasimod in patients with PG over a 12-week treatment period.

8.1.1.2 Safety Objective

To assess the safety and tolerability of etrasimod in patients with PG over a 12-week treatment period.

8.1.2 Hypotheses

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

8.2 Sample Size and Power Calculations

There is no formal sample size estimation for this proof-of-concept open label study. A sample size of 8 subjects is reasonable to assess proof-of-concept of the efficacy of etrasimod in the target population.

8.3 Analysis Populations

Efficacy endpoints will be analyzed in enrolled patients who have baseline and at least 1 post-baseline measure.

Safety endpoints will be analyzed in enrolled patients who received at least 1 dose of the study drug.

8.4 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.

8.5 Efficacy Endpoints

As this is proof-of-concept study all endpoints will be exploratory. The efficacy endpoints will be as follows:

- change from baseline (Day 1 pre-dose) to Week 12 in Physician Global Assessments for active skin manifestations.

  Assessment of target lesion/ulceration
  0: *Total resolution of target ulcer with no signs of active PG*
  1: *almost completely healed target ulcer with only minimal signs of active PG*
  2: *Evidence of target ulcer healing which involves at least 50% of ulcer/ulcer margin*
  3: *Evidence of target ulcer healing which involves less than 50% of ulcer/ulcer margin*
  4: *No evidence of target ulcer healing*
- change from baseline (Day 1 pre-dose) to Week 12 in Patient Global Assessments for active skin manifestations: Visual Analog Scale (VAS) for assessment of severity of the disease and severity of pain by patient.
- change from baseline (Day 1 pre-dose) to Week 12 in Dermatology Life Quality Index (DLQI) (to measure how much a patient's life is affected through their skin problems)
- change from baseline (Day 1 pre-dose) to Week 12 in CRP levels

In addition, the following measures will be assessed as per Schedule of Procedures and Visits:

- Imaging (digital photos) of the target lesion.
- Evaluation of the changes in surface area of target lesion.
- Skin punch biopsies (if performed).

8.6 Statistical Methods

8.6.1 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.

8.6.2 Subgroup Analyses

Not planned.

8.7 Safety Analysis

Safety and tolerability will be assessed by a review of all safety parameters including AEs, laboratory safety parameters, vital signs, and ECG. AEs 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.

8.7.1 Adverse Events

AEs will be coded using the most current 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 CTCAE v4.03; 14Jun2010 definitions [32]). TEAEs will be classified according to system organ class.

8.7.2 Physical Examinations

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

8.7.3 Concomitant Medication

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

8.7.4 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.

8.7.5 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 hematological parameters (e.g. lymphocytes) or other parameters. 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]

[redacted]

9 REGULATORY REQUIREMENTS

9.1 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)
- Curriculum vitae of the PI and sub-investigators, updated within last 2 years
- Current medical licenses for the PI and all sub-investigators
- Financial disclosure form signed by the PI and all sub-investigators listed on the FDA Form 1572
- Copy of the IEC (HREC) approval letter for the study and approved ICF
- IEC (HREC) Membership List
- Copy of the Regulatory Authority approval (if applicable as per local guidelines)

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

9.2 Investigator Obligations

The PI is responsible for ensuring that all study site personnel, including sub-investigators and other study staff members, adhere to all 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.

9.3 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.

9.4 Informed Consent

According to ICH Guideline E6, "Good Clinical Practice: Consolidated Guidance", 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 informed consent should include all the elements outlined in Section 4.8.10 of ICH Guideline E6.

9.5 Independent Ethics Committee (IEC) Human Research Ethics Committee (HREC)

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

10 PROTOCOL MANAGEMENT AND ADMINISTRATIVE CONSIDERATIONS

10.1 Study Documentation

The PI and study staff have the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by the sponsor, representatives of the sponsor, the 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 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 at least 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.

10.2 Protocol Interpretation and Compliance

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

10.3 Study Monitoring

The sponsor or a contracted monitor will visit the study center periodically to monitor adherence to the protocol, compliance with ICH guidelines, adherence to applicable 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.

11 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study as outlined in the protocol entitled "A Phase 2a, Open-label, Proof of Concept Study to Determine the Efficacy and Safety of Etrasimod (APD334) in Patients with Pyoderma Gangrenosum" in accordance with regulatory guidelines, ICH GCP Guidelines and the Declaration of Helsinki; 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 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 IEC.
- Submission of any proposed change in the protocol to the 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 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 IEC within 15 calendar days of their disclosure.
- Submission of timely progress reports to the IEC and sponsor at appropriate intervals on a schedule determined by the 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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SPONSOR PROTOCOL SIGNATURE PAGE

Protocol Title: A Phase 2a, Open-label, Proof of Concept Study to Determine the Efficacy and Safety of Etrasimod (APD334) in Patients with Pyoderma Gangrenosum.

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: APD334-011

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.

Version 1, 20 October 2016

Appendix 2 Physician Global Assessment for Active Skin Manifestations

Pyoderma Gangrenosum Patients

Patients Name:
Study Subject Number:

Number of Ulcers
Please indicate number of ulcers at indicated week

Week	Number of Ulcers
Week 0	
Week 1	
Week 2	
Week 4	
Week 8	
Week 12	

Target Lesion / Ulceration of Pyoderma Gangrenosum
At the beginning of the study, the largest (or one of the largest) lesion is going to be designated "target lesion". A digital photograph with a ruler next to the lesion has to be taken.

Place of target lesion:

Week	Diameter of target Lesion / Ulceration in cm (longest distance)	Assessment of target Lesion / Ulceration	Date and Signature of Investigator
Week 0			
Week 1			
Week 2			
Week 4			
Week 8			
Week 12			

Assessment of target lesion / Ulceration
0: Total resolution of target ulcer with no signs of active PG
1: Almost completely healed target ulcer with only minimal signs of active PG
2: Evidence of target ulcer healing which involves at least 50% of ulcer/ulcer margin
3: Evidence of target ulcer healing which involves less than 50% of ulcer/ulcer margin
4: No evidence of target ulcer healing

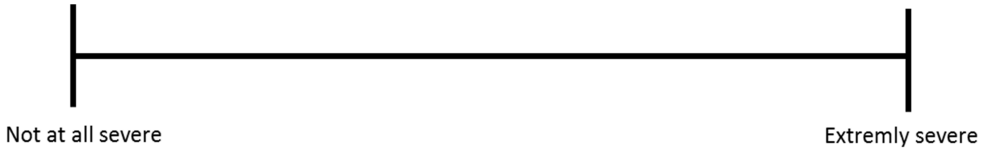
Version 3.0 – 04 January 2017

Appendix 3 Patients Global Assessment for Active Skin Disease VAS (Visual Analogue Scale)

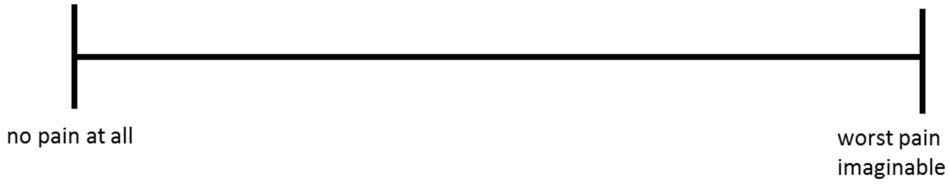
Patient Name:

- Please judge the questions below regarding the past one week
- Please note your answer with a vertical mark (I) on the line below

How do you rate the severity of your skin disease?



How severe is your pain?



(Visual Analogue Scale has to be exactly 10 cm in the print out.)

Version 1.0 – 09 November 2016

Appendix 4 Dermatology Life Quality Index (DLQI) form

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

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: Medical Director Safety / Pharmacovigilance
Date: Wednesday, 08 February 2017, 10:34 AM Pacific Daylight Time
Meaning: Author Approval
==========

UserName: [redacted]
Title:
Date: Thursday, 09 February 2017, 12:08 AM Pacific Daylight Time
Meaning: Approval
==========

UserName: [redacted]
Title: VP, Clinical Development
Date: Thursday, 09 February 2017, 02:59 AM Pacific Daylight Time
Meaning: Approval
==========

UserName: [redacted]
Title: Vice President, Regulatory Affairs and Quality
Date: Thursday, 09 February 2017, 05:52 AM Pacific Daylight Time
Meaning: Approval
==========

UserName: [redacted]
Title: Biostatistician/SAS Programmer
Date: Thursday, 09 February 2017, 06:51 AM Pacific Daylight Time
Meaning: Approval
==========