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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The primary objectives of this study are:1. To evaluate the safety and tolerability of PTG-1002. To evaluate the efficacy of PTG-100 in the induction treatment of subjects with moderate to severe active UC compared to placebo.The secondary…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal ulceration and perforation
Study type	Interventional

Summary

ID

NL-OMON45322

Source
ToetsingOnline

Brief title
PTG-100-02

Condition

- Gastrointestinal ulceration and perforation

Synonym
chronic inflammatory bowel disease, ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Protagonist Therapeutics Inc
Source(s) of monetary or material Support: farmaceutische industrie (Protagonist Therapeutics Inc)

Intervention

Keyword: Phase 2b Randomised, Placebo-controlled, PTG-100, Ulcerative colitis

Outcome measures

Primary outcome

The primary efficacy endpoint is the:

1. 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 primary safety endpoint is:

1. Proportion of subjects with at least 1 AE comparing individual PTG-100 dosing groups with placebo

Secondary outcome

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

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)

Study description

Background summary

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 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 (Cmax), 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 Cmax and AUC from time 0 to the time of the last sample collection [AUC0 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 AUC0-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).

Study objective

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.

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.

Intervention

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

Study burden and risks

PTG-100 has been tested in animals at much higher doses than patient will receive. No specific side effects were observed in these animals for up to 3 months of treatment.

PTG-100 has previously been tested in a study of normal healthy male volunteers. A total of 64 participants were given different doses of PTG-100 up to a maximum dose of 1000 mg for 14 days. The highest dose you would be assigned to in this study is 900 mg. In the completed study, PTG-100 was generally well tolerated by the volunteers. The most frequent side-effects of PTG-100 in this study were:
• headaches
• upper respiratory infections (colds, flu)
• back pain and fatigue (tiredness)

Upper respiratory tract infection and headache events also occurred in some subjects taking placebo. All of the side effects that were observed resolved without complications. There were no abnormalities in blood counts, blood chemistry tests, urine tests or electrocardiograms observed in the participants in the study.

PTG-100 is similar to an approved treatment for ulcerative colitis called vedolizumab (marketed as Entyvio®). Both PTG-100 and vedolizumab block the same *alpha-4*beta-7 integrin target; however, vedolizumab is given through the vein. Vedolizumab has been generally safe and well-tolerated when tested in over 3000 patients who participated in carefully monitored studies. The most common side effects reported with vedolizumab include nasopharyngitis (nasal congestion, throat irritation), headache, arthralgia (joint aches), nausea, pyrexia (fever), upper respiratory tract infection (colds), fatigue, cough, bronchitis (an inflammation of airways in the lungs), influenza (flu), back pain, rash, pruritus (itchiness), sinusitis (sinus infection), oropharyngeal (mouth) pain, and pain in arms and legs. Vedolizumab may increase the risk of

serious infection in some patients. Some patients have had increases in liver function tests while receiving vedolizumab. Vedolizumab must be discontinued in patients who develop jaundice (yellowing skin) or other evidence of significant liver injury. Vedolizumab is also associated with the development of anti-drug antibodies (formation of proteins in the body that may reduce the effectiveness of vedolizumab). It is not known if the risks of these side effects with vedolizumab will be similar while receiving PTG-100. Patient will be carefully monitored for any side effects including infections and liver tests.

Although nothing in pre-clinical (in animals) testing of PTG-100 and the human experience to date indicates that an allergic reaction is likely, a reaction to any drug is possible. Some symptoms of allergic reactions are:
• Rash
• Wheezing, or difficulty breathing
• Dizziness or fainting (also a possible outcome of a drop in blood pressure)
• Swelling around the mouth, throat or eyes
• A fast heart rate
• Sweating

Progressive multifocal leukoencephalopathy (PML)
Another drug which blocks a different integrin receptor has been associated with a rare and often fatal infection of the central nervous system (CNS) called PML. PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised (have severe suppression of the immune system). Typical signs and symptoms associated with PML may be variable, may progress over days to weeks, and include increasing weakness on one side of the body or clumsiness of limbs, changes in vision, and changes in thinking, memory, and orientation (awareness of surroundings) leading to confusion and personality changes. The progression of changes in PML usually leads to death or severe disability over weeks or months.
In clinical trials of vedolizumab, patients were actively monitored for PML with frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. While zero cases of PML were identified among patients with at least 24 months of exposure (and in patients taking vedolizumab since its approval in 2014), it is not possible to definitely exclude a risk of PML in patients taking drugs which block the alpha-4 beta-7 integrin. Therefore, patients taking vedolizumab must be carefully monitored for any new or worsening neurological signs and symptoms.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 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.
Gastrointestinal exclusion criteria
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.
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, 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.

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-11-2017
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PTG-100 also known as PN-10884A
Generic name:	-

Ethics review

Approved WMO Date:	04-01-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-06-2017

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-003452-75-NL
CCMO	NL59662.018.16