A PHASE 2B RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL ADAPTIVE 2-STAGE, MULTI-CENTRE STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ORAL PTG-100 INDUCTION IN SUBJECTS WITH MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS

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for

Protagonist Therapeutics, Inc.
7707 Gateway Boulevard, Suite 140
Newark, California 94560

by

Covance Early Clinical Segment
3402 Kinsman Boulevard
Madison, Wisconsin 53704

STUDY IDENTIFICATION

Sponsor	Protagonist Therapeutics, Inc. +1 (510) 474-0170 (Main Telephone No.)
Sponsor's Study Contact	Lucio A. D. Tozzi +1 (510) 474-0899 (Office Telephone No.)
Sponsor's Medical Monitor	Bittoo Kanwar, MD +1 (510) 474-0854 (Office Telephone No.)

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	anti-drug antibody
ADRC	Adaptive Design Review Committee
AE	adverse event
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of the last sample collection
BP	blood pressure
CD	Crohn's disease
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
C_{trough}	trough (predose) concentration
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
FACS	fluorescence-activated cell sorter
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HCV	Hepatitis C Virus
HIV	human immunodeficiency virus
IA	interim analysis
IB	Investigator's Brochure
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IV	intravenous
IXRS	interactive web/voice response system
JCV	John Cunningham virus
LTBI	latent tuberculosis infection
MAD	multiple ascending dose
MAdCAM-1	mucosal addressin cell adhesion molecule 1

NOAEL	no observed adverse effect level
NOEL	no observed effect level
PB	phosphate buffer
PD	pharmacodynamic
PGA	physician's global assessment
PK	pharmacokinetic
PML	progressive multifocal encephalopathy
QD	once daily
RBC	red blood cell
RE	receptor expression
RO	receptor occupancy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOP	standard operating procedure
TB	tuberculosis
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{max}	time of maximum observed concentration
TNF-α	tumour necrosis factor-alpha
UA	urinalysis
UC	ulcerative colitis
ULN	upper limit of normal
US(A)	United States (of America)
WBC	white blood cell
WOCBP	women of childbearing potential

1 SYNOPSIS

Title of Study:	A Phase 2b Randomised, Double-blind, Placebo-controlled, Parallel Adaptive 2-stage, Multi-centre Study to Evaluate the Safety and Efficacy of Oral PTG-100 Induction in Subjects with Moderate to Severe Active Ulcerative Colitis
Study Phase:	Phase 2b
Indication:	Ulcerative colitis (UC)
Objectives:	The primary objectives of this study are: 1. To evaluate the safety and tolerability of PTG-100 2. To evaluate the efficacy of PTG-100 in the induction treatment of subjects with moderate to severe active UC compared to placebo. The secondary objectives are: 1. To evaluate the dose-response relationship and select PTG-100 induction regimens for continued development 2. To evaluate the pharmacokinetics (PK) of PTG-100 in subjects with active UC 3. To evaluate the pharmacodynamic (PD) effects of PTG-100 including the assessment of receptor occupancy (RO) and α4β7 receptor expression (RE) in peripheral blood lymphocytes 4. To evaluate changes in faecal calprotectin levels for subjects receiving PTG-100 compared to placebo 5. To evaluate the incidence of positive anti-drug antibodies (ADAs) in subjects receiving PTG-100. The exploratory objectives are: 1. To evaluate the ability of subjects receiving PTG-100 to achieve histological improvement in colonic tissue biopsies compared to placebo 2. To characterise immunologic biomarkers in the target population and to evaluate changes in immunological/PD biomarkers in subjects receiving PTG-100 compared to placebo.
Methodology/Study Design:	This will be a randomised, double-blind, placebo-controlled, multi-centre, parallel adaptive 2-stage design study. Subjects will be screened for eligibility within 42 days of dosing. Eligible subjects will return for sigmoidoscopy/ biopsy and baseline Mayo Score within 14 days of randomisation (with all attempts made for this visit to occur as close to randomisation as possible; however, subjects may have a combined Screening visit that includes endoscopy). Randomisation must occur within 7 days of dosing. On Day 0, assessments including physical examination, safety labs, electrocardiogram (ECG), progressive multifocal encephalopathy (PML) assessment, PK, PD, ADA, faecal calprotectin, and Inflammatory Bowel Disease Questionnaire (IBDQ) will be performed predose followed by dosing and physical examination, adverse event (AE) assessment, and blood sampling for PK and PD analysis. Treatment duration will be 12 weeks in order to optimise duration of induction dosing for continued development. There will be a total of 9 visits to the clinical site, including: 2 Screening visits (one for general inclusion/exclusion criteria assessment and a second including recording baseline Mayo scoring and sigmoidoscopy/ biopsy, with the latter occurring within 14 days of randomisation;

	Day -42 to Day -7; however, subjects may have a combined Screening visit that includes endoscopy); dose initiation (Day 0); and assessment visits on Days 14, 28, 42, 56, and 84. Post-treatment sigmoidoscopy/biopsy will be performed on Day 84 (Week 12). Day 70 will be a phone visit in which subjects will be instructed to record the stool frequency and rectal bleeding data preceding Day 70. A final Follow-up visit will occur on Day 112 and a phone call for assessing PML signs and symptoms will occur approximately 6 months after the completion of treatment (or 6 months after discontinuation of treatment if the subject terminates early). Subjects are to be randomised 1:1:1:1 by interactive web/voice response system (IXRS) in Stage 1. Subjects will be stratified by prior treatment with tumour necrosis factor-alpha (TNF-α) antagonist use. Subject enrolment will occur in 2 stages relative to an interim analysis (IA), the purpose of which will be to conduct a futility analysis and to identify which study arms provide optimal data in order to select one (or 2) PTG-100 dose levels and placebo to continue enrolling subjects to the most informative and effective dose arms. After the unblinded IA (Stage 1, see below) by the Adaptive Design Review Committee, additional subjects will be randomised equally (1:1 or 1:1:1, as appropriate) to the selected doses of PTG-100 and placebo with stratification maintained (Stage 2). The IA will be performed after approximately 60 to 80 subjects have been dosed and completed 12 weeks of dosing or terminated early (Stage 1). The IA guidelines for dose selection will be defined in the Data Monitoring Committee charter and will be made in consideration of safety data and sound clinical judgment. Subjects will continue to be randomised across the 4 arms during the IA until dose(s) are selected for Stage 2 of the trial, at which time the randomisation of remaining subjects to be enrolled will be modified to the remaining trial arms. Final analyses will combine all observed data from both stages of the trial. It should be noted that for subjects in the Netherlands, only subjects who have had prior exposure to anti-TNF agents will be allowed to enrol in the study.
Number of Subjects:	It is anticipated that approximately 240 male and non-gravid female subjects aged 18 to 80 years with moderate to severe active UC will be randomised. No study-site target enrolment numbers will be set so as to allow for competitive enrolment among sites.
Number of Study Sites:	Approximately 100 to 120 sites worldwide.
Criteria for Inclusion:	The following are the inclusion criteria. Subjects must meet ALL of the following inclusion criteria to be enrolled. Subjects may be screened up to 3 different times separated by at least 14 days. 1. Male and female subjects aged 18 to 80 years, inclusive. 2. Diagnosis of UC for ≥ 2 months prior to screening, with a history of disease activity extending beyond the rectum; if the UC has been present for > 10 years, a total colonoscopy with biopsy must have been performed within 2 years of screening to rule out dysplasia. Subjects with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance per local standards and guidelines (may be performed during screening). Subjects with extensive colitis or pancolitis of > 8 years duration must have documented evidence that a surveillance colonoscopy was performed within 12

	months of the initial Screening visit (may be performed during screening). 3. Moderate to severe active UC as defined by complete Mayo Score of 6 to 12, inclusive (range 0 to 12), at baseline (pre-randomisation) with endoscopy score of at least 2 (range 0 to 3), extending 15 cm or more from the anal verge, as determined by blinded central read, within 14 days of randomisation. 4. Demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents as defined below: a. Immunomodulators i. Signs and symptoms of persistently active disease despite a history of at least one ≥ 8-week regimen of oral azathioprine (≥ 1.5 mg/kg) or 6-mercaptopurine (6-MP) (≥ 0.75 mg/kg), OR ii. History of intolerance of at least 1 immunomodulator (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopaenia, thiopurine S-methyltransferase genetic mutation, and/or infection) b. TNF-α antagonists i. Signs and symptoms of persistently active disease despite a history of at least 1 induction regimen of at least 6 weeks duration, OR ii. Recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), OR iii. History of intolerance (including, but not limited to, infusion- or injection-related reaction, demyelination, congestive heart failure, and infection) **Note: A maximum of 50% of randomised subjects may have had prior treatment with TNF-α antagonists.** For subjects in the Netherlands, only subjects who have had prior exposure to anti-TNF agents will be allowed to enrol in the study (as confirmed by medical record documentation or by self-reporting). c. Corticosteroids i. Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or intravenous (IV) for 1 week, OR ii. Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions, OR iii. History of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopaenia/ osteoporosis, hyperglycaemia, insomnia, and infection). 5. Subject is unlikely to conceive, as indicated by at least one "yes" answer to the following criteria: a. Subject is a male

	b. Subject is a surgically sterilised female (at least 90 days prior to Screening) c. Subject is a post-menopausal female ≥ 45 years of age with > 1 year since last menses; if a female subject is < 45 years of age, or cessation of menses is < 1 year and > 6 months, follicle-stimulating hormone must be documented as elevated into the post-menopausal range at Screening d. Subject is a non-sterilised, premenopausal female with a non-sterile male partner and agrees to abstain from heterosexual activity, use adequate hormonal contraception, OR use double barrier contraception (ie, a combination of male condom with either cervical cap, diaphragm, or sponge with spermicide) as per local regulations and guidelines during the study and for 28 days after the last dose of study drug. e. If subject is a non-sterilised, premenopausal female with a sterile male partner, the above requirements for contraception do not apply. 6. For women of childbearing potential, a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of study medication. 7. Subject is eligible according to tuberculosis screening criteria. 8. Subject understands the study procedures and agrees to participate in the study by giving written informed consent. Note: Subjects may be permitted to enrol in the study on stable doses of oral 5-aminosalicylic acid (5-ASA) agents, oral corticosteroids, antidiarrhoeals, azathioprine/ 6-MP, or probiotics according to specifications noted in the protocol.
Exclusion Criteria:	The following are the exclusion criteria; subjects must meet NONE of the following exclusion criteria to be enrolled. <u>*Gastrointestinal exclusion criteria*</u> 1. Subject with Crohn's disease (CD), indeterminate colitis, or presence or history of fistula consistent with CD. 2. History of toxic megacolon, abdominal abscess, symptomatic colonic stricture, or stoma; history of extensive colonic resection, or subtotal or total colectomy; or is at imminent risk of colectomy. 3. History or current evidence of colonic dysplasia or adenomatous colonic polyps. Note: Subjects will not be excluded from the study because of a pathology finding of indefinite dysplasia with reactive atypia. Subjects with resected adenomatous polyps may be enrolled. <u>*Infectious disease exclusion criteria*</u> 4. Current bacterial or parasitic pathogenic enteric infection, including *Clostridium difficile* (confirmed by toxin result), current infection with hepatitis B or C virus (subjects treated for HCV infection must have evidence of sustained virologic response 12 weeks after the end of treatment [SVR12], infection requiring hospitalisation or IV antimicrobial therapy, opportunistic infection within 6 months of dosing, any infection requiring antimicrobial therapy within 2 weeks of dosing, history of more than one episode of herpes zoster, history of infection with human immunodeficiency virus (HIV), or any episode of disseminated zoster. Note: Subjects with a history of *C. difficile* infection

	treated with antibiotics with or without faecal microbial transplant may be rescreened after 2 weeks following completion of treatment. 5. Live virus vaccination within 1 month prior to screening. *General exclusion criteria* 6. Subject has a concurrent clinically significant, unstable, or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, haematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the Investigator, might confound the results of the study or pose additional risk to the subject by their participation in the study. Note: Subjects with a history of uncomplicated kidney stones, childhood asthma, or concurrent stable and well-controlled asthma may be enrolled in the study at the discretion of the Investigator. 7. Known primary or secondary immunodeficiency. 8. History of myocardial infarction, unstable angina, transient ischaemic attack, decompensated heart failure requiring hospitalisation, congestive heart failure (New York Heart Association Class 3 or 4), uncontrolled arrhythmias, cardiac revascularisation, stroke, uncontrolled hypertension (systolic blood pressure [BP] > 160 mmHg or diastolic BP > 100 mmHg at Screening), or uncontrolled diabetes (haemoglobin A1c > 9% or > 1 episode of severe hypoglycaemia) within 6 months of screening. 9. Clinically meaningful laboratory abnormalities at Screening including, but not limited to, the ranges below: a. Absolute neutrophil count < 1000/µL b. Platelet count < 100,000/µL c. Haemoglobin < 9 g/dL d. Creatinine ≥ 1.5 mg/dL e. alanine aminotransferase or aspartate aminotransferase ≥ 2.5 x upper limit of normal (ULN) or bilirubin > 1.5 x ULN 10. Pregnant or lactating females. 11. Any surgical procedure requiring general anaesthesia within 1 month prior to screening, or planned elective surgery during the study. 12. History of malignant neoplasms or carcinoma in situ within 5 years prior to screening. (Subjects who are cancer-free for the previous 5 years may be enrolled. Subjects with adequately treated non-metastatic basal cell skin cancer, squamous cell skin cancer that has not recurred for at least 1 year prior to screening, or history of adequately treated cervical dysplasia/cervical intraepithelial neoplasia or cervical carcinoma in situ that has not recurred at least 3 years prior to screening may be enrolled.) 13. History of any major neurological disorders, as judged by the Investigator, or positive PML subjective symptom checklist. 14. Current or recent history of alcohol dependence or illicit drug use within 1 year prior to screening. 15. Subject is mentally or legally incapacitated at the time of Screening visit or has a history of clinically significant psychiatric disorders that would impact the subject's ability to participate in the trial according to the Investigator. Note: Subjects who have had situational depression or adjustment disorder or treated depression may be enrolled at the discretion of the Investigator. 16. Unable to attend study visits or comply with procedures. 17. Concurrent participation in any other interventional study. *Medication exclusion criteria*

	18. Use of topical 5-ASA or corticosteroid enemas/suppositories within 2 weeks of administration of the screening endoscopy. 19. Use of TNF-α antagonists within 60 days prior to screening. 20. Use of ustekinumab within 3 months prior to screening. 21. Use of cyclosporine, thalidomide, tacrolimus, sirolimus, or mycophenolate mofetil within 1 month prior to screening. 22. Have received any investigational or biologic agent within 1 month (or 5 half-lives of the agent, whichever is longer) prior to screening. 23. Prior treatment with vedolizumab or natalizumab.
Test Product(s), Dose, and Mode of Administration:	Subjects will receive the following treatments according to a randomisation schedule generated by IXRS: • PTG-100 (150 mg) once daily (QD) by oral administration • PTG-100 (300 mg) QD by oral administration • PTG-100 (900 mg) QD by oral administration • Placebo QD by oral administration Matching PTG-100 (150 mg or 300 mg unit dose) and placebo capsules will be provided to subjects in prepackaged individual study drug kits, identical in appearance, according to the randomisation schedule. During the double-blind treatment period, subjects will take a total of 3 capsules QD, as indicated below, without regard to meals. • 150 mg PTG-100: 1 × 150-mg capsule, 2 × placebo capsules • 300 mg PTG-100: 2 × 150-mg capsules, 1 × placebo capsule • 900 mg PTG-100: 3 × 300-mg capsules • Placebo: 3 x placebo capsules
Duration of Treatment:	Planned Enrolment/Screening Duration: up to 42 days (Days -42 to -1). Outpatient Visits: Days 14, 28, 42, 56, and 84. A telephone visit will be conducted on Day 70. Follow-up Visit: approximately 28 days (Day 112) after the last dose of study drug. Planned Study Conduct Duration (Screening to Follow-up visit): approximately 17 to 20 months (up to 42 days of screening + 12- to 15-month enrolment + 12 weeks treatment + 28 days follow-up).
Criteria for Evaluation: Efficacy	The primary efficacy endpoint is the: 1. Proportion of subjects receiving PTG-100 with clinical remission at Week 12 compared with placebo <u>Clinical remission</u> is defined as follows, using the Mayo subscores of stool frequency, rectal bleeding, and endoscopy: • Stool frequency subscore of 0 or 1 with a pre-specified change of 1 or more from baseline • Rectal bleeding subscore of 0 • Endoscopy subscore of 0 or 1 (modified so that a score of 1 does not include friability) The secondary efficacy endpoints (all based on comparison of individual PTG-100 dose levels to placebo) are: 1. Proportion of subjects with endoscopic response at Week 12 (Day 84) (defined as an endoscopic subscore of 0 or 1) 2. Proportion of subjects with clinical response at Week 12 (Day 84) (defined as at least 1 point and 30% reduction from baseline in rectal

	bleeding and stool frequency subscores) 3. Mean change in endoscopy subscore from baseline to Week 12 4. Mean change in rectal bleeding and stool frequency subscores from baseline to Weeks 2, 4, 6, 8, 10, 12, and 16 (Days 14, 28, 42, 56, 70, 84, and 112) 5. Proportion of subjects with endoscopic remission at Week 12 (Day 84) (defined as an endoscopic subscore of 0) 6. Mean change in complete Mayo Score (including all 4 subscores) from baseline to Week 12 (Day 84) 7. Mean change in partial Mayo Score (excluding endoscopy subscore) from baseline to Weeks 2, 4, 6, 8, 10, 12, and 16 (Days 14, 28, 42, 56, 70, 84, and 112) 8. Mean change in faecal calprotectin levels from baseline to Weeks 6 (Day 42), 12 (Day 84), and 16 (Day 112) 9. Mean change in IBDQ score from baseline to Week 12 (Day 84) 10. Proportion of subjects developing ADA by Weeks 12 (Day 84) and 16 (Day 112) The exploratory efficacy endpoints (all based on comparison of individual PTG-100 dose levels to placebo) are: 1. Mean change in histological score from baseline to Week 12 (Day 84) 2. Effects of ADA on PK, safety, and efficacy in subjects with positive ADA
Criteria for Evaluation: Safety	The primary safety endpoint is: 1. Proportion of subjects with at least 1 AE comparing individual PTG-100 dosing groups with placebo The secondary safety endpoints (all based on comparison of individual PTG-100 dose levels to placebo) are: 1. Frequency and type of AEs (affecting ≥ 5% of subjects) 2. Proportion of subjects with at least 1 serious AE (SAE) 3. Number and type of SAEs 4. Frequency of AEs of special interest including serious or opportunistic infection (viral, bacterial, fungal including systemic/gut localization), allergic/drug reactions, immune system disorders, and suspected PML. 5. Clinically significant changes in safety labs, ECGs, or physical examination findings (including vital signs)
Criteria for Evaluation: PK, PD, and ADA	The PK/PD/ADA endpoints are: 1. PTG-100 plasma levels 2. Blood α4β7 RO (peripheral blood T cells) 3. Blood α4β7 RE (peripheral blood T cells) 4. Proportion of subjects developing ADA by Weeks 12 (Day 84) and 16 (Day 112) The exploratory PD endpoints are: 1. Analysis of peripheral blood lymphocytes in subjects on individual PTG-100 dose levels compared to placebo 2. Number of β7 positive cells in colonic biopsies as assessed by immunohistochemistry in subjects on individual PTG-100 dose levels compared to placebo 3. Characterisation of immunologic biomarkers in the target population (selected sites only)
Statistical Methods:	Treatment population definitions:

	• All randomised participants who receive any amount of study drug (Safety Population) will be included in the safety analyses. • All randomised participants who receive a Day 0 dose of study drug and who have sufficient PK data for analysis (PK Analysis Population) will be included in the PK analyses. • All randomised participants who receive any amount of study drug and who have results from baseline and from ≥ 1 post-baseline assessment (Full Analysis Set) will be included in the PD and efficacy analyses. Safety and Tolerability: Continuous safety data will be summarised with descriptive statistics (arithmetic mean, standard deviation [SD], median, minimum, and maximum) by dose level. Categorical safety data will be summarised with frequency counts and percentages by dose level. Adverse events will be coded using the most current Medical Dictionary for Regulatory Activities available. A by-participant AE data listing, including verbatim term, preferred term, system organ class, treatment, severity, and relationship to study drug, will be provided. The number of participants experiencing treatment-emergent AEs (TEAEs) and number of individual TEAEs will be summarised by treatment group, system organ class, and preferred term. The TEAEs will also be summarised by severity and by relationship to study drug. Laboratory evaluations, vital signs assessments, and ECG parameters will be summarised by treatment group and protocol-specified collection time point. A summary of change-from-baseline at each protocol-specified time point by treatment group will also be presented. Clinically significant changes in physical examinations will be listed for each participant and described in the text of the final report. Concomitant medications will be listed by participant and coded using the most current World Health Organization drug dictionary. Medical history will be listed by subject. Further details regarding presentation and analysis of safety data will be detailed in the Statistical Analysis Plan (SAP). Anti-drug Antibodies: Serum samples will be evaluated for the presence of ADAs through use of a bridging immunoassay. The evaluation will include assessment of neutralising ADAs, as well as the potential of ADA to cross-react with endogenous mucosal addressin cell adhesion molecule 1. If ADA is detected in clinical samples, the effect of ADA on PK, safety, and efficacy may be explored for all subjects who demonstrate evidence of ADAs. Pharmacokinetics: Individual PTG-100 concentration data will be listed and summarised by treatment group with descriptive statistics (sample size, arithmetic mean, SD, median, minimum, maximum, geometric mean, and geometric coefficient of variation). Individual and mean PTG-100 concentration-time profiles for each treatment group will also be presented graphically. Plasma PTG-100 noncompartmental PK parameters including maximum observed

	concentration (C_{max}), trough (predose) concentration (C_{trough}), time of C_{max} (T_{max}), and area under the concentration-time curve from time 0 to the time of the last sample collection (AUC_{0-t}) will be estimated. Correlations between PTG-100 drug levels and PD or efficacy responses may be explored. Details regarding the statistical analyses of PK data will be provided in the SAP. <u>Pharmacodynamics</u>: Individual data will be listed for each subject and summarised by nominal sampling time point and treatment group with descriptive statistics (arithmetic mean, SD, median, minimum, and maximum). A summary of change-from-baseline at each protocol-specified time point by treatment group will also be presented. The change of PD indicators over time will be demonstrated graphically and will be compared among the dose levels. Receptor occupancy and α4β7 RE in peripheral blood will be listed for each subject and summarised by frequency counts for discrete categories. Additional population PK-PD modelling and immunologic assessment may be performed if deemed necessary. Details regarding the statistical analyses of PD data will be provided in the SAP. It should be noted that PD samples are to be collected at selected sites only. <u>Efficacy Evaluations:</u> Descriptive statistics will be used to evaluate differences in demographic and baseline characteristics. For the primary analysis, proportions of subjects with clinical remission will be compared between each dose and placebo using Cochran-Mantel-Haenszel test, with adjustment for stratification factors. Multiplicity will be addressed via closed testing procedure with combined p-values computed for each of the 2 stages of the trial (Stage 1 and Stage 2; IA and post IA). Each stage p-value will be adjusted as appropriate by a closed testing multiple comparison approach that controls the overall type 1 error at alpha=0.025, 1-sided. All analyses will be based on combined Stage 1 and Stage 2 data and include data from the dose(s) that is (are) dropped for Stage 2. Exploratory analyses will be carried out to assess consistency of results between Stages 1 and 2. Analyses of other binary endpoints will be carried out similarly. Subjects who discontinue prematurely will be considered treatment failures. Rates of clinical response, endoscopic response, and endoscopic remission will be evaluated similarly. Changes from baseline complete Mayo Score, partial Mayo Score, rectal bleeding subscore, stool frequency subscore, endoscopy subscore, IBDQ score, and faecal calprotectin levels will be analysed using repeated measures mixed analysis of covariance model adjusted for treatment, time point, treatment-by-time point interaction, stratification factors, and baseline values. For subjects who withdraw

	prematurely, the last observation will be carried forward. These analyses will be based on the Stage 1 and Stage 2 combined data for exploratory purposes.

2 INTRODUCTION[a]

2.1 Background and Rationale

Protagonist Therapeutics, Inc. is developing PTG-100 as a potential oral therapy for patients with moderate to severe active ulcerative colitis (UC). PTG-100, a peptide dimer comprised of natural and unnatural amino acids and a homologated amide bond, is an orally-stable peptide that binds specifically to α4β7 integrin on leukocytes.

PTG-100 is designed to be stable against various forms of gastrointestinal (GI) degradation and to target α4β7 integrin within the GI tissue compartment. Animal pharmacokinetic (PK) studies have shown these peptides are orally stable because they can be detected as full-length intact peptides in gut tissues and faeces after oral dosing. The PK studies have also shown the oral peptides have high exposure in the colon, small intestine, and to a lesser extent in the mesenteric lymph nodes with less than 0.5% systemic bioavailability; therefore, its presence is largely restricted to the GI tract.

PTG-100 binds specifically to α4β7 integrin on leukocytes, the same target as the approved antibody therapeutic vedolizumab (Entyvio®). PTG-100 is a potent and selective inhibitor of α4β7 integrin with binding selectivity identical to the antibody product vedolizumab. PTG-100 does not bind to α4β1 integrin. The α4β7 integrin, which is primarily involved in the recruitment of leukocytes to the GI tract, is present on the cell surface of a small population of circulating T- and B-lymphocytes. The major ligand for α4β7, mucosal addressin cell adhesion molecule 1 (MAdCAM-1), is selectively expressed on the endothelium of the intestinal vasculature and is present in increased concentrations in inflamed tissue. Through blockade of leukocyte trafficking in the gut, PTG-100 may inhibit inflammation in the GI tract, potentially reducing the signs and symptoms of active UC.

Vedolizumab (Entyvio®), an intravenously administered monoclonal antibody that similarly targets α4β7 integrin, has been approved for the treatment of adult patients with moderate to severe active UC who have had an inadequate response with, lost response to, or were intolerant to a tumour necrosis factor-alpha (TNF-α) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or

[a] Information supplied by the Sponsor.

demonstrated dependence on corticosteroids.[1] Vedolizumab has also been approved for treatment of patients with Crohn's disease (CD).[2] Therefore, it is considered that blockade of this interaction is a safe and effective therapy for inflammatory bowel disease.

Ulcerative colitis is a chronic inflammatory bowel disease characterised by bloody diarrhoea, abdominal cramps, and fatigue.[3] Current medical therapy has important limitations. Aminosalicylates are only modestly effective; glucocorticoids can cause unacceptable adverse events (AEs) and do not provide a benefit as maintenance therapy.[4-6] Tumour necrosis factor-alpha antagonist antibody drugs, although efficacious, may predispose patients to serious infection, a risk of malignancy, and development of anti-drug antibodies (ADA).[7-9] Vedolizumab (Entyvio®) is administered as an intravenous (IV) infusion with potential for systemic infection and risk of immunogenicity.[1,2,10] Therefore, new treatment strategies are needed for patients with UC.

Due to the inconvenience of injectable therapies, associated safety risks of systemic treatment, and risk of development of ADA, PTG-100, an orally-stable, GI-restricted peptide therapeutic candidate that targets α4β7, may provide a significant benefit to patients with moderate to severe UC.

Both in vitro and in vivo pharmacology studies have been conducted to assess the activity, mechanism of action, and toxicity of PTG-100. PTG-100 is a potent and selective inhibitor of α4β7 with binding properties highly similar to the antibody product vedolizumab. Similar to vedolizumab, PTG-100 does not bind α4β1 integrin. A dextran sulphate sodium-induced colitis mouse model demonstrated that PTG-100 administration induced a dose-dependent reduction in α4β7+ memory T cell homing to inflamed gut tissue and a significant improvement in mucosal damage as assessed by blinded endoscopy. Pharmacokinetic studies show that drug levels are much higher in GI tissues compared to blood, which suggests that drug exposure in the GI tissues is the principal driver for the in vivo pharmacology. Fluorescence-activated cell sorter (FACS) analysis of whole blood from healthy cynomolgus monkeys demonstrated that a peripheral blood receptor occupancy (RO) of less than 50% is correlated with in vivo efficacy in the mouse studies. Levels of circulating α4β7+ memory T cells were increased when normalised to total CD4 cells following PTG-100 dosing, confirming that blocking homing of α4β7+ memory T cells redistributes these cells to the blood.

In 42- and 90-day (Good Laboratory Practice [GLP]) toxicology studies, no adverse toxicological findings were observed at once daily (QD) doses up to 90 mg/kg/day and 75 mg/kg/day in rats and monkeys, respectively. The no observed effect level (NOEL) in rats was 90 mg/kg/day, the highest level evaluated. In the monkey study, the no observed adverse effect level (NOAEL) was considered to be 75 mg/kg/day, the highest dose tested. Also, histology from the 90-day toxicology studies demonstrated no adverse testicular findings.

Reproductive and developmental toxicity studies of limited scope (6 dams/group) in rats and rabbits have been completed. There were no maternal or developmental effects noted in either study. The maternal and developmental NOEL for PTG-100 was 90 mg/kg/day in pregnant rats and 75 mg/kg/day in pregnant rabbits, the highest dose levels tested in these studies. Definitive reproductive and developmental toxicity studies to evaluate embryo-foetal development will be completed prior to the Phase 3 clinical program.

PTG-100 did not inhibit the human Ether-à-go-go Related Gene potassium channel current. No effects of PTG-100 were observed on the cardiovascular or respiratory systems in conscious monkeys, or in central nervous system functional assessment (Irwin) or GI motility studies in rats. In vitro GLP genotoxicity tests were negative, indicating a low genotoxic potential.

Protagonist has completed a Phase 1 randomised, double-blind, placebo-controlled, 3-part study (Study PTG-100-01) of PTG-100 in 78 normal healthy male volunteers in Australia. Sixty-four of the 78 subjects were treated with PTG-100. Parts 1 and 2 evaluated single and multiple ascending doses of PTG-100, respectively, up to a maximum daily dose of 1000 mg using a liquid phosphate buffer (PB) formulation of PTG-100. Doses up to 1000 mg/day were tested as a single dose and as QD dosing for 14 days. Part 3 was a single dose cross-over study of PTG-100 capsule formulation compared to solution-based PB formulation. These data informed the selection of doses in Phase 2 (Section 2.2).

In this Phase 1 study, PTG-100 was well tolerated; there were no serious AEs (SAEs) or dose-limiting toxicities observed. All AEs were mild to moderate in severity. No dose-dependent increase in AEs was noted. There were no clinically significant abnormalities or trends in clinical labs, electrocardiograms (ECGs), or vital signs. The maximum dose tested for both single and multiple dosing was 1000 mg; no dose-limiting toxicities were observed at this or any doses.

Consistent with the preclinical data in mice, rats, and cynomolgus monkeys, in Study PTG-100-01, the plasma exposure to PTG-100 was extremely low (< 1%) as determined by the area under the concentration-time curve (AUC) and maximum observed concentration (C_{max}), thus reflecting the GI-restricted nature of the drug. In a small cohort of subjects administered a single dose of PTG-100 (300 mg), the systemic exposure (as measured by C_{max} and AUC from time 0 to the time of the last sample collection [AUC_{0-t}]) of PTG-100 when given to participants after a high-fat meal was approximately 30% of that for PTG-100 administered under fasted conditions. All subjects in the multiple ascending dose (MAD) cohorts in the trial were fed a standard diet. There was minimal drug accumulation at Day 14 in the MAD cohorts, related to the relatively short half-life in the blood.

Dose-dependent increases in blood RO and reduction in receptor expression (RE; eg, receptor down-regulation), as reflecting target engagement in the GI tissue compartment, were observed, thus supporting evidence of sustained target engagement and pharmacologic activity of PTG-100 in healthy volunteers comparable to the data in mouse and cynomolgus monkey studies. Saturating levels of receptor down-regulation were observed at the 300-mg dose level following multiple dose exposure. Blood RO and RE levels in the healthy volunteers (at the 300-mg dose level) exceeded threshold levels in the healthy mice at comparable dose levels (based on allometric scaling; eg, approximately 50 mg/kg/day); this dose threshold also correlated with inhibition of lymphocyte trafficking and improvements in disease activity in the colitis mouse studies. Therefore, the data suggest a potentially efficacious dose of 300 mg in patients with UC.

To support the use of the capsule formulation in Study PTG-100-02, in vivo PK bridging studies in cynomolgus monkey and normal healthy volunteers have demonstrated that the relative bioavailability of the capsule formulation compared to the liquid PB formulation (used in the GLP toxicology studies and Phase 1 single ascending dose and MAD cohorts) was approximately 60% based on AUC_{0-t} and AUC from time 0 to infinity. Despite the lower plasma exposure of the capsule formulation compared to the liquid formulation, the pharmacodynamic (PD) effects (eg, blood RO and RE) were highly similar between the capsule and liquid formulations. These data support the use of the capsule formulation in the Phase 2b clinical trial at doses established by single and multiple dose cohorts using the liquid PB formulation.

Further information about the preclinical and Phase 1 studies are provided in the Investigator's Brochure (IB).

2.2 Study Rationale

This is the first time PTG-100 will be administered to subjects with UC. The principle aims of this study are to evaluate the safety/tolerability and efficacy of PTG-100 administered for 12 weeks as single daily oral doses to UC subjects with moderate to severe active disease. This information, together with PK/PD data, will help establish the doses and duration of induction dosing in subjects with moderate to severe active UC.

The study design and target population described in this protocol is consistent with previous Phase 2 studies evaluating safety and efficacy in patients with moderate to severe active UC. In this trial, a parallel adaptive 2-stage methodology was selected to allow for interim assessment of futility and to drop one (or 2) study arms in order to most efficiently allocate subjects to the most informative dose arms.

As is appropriate for such studies, a placebo group of UC subjects is included with multiple active dose groups to optimise dose finding during induction treatment. A blinded approach will be incorporated.

Subjects will receive dose levels of PTG-100 within the range of doses supported by appropriate GLP toxicology studies and in a healthy volunteer population.

The 12-week (84-day) duration of induction treatment is deemed sufficient for observation of appreciable, quantifiable symptom improvement and to characterise the optimal duration of induction treatment. Prior studies have suggested that shorter induction treatment periods may not be sufficient to identify optimal dose-response outcomes prior to changing to maintenance dosing regimens.[1,11,12] In particular, the Phase 3 study of vedolizumab (Entyvio®), which was not designed to identify the time of maximal effect of vedolizumab as induction therapy, demonstrated greater efficacy beyond the induction treatment of 6 weeks.

The primary endpoint of the trial will be the induction of clinical remission at 12 weeks, a well-established efficacy measure using Mayo Score assessment subscores for stool frequency, rectal bleeding, and endoscopy, but excluding the physician's global assessment (PGA) subscore (see Section 7.4 for details). This definition is in accordance

with recent Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance. Secondary efficacy endpoints will include clinical response, endoscopic response, endoscopic remission, and changes in Mayo Score, partial Mayo Score, rectal bleeding subscore, stool frequency subscore, endoscopic subscore, faecal calprotectin, and Inflammatory Bowel Disease Questionnaire (IBDQ) from baseline. Further details may be found in the appendices and Section 7.4.

2.3 Dose Rationale

This Phase 2b study will initially consist of 4 arms: 3 dose levels of PTG-100 (150 mg, 300 mg, and 900 mg QD) and one placebo arm QD. Following the interim analysis (IA; see Section 7.2), one (or 2) dose levels of PTG-100 will be dropped with additional subjects being randomised to the remaining dose arms. The dose range of 150 to 900 mg is intended to bracket the 300-mg dose that may be a potentially efficacious dose based on translation of animal and Phase 1 PD data (see below). In order to optimise the duration of induction dosing, we will assess efficacy and safety over 12 weeks treatment.

The selection of doses for this study is based on integration of toxicology and PK/PD data from preclinical studies and safety and PK/PD data from the Phase 1 clinical study (PTG-100-01), using exposure (dose levels, plasma exposure) and response data (inhibition of lymphocyte trafficking, disease activity improvement, α4β7 binding saturation, and α4β7 RE on peripheral blood T cells). In 42- and 90-day (GLP) toxicology studies, no adverse toxicological findings were observed with QD doses up to 90 mg/kg/day and 75 mg/kg/day in both rats and monkeys. The NOEL in rats was 90 mg/kg/day, the highest level evaluated. In the monkey study, the NOAEL was considered to be 75 mg/kg/day, the highest dose tested. The high doses used in the repeat dose GLP studies in rats (90 mg/kg/day) and monkeys (75 mg/kg/day) correlate to a human equivalent dose of 14.5 mg/kg and 24.2 mg/kg, respectively. These dose levels in rats and monkeys correlate to doses of 871 mg and 1452 mg, respectively, based on allometric scaling in a 60 kg human. The 900-mg dose does not exceed the maximum dose of 1000 mg tested in the Phase 1 study (see Section 2.1). The blood RO and RE biomarkers have been shown to reflect primary target engagement in the GI tissues in the animal studies, since blood RO and RE measure recirculating lymphocytes with bound drug. At low dose levels, at time points earlier than 4 hours, RO levels in cells in the Peyer's patches and the mesenteric lymph nodes of mice are much higher than those measured in peripheral blood cells.

In mouse colitis models, inhibition of T cells trafficking to the gut and disease activity improvement were observed at doses between approximately 6 and 55 mg/kg/day with corresponding peak peripheral blood α4β7 receptor blockade of < 50%. Doses as low as 6 mg/kg/day in the mouse significantly inhibited lymphocyte homing to the gut, while doses of approximately 55 mg/kg/day significantly reduced disease activity in the colitis mice. The dose range of 6 to 55 mg/kg/day in mouse may be extrapolated to a potentially efficacious dose range of approximately 35 to 300 mg daily dose in humans via allometric scaling by whole body surface area, a conservative assumption for a GI-restricted drug.

Data from the Phase 1 healthy volunteer study (Study PTG-100-01) corroborated target blood RO and α4β7 RE levels that were observed in the mouse and cynomolgus monkey studies. Both blood RO and RE levels at the 300-mg dose level in healthy human volunteers at 24 hours following the last dose in the MAD cohorts (ie, trough exposure) exceeded threshold levels in the healthy mice at a comparable dose level (ie, approximately 50 mg/kg/day). Further, there was evidence of saturation of receptor down-regulation activity at the 300-mg dose in the multiple dose cohorts in Study PTG-100-01. Since inhibition of cell trafficking and mucosal healing was observed at a similar dose in the colitis mice (eg, dose range of 6 to 55 mg/ kg), the data conservatively suggest a potentially efficacious dose of approximately 300 mg in humans. Since PTG-100 exposure in blood and GI tissues of healthy mice is similar to that observed in colitis mice, it was determined that drug tissue exposure is unaffected by the inflammatory status of the mucosal layer. Thus, the highest efficacious dose in the colitis mice (approximately 55 mg/kg/day) corresponds to approximately 300 mg/day in the human.

Based on these data, a dose range of 150 to 900 mg was selected for this Phase 2b study to target corresponding blockade of the α4β7 receptors and saturating levels of target expression in healthy human volunteers that correlated with dose levels inducing pharmacologic and clinical activity in the mouse colitis models. Sustained levels of blood RO and saturation levels of RE at 24 hours postdose in the MAD cohorts on Day 14 (corresponding to trough levels), despite minimal plasma exposure of PTG-100, support the QD dosing regimen.

2.4 Rationale for Target Population

PTG-100 is being developed for the treatment of patients with moderate to severe active UC, similar to the target population for the FDA-approved antibody vedolizumab (Entyvio®). In this study, the target population will include male and non-gravid female adult subjects with diagnosed UC for ≥ 2 months prior to screening and a Mayo Score of 6 to 12, inclusive (total Mayo Score range 0 to 12), at baseline (pre-randomisation) with an endoscopy subscore of at least 2 (range 0 to 3) as determined by blinded central read.

Eligible subjects will have failed treatment with at least 1 or more of the following agents: glucocorticoids, immunosuppressive medications (ie, azathioprine and 6-mercaptopurine [6-MP]), and/ or TNF-α antagonists. A maximum of 50% of randomised subjects may have failed prior treatment with TNF-α inhibitor therapies. Subjects with prior exposure to vedolizumab or natalizumab will be excluded.

As PTG-100 has minimal systemic absorption and a favourable safety/ tolerability profile in toxicology and human subjects to date, Protagonist believes that the proposed criteria define an appropriate population in which PTG-100 will be investigated.

For subjects in the Netherlands, only subjects who have had prior exposure to anti-TNF agents will be allowed to enrol in the study.

2.5 Rationale for Endpoints

This Phase 2b study is designed to assess the safety and efficacy of induction treatment of PTG-100 in subjects with moderate to severe active UC. The selection and definition of efficacy endpoints are consistent with recent FDA and EMA guidance and will be based on patient-reported and endoscopic outcomes.

The study is modelled after other recent clinical studies of a wide range of drugs in mild to severe UC. The Mayo Score will be used as the primary assessment method and will be adapted based on the recent regulatory guidance documents for assessment of the primary and secondary endpoints (see below). Traditional outcome measures in UC trials consist of composite instruments that incorporate symptoms, laboratory criteria, and sigmoidoscopic findings. The Mayo Score is a composite instrument that includes both endoscopic and clinical items.[13] The index has been used in multiple clinical trials of mesalamine, budesonide, infliximab, adalimumab, golimumab, and vedolizumab. In a recent meta-analysis, mucosal healing as assessed by sigmoidoscopy was associated with

long-term clinical remission, avoidance of colectomy, and corticosteroid-free clinical remission.[14] In addition to the traditional endpoint of remission which incorporates symptomatic and endoscopic improvement, the Mayo Score has been adapted to functionally create co-primary endpoints in trials by separating components into symptom-based and endoscopic criteria of response and remission. Symptom-based criteria, that do not include endoscopy, have good correlation with the full Mayo Score.

The primary efficacy endpoint of the trial will be induction of clinical remission at 12 weeks (see Section 7.4). Clinical remission will be based on the following patient-reported and endoscopic criteria from the adapted Mayo Score assessment tool:

1. Stool frequency subscore of 0 or 1 with a pre-specified change of 1 or more from baseline
2. Rectal bleeding subscore of 0
3. Endoscopy subscore of 0 or 1 (modified so that a score of 1 does not include friability)

The secondary endpoints will include clinical response, endoscopic response, endoscopic remission and changes in endoscopy, rectal bleeding and stool frequency subscores, partial Mayo Score, complete Mayo Score, faecal calprotectin, and IBDQ score. Histological outcomes will also be assessed from colonic biopsy samples pre- and post-treatment. Because observer variation in endoscopic assessments can result in differences in response rates compared to placebo, central reading of the recorded endoscopy scans will be performed to confirm eligibility and to assess key endpoints. In UC trials, central reading of endoscopic videos has been shown to be highly reliable and to reduce the rate of placebo response.[15]

3 STUDY OBJECTIVES

The primary objectives of this study are:

1. To evaluate the safety and tolerability of PTG-100
2. To evaluate the efficacy of PTG-100 in the induction treatment of subjects with moderate to severe active UC compared to placebo.

The secondary objectives are:

1. To evaluate the dose-response relationship and select PTG-100 induction regimens for continued development
2. To evaluate the PK of PTG-100 in subjects with active UC

3. To evaluate the PD effects of PTG-100 including the assessment of RO and α4β7 RE in peripheral blood lymphocytes
4. To evaluate changes in faecal calprotectin levels for subjects receiving PTG-100 compared to placebo
5. To evaluate the incidence of positive ADAs in subjects receiving PTG-100.

The exploratory objectives are:

1. To evaluate the ability of subjects receiving PTG-100 to achieve histological improvement in colonic tissue biopsies compared to placebo
2. To characterise immunologic biomarkers in the target population and to evaluate changes in immunological/PD biomarkers in subjects receiving PTG-100 compared to placebo

4 INVESTIGATIONAL PLAN

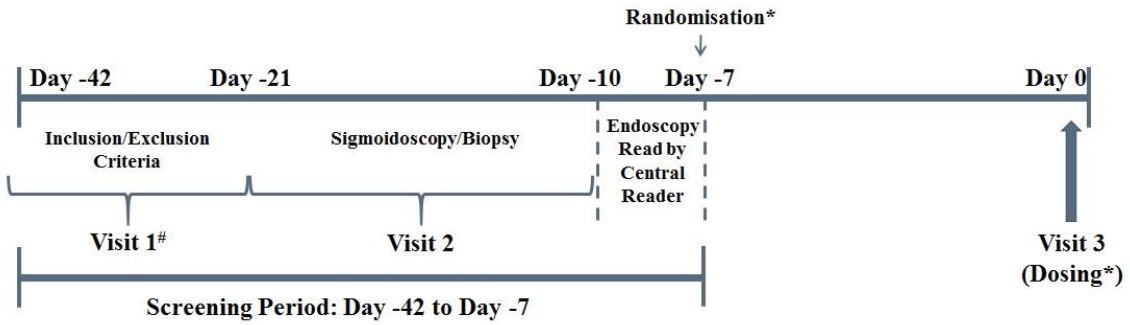
4.1 Study Design Overview

This Phase 2b study will be a randomised, double-blind, placebo-controlled, multi-centre, parallel adaptive 2-stage design to evaluate safety/tolerability and efficacy in subjects with moderate to severe active UC.

Approximately 100 to 120 sites worldwide will participate in this study. No study-site target enrolment numbers will be set so as to allow for competitive enrolment among sites. It should be noted that for subjects in the Netherlands, only subjects who have had prior exposure to anti-TNF agents will be allowed to enrol in the study.

Subjects will be screened for eligibility within 42 days of dosing (see Figure 4-1). Eligible subjects will return for sigmoidoscopy/ biopsy and recording baseline Mayo Score (within 14 days of randomisation; however, subjects may have a combined Screening visit that includes endoscopy). On Day 0, assessments including physical examinations, safety labs, ECG, progressive multifocal encephalopathy (PML) assessment, PK, PD, ADA, faecal calprotectin, and IBDQ, will be performed predose followed by dosing, physical examination, AE assessment, and blood sampling for PK and PD analysis.

Figure 4-1 Screening and Randomisation Design Schematic



#Subjects may have a combined Screening visit that includes endoscopy.

*Dosing to occur within 7 days of randomisation.

Treatment duration will be 12 weeks in order to optimise the duration of induction dosing for continued development. A total of 9 visits to the clinical site will include: 2 Screening visits (one for general inclusion/exclusion criteria assessment and a second including recording baseline Mayo scoring and sigmoidoscopy/ biopsy, with the latter occurring within 14 days of randomisation; Day -42 to Day -7 for both Screening visits; however, subjects may have a combined Screening visit that includes endoscopy); dose initiation (Day 0); assessment visits on Days 14, 28, 42, 56, and 84; and Follow-up visit on Day 112. Day 70 will be a phone visit and subjects will be instructed to record stool frequency and rectal bleeding data preceding Day 70. A phone visit will be conducted at approximately 6 months after the end of study treatment period in which a PML assessment will be performed. Post-treatment sigmoidoscopy/ biopsy will be performed on Day 84 (Week 12). Study design schematics for the screening/randomisation period and overall study are shown in Figure 4-1 and Figure 4-2, respectively. A 3-day window (± 3 days) is allowable for each study visit following dosing with a 7-day window (± 7 days) allowed for the Follow-up visit on Day 112.

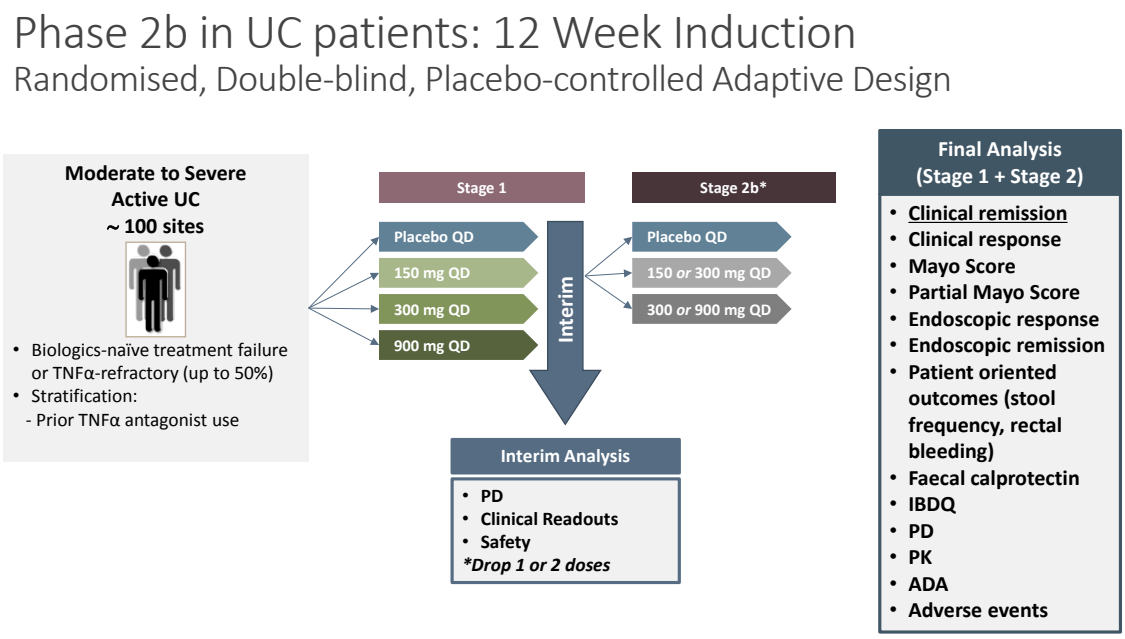
Subjects will be randomised (1:1:1:1) using an interactive web/voice response system (IXRS; Almac, Craigavon, Northern Ireland) to one of the following treatments groups:

- PTG-100 (150 mg) QD by oral administration
- PTG-100 (300 mg) QD by oral administration
- PTG-100 (900 mg) QD by oral administration
- Placebo QD by oral administration

An IA will be performed after approximately 60 to 80 subjects have completed 12 weeks of dosing (Section 7.2). Subject enrolment will occur in 2 stages relative to the IA, the purpose of which will be to conduct a futility analysis and, if futility criteria are not met, to identify which study arms provide optimal data in order to select one (or 2) PTG-100 dose levels and placebo to continue enrolling subjects to the most informative dose arms.

The schematic of the study design is displayed in Figure 4-2. The start of the study is defined as the date the first subject enrolled in the study (ie, signs an Informed Consent Form [ICF]). A subject who completes the Day 112 Follow-up visit is considered to have completed the study. Completion of the study does not include any unplanned Follow-up visits (eg, return to the clinic for repeat clinical laboratory) or the phone visit approximately 6 months after the end of treatment. The end of the study is defined as the date the last subject completes the study (or completes an Early Termination visit). The planned duration of study conduct is approximately 17 to 20 months from Screening through the final subject's Follow-up visit (up to 42 days of screening + 12- to 15-month enrolment + 12 weeks treatment + 28 days follow-up).

Figure 4-2 Study Design Schematic



ADA = anti-drug antibodies; IBDQ = Inflammatory Bowel Disease Questionnaire; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; TNFα = tumour necrosis factor-alpha; UC = ulcerative colitis.

In this study, the primary efficacy endpoint is clinical remission as defined by the rectal bleeding, stool frequency, and endoscopic subscores of the Mayo Score; clinical response, endoscopic response, and endoscopic remission will be determined using designated subscores of the Mayo Score assessment (see Section 7.4 for details). Changes in complete and partial Mayo Score, rectal bleeding subscore, stool frequency subscore, and endoscopic subscore will be evaluated at designated time points. The IBDQ questionnaire will be assessed pre- and post-treatment; sigmoidoscopy and biopsy will be performed at baseline and Day 84 for evaluation of endoscopic response and remission and histological assessment. Stool samples will be collected for faecal calprotectin at designated time points. Subject blood samples will be obtained at designated time points from Day 0 through Day 112 for analysis of safety labs, PK, PD, and ADA parameters.

Safety will be monitored with AE inquiries, assessment of concomitant medication use, clinical laboratory evaluations (Appendix B), vital sign measurements, 12-lead ECGs, and physical examination findings during the study. A PML assessment will also be done at designated time points. A study flow chart is presented in Table 6-1.

Pharmacokinetic analyses will be performed to characterise PTG-100 drug levels and PK parameters (AUC_{0-t}, C_{max}, trough [predose] concentration [C_{trough}], and time of C_{max} [T_{max}]). Pharmacodynamic analyses will be performed to assess the blood PTG-100 RO and α4β7 RE in peripheral blood lymphocytes. The incidence of ADA will be assessed.

Subjects will be stratified by prior treatment with TNF-α antagonist use.

5 SUBJECT SELECTION

Subjects who meet ALL of the inclusion criteria and for whom NONE of the exclusion criteria apply will be eligible to be enrolled into the study. Safety evaluations may be repeated at the Investigator's (or designee's) discretion.

Approximately 240 subjects will be randomised in the trial.

5.1 Inclusion Criteria

The following are the inclusion criteria. Subjects must meet ALL of the following inclusion criteria to be enrolled. Subjects may be screened up to 3 different times separated by at least 14 days.

1. Male and female subjects aged 18 to 80 years, inclusive.
2. Diagnosis of UC for ≥ 2 months prior to screening, with a history of disease activity extending beyond the rectum; if the UC has been present for > 10 years, a total colonoscopy with biopsy must have been performed within 2 years of screening to rule out dysplasia. Subjects with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factor must be up-to date on colorectal cancer surveillance per local standards and guidelines (may be performed during screening). Subjects with extensive colitis or pancolitis of > 8 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial Screening visit (may be performed during screening).
3. Moderate to severe active UC as defined by complete Mayo Score of 6 to 12, inclusive (range 0 to12), at baseline (pre-randomisation) with endoscopy score of at least 2 (range 0 to 3), extending 15 cm or more from the anal verge, as determined by blinded central read, within 14 days of randomisation.
4. Demonstrated over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents as defined below:

a. Immunomodulators
    i. Signs and symptoms of persistently active disease despite a history of at least one ≥ 8-week regimen of oral azathioprine (≥ 1.5 mg/kg) or 6-MP (≥ 0.75 mg/kg), OR
    ii. History of intolerance of at least 1 immunomodulator (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopaenia, thiopurine S-methyltransferase genetic mutation, and/or infection)
b. TNF-α antagonists
    i. Signs and symptoms of persistently active disease despite a history of at least 1 induction regimen of at least 6 weeks duration, OR
    ii. Recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), OR
    iii. History of intolerance (including, but not limited to, infusion- or injection-related reaction, demyelination, congestive heart failure, and infection)

    Note: A maximum of 50% of randomised subjects may have had prior treatment with TNF-α antagonists. For subjects in the Netherlands, only subjects who have had prior exposure to anti-TNF agents will be allowed to enrol in the study (as confirmed by medical record documentation or by self-reporting).
c. Corticosteroids
    i. Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or IV for 1 week, OR
    ii. Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions, OR
    iii. History of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopaenia/ osteoporosis, hyperglycaemia, insomnia, and infection).

5. Subject is unlikely to conceive, as indicated by at least one "yes" answer to the following criteria:
    a. Subject is a male

b. Subject is a surgically sterilised female (at least 90 days prior to Screening)
c. Subject is a post-menopausal female ≥ 45 years of age with > 1 year since last menses; if a female subject is < 45 years of age, or cessation of menses is < 1 year and > 6 months, follicle-stimulating hormone (FSH) must be documented as elevated into the post-menopausal range at Screening
d. Subject is a non-sterilised, premenopausal female with a non-sterile male partner and agrees to abstain from heterosexual activity, use adequate hormonal contraception, OR use double barrier contraception (ie, a combination of male condom with either cervical cap, diaphragm, or sponge with spermicide) as per local regulations and guidelines during the study and for 28 days after the last dose of study drug.
e. If subject is a non-sterilised, premenopausal female with a sterile male partner, the above requirements for contraception do not apply.

6. For women of childbearing potential (WOCBP), a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of study medication.
7. Subject is eligible according to tuberculosis (TB) screening criteria.
8. Subject understands the study procedures and agrees to participate in the study by giving written informed consent.

Note: Subjects may be permitted to enrol in the study on stable doses of oral 5-aminosalicylic acid (5-ASA) agents, oral corticosteroids, antidiarrhoeals, azathioprine/6-MP, or probiotics according to specifications noted in the protocol.

5.2 Exclusion Criteria

The following are the exclusion criteria; subjects must meet NONE of the following exclusion criteria to be enrolled.

Gastrointestinal exclusion criteria

1. Subject with CD, indeterminate colitis, or presence or history of fistula consistent with CD.

2. History of toxic megacolon, abdominal abscess, symptomatic colonic stricture, or stoma; history of extensive colonic resection, or subtotal or total colectomy; or is at imminent risk of colectomy.
3. History or current evidence of colonic dysplasia or adenomatous colonic polyps.
   Note: Subjects will not be excluded from the study because of a pathology finding of indefinite dysplasia with reactive atypia. Subjects with resected adenomatous polyps may be enrolled.

Infectious disease exclusion criteria

4. Current bacterial or parasitic pathogenic enteric infection, including *Clostridium difficile* (confirmed by toxin result), current infection with hepatitis B or C virus (subjects treated for HCV infection must have evidence of sustained virologic response 12 weeks after the end of treatment [SVR12], infection requiring hospitalisation or IV antimicrobial therapy, opportunistic infection within 6 months of dosing, any infection requiring antimicrobial therapy within 2 weeks of dosing, history of more than one episode of herpes zoster, history of infection with human immunodeficiency virus (HIV), or any episode of disseminated zoster. Note: Subjects with a history of *C. difficile* infection treated with antibiotics with or without faecal microbial transplant may be rescreened after 2 weeks following completion of treatment.
5. Live virus vaccination within 1 month prior to screening.

General exclusion criteria

6. Subject has a concurrent clinically significant, unstable, or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, haematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the Investigator, might confound the results of the study or poses additional risk to the subject by their participation in the study.
   Note: Subjects with a history of uncomplicated kidney stones, childhood asthma, or concurrent stable and well-controlled asthma may be enrolled in the study at the discretion of the Investigator.
7. Known primary or secondary immunodeficiency.
8. History of myocardial infarction, unstable angina, transient ischaemic attack, decompensated heart failure requiring hospitalisation, congestive heart failure (New York Heart Association Class 3 or 4), uncontrolled arrhythmias, cardiac revascularisation, stroke, uncontrolled hypertension (systolic blood pressure [BP] > 160 mmHg or diastolic BP > 100 mmHg at Screening), or uncontrolled diabetes (haemoglobin A1c > 9% or > 1 episode of severe hypoglycaemia) within 6 months of screening.

9. Clinically meaningful laboratory abnormalities at Screening, including but not limited to, the ranges below:
    a. Absolute neutrophil count < 1000/μL
    b. Platelet count < 100,000/μL
    c. Haemoglobin < 9 g/dL
    d. Creatinine ≥ 1.5 mg/dL
    e. alanine aminotransferase or aspartate aminotransferase ≥ 2.5 x upper limit of normal (ULN) or bilirubin > 1.5 x ULN
10. Pregnant or lactating females.
11. Any surgical procedure requiring general anaesthesia within 1 month prior to screening, or planned elective surgery during the study.
12. History of malignant neoplasms or carcinoma in situ within 5 years prior to screening. (Subjects who are cancer-free for the previous 5 years may be enrolled. Subjects with adequately treated non-metastatic basal cell skin cancer, squamous cell skin cancer that has not recurred for at least 1 year prior to screening, or history of adequately treated cervical dysplasia/cervical intraepithelial neoplasia or cervical carcinoma in situ that has not recurred at least 3 years prior to screening may be enrolled.)
13. History of any major neurological disorders, as judged by the Investigator, or positive PML subjective symptom checklist.
14. Current or recent history of alcohol dependence or illicit drug use within 1 year prior to screening.
15. Subject is mentally or legally incapacitated at the time of Screening visit or has a history of clinically significant psychiatric disorders that would impact the subject's ability to participate in the trial according to the Investigator. Note: Subjects who have had situational depression or adjustment disorder or treated depression may be enrolled at the discretion of the Investigator.
16. Unable to attend study visits or comply with procedures.
17. Concurrent participation in any other interventional study.

Medication exclusion criteria

18. Use of topical 5-ASA or corticosteroid enemas/suppositories within 2 weeks of administration of the screening endoscopy.
19. Use of TNF-α antagonists within 60 days prior to screening.
20. Use of ustekinumab within 3 months prior to screening.
21. Use of cyclosporine, thalidomide, tacrolimus, sirolimus, or mycophenolate mofetil within 1 month prior to screening.

22. Have received any investigational or biologic agent within 1 month (or 5 half-lives of the agent whichever is longer) prior to screening.
23. Prior treatment with vedolizumab or natalizumab.

5.3 Removal of Subjects from Study Participation

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at an institution. The Investigator (or designee) may remove a subject from the study if, in the Investigator's (or designee's) opinion, it is not in the best interest of the subject to continue the study. Subjects may be withdrawn due to (but not limited to) any of the following:

- change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety
- at the subject's request (withdrawal of consent)
- protocol noncompliance
- occurrence of AEs that, in the Investigator's opinion, require subject removal
- occurrence of pregnancy
- intake of non-permitted concomitant medication that might affect subject safety or study assessments/objectives.

Notification of withdrawal will be made to the Sponsor as soon as is practical. In case of withdrawal, all reasonable efforts will be made to perform all final study day assessments within 10 days of termination (eg, Early Termination visit) (Table 6-1). The date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the subject's Case Report Form (CRF). All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilised.

5.4 Management of Subject Safety

Following dose administration and before leaving the site, each subject will be given a Patient Alert card to carry at all times in case of any emergency outside of the site. The card gives details of the study name and study drug used, name of the relevant Investigator, address and telephone number of the site, as well as emergency out of office contact details if a third party medical professional requires any details or safety information about the study or study drug in case of emergency. Subjects should retain

this card after they have completed or discontinued the study and during the follow-up phase, and destroy the card when directed by study personnel.

6 STUDY PROCEDURES

6.1 Schedule of Study Procedures

A study flow chart is presented in Table 6-1. The total blood volume that will be taken during the study is outlined in Appendix E.

Table 6-1 Study Flow Chart

	Screening	Random-isation Period	Treatment								Follow up		
	Days -42 to -7	Day -7 to Day -1	Day 0 (pre-dose)[1]	Day 0 (dosing, post-dose)	Day 14 ±3 days	Day 28 ±3 days	Day 42 ±3 days	Day 56 ±3 days	Day 70[2] ±3 days	Day 84 ±3 days	Day 112 ±7 days	Day 252[2] ±30 days	Early Termi-nation[3]
Informed Consent	X												
Demographics	X												
Medical History	X												
Prior and Concomitant Medications[4]	X		X	X	X	X	X	X	X	X	X		X
Inclusion/Exclusion	X												
Height	X												
Weight	X		X		X	X	X	X		X	X		X
Physical Examination[5]	X		X	X	X	X	X	X		X	X		X
Vital Signs[6]	X		X	X[7]	X	X	X	X		X	X		X
12-lead ECG[6]	X		X[8]		X			X		X	X[9]		X
Laboratory: Haematology, Coagulation, Serum Chemistry[10]	X		X		X	X		X		X	X		X
Stool *C.diff*, Culture, and Ova and Parasites	X												
Urinalysis (microscopy if abnormal)	X		X		X	X		X		X	X		X
PML Neurological Assessment[11]	X		X		X	X	X	X	X	X	X	X	X
Hepatitis B & C; TB Test	X												
Serum Pregnancy (WOCBP)	X									X	X		X

	Screening	Random-isation Period	Treatment								Follow up		
	Days -42 to -7	Day -7 to Day -1	Day 0 (pre-dose)[1]	Day 0 (dosing, post-dose)	Day 14 ±3 days	Day 28 ±3 days	Day 42 ±3 days	Day 56 ±3 days	Day 70[2] ±3 days	Day 84 ±3 days	Day 112 ±7 days	Day 252[2] ±30 days	Early Termi-nation[3]
Sigmoidoscopy	X[12]									X			X
Colonic Biopsy	X[12]									X			X
Mayo Score[13]	X[12]				X	X	X	X	X	X	X		X
JCV Antibody Testing[14]	X[14]												
Confirmation of Eligibility			X										
Randomisation[15]		X											
Adverse Events			X	X	X	X	X	X	X	X	X		X
IBDQ			X							X			X
Faecal Calprotectin			X				X			X	X		X
Urine Pregnancy (WOCBP)			X		X	X	X	X					
PK Blood Collection[16]			X	X[17]	X	X	X	X		X[17]			X[17]
PD Blood Collection[16]			X	X[17]	X	X	X	X		X[17]			X[17]
ADA Testing			X			X		X		X	X		X
Exploratory Immunologic Assessment Blood Sample[18]			X										
IP Administration[19]				X	X	X	X	X	X	X			

ADA = anti-drug antibodies; AE = adverse event; ECG = electrocardiogram; IBDQ = Inflammatory Bowel Disease Questionnaire; IP = investigational product; JCV= John Cunningham virus; PD = pharmacodynamics; PK = pharmacokinetics; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; WOCBP = women of childbearing potential.

[1] All predose procedures should be completed prior to dosing.

[2] Day 70 AE monitoring will be obtained via phone call and data to calculate rectal bleeding and stool frequency subscores will be obtained; 6-month follow-up PML assessment will be obtained via phone call (the phone call should occur 6 months following discontinuation of treatment if the subject terminates early).

[3] Procedures to be performed within 10 days of Early Termination.

[4] All prior medications taken within 3 months before Screening should be recorded.
[5] Complete physical examinations (including a neurological examination) should be conducted at Screening. Complete physical examinations should also be conducted at Day 84, Day 112, and/or Early Termination. Directed physical examinations should be conducted at other time points. The Day 0 postdose examination will occur 4 hours postdose.
[6] Participants should be rested in a supine or semi-recumbent position for ≥ 5 minutes prior to recording of ECGs and vital signs. The ECGs and vital signs should be assessed prior to blood draws. Temperature by oral, axillary, or tympanic route may be permitted provided the same route is used for the participant throughout the study.
[7] Vital signs will be done at 1, 2, and 4 hours ± 20 minutes postdose following the first dose of study drug.
[8] Predose (baseline) ECGs should be repeated 3 times with 1- to 2-minute intervals between ECG readings, all within 2 hours prior to dosing.
[9] ECG only to be performed if previously abnormal.
[10] Laboratory samples collected at Screening and on Day 0 (predose), Day 28, Day 84 (or Early Termination), and Day 112 MUST be after the participant has FASTED from all food and drink except water for ≥ 8 hours (except for any dietary requirements that are part of sigmoidoscopy prep). Chemistry Panel at these fasting visits will include cholesterol and glucose analytes. All other non-fasting visits will have Chemistry Panel completed without cholesterol and glucose analytes. See Appendix B for list of analytes assessed.
[11] PML Assessment Questionnaire subjective checklist will be performed at Screening and at designated study visits (see Appendix D). If the Screening PML subjective checklist was performed within 14 days of Day 0, it will not need to be repeated on Day 0. At Day 0 (predose), subjects will be educated on the signs and symptoms of PML and advised to report if they experience any of those signs or symptoms at any time during the study.
[12] Sigmoidoscopy, biopsy, and a baseline complete Mayo Score are to be completed within 14 days of randomisation (as close to randomisation as possible; however, subjects may have a combined Screening visit that includes endoscopy) after confirmation of eligibility from other screening tests. Mayo Score for stool frequency and rectal bleeding should be done before the day of sigmoidoscopy. Mayo Score for physician's global assessment will be completed on the day of the sigmoidoscopy. Sigmoidoscopy should be the last procedure before randomisation. Subjects must meet eligibility criteria of Mayo Score 6 to 12 and endoscopy subscore of ≥ 2 in order to be randomised.
[13] Complete Mayo Score (including all 4 subscores) to be assessed at Screening, Day 84, and Early Termination (if possible); partial Mayo Score (without endoscopy subscore) to be assessed at all other time points except Day 70 where only rectal bleeding and stool frequency subscores will be reported via phone.
[14] JCV antibody testing must be performed within 90 days prior to dosing. Testing will be performed at the time of the pretreatment sigmoidoscopy if no prior results (within the 90-day timeframe) are available, and if the subject is eligible for study enrolment. Results will not determine eligibility for the trial.
[15]Randomisation will occur after all subject eligibility has been confirmed in the screening period. Randomisation in the interactive web/voice response system must be completed in advance of Day 0. Dosing should occur within 7 days of randomisation.
[16] Baseline (Day 0 predose) PK and PD blood samples will be taken within 2 hours prior to dosing. PD samples to be taken at selected sites only.
[17] PK samples are to be collected at 1, 2, and 4 hours ± 20 minutes postdose on Day 0 and Day 84 or Early Termination (if possible) only. PD samples to be collected 4 hours ± 20 minutes postdose on Day 0 and Day 84 or Early Termination (if possible) only. For every visit other than Day 0, a single PK and PD sample will be obtained within 1 hour prior to taking the regularly scheduled dose.
[18] A separate blood sample will be collected at selected sites (Day 0 predose only) for immunologic assessment.
[19] IP will be administered once daily for 84 days. The first drug will be administered at the study centre and subjects will be observed for at least 4 hours. On visits to study site, subjects should take the daily dose of study medication after completion of all blood collections. On Day 0, if the IP shipment is delayed, late dosing will not be considered a protocol deviation.

6.2 Study Treatment

6.2.1 Drug Supplies and Accountability

Specific instructions about the storage, dispensation, and administration of PTG-100 to subjects will be provided in the pharmacy manual.

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of the study drugs (Table 6-2).

Table 6-2 Study Drug

Study Drug	Placebo	PTG-100	PTG-100
Form[a]	Powder in a hard gelatin capsule	Powder in a hard gelatin capsule	Powder in a hard gelatin capsule
Strength	0 mg	150 mg	300 mg
Supplier	Protagonist	Protagonist	Protagonist
Manufacturer	Catalent	Catalent	Catalent

[a] Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug.

The lot numbers for the study drug will be provided to the clinical sites by the supplier/manufacturer.

Study drugs will be supplied in blister packs and **stored refrigerated at 2°C to 8°C under secure conditions**.

The Investigators (or designees) will maintain an accurate record of the receipt of the clinical trial materials as shipped by the Sponsor (or designee), including the date received. One copy of this receipt will be returned to the Sponsor (or designee) when the contents of the shipment have been verified. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor on request.

At the completion of the study, all unused drug supplies will be returned to the Sponsor (or designee) or disposed of by the clinical site(s), per the Sponsor's (or designee's) written instructions.

6.2.2 Subject Number and Identification

Subjects will be assigned a number by an Interactive Web Response System . Assignment of numbers will be in ascending order and no numbers will be omitted. Subject numbers will be used on all study documentation. For subjects who are withdrawn by the Investigator (or designee) or who voluntarily withdraw prematurely from the study, replacement subjects will be enrolled only if deemed necessary by the Sponsor. Replacement subjects will be assigned a subject number by adding 300 to the number of the subject they are replacing (eg, Subject No. 305 replaces Subject No. 005) and will be enrolled into the same randomisation arm as the subject whom they are replacing.

6.2.3 Dose Preparation and Administration

Study drug (PTG-100 or placebo) will be administered by subjects orally QD.

Matching PTG-100 (150-mg or 300-mg capsule) and placebo capsules will be provided to subjects in prepackaged individual study drug wallet kits, identical in appearance, according to the randomisation schedule. Each prepackaged kit will be appropriately labelled. Each day during the double-blind treatment period (preferably in the morning), subjects will take a total of 3 capsules, without regard to meals, according to their blinded treatment assignment, as follows:

- 150 mg PTG-100 group will receive: 1 × 150-mg capsule, 2 × placebo capsules
- 300 mg PTG-100 group will receive: 2 × 150-mg capsules, 1 × placebo capsule
- 900 mg PTG-100 group will receive: 3 × 300-mg capsules
- Placebo group will receive: 3 × placebo capsules

Study drug will be prepared in blinded blister packs and dispensed by the pharmacist (or appropriate designee) at study site visits; the subject will return any unused study drug at site visits during which site personnel will record used and unused capsules.

Subjects will be encouraged to take their daily study drug in the morning at approximately the same time each day. If the subject forgets to take a morning dose, the subject will be advised to take the dose on the same day. If it has been more than 12 hours since they were due to take the dose, they will be advised to skip that dose and resume the daily schedule with the next dose. Subjects will be told to not “double-up” on the doses if doses are missed.

All study personnel including the Sponsor, Contract Research Organization (CRO), Medical Monitors, Investigator, site pharmacist (or designee), site personnel involved in

study conduct, and subjects will remain blinded to study medication assignment. Appropriate unit doses, as described above, will be administered to consecutively-numbered subjects.

For all site visit days, doses will be administered orally after PK and PD blood collections. Doses will be preceded by an overnight fast (ie, at least 8 hours) from food (not including water) on Days 0, 28, 84, and 112 only prior to safety lab collection. Subjects may resume food after the blood collection.

At all other times during the study, subjects will have no water or meal restrictions or requirements.

6.2.4 Blinding

This will be a double-blind, placebo-controlled study. As such, the Sponsor, CRO, Medical Monitors, Investigator, site pharmacist (or designee), site personnel involved in study conduct, and subjects will remain blinded to study medication assignment.

An independent Data Monitoring Committee (DMC) will monitor safety throughout the study period and may be unblinded as necessary. Limited personnel required for conducting the analyses may also be unblinded to allow necessary safety oversight. The DMC will also be involved in the IA. Limited personnel required for conducting the IA will also be unblinded. Unblinded personnel required for the IA will be defined in the DMC charter.

Unblinding of individual subject treatment assignment may be permitted in the event of an emergency situation requiring knowledge of treatment assignment; however, subject assignment should not be routinely unblinded. Unblinding will be performed via the IXRS. This randomisation information may be opened and the randomisation for each individual subject made available to the Investigator (or designee) only in the event of a medical emergency or an AE that necessitates identification of the clinical trial material for the welfare of that subject. Except in a medical emergency, the Investigator (or designee) and blinded clinical site staff will remain blinded during the conduct of the study and until such time that all discrepancies in the clinical database are resolved (ie, at the database lock). The date/initials and reason for the Investigator (or designee) removing the study blind will be documented. Although the Investigator (or designee) will remain blinded as to treatment, the Investigator (or designee) will assess the data in

aggregate for safety and tolerability review. Unblinding for any other reason will be considered a protocol violation.

6.3 Study Restrictions

6.3.1 Diet, Fluid, and Activity Control

Subjects will adhere to recommended dietary and activity restrictions prior to sigmoidoscopy/ biopsy according to the Investigator (or designee).

Subjects will maintain their normal level of physical activity throughout the entire study (ie, will not begin a new exercise program or participate in any unusually strenuous physical exertion). There are no dietary restrictions throughout the study except for fasting for at least 8 hours prior to study visits on Days 0, 28, 84, and 112 (except for dietary requirements that are part of the preparations for a sigmoidoscopy).

6.3.2 Concomitant Medications

Subjects will refrain from participation in any other investigational study drug trial in which receipt of any investigational drug occurred within 5 half-lives or 1 month, whichever is longer, prior to Screening and during the entire study.

Subjects will be expected to continue their existing medication regimen, provided those treatments are permitted in the protocol.

Subjects may be receiving the following drugs at enrolment and must maintain stable doses throughout the treatment and follow-up period:

- Oral 5-ASA therapy may be continued provided that subjects have been on treatment for at least 6 weeks with a stable dose for the 2 weeks immediately prior to screening endoscopy
- Oral corticosteroid therapy (prednisone at a stable dose ≤ 20 mg/day, or equivalent steroid) may be continued provided that subjects have been on treatment for at least 4 weeks with a stable dose for at least 2 weeks immediately prior to screening endoscopy
- Azathioprine or 6-MP may be continued provided that the dose has been stable for the 4 weeks immediately prior to screening endoscopy
- Antidiarrhoeals (eg, loperamide, diphenoxylate with atropine) may be continued at a stable dose for control of chronic diarrhoea

- Probiotics (eg, Culturelle, Saccharomyces boulardii) may be continued provided that the dose has been stable for the 2 weeks immediately prior to screening.

The following drugs must be discontinued and may not be used during the study:

- Use of topical 5-ASA or corticosteroid enemas/suppositories must be discontinued within 2 weeks prior to the screening endoscopy
- TNF-α antagonist drugs must not be used within 60 days prior to screening
- Ustekinumab must not be used within 3 months prior to screening
- Cyclosporine, thalidomide, tacrolimus, sirolimus, or mycophenolate mofetil must not be used within 1 month prior to screening
- Investigational drugs or biologic agents must not be used within 1 month (or 5 half-lives) prior to screening
- Vedolizumab, natalizumab, or other biologic therapy must not be used during the study. Subjects with prior treatment with vedolizumab or natalizumab are not eligible for participation in the study.
- No live viral vaccines should be administered within 1 month prior to screening
- Subjects must have discontinued antibiotics for treatment of infection according to the criteria listed in Section 5.2.

The Investigator (or designee) will review all subject medications prior to study entry and consult with the Medical Monitor if any questions or concerns arise. In general, subjects may continue concomitant treatments for stable or controlled concurrent medical conditions.

When concomitant use of a medication is in doubt, an evaluation will be made by the Investigator(s) (or designee[s]) and Medical Monitor to allow on-study use of some medications that are stable and unlikely to interfere with study medications and assessments.

Use of any newly prescribed, intermittent, or as-needed medication taken by a subject during the course of the study and the reason for its use (eg, to address an AE) will be documented in the source documents and the concomitant medication CRF. The administration of any of the disallowed concomitant medications noted above is prohibited.

6.3.3 Contraception

Female participants must be unlikely to conceive according to the criteria listed in Section 5.1.

Females of non-childbearing potential are defined as females who are ≥ 45 years of age with > 1 year since last menses. Female subjects who are of non-childbearing potential will not be required to use contraception.

If a female subject is < 45 years of age, or cessation of menses is < 1 year and > 6 months, FSH must be documented as elevated into the post-menopausal range at Screening or the subject must have been surgically sterile (eg, bilateral oophorectomy, hysterectomy) for at least 90 days.

Women of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of study medication in order to receive study drug.

Women of childbearing potential when sexually active with male partners who are not sterile will be required to use adequate hormonal contraception or use appropriate double barrier contraception (such as a combination of male condom with either cervical cap, diaphragm, or sponge with spermicide) as per local regulations and guidelines from the time of signing the ICF until 28 days after the last dose of study drug.

Any subject who becomes pregnant during the study must immediately discontinue further treatment with study drug and will be followed through the pregnancy's outcome (see Appendix F).

6.4 Screening Procedures (Days -42 to -7)

Subjects will undergo study-specific screening within 42 days prior to dosing (Day 0). Prior to the Screening visit, subjects will have fasted for ≥ 8 hours.

Subjects will sign the study-specific consent form in the presence of a study site physician (or appropriate designee), prior to any screening procedures being performed. The information recorded for all subjects, regardless of their suitability for the study, will be retained and archived.

The following information and procedures will be recorded and performed as part of the screening assessments for the first Screening visit:

- demographic data
- medical history
- prior medications (including all prescription medications within 3 months prior to screening)
- review of inclusion/exclusion criteria
- height and weight
- complete physical examination, including neurological examination; any subject with abnormal neurological examination will be excluded from study participation
- vital signs (including BP, heart rate, respiration rate, and temperature)
- 12-lead ECG
- clinical laboratory evaluations (including haematology, coagulation factors, serum chemistry, and C-reactive protein [CRP]; see Appendix B)
- stool for *C.difficile* (confirmed by toxin result), culture, and ova and parasites
- urinalysis (UA; see Appendix B)
- PML subjective checklist (see Appendix D)
- TB test (QuantiFERON-TB Gold assay or TB skin test) and chest x-ray (if indicated for positive TB test; see Appendix C)
- hepatitis B and C testing
- serum pregnancy test (for WOCBP)

Subjects who meet all of the preceding screening criteria will attend a second Screening visit (however, subjects may have a combined Screening visit that includes endoscopy), where they will undergo:

- sigmoidoscopy and biopsy (within 14 days of randomisation)
- complete Mayo Score assessment (within 14 days of randomisation; see Appendix A). Eligibility/baseline Mayo Score and sigmoidoscopy/biopsy should be done as close to randomisation as possible. Mayo Score for stool frequency and rectal bleeding should be done before the day of sigmoidoscopy. However, if the subject has a combined Screening visit, then the Mayo Score for stool frequency and rectal bleeding should be done before the day of randomization for final determination of eligibility. Mayo Score for PGA will be completed on the day of the sigmoidoscopy. Sigmoidoscopy should be the last procedure before randomisation. Subjects must meet eligibility criteria of Mayo Score 6 to 12 and endoscopy subscore of ≥ 2 in order to be randomised

- John Cunningham virus (JCV) antibody testing (within 90 days prior to dosing; a sample will be obtained for testing at the second Screening visit in the absence of prior JCV testing).

Subjects will be randomised within 7 days of dosing.

6.5 Clinical Site Admission (Day 0)

6.5.1 Predose Procedures

On arrival at the study site on Day 0, subjects will undergo the following assessments prior to dosing (see Table 6-1):

- confirmation of eligibility
- prior and concomitant medications
- AEs
- weight
- vital signs
- 12-lead ECG
- directed physical examination
- clinical laboratory evaluations (including haematology, coagulation, serum chemistry [fasting], CRP, and UA; see Appendix B)
- PML subjective checklist (see Appendix D); subjects will be educated on the signs and symptoms of PML and advised to report to designated site personnel if they experience any of those signs or symptoms at any time during the study
- IBDQ (see Appendix G)
- faecal calprotectin
- urine pregnancy test (for WOCBP; subject must have negative pregnancy test to be dosed)
- PK blood sample (within 2 hours prior to dosing)
- PD blood sample (within 2 hours prior to dosing; at selected sites only)
- ADA testing
- blood sample for exploratory immunologic assessment (selected sites only)
- dose administration (after completion of the preceding procedures); it should be noted that a delay to dosing on Day 0 due to IP shipment delay will not be considered a protocol deviation

6.5.2 Postdose Procedures

Subjects will be observed for up to 4 hours after the first dose of study drug. Following dose administration, the following assessments will be performed in the clinic:

- AEs
- concomitant medications
- vital signs (at 1, 2, and 4 hours ± 20 minutes postdose)
- directed physical examination (4 hours postdose)
- PK blood sample (1, 2, and 4 hours ± 20 minutes postdose)
- PD blood sample (4 hours ± 20 minutes postdose; at selected sites only)

6.6 Clinical Site Visits (Days 14, 28, 42, and 56)

Subjects will be instructed to take the study drug QD, preferably in the morning. Subjects will be instructed not to take their study drug dose the morning of their study site visits to allow for predose blood sampling. On these visits, subjects will take the study drug dose following completion of the blood collection. Details on dosing times and allowable dosing windows will be provided in the pharmacy manual and explained to the subject prior to their dismissal from the study site.

Subjects will return to the study site at designated visits according to the study schedule and will arrive without having taken their dose for the day. *Subjects will have fasted for ≥ 8 hours on Day 28 prior to arrival at the study site*. The following assessments will be performed prior to dose administration:

- AEs
- concomitant medications
- weight
- vital signs
- 12-lead ECG (Days 14 and 56 only)
- directed physical examination
- PML subjective checklist (see Appendix D); any positive responses to the PML subjective checklist will require that the PML objective checklist be performed by the Investigator according to Appendix D and the study manual
- urine pregnancy test (for WOCBP). Subjects must have negative urine pregnancy test to proceed with dosing
- partial Mayo Score assessment (rectal bleeding, stool frequency, PGA subscores only; see Appendix A)
- PK blood sample (within 1 hour prior to dosing)

- PD blood sample (within 1 hour prior to dosing; selected sites only)
- clinical laboratory evaluations (including haematology, coagulation, serum chemistry, CRP, and UA; see Appendix B) (Days 14, 28 [fasting], and 56 only)
- ADA testing (Days 28 and 56 only)
- faecal calprotectin (Day 42 only)

6.7 Day 70 (Phone Visit)

Sites will conduct the subject visit by phone.

The following assessments should be performed during this phone visit:

- AEs
- concomitant medications
- recording of rectal bleeding and stool frequency subscores only via diary record (see Appendix A)
- PML subjective checklist (see Appendix D); any positive responses to the PML subjective checklist will require that the PML objective checklist be performed by the Investigator at the study site according to Appendix D and the study manual

6.8 Final Treatment Day Clinical Site Visit (Day 84 or Early Termination)

The following assessments should be performed:

- AEs
- concomitant medications
- weight
- vital signs
- 12-lead ECG
- complete physical examination
- clinical laboratory evaluations (including haematology, coagulation, serum chemistry [fasting], CRP, and UA; see Appendix B)
- PML subjective checklist (see Appendix D); any positive responses to the PML subjective checklist will require that the PML objective checklist be performed by the Investigator according to Appendix D and the study manual
- serum pregnancy test (WOCBP)
- sigmoidoscopy and biopsy
- complete Mayo Score assessment (rectal bleeding, stool frequency, PGA, and endoscopy subscores; see Appendix A)
- IBDQ (see Appendix G)

- faecal calprotectin
- PK blood sample (within 1 hour prior to dosing and 1, 2, and 4 hours ± 20 minutes postdose)
- PD blood sample (within 1 hour prior to dosing and 4 hours ± 20 minutes postdose; at selected sites only)
- ADA testing

Subjects who experience a flare of UC requiring rescue treatment that is prohibited in the protocol (in the judgement of the Investigator) will be discontinued from further treatment with study drug. Subjects who terminate early from treatment may be placed on appropriate therapy by the treating physician. Subjects will complete an Early Termination visit (including endoscopy) within 10 days following discontinuation, undergo the study procedures detailed in the Study Flow Chart (Table 6-1), and will be encouraged to be followed for all safety assessments through 28 days.

6.9 Follow-up/End of Study Visit (Day 112)

Subjects will return to the study site having fasted for ≥ 8 hours, and the following assessments will be performed:

- AEs
- concomitant medications
- weight
- vital signs
- 12-lead ECG (if previously abnormal)
- complete physical examination
- clinical laboratory evaluations (including haematology, coagulation, serum chemistry [fasting], CRP, and UA; see Appendix B)
- PML subjective checklist (see Appendix D); any positive responses to the PML subjective checklist will require that the PML objective checklist be performed by the Investigator according to Appendix D and the study manual
- serum pregnancy test (WOCBP)
- partial Mayo Score assessment (rectal bleeding, stool frequency, PGA subscores only)
- faecal calprotectin
- ADA testing

Subjects will also be asked to confirm and provide all relevant contact information for the 6-month phone visit.

6.10 6 Months Post-Treatment (Final Phone Follow-up)

Study subjects will receive a follow-up phone call at the 6-month post-treatment time point (Day 252) or earlier if the subject terminates early from the study. During this call, the PML subjective checklist (Appendix D) will be administered and the data recorded in the CRF. Any positive responses to the PML subjective checklist will necessitate the scheduling of an additional site visit so that the PML objective checklist may be performed by the Investigator according to Appendix D and the study manual.

6.11 Efficacy Assessments

6.11.1 Mayo Score

Clinical remission, clinical response, endoscopic response, endoscopic remission, complete and partial Mayo Score and individual endoscopy, rectal bleeding, and stool frequency subscores will be assessed using the Mayo Score (see Appendix A).

Subjects will record stool frequency and rectal bleeding subscores in an electronic subject diary each day through the entire treatment and follow-up periods. Subjects will be provided standardised instructions for recording the number of stools and their worst rectal bleeding over a 24-hour period (Appendix A). Each subscore ranges from 0 to 3, with higher scores indicating more severe disease. For visits that include a sigmoidoscopy, data collected on the day of the bowel preparation will not be used to assess the Mayo Score. The nearest 3 available days preceding the study visit (or bowel preparation) will be used to assess the Mayo Score, allowing for discontinuous days if a day is missing (eg, Day -4, Day -3, Day -1 [with Day -2 missing]). However, if the subject has a combined Screening visit, then the baseline Mayo Score for stool frequency and rectal bleeding should be done before the day of randomization for final determination of eligibility.

Endoscopic subscore will be assessed by a central reading of recorded endoscopy scans. Sigmoidoscopy will be performed by the site endoscopist and scored by a blinded central reader reviewing video recordings of the procedure. Further details to standardise procedures, video recordings/equipment, and assessment of endoscopy will be provided in the laboratory manual.

The complete Mayo Score is a sum of 4 subscores (ie, stool frequency, rectal bleeding, endoscopic findings, and PGA). The complete Mayo Score ranges from 0 to 12 using all 4 subscores.

Partial Mayo Score (range 0 to 9) will include the PGA, stool frequency, and rectal bleeding subscores only.

At baseline and Day 84 (or Early Termination), complete Mayo Score will be assessed and recorded.

For evaluation of the primary endpoint clinical remission, the PGA subscore will **not** be evaluated, only the stool frequency, rectal bleeding, and endoscopic subscores will be assessed (Section 7.4). Clinical response will be assessed using the stool frequency and rectal bleeding subscores.

6.11.2 Colonic Biopsy

Colonic biopsies will be obtained from subjects during sigmoidoscopy at baseline (within 14 days prior to randomisation) and at Week 12 (Day 84). Biopsies will be taken from the most inflamed area of the colon, while avoiding necrotic areas of ulcerated mucosa or suture sites in patients with previous colonic resection. Biopsies should be repeated from the same area at baseline and at Week 12. Biopsies will be placed into RNA*later*® (Life Technologies Corporation, Carlsbad, CA, United States of America [USA]) or formalin for storage and subsequent processing. Further details regarding the biopsy collection, processing, storage, and shipment will be provided in the laboratory manual. Colonic biopsies will be subjected to histologic evaluation and immunohistochemistry. Histologic assessment will be performed.

All biopsies will be read by a central laboratory. Further details will be provided in the laboratory manual.

6.11.3 Faecal Calprotectin

Stool samples will be collected by the study subjects and brought to the study centre for faecal calprotectin assessment at the designated time points. The stool should be a morning specimen. Subjects will be provided instructions regarding the proper means of collecting (including proper collection time), processing (eg, mixing), and storing the stool samples.

Further details will be provided in the laboratory manual.

6.11.4 IBDQ

Health-related quality of life will be assessed by the IBDQ (see Appendix G),[16] a standardised validated questionnaire with scores ranging from 32 to 224 points, at time points designated in the study schedule (Table 6-1).

6.12 Pharmacokinetic and Pharmacodynamic Assessments

6.12.1 Pharmacokinetic Blood Sample Collection, Processing, and Analysis

Blood (4 mL) samples for PK analysis will be obtained in K_2EDTA tubes according to the site standard operating procedures (SOPs) prior to dosing and at the time points delineated in the study schedule (Table 6-1). All samples (except those collected postdose on Days 0 and 84) should be obtained prior to the daily dosing of study drug (ie, C_{trough}). The actual collection time of each sample must be recorded in the source data, collection tube, and on the electronic CRF (eCRF). The allowed time deviation window for blood sample collection is ± 20 minutes for the samples up to 4 hours postdose on Days 0 and 84.

The Sponsor will supply complete written instructions for collection, handling, processing, storage, and shipping of samples in the laboratory manual.

Plasma PK sample analysis will be performed using validated procedures and methods.

6.12.2 Pharmacodynamic Blood Sample Collection, Processing, and Analysis

Pharmacodynamic assessments will be measured from 2 mL blood samples collected in heparinised blood collection tubes from subjects at selected sites according to the study schedule (Table 6-1). The blood samples will be analysed by FACS for PTG-100 RO and α4β7 RE in peripheral blood lymphocytes. The percentages of circulating lymphocytes will also be measured.

An additional 3 mL blood sample will be collected in heparinised blood collection tubes at selected sites (Day 0 predose only) with plasma stored for exploratory immunologic assessments.

The Sponsor will supply complete written instructions for the collection, handling, processing, storage, and shipping of samples in the laboratory manual. The samples will be analysed using validated assay methods.

6.12.3 Anti-drug Antibody Blood Sample Collection and Processing

Blood samples (3 mL) will be collected in heparinised blood collection tubes according to the study schedule (Table 6-1) and serum will be evaluated for the presence of ADAs with a bridging immunoassay.

The Sponsor will supply complete written instructions for the collection, handling, processing, storage, and shipping of samples in the laboratory manual.

6.13 Safety Monitoring

Subjects will be monitored for AEs and concomitant medication use throughout the study. Physical examination (including weight and vital signs), clinical safety labs, PML assessments, and ECGs will be done periodically throughout the study according to the schedule specified in Table 6-1. Safety evaluations may be repeated at the Investigator's (or designee's) discretion.

The following will constitute AEs of special interest that will be monitored at each visit: serious or opportunistic infection (viral, bacterial, fungal including systemic/gut localization), allergic/drug reactions, immune system disorders, and/or suspected PML. Adverse events of special interest will not constitute Investigational New Drug safety reports unless they are defined as serious events and there is evidence suggesting a causal relationship between the drug and the event.

The JCV antibody testing must have been performed and documented on all randomised subjects within 90 days prior to dosing. All subjects will be closely monitored for signs and symptoms of PML through directed questionnaires that assess recent changes in vision, speech, gait, sensation, comprehension, coordination, and personality, with any positive responses prompting objective testing by the Investigator (see Appendix D).[1,17]

An independent DMC will be appointed to monitor the safety of the subjects in the study. The DMC will meet approximately quarterly to review the safety data and will make recommendations regarding the continuation, modification, suspension, or termination of the study. Operational guidelines will be specified in the DMC charter.

Every effort will be made to schedule and perform the procedures in accordance with the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same time point. Acceptable

windows for study visits are provided in Section 6.1. The order of priority for scheduling procedures around a time point is (in descending order of priority):

- dosing
- PK blood sampling
- PD blood sampling
- vital sign measurements
- ECGs
- blood and urine samples for clinical laboratories
- physical examinations

6.13.1 PML Monitoring

Any subject with abnormal neurological examination at Screening will be excluded from participation in the study.

The JCV antibody testing must have been performed and documented on all randomised subjects within 90 days prior to dosing.

All randomised subjects will be closely monitored for signs and symptoms of PML through directed questionnaires that assess recent changes in vision, speech, gait, sensation, comprehension, coordination, and personality, with any positive responses prompting objective testing by the Investigator (see Appendix D).[1,17,26,27] All randomised study subjects will be closely monitored for the onset of any new neurological signs or symptoms or suspected PML during treatment and follow-up. The study's monitoring program will include education of site personnel and subjects about the signs and symptoms of PML and will advise subjects to report to designated personnel should they experience any signs and symptoms suggestive of PML.

Study sites will be provided a stepwise algorithm for the action plan for all subjects with suspected PML during the study and follow-up period; details regarding this algorithm will be provided in the study manual. Appropriately qualified site staff will complete the subjective PML checklist using the questionnaire (Appendix D) at all study visits per the schedule in Section 6.1. If any subject has a positive response based on the PML subjective checklist, the site will immediately schedule a visit where the Investigator will perform the PML objective checklist (involving tests of visual fields, ocular motility, speech, muscle strength, gait, memory, and sensation) per Appendix D and the study manual. If a study subject has both positive subjective and objective checklists, the subject will be referred to a local neurologist for further evaluation to rule out PML. If

the neurologist cannot rule out PML, the case will be referred to the Independent Adjudication Committee (that will include at least one neurologist) for the final determination of PML.

6.13.2 Adverse Events

Adverse event definitions; assignment of severity, causality, action taken, and outcome; and procedures for reporting SAEs are detailed in Appendix F.

Subjects will be asked a nonleading question such as "Have there been any changes in your health status since Screening/since you were last asked?" at the time points specified in Table 6-1 to assess for the occurrence of AEs. Subjects will also be encouraged to voluntarily report AEs occurring at any other time during the study.

All nonserious AEs, whether volunteered, elicited, or noted on physical examination, will be recorded from Day 0 until study completion. Serious AEs will be recorded from the time the subject signs the ICF until study completion.

All AEs (nonserious and serious) should be followed until the event has resolved, returned to baseline, or is assessed as stable by the Investigator (or designee).

6.13.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations (including clinical chemistry panel [fasted at least 8 hours on designated study days], coagulation parameters, haematology, and UA; Appendix B) will be collected at the time points specified in Table 6-1. Medically indicated laboratory tests (emergency or unscheduled tests) will be conducted at the local laboratory as needed.

A blood sample will be taken from each subject for haematology, coagulation, and serum chemistry analysis at the time points delineated in the study schedules. Additional clinical laboratory tests may be performed at other times if deemed necessary.

Urinalysis will be performed at the Screening visit and at other times according to the study schedule. Urine microscopy will be performed in the event of abnormal macro analysis.

Screen for a hepatitis panel and TB testing (Appendix C) will be performed at Screening. Stool samples for *C. difficile* (confirmed by toxin result), culture, and ova, and parasite

examination will be obtained at Screening. An HIV antibody test will not be performed, but history of positive HIV test is exclusionary. Serum and urine pregnancy tests (WOCBP only) will be performed at the time points specified in Table 6-1.

6.13.4 Vital Signs

Vital sign measurements (including oral temperature, respiratory rate, and BP and pulse) will be obtained at the time points specified in Table 6-1. Blood pressure and pulse will be taken with the subject in a supine or semi-recumbent position; subjects will have rested in a supine or semi-recumbent position for at least 5 minutes prior to and during vital sign measurements. Temperature may be taken by oral, axillary, or tympanic route provided the same route is used for the participant throughout the study. When the time of vital sign measurements coincides with a blood draw, the vital signs will be taken before the scheduled blood draw where possible.

6.13.5 Twelve-lead Electrocardiograms

A 12-lead ECG will be obtained at the time points specified in Table 6-1. Additional ECG monitoring may be performed at other times if deemed necessary. Subjects will be supine or semi-recumbent for at least 5 minutes prior to obtaining an ECG measurement.

The predose (baseline) ECG will be repeated 3 times with 1- to 2-minute intervals between ECG readings within 2 hours prior to dosing. The ECG measurements will be single measurements performed according to the study schedule. Electrocardiogram parameters (including heart rate; PR, QRS, and QT intervals; and QT interval corrected for heart rate using Fridericia's formula) and the Investigator's overall interpretation of the ECG will be recorded in the CRF. When the time of ECG monitoring coincides with a blood draw, the ECG will be taken before the scheduled blood draw.

6.13.6 Physical Examinations

A complete physical examination will be performed at the time points specified in Table 6-1. A directed exam (including exam of general appearance, skin, thorax/lungs, cardiovascular system, and abdomen) will be performed at the time points specified in Table 6-1.

The time and date of the physical examination findings will be recorded in the CRF and any clinically significant findings will be recorded as AEs.

6.14 Study Termination

The study or specific participating sites may be terminated if significant violations of Good Clinical Practice (GCP) that compromise the ability to achieve the study objectives or compromise participant safety are observed at any time during the study. With regard to safety, the study may be temporarily suspended or terminated should the DMC determine that the safety of study participants is significantly jeopardised. Additional reasons for termination of the study may include: medical or ethical reasons affecting continued performance of the study, inability to recruit subjects, or suspension or cancellation of the drug development program. The decision for a temporary or permanent study hold will depend on the nature, frequency, and severity of AEs that were observed in all enrolled participants to date. In a temporary study hold, no additional participants will be enrolled into the study or dosed with study drug until the DMC determines it is safe to proceed with the study.

7 DATA ANALYSES AND SAMPLE SIZE

7.1 Sample Size

Approximately 240 male and non-gravid female subjects aged 18 to 80 with moderate to severe active UC will be randomised. If only 2 arms are selected for continuation following the IA, then up to approximately 210 subjects will be randomised in the study; see Section 7.2.

Prior studies[1,17-21] suggest treatment effects of approximately 21 percentage point differences from placebo clinical remission rate of approximately 10%. Those values were assumed for purposes of design of this 12-week trial.

The table below shows power for representative scenarios of potential TRUE underlying dose-response relationships, as well as that for no drug effect to assess type 1 error (calculations via Cytel's EAST COMPASS adaptive dose-finding software based on 1000 simulations of each design, with each simulated trial analysed as described in the statistical methods section).[22]

TRUE underlying response rates				power (alpha=0.025, 1-sided)			
placebo	150 mg	300 mg	900 mg	N=260	N=240	N=220	N=200
0.1	0.2	0.31	0.31	93%	91%	90%	84%
0.1	0.17	0.24	0.31	83%	82%	78%	75%
0.1	0.1	0.1	0.1	3.4%	2.2%	1.7%	2.1%

7.2 Interim Analysis

An unblinded IA will be performed by the Adaptive Design Review Committee (ADRC) after approximately 60 to 80 subjects have been dosed and completed 12 weeks of dosing or terminated early (Stage 1).[23] A futility analysis will be performed; if the trial does not meet criteria for futility, further analysis will be conducted in order to drop one (or 2) of the PTG-100 dose arms (Stage 1, see below). Following the IA, randomisation will continue to the remaining dose arms (Stage 2).

Conditional power will also be computed at the IA. It is the probability that the trial will yield a statistically significant difference for clinical remission at the higher chosen dose for Stage 2 if the observed difference at the IA is the TRUE underlying difference and the trial is continued to completion. If this probability is low (eg, less than 10% to 20%), the decision could be made to stop the trial for futility.

The PD, efficacy, and safety data will be analysed to model dose- and exposure-response from Stage 1 of the trial to allow dropping of an ineffective or redundant arm(s). Since the trial provides for a 12-week treatment period, it is expected that an additional approximately 60 subjects would be randomised in equal proportions to the 4 treatment groups while the first approximately 60 to 80 subjects' 12-week data are accumulated and analysed. Hence, in Stage 2, the remaining subjects would be randomised in equal proportions to the selected dose(s) and placebo. This would yield approximately 70 to 80 subjects per treatment group for the selected doses. Final analysis will combine all observed data from both Stages 1 and 2.

The IA guidelines for futility and dose selection will be defined in the DMC charter and will be made in consideration of safety data and sound clinical judgment. Dose selection for Stage 2 will be made by the ADRC, which will be comprised of the DMC and a representative of the Sponsor (not involved in the direct conduct of the study). No pre-specified algorithm will be defined for the IA, although specific guidelines for dropping a dose(s) will be provided in the DMC charter. Only the ADRC, which will make the dose selection for Stage 2, and the Independent Statistical Centre, which will perform the IA, will be unblinded.

Stratification by prior treatment with TNF-α antagonist use will be maintained in both Stage 1 and 2.

7.3 Study Populations

Safety Population: All randomised participants who receive any amount of study drug will be included in the safety analyses.

Pharmacokinetic Analysis Population: All randomised participants who receive a Day 0 dose of study drug and who have sufficient PK data (meeting the required minimum blood volume collected along with the sampling schedule, with an accurate record of dosing and sampling time, and without vomiting) for analysis will be included in the PK analyses.

Full Analysis Set: All randomised participants who receive any amount of study drug and who have results from baseline and from ≥ 1 post-baseline assessment will be included in the PD and efficacy analyses.

7.4 Statistical Analysis of Efficacy Data

The primary efficacy endpoint for this study is the proportion of subjects receiving PTG-100 with clinical remission at Week 12 compared with placebo.

Clinical remission is defined as follows, using the Mayo subscores of stool frequency, rectal bleeding, and endoscopy:

- Stool frequency subscore of 0 or 1 with a pre-specified change of 1 or more from baseline
- Rectal bleeding subscore of 0
- Endoscopy subscore of 0 or 1 (modified so that a score of 1 does not include friability)

The secondary endpoints, all based on comparison of individual PTG-100 dose levels with placebo, include:

1. Proportion of subjects with endoscopic response at Week 12 (Day 84) (defined as an endoscopic subscore of 0 or 1)
2. Proportion of subjects with clinical response at Week 12 (Day 84) (defined as at least 1 point and 30% reduction from baseline in rectal bleeding and stool frequency subscores)
3. Mean change in endoscopy subscore from baseline to Week 12 (Day 84)
4. Mean change in rectal bleeding and stool frequency subscores from baseline to Weeks 2, 4, 6, 8, 10, 12, and 16 (Days 14, 28, 42, 56, 70, 84, and 112)

5. Proportion of subjects with endoscopic remission at Week 12 (Day 84) (defined as an endoscopic subscore of 0)
6. Mean change in complete Mayo Score (including all 4 subscores) from baseline to Week 12 (Day 84)
7. Mean change in partial Mayo Score (excluding endoscopy subscore) from baseline to Weeks 2, 4, 6, 8, 10, 12, and 16 (Days 14, 28, 42, 56, 70, 84, and 112)
8. Mean change in faecal calprotectin levels from baseline to Weeks 6, 12, and 16 (Days 42, 84, and 112)
9. Mean change in IBDQ score from baseline to Week 12 (Day 84)

The exploratory endpoints (all based on comparison of individual PTG 100 dose levels to placebo) include:

1. Mean change in histological score from baseline to Week 12 (Day 84) (assessment tool to be determined)
2. Effects of ADA on PK, safety, and efficacy in subjects with positive ADA

Descriptive statistics will be used to evaluate differences in demographic and baseline characteristics.

For the primary analysis, proportions of subjects with clinical remission will be compared between each dose and placebo using Cochran-Mantel-Haenszel test, with adjustment for stratification factors. Rates of clinical response, endoscopic response, and endoscopic remission will be evaluated similarly.

Multiplicity will be addressed via closed testing procedure with combined p-values computed for each of the 2 stages of the trial (IA and post-IA). Each stage p-value will be adjusted as appropriate by closed testing multiple comparison approach per Simes.[24] This approach controls the overall type 1 error at alpha=0.025, 1-sided.

All analyses will be based on combined Stage 1 and Stage 2 data and include data from the dose(s) that is (are) dropped for Stage 2. Exploratory analyses will be carried out to assess consistency of results between Stages 1 and 2. Analyses of other binary endpoints will be carried out similarly.

Subjects who discontinue prematurely will be considered treatment failures.

Changes from baseline complete Mayo Score, partial Mayo Score, rectal bleeding subscore, stool frequency subscore, endoscopic subscore, IBDQ score, and faecal

calprotectin levels will be analysed using repeated measures mixed analysis of covariance model adjusted for treatment, time point, treatment-by-time point interaction, stratification factors, and baseline values. For subjects who withdraw prematurely, the last observation will be carried forward. These analyses will be based on the Stage 1 and Stage 2 combined data for exploratory purposes.

Details regarding the statistical analyses of efficacy data will be provided in the Statistical Analysis Plan (SAP).

7.5 Statistical Analysis of Safety Data

The primary safety endpoint is the proportion of subjects with at least 1 AE comparing individual PTG-100 dosing groups with placebo.

The secondary endpoints (all based on comparison of individual PTG-100 dose levels to placebo) will include:

1. Frequency and type of AEs (affecting ≥ 5% of subjects)
2. Proportion of subjects with at least 1 SAE
3. Number and type of SAEs
4. Frequency of AEs of special interest including serious or opportunistic infection (viral, bacterial, fungal including systemic/gut localization), allergic/drug reactions, immune system disorders, and suspected PML
5. Clinically significant changes in safety labs, ECGs, or physical examination findings (including vital signs).

Continuous safety data will be summarised with descriptive statistics (arithmetic mean, standard deviation [SD], median, minimum, and maximum) by dose level. Categorical safety data will be summarised with frequency counts and percentages by dose level. Adverse events will be coded using the most current Medical Dictionary for Regulatory Activities available, which will be indicated in the Data Management Plan. A by-participant AE data listing, including verbatim term, preferred term, system organ class, treatment, severity, and relationship to study drug, will be provided. The number of participants experiencing treatment-emergent AEs (TEAEs) and number of individual TEAEs will be summarised by treatment group, system organ class, and preferred term. The TEAEs will also be summarised by severity and by relationship to study drug.

Laboratory evaluations, vital signs assessments, and ECG parameters will be summarised by treatment group and protocol-specified collection time point. A summary of change-

from-baseline at each protocol-specified time point by treatment group will also be presented.

Clinically significant changes in physical examinations will be listed for each participant and described in the text of the Clinical Study Report.

Medical history will be listed by subject.

Concomitant medications will be listed by participant and coded using the most current World Health Organization drug dictionary.

Further details regarding presentation and analysis of safety data will be detailed in the SAP.

7.6 Pharmacokinetic Analysis

Noncompartmental PK analyses will be performed on individual PTG-100 plasma concentration data. The C_{max}, C_{trough}, and T_{max} will be taken directly from the observed data. The AUC_{0-t} will be calculated using the linear trapezoidal rule.

The PK analyses will be performed using commercial software such as Phoenix™ WinNonlin® Version 6.4 or higher (Certara USA Inc.). All PK calculations will be performed using published noncompartmental relationships. Actual dose administration times and sample collection times will be used for the analyses as recorded on the CRF. Plasma concentrations below the lower limit of quantification will be set to zero for the analysis.

As a secondary endpoint, individual PTG-100 concentration data will be listed and summarised by treatment group with descriptive statistics (sample size, arithmetic mean, SD, median, minimum, maximum, geometric mean, and geometric coefficient of variation). Mean and individual PTG-100 concentration-time profiles will be presented graphically on both linear and semilogarithmic scales. All statistical analyses will use non-rounded parameter estimates. Plasma concentration data and the PK parameter estimates will be presented by study group. Pharmacokinetic parameter estimates will be 3 or 4 significant figures for presentation. No attempt will made to estimate missing data. Other parameters and data handling procedures may be added as appropriate. Final PK parameters reported and statistical approaches will be detailed in the SAP.

7.7 Pharmacodynamic Analysis

Quantitation of PTG-100 RO and α4β7 RE on peripheral blood T cells will be evaluated as secondary endpoints.

The exploratory endpoints will include:

1. Analysis of peripheral blood lymphocytes in subjects on individual PTG-100 dose levels compared to placebo
2. Number of β7 positive cells in colonic biopsies as assessed by immunohistochemistry in subjects on individual PTG-100 dose levels compared to placebo

Individual data will be listed for each individual and summarised by nominal sampling time point and treatment group with descriptive statistics (arithmetic mean, SD, median, minimum, and maximum). A summary of change-from-baseline at each protocol-specified time point by treatment group will also be presented. The change of PD indicators over time will be demonstrated graphically and will be compared among the dose levels. Details regarding the statistical analyses of PD data will be provided in the SAP.

Receptor occupancy and α4β7 RE in peripheral blood will be listed for each individual and summarised by frequency counts for discrete categories.

Additional population PK-PD modelling may be performed and will be detailed in the SAP.

Details regarding the statistical analyses of PD data will be provided in the SAP.

7.8 Immunogenicity Analysis

The proportion of subjects developing ADA by Weeks 12 (Day 84) and 16 (Day 112) will be characterised.

Serum samples will be evaluated for the presence of ADA through use of a validated bridging immunoassay. This will involve conjugating PTG-100 to biotin or horseradish peroxidase (HRP) enzyme using a flexible PEG linker. The biotin conjugate will be used to immobilize PTG-100 to streptavidin coated wells of assay plates. Clinical serum samples containing anti-PTG-100 antibodies will bind to the plate and binding can be detected using horseradish peroxidase-conjugated PTG-100. To validate the ADA assay,

we will spike positive control antibodies into the matrix selected for the assay to measure assay sensitivity and specificity as recommended by the FDA guidance.[25] We will also establish a negative control by pooling the sera from 5 to 10 non-exposed individuals. The evaluation will include assessment of neutralizing ADAs, as well as the potential of ADA to cross-react with endogenous MAdCAM-1. If ADA is detected in clinical samples, the effect of ADA on PK, safety, and efficacy may be explored for all subjects who demonstrate evidence of ADAs.

7.9 Data Handling and Record Keeping

Any changes to the information in the trial progress notes and other source documents will be initialled and dated on the day the change is made by a clinical site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

The Data Management Plan will be approved by the Sponsor.

Data will be validated during data entry by the clinical site and verified by the Study Monitor. Data will then be reviewed by the data management group to resolve any outstanding issues. Listings will be generated after the database is cleaned by Data Management and will be reviewed by the Covance scientific team. The CRF/eCRF and ancillary data will be converted into final SAS® datasets following Study Data Tabulation Model or client-provided specifications. The final datasets structure will be verified (eg, by using a data management system such as Web Submission Data Manager®) while the dataset content will be peer-reviewed by an independent programmer.

The tables, figures, and listings (TFLs) will be programmed per the final SAP. All TFLs will be peer-reviewed by an independent programmer. In addition, draft TFLs will be reviewed by the Covance scientific team during the dry run and data review meetings.

The peer-review will be performed by independent programmers following the quality control process and programming checklists.

7.10 Quality Control and Quality Assurance

Quality control and quality assurance will be performed according to Covance SOPs or per client request and as applicable according to the contract between Covance and the Sponsor.

Prior to participation, investigational sites and Investigators will be evaluated for appropriate qualifications and ability to execute the study. Each investigational site must undergo appropriate training on the study protocol and ancillary study procedures and documents, through participation in an initiation visit or Investigator Meeting. Training must take place before any subjects are enrolled at that site. Initiation visits and Investigator Meetings will include (but may not be limited to) review of GCP guidelines, study drug dispensation and administration procedures, data collection requirements, and subject eligibility requirements.

The Sponsor and/or its representative may make periodic visits to the investigational site to assess compliance with study procedures and regulatory requirements; to ensure that the safety, welfare, and privacy of subjects are being protected; and to verify the accuracy and integrity of the study data. In addition, independent quality assurance site audits may be conducted as verification of the quality and compliance of study conduct.

The Sponsor and/or its representative will periodically review the study data to ensure that data are being appropriately collected and reported. Queries and corrections will be made as needed.

8 ADMINISTRATIVE ASPECTS

8.1 Change in Protocol

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator.

There will be no alterations in the protocol affecting subject safety without the expressed written approval of the Sponsor, Investigator, and the Institutional Review Board (IRB; see Form FDA 1572) or Independent Ethics Committee (IEC).

8.2 Site Initiation Visit/Investigator Meeting

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the Investigator(s) and appropriate clinical staff to familiarise the Investigator(s) and clinical staff with the protocol and the materials necessary for conducting the clinical study.

8.3 Disclosure

All information provided regarding the study, as well as all information collected/documented during the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

8.4 Publication

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing study results within 12 months after the last data become available. The Sponsor will post a synopsis of study results for approved products on www.clinicaltrials.gov by 12 months after the last patient's last visit or within 7 days of product approval in any major markets (US, Europe, or Japan), whichever is later. These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties.

Authors of the primary results manuscript will be provided the relevant results from the Clinical Study Report, subject to the confidentiality agreement. For this multicentre study, subsequent to the multicentre publication (or after public disclosure of the results online if a multicentre manuscript is not planned), an Investigator and his/her colleagues may publish their data independently. In most cases, publication of individual site data does not add value to complete multicentre results, due to statistical concerns. In rare cases, publication of single-site data prior to the main paper may be of value. Limitations of single-site observations in a multicentre trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article

or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Significant contributions to study execution may also be taken into account to determine authorship, provided that contributions have also been made to all of the preceding authorship criteria. Contributors who do not meet the criteria for authorship will not be listed as authors, but should be acknowledged. The collection of data, or general supervision of the research group, by themselves, does not justify authorship. Although publication planning may begin before conducting the study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend the integrity of the data, method(s) of data analysis, and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission. Sponsor review can be expedited to meet publication timelines.

8.5 Monitoring

The Sponsor will designate a Sponsor's Study Monitor who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor will monitor the study conduct, proper CRF and source documentation completion and retention, and accurate study drug accountability. To this end, the Sponsor's Study Monitor will visit the clinical site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Sponsor's Study Monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Sponsor's Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

8.6 Institutional Review Board/Institutional Ethics Committee

In accordance with US Title 21 Code of Federal Regulations (CFR) 56, the protocol, advertisement, ICF, and any other information provided to subjects will be reviewed and

approved by the IRB/IEC. The Sponsor will supply relevant material for the Investigator (or designee) to submit to the IRB/IEC for the protocol's review and approval. Verification of the IRB/IEC unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator (or designee).

The IRB/IEC will be informed by the Investigator (or designee) of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the Investigator (or designee). If requested, the Investigator (or designee) will permit audits by the IRB/IEC and regulatory inspections by providing direct access to source data/documents.

The Investigator (or designee) will provide the IRB/IEC with progress reports at appropriate intervals, as per local regulations, and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

8.7 Informed Consent

Written informed consent for the study will be obtained from all subjects before protocol-specific procedures are carried out. The ICF will be approved (along with the protocol) by the IRB/IEC and will be acceptable to the Sponsor.

The Investigator (or designee) will explain the nature of the study and the action of the test product. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the IRB/IEC and signed by the subject prior to protocol-specific procedures being performed.

The subject will sign the ICF; a copy will be given to the subject, and the other will be maintained with the subject's records.

8.8 Records

The results from data collected at Screening and during the study will be recorded in the subject's CRF (paper or eCRF). To maintain confidentiality, the subjects will be identified only by numbers, initials, or both.

The completed CRFs will be transferred to the Sponsor (or designee). Copies of each CRF will be retained by the Investigator (or designee). All source documents, records, and reports will be retained by the clinical site in accordance with 21 CFR 312.62(c).

All primary data, or copies thereof (eg, laboratory records, CRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the clinical site archives.

8.9 Reference to Declaration of Helsinki/Basic Principles

The study procedures outlined in this protocol will be conducted in accordance with the US CFR governing Protection of Human Patients (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRB/IECs (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Applications for FDA Approval to Market a New Drug (21 CFR 314), as appropriate. As such, these sections of US Title 21 CFR, along with the applicable International Council on Harmonisation (ICH; formerly International Conference on Harmonisation) Guidelines, are commonly known as GCP, which are consistent with the Declaration of Helsinki.

8.10 Investigator Responsibilities

The Investigator agrees to:

- Conduct the study in accordance with the relevant, current protocol and make changes only after notifying Sponsor or its representative, except where necessary to eliminate apparent immediate hazards to human subjects
- Comply with the ICH Tripartite Guideline on GCP plus appropriate regional regulatory laws and requirements
- Personally conduct or supervise the described investigation
- Inform any subjects or persons used as controls that the study drugs are being used for investigational purposes
- Ensure requirements relating to obtaining informed consent and regional IEC/IRB approval have been met
- Report to the Sponsor or its representative any AEs that occur in the course of the investigations, as specified in Appendix F
- Read and understand the IB, including potential risks and side effects of the drug
- Ensure all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting their commitments

- Maintain adequate and accurate records and make these available for inspection by the Sponsor and/or its representative, or any regulatory agency authorised by law
- Promptly report to the regional IEC/IRB all changes in research activity and all unanticipated problems involving risks to human subjects or others
- Comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements
- Administer study drug only to subjects who meet study entry criteria and are enrolled in the study, and only according to the guidelines set forth in this protocol

8.11 Financing and Insurance

Financing and insurance will be addressed in a separate agreement.

SPONSOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein.

17 NOV 2017

Bittoo Kanwar, MD
Senior Medical Director
Protagonist Therapeutics, Inc.

Date

INVESTIGATOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein.

Printed Name of PI

Signature of PI

Date

REFERENCES

1. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699-710.
2. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711-721.
3. Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med*. 2011;365(18):1713-1725.
4. Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;10: CD000543. doi: 10.1002/14651858.CD000543.pub3.
5. Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;10:CD000544. doi: 10.1002/14651858.CD000544.pub3.
6. Ford AC, Khan KJ, Achkar JP, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107(2):167-176.
7. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med*. 2001;345(15):1098-1104.
8. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353(23):2462-2476.
9. Sandborn WJ, Van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142(2):257-265.e1-3.
10. ENTYVIO (Vedolizumab) for Injection, for Intravenous Use [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014. Available at: http://general.takedapharm.com/content/file.aspx?FileTypeCode=ENTYVIOPI&cacheRandomizer=1b94c181-3ea4-4aa4-8ac5-3a0592873792.
11. Gies N, Kroeker KI, Wong K, Fedorak RN. Treatment of ulcerative colitis with adalimumab or infliximab: long-term follow-up of a single centre cohort. *Aliment Pharmacol Ther*. 2010;32(4):522-528.
12. Kobayashi T, Suzuke Y, Motoya S, et al. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis – results from a multicenter prospective randomized controlled trial and its post hoc analysis. *J Gastroenterol*. 2016;51:241-251.

13. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987 Dec 24;317(26):1625-1629.
14. Shah SC, Colombel JF, Sands BE, Narula N. Mucosal Healing is Associated with Improved Long-term Outcomes of Patients With Ulcerative Colitis: a Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14(9):1245-1255.e8.
15. Feagan BG Sandborn WJ, D'Haens G, et al. The Role of Centralized Reading of Endoscopy in a Randomized Controlled Trial of Mesalamine for Ulcerative Colitis. *Gastroenterology*. 2013;145(1):149-157.e2.
16. Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology*. 1994;106(2):287-296.
17. Vermeire S, O'Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet*. 2014;384:309-318.
18. Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the α4β7 integrin. *N Engl J Med*. 2005;352(24):2499-2507.
19. Sandborn WJ, Feagan BG, Wolf DC, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. *N Engl J Med*. 2016;374(18):1754-1762.
20. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med*. 2012;367:616-624.
21. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastro*. 2014;46:85-95.
22. COMPASS User Manual, Cytel Inc., Cambridge, MA, 2012.
23. Posch M, Koenig F, Branson M, Brannath W, Dunger-Baldauf C, Bauer P. Testing and Estimation in Flexible Group Sequential Designs with Adaptive Treatment Selection. *Stat Med*. 2005;24:3697-3714.
24. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. *Biometrika*. 1986;73:751-754.
25. Department of Health and Human Services, Food and Drug Administration. Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products; Guidance for Industry. April 1, 2016. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf.

26. Parikh A, Leach T, Wyant T, et al. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. *Inflamm Bowel Dis*. 2012;18:1470–9. doi:10.1002/ibd.21896.
27. Parikh A, Mcauliffe M, Stephens K, Major E, Fox I, Milch C, et al. Risk assessment and minimization for progressive multifocal leukoencephalopathy (PML) (RAMP): a program to assess for potential early signs and symptoms of PML during clinical development of vedolizumab. Poster presented at: United European Gastroenterology Week 2013; 14 October 2013.

APPENDIX A - COMPONENTS OF THE MAYO SCORE

Stool Frequency

0 = Normal
1 = 1–2 stools/day more than normal
2 = 3–4 stools/day more than normal
3 = >4 stools/day more than normal

Rectal bleeding[a]

0 = None
1 = Visible blood with stool less than half the time
2 = Visible blood with stool half of the time or more
3 = Passing blood alone

Mucosal appearance at endoscopy[b]

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

Physician rating of disease activity

0 = Normal
1 = Mild
2 = Moderate
3 = Severe

[a]A score of 3 for bleeding required patients to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.

[b]The mucosal appearance at endoscopy is not included in the partial Mayo Score.

Study sites will use the following standardised instructions to advise subjects on recording the stool frequency and rectal bleeding over a 24-hour period.

Category of Instructions	Specific Instructions to Patients
Definition of *Stool*	• Patients should be instructed that a stool is defined as a trip to the toilet when the patient has either a bowel movement, or passes blood alone, blood and mucus, or mucus only
Most Severe Category of Rectal Bleeding (in a given 24-hour period)	• Patients should be instructed to indicate the most severe category that describes the amount of blood they had in their stools for a given day • Categories of rectal bleeding should be defined as follows: – No blood seen – Streaks of blood with stool less than half the time – Obvious blood (more than just streaks) or streaks of blood with stool most of the time – Blood alone passed • Patients should be instructed to select "No Blood Seen" in the rectal bleeding section if they do not have stool during a given day

APPENDIX B - CLINICAL LABORATORY EVALUATIONS

Clinical Chemistry Panel (Fasted):
Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Blood urea nitrogen
Calcium
Chloride
Cholesterol*
Creatinine
Glucose*
Potassium
Sodium
Total bilirubin
Total protein
Triglycerides
Uric acid

Haematology Parameters:
Haematocrit
Haemoglobin
Mean corpuscular haemoglobin
Mean corpuscular haemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell (RBC) count
RBC distribution width
White blood cell (WBC) count
WBC differential (absolute):
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils

Coagulation:
Activated partial thromboplastin time
Prothrombin time

Urinalysis:
Bilirubin
Colour and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic exam including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)

Other Tests:
Hepatitis B surface antigen
Hepatitis C virus antibody
Pregnancy test (females only; serum qualitative)
Pregnancy test (females only; urine quantitative)
Follicle-stimulating hormone (postmenopausal females only)
C-reactive protein
Enteric pathogens (stool sample)

*Required only on visits requiring fasting, ie, Day 0 (predose), Day 28, Day 84 (Early Termination), and Day 112 (Follow-up).

APPENDIX C - TB SCREENING CRITERIA

Subject is eligible according to the following tuberculosis (TB) screening criteria:

a. Has no history of untreated latent or active TB prior to screening. (Prophylactic treatment for latent TB as per local guidelines must be initiated within at least 28 days prior to first administration of study medication.)
b. Has no signs or symptoms suggestive of active TB upon medical history and/or physical examination
c. Has had no recent contact with a person with active TB or, if there has been such contact, will be referred to a physician specialising in TB to undergo additional evaluation and, if warranted, complete appropriate course of treatment for latent TB prior to the first administration of study drug
d. Within 42 days prior to first administration of study medication, either has negative diagnostic TB test results defined as either a negative tuberculin skin test or a negative QuantiFERON-TB Gold test
e. A subject who has a positive intradermal skin or positive QuantiFERON-TB Gold test, or who has had recent close contact with a person with active TB, or has signs or symptoms suggestive of active TB upon medical history and/or physical examination, or if required by local guidelines or regulations as part of routine TB screening, must have a negative chest radiograph (both posterioranterior and lateral views) or chest computed tomography scan, taken within 3 months prior to the first dose of study drug and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.

Note: If either the tuberculin skin test or QuantiFERON-TB gold test is positive AND the chest x-ray (or computed tomography scan) is negative, the subject is considered to have latent TB infection (LTBI). Subjects with LTBI may be included only if they have previously completed an adequate course of prophylactic treatment (per local guidelines or regulations) without subsequent new exposure to active TB. The need for repeat of prophylactic therapy if there is a history of new exposure to active TB subsequent to completion of prior LTBI treatment, or if prior LTBI treatment was completed > 3 months prior to screening, should be determined by the Investigator in consultation with a TB specialist.

APPENDIX D - PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) ASSESSMENT [26,27]

A subjective PML checklist (see table below) is to be administered by appropriately qualified site personnel (Investigator or Study Coordinator) to all subjects at Screening, at the designated time points as noted in Table 6-1, and whenever new neurologic symptoms manifest. For each symptom in the subjective checklist that had positive findings, results of an objective evaluation (see below), administered by the Investigator to assess corresponding neurologic function, are to be recorded on the objective checklist and an AE recorded.

Subjective 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 Objective 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 with 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 patients to name a few objects and repeat a multipart phrase.
3. Have you been experiencing any persistent weakness in an arm or a leg?				Test for pronator drift (Barré maneuver) and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test symmetric 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 (Close your eyes, stick out your tongue, and touch your left finger to your left ear)
6. Have you had persistent problems with your memory or thinking?				Recall of 3 objects over 1 minute with distraction; ability to follow commands.
7. Have you been experiencing any persistent numbness or other loss of sensation?				Test sensation side to side with pinprick.

Objective PML Checklist

Positive Symptom(s)	Applicable Objective Test(s)	Test Result(s)		If test result is abnormal, briefly describe result
		Normal	Abnormal	
1. Difficulty with vision or reading	Test visual fields and ocular motility			
2. Difficulty with speaking	Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.			
3. Weakness in an arm or a leg	Test for pronator drift and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test muscle strength.			
4. Bumping into things or difficulty writing	Ask for sponaneous written sample and observe finger to nose, heel to shin, and tandem gait			
5. Difficulty understanding others	Ability to follow serial commands (Close your eyes, stick out your tongue, and touch your left finger to your left ear)			
6. Problems with memory or thinking	Recall of 3 objects over 1 minute with distraction; ability to follow commands.			
7. Problems with numbness	Test sensation side to side with pinprick.			

If the objective test corroborates the reported symptom, the subject will be referred to a neurologist. Otherwise, the subject will receive a follow-up call 1 week after administration of the objective checklist to ensure that symptoms are not recurring.

APPENDIX E - BLOOD SAMPLING SUMMARY

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Hepatitis screen	3.5	1	3.5
Pregnancy tests	3	3	9
Pharmacokinetic sampling	4	12	48
Pharmacodynamic sampling	2	7	14
Haematology	4	7	28
Clinical laboratory tests	3.5	7	24.5
Coagulation	1.8	7	12.6
Anti-drug antibody test	3	5	15
Immunologic analysis	3	1	3
Total			157.6

APPENDIX F - ADVERSE EVENTS

ADVERSE EVENTS

Definition of Adverse Events

An adverse event (AE; or adverse experience) is defined as any untoward medical occurrence experienced by a patient or healthy subject, whether or not considered drug related by the Investigator (or designee). A treatment-emergent AE is an AE that is reported after a dose of study drug.

The following are all AEs:

- unfavourable changes in general condition;
- subjective or objective signs/symptoms;
- concomitant diseases or accidents;
- clinically relevant adverse changes in laboratory parameters observed in a subject during a clinical study.

Adverse events comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods, under placebo, or in a reference group receiving drug or nondrug therapy are also to be designated as AEs.

Categorization of Adverse Events

The severity of AEs will be categorized as follows:

- **MILD** = of little concern to the subject and/or of no clinical significance, is not expected to affect the subject's health or well-being;
- **MODERATE** = discomforting enough to cause interference with or change in usual activities, is likely to require medical intervention or close follow-up;
- **SEVERE** = incapacitating or causing inability to work or participate in many or all usual activities, is of concern to the subject or poses substantial risk to the subject's health or well-being, is likely to require medical intervention or close follow-up.

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- **NOT RELATED** = an AE that does not follow a reasonable temporal sequence from administration of the drug and can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment;
- **UNLIKELY RELATED** = an AE that follows a reasonable temporal sequence from the administration of the drug (including after withdrawal of the drug) and cannot be excluded as being possibly caused by the drug (eg, existence of similar reports attributed to the suspected drug and/or its analogues, reactions attributable to the pharmacological effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable;
- **POSSIBLY RELATED** = an AE that follows a reasonable temporal sequence from administration of the drug (including after withdrawal of the drug) and can be excluded as being possibly caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment;
- **RELATED** = an AE that follows a reasonable temporal sequence from administration of the drug (including after withdrawal of the drug), follows a known or hypothesized cause-effect relationship, and (if appropriate) satisfies the following:
  - positive results obtained in drug sensitivity tests;
  - toxic level of the drug present in blood or other body fluids.

An AE is associated with the use of the drug if there is a reasonable possibility that the experience may have been caused by the drug.

The following categories will be used for the action taken with the study drug for the AE: drug withdrawn, dose not changed, drug interrupted, unknown, and not applicable.

The following categories will be used for the outcome of the AE: resolved, resolved with sequelae, ongoing, fatal, and unknown.

Notification of the Independent Ethics Committees/Institutional Review Boards

Notification of the Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) about all relevant events (eg, serious AEs [SAEs], Suspected Unexpected Serious Adverse Reactions) will be performed by the Sponsor and/or by the Investigator according to all applicable regulations.

Pregnancy

The Investigator must report to the Sponsor any pregnancy occurring in a study subject (or subject's partner) during the subject's participation. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE. A pregnancy should be followed-up until reporting of the pregnancy's outcome and the birth date.

As information is available, a pregnancy diagnosed during the study will be reported immediately to the Investigator (or designee) or Sponsor, including pregnancy in female partners of male subjects. The pregnancy will be followed to term or outcome and this outcome will be reported to the Sponsor. Pregnancy, in and of itself, is not regarded as an AE or SAE unless the birth results in a congenital anomaly/birth defect or there is suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication or method.

Definition of Serious Adverse Events

An SAE (by Food and Drug Administration [FDA] definition) is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death;
- a life-threatening adverse drug experience (ie, places the subject, in the view of the Investigator [or designee], at immediate risk of death);
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant disability/incapacity;
- a congenital anomaly/birth defect;
- important medical event that may require medical or surgical intervention to prevent one of the above outcomes.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment,

they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. All SAEs must be collected that occur after the subject signs the Informed Consent Form.

Unexpected Adverse Drug Experience

An unexpected adverse drug experience is any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator's Brochure (IB) or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Reporting

Food and Drug Administration-reportable AEs are AEs that are associated with the use of the drug and are serious and unexpected. Food and Drug Administration-reportable AEs will be reported by the clinical site to the Sponsor, Medical Monitor assigned by the Sponsor, and the responsible IRB/IEC.

The Sponsor and Medical Monitor will be notified in writing (eg, facsimile) within 24 hours of when an AE that is potentially FDA-reportable is first recognized or reported.

Subsequently, a written confirmation or summary of the AE (using FDA Form 3500A, or equivalent) will be sent to the Sponsor within 3 working days of the original notification. (Instructions for completion of FDA Form 3500A may be obtained from the FDA website at www.fda.gov/medwatch/how.htm.)

The IRB/IEC will be notified of any FDA-reportable AE within the timeframe required by the IRB/IEC. The IRB/IEC Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

APPENDIX G - INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

INSTRUCTIONS FOR SELF-ADMINISTERED INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has graded response choices numbered from 1 to 7. Please read each question carefully and answer the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS THE MOST FREQUENT YOU HAVE EVER EXPERIENCED
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME

3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME

3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a toilet? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME

7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no toilet close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of wind? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME

4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a

feeling of having to go to the toilet even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME

4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or an upset stomach? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from

others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED