Official Protocol Title:	A Phase 1b, Randomized, Adaptive, Double-Blind, Placebo-Controlled, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of PT101 in Subjects with Active Ulcerative Colitis
NCT number:	NCT04924114
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Protocol Number:	PT101-201
Version:	Amendment 8; 13-May-2022
Protocol Title:	A Phase 1b, Randomized, Adaptive, Double-Blind, Placebo-Controlled, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of PT101 in Subjects with Active Ulcerative Colitis
Investigational Drug:	PT101
Phase:	Phase 1b
IND Number:	148373
EudraCT Number:	2021-000093-28
Sponsor:	Pandion Therapeutics, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA (known as MSD outside the United States and Canada) 134 Coolidge Ave Watertown, MA 02472 USA
Medical Monitor:	PPD

PROTOCOL SYNOPSIS

Protocol Number	**Product Name**
PT101-201	PT101
Version	**Sponsor**
Amendment 8; 13-May-2022	Pandion Therapeutics, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA (known as MSD outside the United States and Canada) 134 Coolidge Ave Watertown, MA 02472 USA
Phase	
Phase 1b	

Protocol Title

A Phase 1b, Randomized, Adaptive, Double-Blind, Placebo-Controlled, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of PT101 in Subjects with Active Ulcerative Colitis

Study Objectives

Primary

- To evaluate the safety and tolerability of PT101 in subjects with active ulcerative colitis (UC) following multiple subcutaneous (SC) doses

Secondary

- To assess the pharmacokinetics (PK) of PT101 in subjects with UC following multiple SC doses
- To assess the pharmacodynamics (PD) of PT101 in subjects with UC following multiple SC doses
- To assess the immunogenicity of PT101 in subjects with UC following multiple SC doses
- To assess the PK/PD relationship of PT101 in subjects with UC following multiple SC doses

Exploratory

- To assess improvement in disease activity in subjects with UC following multiple SC doses of PT101
- To evaluate changes in PT101- and UC-associated biomarkers following multiple SC doses of PT101

Study Endpoints

Primary

- Safety and tolerability as assessed by incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and changes in laboratory values, electrocardiograms (ECGs), physical exam findings, and vital signs through Week 12

Secondary

- PK parameters of PT101 through Week 12
- PD parameters of PT101 through Week 12
- Anti-drug antibodies (ADA) to PT101 through Week 12
- The relationship between the PT101 PK and PD response

Exploratory

- Mean change from baseline in modified Mayo Score at Week 12
- Mean change from baseline in total Mayo Score at Week 12
- Mean change from baseline in partial Mayo Score at Weeks 2, 4, 6, 8, 10, and 12
- Mean change from baseline in Robarts Histopathology Index (RHI) score at Week 12
- Mean change from baseline in UC-100 score at Week 12
- Mean change from baseline in fecal calprotectin (FC) at Weeks 4 and 12
- Mean change from baseline in high sensitivity C-reactive protein (hs-CRP) levels at Weeks 2, 4, 8, and 12

- Mean change from baseline in patient-reported outcome (PRO) measures at Week 12:
    - Inflammatory Bowel Disease Questionnaire (IBDQ)
    - Short Form-36 (SF-36)
- Proportion of subjects achieving clinical remission at Week 12
- Proportion of subjects achieving endoscopic improvement at Week 12
- Proportion of subjects achieving clinical response at Week 12
- Proportion of subjects achieving symptomatic remission at Weeks 2, 4, 6, 8, 10, and 12
- Proportion of subjects achieving symptomatic response at Weeks 2, 4, 6, 8, 10, and 12
- Proportion of subjects achieving endoscopic remission at Week 12
- Proportion of subjects achieving histologic remission at Week 12
- Proportion of subjects achieving histologic response at Week 12
- Proportion of subjects achieving mucosal healing at Week 12
- Change from baseline in partial Mayo Score beyond Week 12
- Incidence and characterization of TEAEs and laboratory abnormalities beyond Week 12
- Changes in PT101- and UC-associated biomarkers

Study Population

Inclusion Criteria

1. Male or female, 18 to 80 years of age, inclusive.

2. Diagnosis of UC at least 3 months prior to screening; diagnosis must be confirmed by endoscopy during the screening period. Source documentation of biopsy results (e.g., histopathology report) and endoscopic evidence consistent with the diagnosis of UC in the assessment of the Investigator is required.

3. Active UC as follows: subjects with mildly to severely active UC (i.e., 3-component modified Mayo Score of 4 to 9, with a rectal bleeding (RB) subscore of ≥ 1, stool frequency (SF) subscore of ≥ 1, and endoscopic subscore ≥ 1 excluding physician global assessment [PGA] subscore); and PGA score ≥ 1.

*Note: The SF and RB Mayo subscores must be calculated based on the subject's Mayo Score diary data recorded over the **3 consecutive days prior to the endoscopy** (excluding the bowel preparation day; see Section 7.2.1 and Appendix 3).*

4. Inadequate response, loss of response, or intolerance to at least 1 prior conventional therapy, and no more than 2 prior advanced therapies.

   - **Conventional Therapies**
     - Oral 5-aminosalicylates
     - Rectal corticosteroids
     - Oral and/or intravenous (IV) corticosteroids
     - Oral thiopurines
   - **Advanced therapies:**
     - Biologic therapy (e.g., anti-tumor necrosis factor-alpha (TNF-α), anti-integrin, anti-interleukin therapies)
     - Janus kinase (JAK) inhibitors
     - Sphingosine-1-phosphate receptor 1 (S1P1) inhibitors

5. Subjects at risk for colorectal cancer must have a colonoscopy prior to or at screening as follows:

   - Subjects > 50 years of age must have documentation of a colonoscopy within 3 years of the screening visit to exclude adenomatous polyps. Subjects whose adenomas have been completely excised at screening are eligible.
   - Subjects with extensive colitis for ≥ 8 years, or disease limited to the left side of the colon for ≥ 10 years, must either have had a full colonoscopy to assess for the presence of dysplasia within 1 year before first administration of study drug or a full colonoscopy to assess for the presence of malignancy at the screening visit.

6. Meets the following tuberculosis (TB) screening criteria:

   - No evidence of active TB, latent TB, or inadequately treated TB as evidenced by 1 of the following:
     - Negative QuantiFERON test or equivalent assay reported by the central lab at screening or within 90 days prior to randomization date OR
     - History of fully treated active or latent TB according to local standard of care. Investigator must verify adequate previous anti-TB treatment and provide

documentation; these subjects do not require QuantiFERON testing and eligibility must be approved by the Sponsor or Medical Monitor prior to enrollment in the study.

7. Women of childbearing potential (WOCBP) and males with female partners of childbearing potential must utilize highly effective contraceptive methods beginning 4 weeks prior to first dose of study drug and continue for 30 days after the last dose of study drug.

8. Body mass index (BMI) 18 to 35 kg/m^2 inclusive and weight ≥ 50 kg.

9. Willing and able to comply with this protocol and be available for the entire duration of the study.

Exclusion Criteria

1. Prior treatment with recombinant IL-2 or modified IL-2 therapy, including PT101.

2. Known sensitivity to PT101 or its excipients.

3. Known history of hypersensitivity to IL-2.

4. Disease limited to the rectum (i.e., within 15 cm of the anal verge).

5. Diagnosis of toxic megacolon.

6. Suspected or known colon stricture or stenosis.

7. Diagnosis of Crohn's disease, or indeterminant colitis.

8. Has severe colitis as evidenced by:

    - Current hospitalization for the treatment of UC

    - Likely to require a colectomy within 12 weeks of Day 1 visit, according to the Investigator

    - Symptom complex at screening or Day 1 visit that includes at least 4 of the following:

        - Diarrhea with ≥ 6 bowel movements/day with macroscopic blood in stool

        - Focal severe or rebound abdominal tenderness

        - Persistent fever (≥ 37.5°C) for at least 3 consecutive days within 28 days prior to Day 1 dosing

        - Tachycardia (> 90 beats/minute)

- Anemia (hemoglobin < 8.5 g/dL).

9. Previously had surgery for UC (e.g., subtotal colectomy with ileo-rectal anastomosis or colectomy with ileoanal pouch, Koch pouch, or ileostomy) or, per the Investigator, likely to require surgery for UC during the study conduct CCI [redacted] CCI [redacted]

10. Stool positive for enteric pathogens (e.g., Clostridium difficile toxin, pathogenic Escherichia coli, Salmonella species (spp), Shigella spp, Campylobacter spp, Yersinia spp), as well as ova and parasites at screening:

    Note: Subjects who are positive for enteric pathogens at screening, and who are considered screen failures, may be rescreened after complete resolution of the infection following discussion with the Medical Monitor. Rescreening should include all screening procedures.

11. History of abnormal thallium stress test or functional cardiac function test.

12. History of significant cardiac, pulmonary, renal, hepatic, or central nervous system (CNS) impairment, including but not limited to: myocardial infarction, unstable ischemic heart disease, stroke, heart failure, pulmonary edema, pulmonary fibrosis, interstitial lung disease, estimated glomerular filtration rate (eGFR) < 60 mL/min, cirrhosis, or history of anaphylaxis.

13. Active clinically significant infection, or any infection requiring hospitalization or treatment with intravenous anti-infectives up to 8 weeks prior to Day 1 visit, or any infection requiring oral anti-infective therapy up to 6 weeks prior to Day 1 visit.

14. History of opportunistic infection.

15. History of symptomatic herpes zoster within 16 weeks of randomization, or any history of disseminated herpes simplex, disseminated herpes zoster, ophthalmic zoster, or CNS zoster.

16. Currently on any chronic systemic (oral or IV) anti-infective therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, or atypical mycobacteria).

17. Currently receiving lymphocyte depleting therapy.

18. History of abnormal pulmonary function tests:

    Note: Subjects with history of pulmonary function abnormality that have been isolated/distant (≥ 12 months) and considered within normal range in standard of care follow-up testing, may be enrolled upon consultation with the Sponsor.

19. Subjects with organ or tissue allograft.

20. Tests positive for hepatitis B virus surface antigen (HBVsAg), hepatitis C virus (HCV) antibody (unless treated with demonstration of viral clearance) or human immunodeficiency virus (HIV) at screening as follows:

    - Subjects with positive HCV antibody at screening must have further testing for HCV RNA. Subjects with HCV RNA ≥ lower limit of quantification (LLOQ) are not eligible for the study. Subjects with positive HCV antibody but HCV RNA < LLOQ are eligible.

    - Subjects with positive HBVsAg are excluded from the study. Subjects with negative HBVsAg and positive HBV core antibody (HBVcAb) must have further testing for HBV DNA. Subjects with HBV DNA ≥ LLOQ are not eligible for the study. Subjects with HBV DNA < LLOQ are eligible at the discretion of the investigator. Such subjects will undergo HBV DNA monitoring every 12 weeks while receiving study drug and if HBV DNA ≥ LLOQ they will be discontinued from the study.

    - Subjects who have HIV infection (positive antibody test) regardless of virologic status are excluded from the study.

21. Known history of drug or alcohol abuse within 1 year of screening.

22. Malignancy within 5 years of screening, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or carcinoma in situ of the uterine cervix. Subjects with a malignancy that occurred > 5 years prior to screening are eligible with documentation of disease-free state since treatment.

23. Immunosuppressive therapy with either cyclosporine A, tacrolimus, or mycophenolate mofetil within 2 weeks of the Day 1 visit.

24. Exposure to advanced therapy within 5 half-lives of the specific therapy of the Day 1 visit or documentation of detectable drug during screening.

25. Subjects receiving concomitant medications for UC (i.e., oral probiotics, aminosalicylates, thiopurines, and/or oral corticosteroids) that have not been administered at stable doses 2 weeks prior to the screening endoscopy or subjects unable or unwilling to maintain stable doses of medications through Week 12 CCI [redacted] of the study conduct. Subjects taking oral prednisone or equivalent not greater than 20 mg per day, or budesonide 9 mg per day are eligible.

26. Subjects unable to discontinue topical enemas within 2 weeks prior to endoscopy.

27. Received a live attenuated vaccine < 4 weeks prior to screening or is planning to receive a live attenuated vaccine during the study conduct or up to 12 weeks after the last dose of study drug.

28. Any clinically significant laboratory abnormality, which, in the opinion of the investigator, presents a safety concern to the subject, will prevent the subject from completing the study or will interfere with the interpretation of the study results.

29. Currently enrolled in another investigational device or drug study, or it has been less than 30 days or 5 half lives (whichever is the longest) since ending another investigational device or drug study, or receiving another investigational agent.

30. Is pregnant or nursing or is planning to become pregnant during the study.

31. Any uncontrolled or clinically significant concurrent systemic disease other than UC.

32. Any condition or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with study evaluation, procedures or completion.

33. Has a median QTc interval > 450 ms on screening triplicate ECG, has a history of risk factors for Torsades de Pointes (e.g., heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia, or is taking concomitant medications that prolong the QT/QTc interval.

Number of Planned Subjects

Up to approximately 60 subjects

Number of Study Centers

Approximately 20

Study Design

This is a Phase 1b, adaptive, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study in subjects with active UC.

The study will enroll up to approximately 60 subjects with mildly to severely active UC in up to 6 cohorts of at least 10 subjects each (randomized 4:1 [PT101:placebo]) in a MAD design. There will be 3 planned cohorts (Cohorts 1-3) and up to 3 optional cohorts (Cohorts 4-6).

Subject randomization will be stratified by prior advanced therapy use (yes or no). Enrollment of subjects with a prior history of inadequate response, loss of response, or intolerance to 2 advanced therapies (as assessed by the Investigator) will be capped at 20% of subjects per cohort.

An independent Data Review Committee (DRC) composed of unblinded members not involved in any way in the conduct of this trial will assess safety, PK, and PD data and provide recommendations on dose escalation/dosing regimen [redacted] study continuation, and enrollment of subjects into planned and optional dosing cohorts, as well as provide recommendations on dose and dosing regimen selection to inform future clinical development.

[redacted] New information, that was not available when the original protocol was developed and now presented in the protocol, [redacted] This new information included 1) additional safety, PK, and PD data with PT101 in the first-in-human trial (Sections 1.3 and 3.2.2), 2) recently presented data of other interleukin-2 mutein [redacted] demonstrating sustained regulatory T cell (Treg) expansion with good tolerability (Section 3.2.2), and 3) a new MAD trial of PT101 in healthy subjects (MK-6194-003) (Section 1.3) initiated in November 2021 to assess the safety, PK, and PD of PT101 administered as [redacted]

[redacted]

In addition to the safety and PK rationale noted above, [redacted] is expected to have a greater effect on Treg expansion than the dose of [redacted] and therefore has a greater potential to benefit subjects with UC. Based on safety data review of 6 weeks of data from 5 participants from Cohort 2, the DRC may recommend progression to Cohort 3, [redacted]

Initial Blinded Treatment Phase

Planned Cohorts (Cohorts 1–3)

[redacted]

Enrollment in Cohorts 1-3 will occur sequentially. Progression from Cohort 1 to Cohort 2 per protocol will be based on DRC recommendations from all available unblinded safety and PK/PD data reviewed from Cohort 1 in the current study along with all available unblinded safety data [redacted] in a concurrent PT101 study conducted in a young adult healthy volunteer population (study MK-6194-003). Recommendations from DRC may also include modification to the study design, including but not limited to assessment of a lower dose or repeating a dose/dosing regimen, changes to subject safety monitoring assessments or addition of sampling timepoints. [redacted] The DRC will review all

safety and available PK/PD data from Cohort 2, and make recommendations for the next cohort (Cohort 3) regarding study continuation, dose escalation per protocol, or any modification to the study design. Moving sequentially from Cohort 1 through 3 will require demonstration of adequate safety, guided by the in-cohort stopping rules and the cohort progression criteria. At Week 12, subjects may be eligible to receive PT101 in a subsequent open-label (OL) treatment phase (non-responders only) or continue in a subsequent blinded treatment phase (responders only) for a maximum duration of up to 9 months. For subjects who do not continue into the OL or continued blinded treatment (CBT) phase, the clinic will perform a follow-up call approximately 90 days after the last dose of study drug to assess any changes in UC disease status.

Optional Cohorts (Cohorts 4–6)

Up to 3 optional cohorts may be added following DRC review of all available data from the previous planned cohorts (Cohorts 1-3) to (a) assess additional dose levels of PT101 either in CCI and/or (b) repeat a previously studied dose level/dosing regimen. The purpose of these optional cohorts is to assess the range of doses and dosing frequency that provides optimal expansion of Tregs in the periphery while maintaining appropriate safety and tolerability. Operating principles for inclusion of optional cohorts in this study are listed below:

1. Optional cohorts will enroll subjects only after DRC recommendation and may be enrolled concurrently with the planned cohorts, if appropriate.

CCI

Definition of Dose-limiting Toxicity

A dose-limiting toxicity (DLT) is defined as any treatment-related adverse event (AE) reported within 4 weeks from dosing that meets both of the following criteria:

- Grade 3 or higher in severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0
- A shift of ≥ 2 NCI CTCAE grades from baseline (initial presentation of the AE)

Definition of Maximum Tolerated Dose

Cohort-Progression Criteria

Cohort-progression criteria will be included in the overall data package reviewed by DRC to determine whether or not investigation of a higher or more frequent dose level of PT101 CCI [redacted] CCI

In-Cohort Stopping Rules

During a given cohort, if 3 or more subjects experience a DLT, 2 or more subjects experience similar DLTs, or 1 subject experiences a DLT of Grade 4 or higher in severity, further enrollment to the respective cohort will be paused pending DRC evaluation of all available safety, PK, PD, biomarker and measures associated with UC disease activity data. After the DRC convenes to review these data, they may recommend study continuation (with or without modification) or termination of dosing within the cohort; DRC may also recommend de-escalation to lower doses/reduced frequency dosing regimen. If dosing within a cohort is terminated, the next-lower dose may be declared the maximum tolerated dose (MTD). Alternatively, an additional cohort at an intermediate dose may be added to better define the MTD.

The study may be stopped at the discretion of the Sponsor based on recommendations of the DRC. All necessary measures will be taken to ensure appropriate safety follow-up for all subjects in the trial.

Continued Blinded Treatment and Open-Label Phases

Subjects who have achieved clinical response (based on the modified Mayo Score using the endoscopic score derived by the Investigator) at Week 12 will be eligible to enter the CBT phase of the study. Subjects in the CBT phase will receive the same treatment allocation (PT101 or placebo) as during the IBT phase; subjects who received PT101 will continue receiving PT101 at the same dose/regimen. Corticosteroid tapering will be initiated at Week 12 of the IBT phase for subjects entering the CBT phase.

Subjects who do not achieve clinical response at Week 12 will have the option to enter an open-label (OL) phase of the study. Subjects in the OL phase will receive PT101 at the same dose/regimen as received by subjects in their cohort during the IBT phase. Subjects who achieve a clinical response using the partial Mayo Score at Week 24 of the OL phase will also undergo corticosteroid tapering. Subjects who do not achieve a clinical response using the partial Mayo Score at Week 24 of the OL phase may continue on open label treatment if it is considered in the best interest of the subject at the discretion of the Investigator.

Subjects with insufficient data to assess clinical response at Week 12 of the IBT phase will not be eligible to enter the CBT or OL phases and will be discontinued from the study.

Participation in the CBT and OL phase is for a maximum of 9 months. The clinic will perform a follow-up call approximately 90 days after the last dose of study drug to assess any changes in UC disease status.

Study Periods

The study will be conducted as follows:

- **Screening Period:** will begin when the informed consent form (ICF) is signed. During this period, a subject will undergo baseline assessments to determine eligibility for study participation. Endoscopy (flexible sigmoidoscopy or colonoscopy as indicated) will be performed, a stool sample will be collected and additional disease assessment tools will be completed. The screening period will be approximately 4 weeks (± 1 week); it will end after all assessments required to assess eligibility have been completed. If a subject meets all eligibility criteria, they will be offered enrollment into the study.

- **Initial Blinded Treatment Phase:** will begin on Day 1 with randomization and the first dose of study drug (PT101 or placebo) administered. The IBT phase will have a duration of 12–14 weeks with the last dose of study drug administered on CCI [redacted] CCI

- Following completion of the IBT phase, subjects who are eligible may decide to enter into the 9 -month CBT or OL phase.

Early Termination or Unscheduled Visits

Subjects who receive ≥ 1 dose of study drug should be encouraged to complete all study visits within the IBT phase. If subjects discontinue study drug and terminate early from the study, they will be asked to return to the study site for an early termination (ET) visit approximately 28 days after the last dose of study drug administration. If a subject has an ET Visit, the assessments designated in the schedule of events (SOE) should be conducted. In addition, if at any time up to Study CCI [redacted] a subject has an unscheduled study visit, all procedures that were conducted at that visit will be collected in the electronic case report form (eCRF) as an unscheduled visit.

Dose Modification and Dose Schedule Deviation

If a subject has a DLT during study conduct, study drug dosing will be discontinued for that subject and the subject will be asked to return to the clinic 28 days after last dose of study drug for their ET visit.

Study Drug Interruption Considerations

When feasible, the medical monitor should be consulted prior to study drug interruption. The medical monitor must be informed of all cases of study drug interruption for medical reasons.

Study drug interruption must occur in the following circumstances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- A nonserious infection (e.g., acute upper respiratory tract infection, simple urinary tract infection)
- Positive urine pregnancy test (pending confirmation of pregnancy)
- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia)

Study drug administration may be resumed only after resolution of the condition causing interruption and requires consultation with and approval by the medical monitor.

During the time of study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments if deemed medically appropriate by the investigator. Subjects with SARS-CoV 2 infection (or suspected infection) must follow local site-specific regulations and the PT101-201 COVID-19 Risk Management Plan regarding study visits and procedures.

Individual Stopping Rules

Dosing of study drug will be permanently discontinued in a subject if any of the following occurs:

- Subject withdraws consent
- Severe worsening of UC disease activity defined as:
  - Requirement for hospitalization due to UC worsening; or
  - Partial Mayo Score increase of ≥ 3 points from baseline value to at least 5 points on 2 consecutive visits; or
  - An increase in partial Mayo Score to 9 points on 2 consecutive visits if the baseline partial Mayo Score is > 6

  Disease worsening visits may include unscheduled visits.
- Elevated absolute eosinophil count (AEC):
  - Severe eosinophilia defined as AEC > 5.0 giga/L confirmed on repeat measurement after at least 24 hours

- Persistent moderate eosinophilia defined as AEC > 1.5 to < 5.0 giga/L confirmed on repeat measurement after at least 24 hours; recurring after 2 consecutive administrations of study drug

- Any new elevation of AEC > upper limit of normal (ULN) confirmed on repeat measurement after at least 24 hours and associated with new onset of suspected eosinophil-related end organ injury (see below)

Eosinophil-Related Organ Injury

Manifestations of eosinophil-related organ injury may include but are not limited to the following:

- Gastrointestinal: new onset eosinophilic esophagitis/gastritis

- Hepatic: significant elevation in liver aminotransferases, liver fibrosis, hepatic impairment

- Pulmonary: eosinophilic pneumonia or new onset or worsening of asthma

- Cardiac: heart failure, dysrhythmia, intraluminal thrombus

- Neurologic: peripheral neuropathy or cranial neuropathy

- Cutaneous: cutaneous fibrosis

- Renal: interstitial nephritis, eosinophiluria, impaired renal function

- Potential drug-induced liver injury (DILI) defined by new onset of an elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory value that is ≥ 3X the ULN and an elevated total bilirubin laboratory value that is ≥ 2X the ULN and, at the same time, an alkaline phosphatase laboratory value < 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing

  - Subjects with potential DILI should stop further study drug administration and the Investigator should follow directions provided in the DILI Guidance Document (Appendix 7).

- Subjects with a marked prolongation of the QTc interval identified on ECG during the study (e.g., increase in QTc to > 500 ms, or > 60 ms over baseline, Appendix 8)

- New onset of clinically significant cardiovascular disease such as myocardial infarction, unstable ischemic heart disease, stroke, heart failure, or clinically significant changes in ECG

- New onset of pulmonary edema, interstitial lung disease, or clinically significant dyspnea
- New onset of clinically significant peripheral edema or reduced blood pressure (semirecumbent [supine or seated also acceptable, per site standard procedures] SBP < 90 mmHg associated with symptoms such as lightheadedness, sustained over at least the next 90 minutes):
    - Semi recumbent (supine or seated also acceptable) BP will be obtained as triplicate measurements every 30 minutes over the following 90 minutes (i.e. at 30, 60, and 90 minutes). If a subject's SBP remains < 90 mmHg for the median of all 3 measurements over the 90 minute period, this is defined as a sustained finding, and dosing will end for that particular subject.
- Reduction of eGFR < 60 mL/min confirmed on repeat measurement after at least 24 hours
- Serious infection requiring hospitalization or intravenous antibiotics
- Investigator or Sponsor determines that the subject will not benefit from further study drug
- Adverse event or laboratory or physical examination finding that per the Investigator or Sponsor presents excessive risk to the subject
- Adverse event of Grade 3 or higher in severity that is attributable to study drug, or any unexplained ≥ Grade 3 AE that is not reasonably related to the underlying disease process
- Subject becomes pregnant or plans a pregnancy within the study conduct
- Subject is unable to comply with the protocol requirements
- Sponsor or Regulatory Agency terminates the study

Study Drug, Dose, and Mode of Administration

PT101 is a [redacted] Subjects within each cohort will be randomized to receive PT101 or placebo administered SC. Placebo will be similar in color and presentation to PT101 to ensure blinding is maintained but will contain no active ingredients. All study drug is stored per storage conditions written on the label.

[redacted] Additional dose levels or regimens of PT101 to be evaluated in the optional cohorts will be determined by the DRC following cumulative review of available safety, PK, PD, measures of UC disease activity, and biomarker data.

Duration of Treatment/Study Participation

The duration of the IBT phase for an individual subject is anticipated to be approximately 16 to 18 weeks, including:

- Up to a 4-week screening period
- 12 to 14-week study conduct

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Efficacy Assessments

Disease activity will be assessed using the Mayo Score, the Geboes score, the RHI, and the UC-100.

Pharmacokinetic and Immunogenicity Assessments

Blood samples for PK and ADA analysis will be collected at baseline and at specified timepoints.

PK parameters that will be assessed include Cmax, Tmax, AUC_{0-t}, Cmin, AUC_{0-inf}, $t_{½}$, CL/F, and Vd/F. ADA to PT101 will be assessed using a standard 3-tier approach to measure binding antibody with a screening assay, ADA titer using a confirmatory assay, and neutralizing antibody to PT101 in subjects with confirmed positive titers.

Pharmacodynamic Assessments

Whole blood will be collected for PD assessments, including immunophenotyping (IPT) and receptor occupancy (RO) and analyzed by flow cytometry to enumerate immune cell subsets and assess CD25 (IL-2Rα) RO on Tregs.

Biomarker Assessments

CRP will be assayed using a validated, high-sensitivity CRP assay. FC will be evaluated in stool samples using a validated method. Changes in additional PT101- and UC-associated exploratory biomarkers will be assessed in serum, blood, PBMCs, stool, and colonic tissue biopsy samples.

Safety Assessments

Safety assessments will include the surveillance and recording of adverse events, ECGs, vital signs, physical examination findings, and laboratory tests.

PRO Assessments

Paper questionnaires will be used to record the following PRO assessments during this study:

- IBDQ
- SF-36

Statistical Methods

Sample Size Determination

A sample size of 10 subjects at each dose level (4:1 ratio: 8 subjects treated with PT101 and 2 subjects administered placebo) was chosen so that there is a probability of 80% to detect a ratio of 2 in the mean change from baseline in the absolute number of peripheral Tregs as measured in whole blood. This assumes a -one-sided alpha level of 0.1 CCI CCI At least 30 subjects are expected to be evaluated at Week 12 (planned Cohorts 1-3) and a total of approximately 60 subjects will be enrolled.

Details of all statistical analyses will be provided in a statistical analysis plan (SAP) that will be finalized prior to DRC review of Cohort 1 data.

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ABBREVIATIONS

Abbreviation	Definition
6-MP	6-mercaptopurine
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AEC	absolute eosinophil count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under the curve from time 0 to infinity
$AUC_{0\text{-}t}$	area under the curve from time 0 to time t
AZA	azathioprine
BCG	bacille Calmette-Guerin
β-hCG	beta human chorionic gonadotropin
BLRM	Bayesian Logistic Regression Model
BMI	body mass index
BP	blood pressure
C_{max}	maximum concentration
C_{min}	minimum concentration (trough)
CBC	complete blood count
CBT	continued blinded treatment
CL/F	apparent clearance
CMH	Cochran–Mantel–Haenszel test
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DRC	data review committee
ECI	events of clinical interest
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
ET	early termination
EWOC	Escalation With Overdose Control
FAS	full analysis set
Fc	fragment crystallizable
FC	fecal calprotectin
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
HBV	hepatitis B virus

Abbreviation	Definition
HBVcAb	HBV core antibody
HBVsAg	HBV surface antigen
HCV	hepatitis C virus
HCP	health care professional
HIV	human immunodeficiency virus
hs-CRP	high sensitivity C-reactive protein
HR	heart rate
HV	Healthy volunteer
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBT	initial blinded treatment
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG1	immunoglobulin G1
IL-2	interleukin-2
IL-2M	interleukin-2 mutein
IL-2R	interleukin-2 receptor
IL-2Rα	interleukin-2 receptor alpha (also known as CD25)
IL-2Rβ	interleukin-2 receptor beta (also known as CD122)
IL-2Rγ	interleukin-2 receptor gamma (also known as CD132)
IND	investigational new drug
INR	International Normalized Ratio
IPT	immunophenotyping
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
JAK	Janus kinase
LAIV	live attenuated influenza vaccine
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles, mumps, and rubella
MMRM	mixed-model-repeated measure
MMRV	measles, mumps, and rubella plus varicella
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no observed adverse effect level
OL	open-label
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PGA	physician global assessment
PK	pharmacokinetics

Abbreviation	Definition
PP	per protocol analysis set
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
CCI	[redacted]
RB	rectal bleeding
RHI	Robarts histopathology index
RO	receptor occupancy
S1P1	sphingosine-1-phosphate receptor 1
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
SF	stool frequency
SF-36	Short Form-36
SOE	schedule of events
Spp	species
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
$t_{1/2}$	half-life
T_{max}	time at which the maximum concentration occurs
TMF	Trial Master File
TNF-α	tumor necrosis factor α
Treg	regulatory T cell
Tconv	conventional T cell
UC	ulcerative colitis
ULN	upper limit of normal
V_d/F	apparent volume of distribution
WHO	World Health Organization
WOCBP	women of child-bearing potential

1 INTRODUCTION

1.1 Ulcerative Colitis

Ulcerative colitis (UC) is a chronic inflammatory disease of the rectal and colonic mucosa that is characterized by periods of remission and relapse. UC often first appears during young adulthood, and typically presents with blood in the stool and diarrhea. Additional symptoms vary depending on the severity of inflammation and extent of disease and can include incontinence, increased frequency of bowel movements, mucus discharge, and abdominal discomfort. Up to 15% of patients initially present with severe disease, which is often associated with systemic symptoms, including fever, weight loss, and malaise. Furthermore, UC is associated with an increased risk of colorectal cancer (Ungaro, 2017). With poorly controlled disease, the risk of developing colorectal cancer increases with time (Jess, 2012).

The pathogenesis of UC is multifactorial, involving genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors (Chang, 2020). Although the precise cause of UC is unknown, genetically susceptible individuals appear to have a dysregulated mucosal immune response to commensal gut flora and studies show that the homeostatic balance between regulatory T cells (Tregs) and effector T cells is disturbed in the colonic mucosa of patients with UC (Ordás, 2012; Ungaro, 2017).

The incidence and prevalence of UC have been increasing worldwide. In a systematic review of population-based studies, the highest reported prevalence values were reported in Europe and North America. In Europe, the incidence and prevalence ranged from approximately 1-58 per 100,000 person years and 2.4–505 per 100,000 person years, respectively and in North America, the incidence and prevalence ranged from 8.8–23.1 per 100,000 person years and 139.8–286.3 per 100,000 person years, respectively. Since the end of the 20th century, the incidence of both Crohn's disease and UC have also been increasing in newly industrialized countries in Africa, Asia, and South America (Ng, 2018).

1.2 Current Treatment Options for Patients with Ulcerative Colitis

While several treatment options are available and in development for the treatment of UC, there are currently no curative therapies. Goals of treatment include improved quality of life, reduction in long-term corticosteroid use, and minimization of cancer risk. Treatment of UC is dependent on the severity and the location of disease. Mild to moderate UC treatment may be treated with oral aminosalicylates, topical mesalamine, or topical steroids. For moderately active disease, oral corticosteroids and immunomodulators such as azathioprine (AZA) and 6-mercaptopurine (6-MP) may be utilized (Danese and Fiocchi, 2011). For more severe disease, tumor necrosis factor-alpha (TNF-α) antagonists such as infliximab (Remicade®), adalimumab (Humira®), and golimumab (Simponi®), or an α4β7 integrin antagonist such as vedolizumab (Entyvio®) are often employed. Tofacitinib (Xeljanz®), an oral Janus kinase (JAK) inhibitor is also approved for the treatment of adult patients with moderately to severely active disease (Harbord, 2017). Although these agents may be effective in inducing disease remission, many are associated with toxicities. The use of 6-MP and AZA can result in neutropenia, pancytopenia, pancreatitis, nephrotoxicity, hepatotoxicity, and in rare cases, hepatosplenic T-cell lymphoma (Bousvaros, 2010; Carter, 2004; Chaparro, 2009; Turner and

Griffiths, 2011). Treatment with corticosteroids is associated with multiple adverse effects including cataracts, acne, hypertension, and diabetes. Furthermore, although effective in induction of response, many patients who initially respond to corticosteroids either become steroid-dependent or require surgery (Bradley and Oliva-Hemker, 2012; Tung, 2006).

1.3 PT101

Interleukin-2 muteins (IL-2M) are recombinant forms of IL-2 with amino acid substitutions designed to alter binding of IL-2 to the different interleukin-2 receptor (IL-2R) subunits. IL-2Ms that bind less favorably to IL-2Rβ and with greater affinity to IL-2Rα induce a signal via IL-2Rβ and IL-2Rγ only when IL-2Rα is expressed and therefore preferentially activate Tregs. PT101 is a recombinant IL-2M that is fused at its C-terminus to the N-terminus of an effector function ablated human immunoglobulin G1 (IgG1) fragment crystallizable (Fc) domain using a 20 amino acid glycine/serine rich linker. Compared with wild-type human IL-2, the modified IL-2M component of PT101 contains mutations, which collectively lead to PT101 selectively activating Tregs over other cell types. The Fc component of PT101 contains alanine mutations in the base of the IgG1 hinge region, which reduce antibody effector functions.

A series of nonclinical studies have demonstrated that PT101 selectively activates and expands human and cynomolgus monkey Tregs without activating or expanding other populations of immune cells or inducing plasma proinflammatory cytokines. CCI [redacted] CCI [redacted] Maximum expansion of Tregs occurred between Days 8 and 10 after PT101 administration at all dose levels except the highest CCI [redacted] CCI [redacted] CCI [redacted] Treg numbers returned to near baseline by Day 29. No significant expansion in conventional T cells (Tconv), natural killer (NK) cells, or B cells was observed at any dose of PT101, and no meaningful change in plasma cytokine concentrations was observed. All adverse events (AEs) were Grade 1 or 2 in severity and most frequently involved cutaneous events including injection site reactions. CCI [redacted] CCI [redacted]

Pandion Therapeutics, which initially developed PT101 and conducted the PT101-101 study, was acquired by Merck & Co. on April 1, 2021. PT101 is designated within Merck as MK-6194.

An additional multiple ascending dose (MAD) trial of MK-6194 (PT101) is currently in progress (MK-6194-003). This is a Phase 1, randomized, double-blind, placebo-controlled, MAD study in healthy subjects. The first subject was dosed in the trial in November 2021. The study is currently ongoing and plans to enroll up to 56 subjects in up to 7 panels of 8 subjects each (randomized 6:2 [PT101/MK-6194:PBO]) in a MAD design, after a recent protocol amendment to add additional dose escalation panels.

CCI [redacted]

Dose escalation between panels is determined based on review of the safety data for at least 7 days after the last dose in each panel jointly by the investigator and the Sponsor. CCI [redacted]

CCI [redacted]

CCI [redacted] There have been no discontinuations related to AEs, serious adverse events (SAEs) have not occurred and stopping rules have not been met. The most common AEs have been injection site reactions and mild eosinophilia.

The primary objectives of MK-6194-003 are to evaluate the safety, tolerability and Treg pharmacodynamics (PD) of PT101 (MK-6194) in healthy subjects following multiple SC doses. Secondary objectives are to evaluate the pharmacokinetics (PK) and receptor occupancy of PT101 (MK-6194). Exploratory endpoints include exploratory PD biomarkers and ADA.

A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the PT101 Investigator's Brochure (IB).

1.4 Rationale for Current Study

Despite a number of available therapeutic options for patients with UC, there remains an unmet medical need because existing agents are limited by low efficacy and/or toxicities. Moderately to severely active UC remains a serious, life-threatening disease for which new therapies are needed to prevent disease progression, restore quality of life, and reduce the risk of colorectal cancer.

Autoimmune and inflammatory diseases result from disrupted immune homeostasis and inappropriate immune system activity, often driven by effector T cells. Tregs attenuate inflammatory processes by a variety of mechanisms that suppress the activity of effector T cells (Klatzmann, 2015). Studies show that the homeostatic balance between Tregs and effector T cells is disturbed in the colonic mucosa of patients with UC (Ordás, 2012; Ungaro, 2017). Furthermore, expansion of Tregs using repeated administration of low doses of IL-2 has shown preliminary evidence of clinical efficacy in small proof-of-concept clinical trials in patients with a variety of autoimmune diseases (Castela, 2014; Hartemann, 2013; He, 2016; Koreth, 2011; Rosenzwajg, 2015; Rosenzwajg, 2018; Saadoun, 2011). Low dose IL-2 resulting in at least 2-fold expansion in Tregs was associated with clinical response in an open-label trial in patients with moderate to severe UC (Allegretti, 2021). PT101 is an IL-2M that selectively activates Tregs over other cell types and may therefore represent a unique opportunity to rebalance the immune system in patients with a variety of autoimmune and inflammatory diseases including UC.

2 OBJECTIVES AND ENDPOINTS

Trial objectives and endpoints are listed below. Definitions of the efficacy and response assessments are provided in Section 7.2.

2.1 Objectives

2.1.1 Primary Objective

- To evaluate the safety and tolerability of PT101 in subjects with active UC following multiple SC doses

2.1.2 Secondary Objectives

- To assess the PK of PT101 in subjects with UC following multiple SC doses
- To assess the PD of PT101 in subjects with UC following multiple SC doses
- To assess the immunogenicity of PT101 in subjects with UC following multiple SC doses
- To assess the PK/PD relationship of PT101 in subjects with UC following multiple SC doses

2.1.3 Exploratory Objectives

- To assess improvement in disease activity in subjects with UC following multiple SC doses of PT101
- To evaluate changes in PT101- and UC-associated biomarkers following multiple SC doses of PT101

2.2 Endpoints

2.2.1 Primary Endpoint

- Safety and tolerability as assessed by incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and changes in laboratory values, electrocardiograms (ECGs), physical exam findings, and vital signs through Week 12

2.2.2 Secondary Endpoints

- PK parameters of PT101 through Week 12
- PD parameters of PT101 through Week 12
- Anti-drug antibodies (ADA) to PT101 through Week 12
- The relationship between the PT101 PK and PD response

2.2.3 Exploratory Endpoints

- Mean change from baseline in modified Mayo Score at Week 12
- Mean change from baseline in total Mayo Score at Week 12
- Mean change from baseline in partial Mayo Score at Weeks 2, 4, 6, 8, 10, and 12
- Mean change from baseline in Robarts Histopathology Index (RHI) score at Week 12
- Mean change from baseline in UC-100 score at Week 12
- Mean change from baseline in fecal calprotectin (FC) at Weeks 4 and 12
- Mean change from baseline in high sensitivity C-reactive protein (hs-CRP) levels at Weeks 2, 4, 8, and 12
- Mean change from baseline in patient-reported outcome (PRO) measures at Week 12
    - Inflammatory Bowel Disease Questionnaire (IBDQ)
    - Short Form-36 (SF-36)
- Proportion of subjects achieving clinical remission at Week 12
- Proportion of subjects achieving endoscopic improvement at Week 12
- Proportion of subjects achieving clinical response at Week 12
- Proportion of subjects achieving symptomatic remission at Weeks 2, 4, 6, 8, 10, and 12
- Proportion of subjects achieving symptomatic response at Weeks 2, 4, 6, 8, 10, and 12
- Proportion of subjects achieving endoscopic remission at Week 12
- Proportion of subjects achieving histologic remission at Week 12
- Proportion of subjects achieving histologic response at Week 12
- Proportion of subjects achieving mucosal healing at Week 12
- Change from baseline in partial Mayo Score beyond Week 12
- Incidence and characterization of TEAEs and laboratory abnormalities beyond Week 12
- Changes in PT101- and UC-associated biomarkers

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a Phase 1b, adaptive, randomized, double-blind, placebo-controlled, multiple dose study in subjects with active UC. The study will be conducted at approximately 20 sites worldwide. A study schematic is presented in Figure 1.

The study will enroll up to approximately 60 subjects with mildly to severely active UC in up to 6 cohorts of at least 10 subjects each (randomized 4:1 [PT101:placebo]) in a MAD design. There will be 3 planned cohorts (Cohorts 1–3) and up to 3 optional cohorts (Cohorts 4–6). CCI [redacted] CCI [redacted] Subject randomization will be stratified by prior advanced therapy use (yes or no). Enrollment of subjects with a prior history of inadequate response, loss of response, or intolerance to 2 advanced therapies as assessed by the Investigator will be capped at 20% of subjects per cohort.

A Data Review Committee (DRC) composed of unblinded members not involved in any way in the conduct of this trial will assess safety, PK, and PD data and provide recommendations on dose escalation/dosing regimen CCI [redacted] study continuation, and enrollment of subjects into the 3 planned cohorts (Cohorts 1-3) and the 3 optional cohorts (Cohorts 4-6) as well as provide recommendations on dose and dosing regimen selection to inform future clinical development.

Because this is a Phase 1 assessment of PT101 in humans, the PK, PD, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 6.5 for examples of modifications permitted within the protocol parameters.

CCI [redacted] CCI [redacted] New information, that was not available when the original protocol resented in the protocol, CCI [redacted] CCI [redacted] This new information included 1) additional safety, PK, and PD data with PT101 in the FIH trial (Sections 1.3 and 3.2.2), 2) recently presented data of other IL-2M CCI [redacted] sustained Treg expansion with good tolerability (Section 3.2.2), and 3) a new MAD trial of PT101 in healthy subjects (MK-6194-003) (Section 1.3) initiated in November 2021 to assess the safety, PK, and PD of PT101 administered as multiple doses CCI [redacted] CCI [redacted] Safety data from MK-6194-003 was reviewed by the DRC to support initiation of Cohort 2 of this trial. PT-101 safety profile was considered acceptable by the DRC at CCI [redacted] CCI [redacted]

With the modification of the CCI [redacted] CCI [redacted]

In addition to the safety and PK rationale noted above, [redacted]

[redacted]

3.1.1 Initial Blinded Treatment Phase

3.1.1.1 Planned Cohorts (Cohorts 1–3)

Subjects in Cohorts 1-3 will be randomly assigned in a 4:1 ratio to receive PT101 or placebo at [redacted]
Enrollment in Cohorts 1–3 will occur sequentially. Progression from Cohort 1 to Cohort 2 per protocol will be based on DRC recommendations from all available unblinded safety, PK, and PD data reviewed from Cohort 1. All available unblinded safety data (all 8 subjects [PT101:PBO; 6:2] up to 1 week after the third dose of study drug received [redacted] in a concurrent PT101 study conducted in a young adult healthy volunteer population (study MK-6194-003) was reviewed by DRC and considered acceptable. Recommendations from DRC may also include modification to the study design, including but not limited to assessment of a lower dose or repeating a dose/dosing regimen, changes to subject safety monitoring assessments, addition of sampling timepoints or closing enrollment in an ongoing cohort prior to completion, if appropriate. [redacted] The DRC will review all safety and available PK and PD data from Cohort 2 and make recommendations for the next cohort (Cohort 3) regarding study continuation, dose escalation per protocol, or any modification to the study design. Moving sequentially from Cohort 1 through 3 requires

demonstration of adequate safety, guided by the in-cohort stopping rules and the cohort progression criteria (see Sections 3.1.1.4 and 9.3.4).

3.1.1.2 Optional Cohorts (Cohorts 4–6)

Up to 3 optional cohorts may be added following DRC review of all available data from the previous planned cohorts (Cohorts 1-3) to (a) assess additional dose levels of PT101 either in CCI and/or (b) repeat a previously studied dose level/dosing ional cohorts is to assess the range of doses and dosing frequency that provides optimal expansion of peripheral Tregs while maintaining appropriate safety and tolerability. Operating principles for inclusion of optional cohorts in this study are listed below, and will be detailed in the DRC charter:

1. Optional cohorts will enroll subjects only after DRC recommendation and may be enrolled concurrently with the planned cohorts, if appropriate.

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3.1.1.3 Dose-Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as any treatment-related adverse event (AE) reported within 4 weeks from dosing that meets both of the following criteria:

- Grade 3 or higher in severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0
- A shift of ≥ 2 NCI CTCAE grades from baseline (initial presentation of the AE)

3.1.1.4 Cohort Progression Criteria

Cohort progression criteria will be included in the overall data package reviewed by DRC to determine whether or not investigation of CCI

CCI

3.1.1.5 In-Cohort Stopping Rules

During a given cohort, if 3 or more subjects experience a DLT, 2 or more subjects experience similar DLTs, or 1 subject experiences a DLT of Grade 4 or higher in severity, further enrollment to the respective cohort will be paused pending DRC evaluation of all available safety, PK, PD, biomarker, and UC disease activity data. After the DRC convenes to review these data, they may recommend study continuation (with or without modification) or

termination of dosing within the cohort; DRC may also recommend de-escalation to lower doses/reduced frequency dosing regimen. If dosing within a cohort is terminated, the next-lower dose may be declared the maximum tolerated dose (MTD). Alternatively, an additional cohort at an intermediate dose may be added to better define the MTD.

The study may be stopped at the discretion of the Sponsor based on recommendations of the DRC. In all cases, necessary measures will be taken to ensure appropriate safety follow-up for all subjects in the trial.

3.1.2 Continued Blinded Treatment and Open-Label Phases

Subjects who have achieved clinical response (based on the modified Mayo Score using the endoscopic score derived by the Investigator) at Week 12 will be eligible to enter the continued blinded treatment (CBT) phase of the study. Subjects in the CBT phase will receive the same treatment allocation (PT101 or placebo) as received during the IBT phase; subjects who received PT101 will continue receiving PT101 at the same dose/regimen. Corticosteroid tapering will be initiated at Week 12 of the IBT phase for subjects entering the CBT phase.

Subjects who do not achieve clinical response at Week 12 will have the option to enter an open-label (OL) phase of the study. Subjects in the OL phase will receive PT101 at the same dose/regimen as received by subjects in their cohort during the IBT phase. Subjects participating in the OL phase who achieve a clinical response using the partial Mayo Score at Week 24 of the OL phase will also undergo corticosteroid tapering. Subjects who do not achieve a clinical response using the partial Mayo Score at Week 24 of the OL phase may continue on open-label treatment if it is considered in the best interest of the subject at the discretion of the Investigator.

Subjects with insufficient data to assess clinical response at Week 12 of IBT will not be eligible to enter the CBT or OL phases and will be discontinued from the study.

For subjects not entering the CBT or OL phases, the site will conduct a follow-up phone call approximately 48 hours after the Day 85 visit to confirm no adverse events related to study procedures had occurred.

Participation in the CBT and OL is for a maximum of 9 months.

The clinic will perform a follow-up call approximately 90 days after the last dose of study drug for all subjects in the trial (those who complete IBT only or enter the CBT or OL phase) to assess any changes in UC disease status.

3.1.3 Study Periods

The study will be conducted as follows:

- **Screening Period:** will begin when the informed consent form (ICF) is signed. During this period, a subject will undergo baseline assessments to determine eligibility for study participation. Endoscopy (flexible sigmoidoscopy or colonoscopy as indicated)

will be performed, a stool sample will be collected, and additional disease assessment tools will be completed. The screening period will last approximately 4 weeks (± 1 week); it will end after all assessments required to assess eligibility have been completed. If a subject meets all eligibility criteria, they will be offered enrollment into the study.

- **Initial Blinded Treatment Phase:** will begin on Day 1 with randomization and the first dose of study drug (PT101 or placebo) administered. The IBT phase will have a duration of 12–14 weeks CCI [redacted] CCI

- Following completion of the IBT phase, subjects who are eligible may decide to enter into the 9-month CBT or OL phase.

3.1.4 Early Termination or Unscheduled Visit

Subjects who receive ≥ 1 dose of study drug should be encouraged to complete all study visits within the IBT phase. If subjects discontinue study drug and terminate early from the study, they will be asked to return to the study site for an early termination (ET) visit approximately 28 days after the last dose of study drug administration. If a subject has an ET visit, the assessments designated in the schedule of events (SOE) should be conducted. In addition, if at any time up to CCI [redacted] CCI all procedures that were conducted at that visit will be collected in the electronic case report form (eCRF) as an unscheduled visit.

3.1.5 Dose Modification and Dose Schedule Deviation

If a subject has a DLT during study conduct, study drug dosing will be discontinued for that subject and the subject will be asked to return to the clinic 28 days after last dose of study drug for their ET visit. The AE triggering the DLT should be monitored through safety follow-up phone call and/or additional site visits as needed until the ET visit.

3.1.6 Study Drug Interruption Considerations

When feasible, the medical monitor should be consulted prior to study drug interruption. The medical monitor must be informed of all cases of study drug interruption for medical reasons.

Study drug interruption must occur in the following circumstances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.

- A nonserious infection (e.g., acute upper respiratory tract infection, simple urinary tract infection)

- Positive urine pregnancy test (pending confirmation of pregnancy)

- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia)

Study drug administration may be resumed only after resolution of the condition causing interruption, and requires consultation with and approval by the medical monitor.

During the time of study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments if deemed medically appropriate by the investigator. Subjects with SARS-CoV 2 infection (or suspected infection) must follow local site specific regulations and the PT101-201 COVID-19 Risk Management Plan regarding study visits and procedures.

3.1.7 Individual Stopping Rules

Dosing of study drug will be permanently discontinued in a subject if any of the following occurs:

- Subject withdraws consent
- Severe worsening of UC disease activity defined as:
    - Requirement for hospitalization due to UC worsening; or
    - Partial Mayo Score increase of ≥ 3 points from baseline value to at least 5 points on 2 consecutive visits; or
    - An increase in partial Mayo Score to 9 points on 2 consecutive visits if the baseline partial Mayo Score is > 6

    Disease worsening visits may include unscheduled visits.
- Elevated absolute eosinophil count (AEC):
    - Severe eosinophilia defined as AEC > 5.0 giga/L confirmed on repeat measurement after at least 24 hours
    - Persistent moderate eosinophilia defined as AEC > 1.5 to < 5.0 giga/L confirmed on repeat measurement after at least 24 hours; recurring after 2 consecutive administrations of study drug
    - Any new elevation of AEC > upper limit of normal (ULN) confirmed on repeat measurement after at least 24 hours and associated with new onset of suspected eosinophil-related end organ injury (see below)

Eosinophil-Related Organ Injury

Manifestations of eosinophil-related organ injury may include but are not limited to the following:

- Gastrointestinal: new onset eosinophilic esophagitis/gastritis
- Hepatic: significant elevation in liver aminotransferases, liver fibrosis, hepatic impairment
- Pulmonary: eosinophilic pneumonia or new onset or worsening of asthma
- Cardiac: heart failure, dysrhythmia, intraluminal thrombus
- Neurologic: peripheral neuropathy or cranial neuropathy
- Cutaneous: cutaneous fibrosis
- Renal: interstitial nephritis, eosinophiluria, impaired renal function

- Potential drug-induced liver injury (DILI) defined by new onset of an elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory value that is ≥ 3X the ULN and an elevated total bilirubin laboratory value that is ≥ 2X the ULN and, at the same time, an alkaline phosphatase laboratory value < 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing
  - Subjects with potential DILI should stop further study drug administration and the Investigator should follow directions provided in the DILI Guidance Document (Appendix 7).
- New onset of clinically significant cardiovascular disease such as myocardial infarction, unstable ischemic heart disease, stroke, heart failure, or clinically significant changes in ECG
- Subjects with a marked prolongation of the QTc interval identified on ECG during the study (e.g., increase in QTc to > 500 ms, or > 60 ms over baseline, Appendix 8)
- New onset of pulmonary edema, interstitial lung disease, or clinically significant dyspnea
- New onset of clinically significant peripheral edema or reduced blood pressure (semi recumbent [supine or seated also acceptable, per site standard procedures]) SBP < 90 mmHg associated with symptoms such as lightheadedness, sustained over at least the next 90 minutes):

  - SBP (supine or seated also acceptable) will be obtained as triplicate measurements every 30 minutes over the following 90 minutes (i.e. at 30, 60- and 90 minutes). If a subject's SBP remains < 90 mmHg for the median of all 3 measurements over the 90 minute period, this is defined as a sustained finding, and dosing will end for that particular subject.

- Reduction of estimated glomerular filtration rate (eGFR) < 60 mL/min confirmed on repeat measurement after at least 24 hours
- Serious infection requiring hospitalization or intravenous antibiotics
- Investigator or Sponsor determines that the subject will not benefit from further study drug
- Adverse event or laboratory or physical examination finding that in the opinion of the Investigator or Sponsor presents excessive risk to the subject
- Adverse event of Grade 3 or higher in severity that is attributable to study drug, or any unexplained ≥ Grade 3 AE that is not reasonably related to the underlying disease process
- Subject becomes pregnant or plans a pregnancy within the study conduct
- Subject is unable to comply with the protocol requirements
- Sponsor or Regulatory Agency terminates the study

3.2 Discussion and Rationale for Study Design

This study is a double-blind, randomized, placebo-controlled trial.

The efficacy endpoints utilize subject-reported and physician-reported components of the Mayo Score; therefore, the use of a double-blind, randomized design will minimize bias that could be introduced by subject or Investigator knowledge of the treatment assignment. As UC has a relapsing and remitting course, the use of a placebo comparator will ensure that a true treatment effect is being assessed.

3.2.1 Method of Assigning Patients to Treatment Groups

Centralized registration and treatment assignment for eligible subjects will be completed using an interactive web response system (IWRS).

3.2.2 Rationale for Selection of Doses

Study PT101-201 will represent the initial multiple-dose regimen of PT101 in patients with UC to determine an improved benefit-risk profile for the proposed study duration of 12 weeks

or longer. Dose selection for the study has been guided by the objectives of maximizing subject safety while inducing a sufficient PD response to potentially benefit subjects with active UC.

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CCI resulted in the desired PD effect of Treg expansion and were well tolerated; all AEs were Grade 1 or 2, monitorable, and self-limited. A starting dose of CCI has the potential for Treg expansion and provide clinical efficacy in UC patients who have not adequately responded to previous therapies. However, CCI CCI as this level of Treg expansion has been shown to be associated with clinical responses in patients with autoimmune diseases treated with low dose IL-2. CCI CCI

CCI

CCI have been selected based on results from preclinical multiple-dose studies and GLP toxicology studies, PD results from the PT101-101 SAD study, and published results of clinical trials using low-dose IL-2 and modified forms of IL-2 for the treatment of autoimmune diseases. Recent data from multiple dose trials of modified forms of IL-2 in patients with autoimmune disease CCI CCI

MK-6194-003, a multiple ascending dose trial of PT101 conducted concurrently in healthy subjects, initiated in November 2021 to assess the safety, PK, and PD of PT101 administered as CCI CCI Safety data from MK-6194-003 was reviewed by the DRC to support initiation of Cohort 2 of this trial. The PT101 safety profile was considered acceptable by the DRC CCI Emerging data from MK-6194-003 at higher dose levels may also be reviewed during DRC meetings.

The observed safety profile from the PT101 FIH trial supports CCI CCI as all AEs were monitorable, of Grade 1 toxicity, and

resolved without medical intervention. [redacted] In each case, the symptoms lasted between 1 hour and 5 days and resolved spontaneously without medical intervention.

No clinically significant laboratory abnormalities were observed during the FIH study. [redacted] No clinically significant abnormalities in vital signs, physical examination findings, or other observations related to safety were noted. The collective safety, PK, and PD profile of single doses of PT101 support the review of safety data up to 6 weeks [redacted] for cohort progression decisions.

3.2.3 Randomization and Blinding

The randomization schedule will be generated using an IWRS. The Investigator should assign the responsibility of unblinded health care professional (HCP) to a qualified person who will prepare study drug and will not participate in the evaluation of any study subject. All randomization information will be stored in a secured area, accessible only by the unblinded HCP. This permits the Investigator and designated Investigator site staff to remain blinded to treatment assignments. The designated unblinded HCP should be fully trained in the relevant aspects of the study. The unblinded HCP will prepare and transfer study drug (PT101 and placebo) to the Investigator or qualified designee for study drug administration. Contact between the unblinded HCP and study subjects should be avoided to protect the blind.

Information necessary to unblind a treatment assignment at the Investigator's site is held by the unblinded HCP in the form of treatment codes. The Medical Monitor should be consulted prior to any unblinding. Should a situation arise which requires unblinding of the treatment assignment, the treatment code(s) will be provided according to the process defined in the Pharmacy Manual. Upon unblinding, the subject should undergo the end of study (EOS) visit if possible and be followed for safety purposes. In the event of an accidental unblinding of treatment assignment, the Medical Monitor should be promptly notified. At the end of the study, all records for premature unblinding must be returned to the Sponsor and filed in the Trial Master File (TMF).

Selected individuals from the Sponsor, contract research organization (CRO), an independent statistician, and the DRC will be unblinded to treatment assignments. The purpose of having unblinded personnel is to monitor study conduct, prepare data for presentation to the DRC, and

to facilitate planning for subsequent dosing cohorts. All unblinded personnel will be fire-walled from the operational study team at the Sponsor and CRO to prevent inadvertent unblinding of treatment assignment and to minimize the risk of introducing bias into the study results. Designation of unblinded study personnel will be authorized by the Sponsor's Chief Medical Officer and the lead study biostatistician. A roster of unblinded personnel will be maintained in the TMF. All unblinded personnel will be trained in steps necessary to maintain an adequate firewall.

3.2.4 Risk-Benefit Profile

Although a number of therapeutic options are available for patients with UC, existing agents are limited by low efficacy and/or toxicities. Moderately to severely active UC remains a serious, life-threatening disease for which new therapies are needed. PT101 is an IL-2M that selectively activates Tregs over other cell types and may therefore represent a unique opportunity to rebalance the immune system in patients with UC.

Adverse events associated with PT101 in cynomolgus monkey studies and the Phase 1a SAD study are detailed in the Investigator Brochure. Overall, on the basis of the available nonclinical and clinical data the risk-benefit profile of PT101 is judged acceptable for the proposed clinical study. The information obtained in this study will be used for the further clinical development of PT101.

Sites will adhere to COVID-19 rules and regulations as mandated by local authorities. Trial subject safety and data validity will be prioritized. In case of conflict, safety will be given priority. Further information can be found in the PT101-201 COVID-19 Risk Management Plan.

4 STUDY POPULATION

Subjects must meet all of the inclusion and none of the exclusion criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator.

4.1 Inclusion Criteria

1. Male or female, 18 to 80 years of age, inclusive.

2. Diagnosis of UC at least 3 months prior to screening; diagnosis must be confirmed by endoscopy during the screening period. Source documentation of biopsy results (e.g., histopathology report) and endoscopic evidence consistent with the diagnosis of UC in the assessment of the Investigator is required.

3. Active UC as follows: subjects with mildly to severely active UC (i.e., 3-component modified Mayo Score of 4 to 9, with a rectal bleeding subscore of ≥ 1, stool frequency subscore of ≥ 1, and endoscopic subscore ≥ 1 excluding physician global assessment [PGA] subscore) and PGA score ≥ 1.

*Note: The stool frequency (SF) and rectal bleeding (RB) Mayo subscores must be calculated based on the subject's Mayo Score diary data recorded over the **3 consecutive days prior to the endoscopy** (excluding the bowel preparation day; see Section 7.2.1 and Appendix 3).*

4. Inadequate response, loss of response, or intolerance to at least 1 prior conventional therapy, and no more than 2 prior advanced therapies.

   - **Conventional Therapies**
     - Oral 5-aminosalicylates
     - Rectal corticosteroids
     - Oral and/or intravenous (IV) corticosteroids
     - Oral thiopurines
   - **Advanced therapies:**
     - Biologic therapy (e.g., anti- tumor necrosis factor-alpha (TNF-α), anti-integrin, anti-interleukin therapies)
     - Janus kinase (JAK) inhibitors
     - Sphingosine-1-phosphate receptor 1 (S1P1) inhibitors

5. Subjects at risk for colorectal cancer must have a colonoscopy prior to or at screening as follows:

   - Subjects > 50 years of age must have documentation of a colonoscopy within 3 years of the screening visit to exclude adenomatous polyps. Subjects whose adenomas have been completely excised at screening are eligible.
   - Subjects with extensive colitis for ≥ 8 years, or disease limited to the left side of the colon for ≥ 10 years, must either have had a full colonoscopy to assess for the presence of dysplasia within 1 year before first administration of study drug or a full colonoscopy to assess for the presence of malignancy at the screening visit.

6. Meets the following tuberculosis (TB) screening criteria:

   - No evidence of active TB, latent TB, or inadequately treated TB as evidenced by 1 of the following:
     - Negative QuantiFERON test or equivalent assay reported by the central lab at screening or within 90 days prior to randomization date, OR

- History of fully treated active or latent TB according to local standard of care. Investigator must verify adequate previous anti-TB treatment and provide documentation; these subjects do not require QuantiFERON testing, and eligibility must be approved by the Sponsor or Medical Monitor prior to enrollment in the study.

7. Women of childbearing potential (WOCBP) and males with female partners of childbearing potential must utilize highly effective contraceptive methods beginning 4 weeks prior to first dose of study drug and continue for 30 days after the last dose of study drug (see Appendix 2 for details).

8. Body mass index (BMI) 18 to 35 kg/m^2 inclusive and weight ≥ 50 kg.

9. Willing and able to comply with this protocol and be available for the entire duration of the study.

4.2 Exclusion Criteria

1. Prior treatment with recombinant IL-2 or modified IL-2 therapy, including PT101.

2. Known sensitivity to PT101 or its excipients.

3. Known history of hypersensitivity to IL-2.

4. Disease limited to the rectum (i.e., within 15 cm of the anal verge).

5. Diagnosis of toxic megacolon.

6. Suspected or known colon stricture or stenosis.

7. Diagnosis of Crohn's disease, or indeterminant colitis.

8. Has severe colitis as evidenced by:

   - Current hospitalization for the treatment of UC
   - Likely to require a colectomy within 12 weeks of Day 1 visit, in the opinion of the Investigator
   - Symptom complex at screening or Day 1 visit that includes at least 4 of the following:
     - Diarrhea with ≥ 6 bowel movements/day with macroscopic blood in stool
     - Focal severe or rebound abdominal tenderness
     - Persistent fever (≥ 37.5°C) for at least 3 consecutive days within 28 days prior to Day 1 dosing

- Tachycardia (> 90 beats/minute)
- Anemia (hemoglobin < 8.5 g/dL).

9. Previously had surgery for UC (e.g., subtotal colectomy with ileo-rectal anastomosis or colectomy with ileoanal pouch, Koch pouch, or ileostomy) or, in the opinion of the Investigator, likely to require surgery for UC during the study conduct CCI [redacted] CCI [redacted]

10. Stool positive for enteric pathogens (e.g. Clostridium difficile toxin, pathogenic Escherichia coli, Salmonella species (spp), Shigella spp, Campylobacter spp, Yersinia spp), as well as ova and parasites at screening:

    Note: Subjects who are positive for enteric pathogens at screening, and who are considered screen failures, may be rescreened after complete resolution of the infection following discussion with the Medical Monitor. Rescreening should include all screening procedures listed in the SOEs (see Section 6.2.2 for details and exception).

11. History of abnormal thallium stress test or functional cardiac function test.

12. History of significant cardiac, pulmonary, renal, hepatic, or central nervous system (CNS) impairment, including but not limited to: myocardial infarction, unstable ischemic heart disease, stroke, heart failure, pulmonary edema, pulmonary fibrosis, interstitial lung disease, eGFR < 60 mL/min, cirrhosis, or history of anaphylaxis.

13. Active clinically significant infection, or any infection requiring hospitalization or treatment with intravenous anti-infectives up to 8 weeks prior to Day 1 visit, or any infection requiring oral anti-infective therapy up to 6 weeks prior to Day 1 visit.

14. History of opportunistic infection.

15. History of symptomatic herpes zoster within 16 weeks of randomization, or any history of disseminated herpes simplex, disseminated herpes zoster, ophthalmic zoster, or CNS zoster.

16. Currently on any chronic systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, or atypical mycobacteria).

17. Currently receiving lymphocyte depleting therapy.

18. History of abnormal pulmonary function tests:

    Note: Subjects with history of pulmonary function abnormality that have been isolated/distant (≥ 12 months) and considered within normal range in standard of care follow-up testing, may be enrolled upon consultation with the Sponsor.

19. Subjects with organ or tissue allograft.

20. Tests positive for hepatitis B virus surface antigen (HBVsAg), hepatitis C virus (HCV) antibody (unless treated with demonstration of viral clearance) or human immunodeficiency virus (HIV) at screening as follows:

    - Subjects with positive HCV antibody at screening must have further testing for HCV RNA. Subjects with HCV RNA ≥ lower limit of quantification (LLOQ) are not eligible for the study. Subjects with positive HCV antibody but HCV RNA < LLOQ are eligible.

    - Subjects with positive HBVsAg are excluded from the study. Subjects with negative HBVsAg and positive HBV core antibody (HBVcAb) must have further testing for HBV DNA. Subjects with HBV DNA ≥ LLOQ are not eligible for the study. Subjects with HBV DNA < LLOQ are eligible at the discretion of the investigator. Such subjects will undergo HBV DNA monitoring every 12 weeks while receiving study drug and if HBV DNA ≥LLOQ they will be discontinued from the study.

    - Subjects who have HIV infection (positive antibody test) regardless of virologic status are excluded from the study.

21. Known history of drug or alcohol abuse within 1 year of screening.

22. Malignancy within 5 years of screening, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or carcinoma in situ of the uterine cervix. Subjects with a malignancy that occurred > 5 years prior to screening are eligible with documentation of disease-free state since treatment.

23. Immunosuppressive therapy with either cyclosporine A, tacrolimus, or mycophenolate mofetil within 2 weeks of the Day 1 visit.

24. Exposure to advanced therapy within 5 half-lives of the specific therapy of the Day 1 visit or documentation of detectable drug during screening.

25. Subjects receiving concomitant medications for UC (i.e., oral probiotics, aminosalicylates, thiopurines, and/or oral corticosteroids) that have not been administered at stable doses 2 weeks prior to the screening endoscopy or subjects unable or unwilling to maintain stable doses of medications through CCI [redacted] of the study conduct. Subjects taking oral prednisone or equivalent not greater than 20 mg per day, or budesonide 9 mg per day are eligible.

26. Subjects unable to discontinue topical enemas within 2 weeks prior to endoscopy.

27. Received a live attenuated vaccine < 4 weeks prior to screening or is planning to receive a live attenuated vaccine during the study conduct or up to 12 weeks after the last dose of study drug.

28. Any clinically significant laboratory abnormality, which, in the opinion of the investigator, presents a safety concern to the subject, will prevent the subject from completing the study or will interfere with the interpretation of the study results.

29. Currently enrolled in another investigational device or drug study, or it has been less than 30 days or 5 half-lives (whichever is the longest) since ending another investigational device or drug study, or receiving another investigational agent.

30. Is pregnant or nursing or is planning to become pregnant during the study.

31. Any uncontrolled or clinically significant concurrent systemic disease other than UC.

32. Any condition or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with study evaluation, procedures or completion.

33. Has a median QTc interval >450 ms on screening triplicate ECG, has a history of risk factors for Torsades de Pointes (e.g., heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia, or is taking concomitant medications that prolong the QT/QTc interval.

4.3 Lifestyle Considerations

4.3.1 Activity Restrictions

Subjects will avoid unaccustomed strenuous physical activity from the screening visit until administration of the initial dose of study drug and until completion of the initial blinded treatment phase [redacted]

4.4 Childbearing Potential

A WOCBP is any female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological, physiological, or pharmacological causes.

4.5 Removal of Patients from Therapy or Assessment

The Sponsor or their designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's eCRF.

4.5.1 Discontinuation of Study Treatment

A subject's study treatment may be discontinued for any of the reasons listed in Section 3.1.7.

4.5.2 Subject Withdrawal From Study

A subject may be discontinued from the study for any of the following reasons:

- Completed study per protocol
- Subject withdrawal of consents including future research and genetic analysis consents*
- Study termination by sponsor
- Lost to follow-up
- Lack of compliance
- Other (as specified by the investigator)

*Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received. In the event that the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

4.6 Subject Replacement Strategy

If a subject discontinues from study drug or withdraws from the study, a replacement subject may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement subject will generally receive the same study drug as the subject being replaced. The replacement subject will be assigned a unique screening/randomization number.

5 TREATMENTS

5.1 Investigational Study Drug

5.1.1 Description

PT101 is a recombinant mutant form of human IL-2 fused at its C-terminus to an effector function ablated human IgG1 Fc domain.[redacted]

Placebo is similar in color and presentation to PT101 to ensure blinding is maintained but will contain no active ingredients. Placebo will be administered as 5% dextrose or 5% D-glucose

sourced by the investigative site. All study drug (PT101 and placebo) is stored per storage conditions written on the label.

5.1.2 Dose and Administration

[redacted] administered by SC injection. Additional dose levels or regimens of PT101 to be evaluated in the optional cohorts will be determined by the DRC following cumulative review of available safety, PK, PD, measures of UC disease activity, and biomarker data.

On visit days where the study drug is being administered, all safety, PK, and PD procedures are to be conducted before administration of study drug, unless otherwise specified [redacted]

5.1.3 Storage and Handling

Upon receipt, PT101 should be visually inspected and then stored per storage conditions written on the label in a secured location accessible only to authorized study staff.

5.1.4 Packaging and Labeling

Packaging and labelling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines. PT101 will be packed in boxes containing a suitable number of vials. The information on the boxes and vials will be in accordance with approved submission documents.

5.1.5 Preparation

Study drug will be prepared and dispensed by the unblinded HCP according to the instructions in the Pharmacy Manual. PT101 must be administered within 4 hours from the time the vial seal was opened. Placebo will be 5% dextrose or 5% D-glucose, which will be provided by the investigative site.

Source documentation will be maintained by both the unblinded HCP and site staff on both the preparation and administration of study drug.

The Investigator, or a qualified designee, will administer study drug according to the instructions in the Pharmacy Manual.

5.2 Concomitant Therapy

All concomitant medications administered will be recorded from randomization through the safety reporting period. Any concomitant medication given for AEs that are the result of a study protocol-specified intervention should be recorded from the time of informed consent.

5.2.1 Vaccine Guidelines

Prior to study participation, it is recommended that the subject's vaccinations be brought up to date according to local vaccination standards.

Inactivated vaccines (such as inactivated influenza vaccines) should be administered according to local vaccination standards whenever medically appropriate; however, there are no available data on the concurrent use of PT101 and its impact on immune responses following vaccination.

Live or attenuated vaccines (including, but not limited to varicella, measles, mumps, and rubella [MMR], MMR plus varicella [MMRV], live attenuated influenza vaccine [LAIV], yellow fever, Ty21a oral typhoid, bacille Calmette-Guerin [BCG], smallpox, and rotavirus) are prohibited within 4 weeks of screening, throughout the study, and for 12 weeks after the last dose of study drug.

Regarding precautions related to the vaccination of household or close contacts, subjects participating in this study are recommended to follow country-specific guidelines or those of the US Centers for Disease Control regarding contacts as appropriate (https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html). In general, household contacts and other close contacts of subjects in this trial may receive all age- and exposure-appropriate vaccines.

5.2.2 Prohibited Concomitant Therapy

Some medications and treatments may have an impact on the safety of the subjects and/or efficacy assessments of this study. Prohibited concomitant medications that may impact efficacy assessments or impact subject safety are presented in Table 1. Subjects who initiate any of these concomitant medications at any time during the IBT phase of the study must be discontinued from study drug and will not be eligible for the OL or CBT phase of the study. Subjects who initiate any of these concomitant medications at any time during the OL or CBT phase of the study must be discontinued from study drug.

Medications or vaccinations specifically prohibited in the exclusion criteria and in Table 1 are not allowed during the ongoing study. If there is a clinical indication for any medications or vaccinations specifically prohibited (i.e., as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician), discontinuation from study drug may be required. The investigator should discuss any questions regarding this with the Medical Monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study drug requires the mutual agreement of the investigator, the Sponsor, and the subject.

Table 1: Prohibited Concomitant Medications that May Impact Efficacy Assessments or Impact Subject Safety

Drug Class	Agents Disallowed	Prohibited Period
TNFα antagonist	Infliximab (t½: 9.5 days) Adalimumab (t½: 10-20 days) Golimumab (t½: 12-14 days) Certolizumab (t½: 14 days)	5 half-lives prior to Day 1* through the end of treatment
Integrin antagonist	Vedolizumab (t½: 25 days) Natalizumab (t½: 11 days)	5 half-lives prior to Day 1* through the end of treatment
Interleukin antagonist	Ustekinumab (t½: 19 days)	5 half-lives prior to Day 1* through the end of treatment
JAK inhibitor	Baricitinib (t½: 12 hours) Tofacitinib (t½: 3 hours) Tofacitinib XR (t½: 6-8 hours) Upadacitinib (t½: 8-14 hours)	5 half-lives prior to Day 1* through the end of treatment
S1P1 inhibitor	Fingolimod (t½: 6-9 days) Ozanimod (t½: 11 days) Siponimod (t½: 30 hours)	5 half-lives prior to Day 1* through the end of treatment
Rectal compounds	Rectal mesalamine, rectal corticosteroids	2 weeks prior to screening endoscopy through the end of treatment
Antidiarrheal agents**	Loperamide, diphenoxylate/atropine	2 weeks prior to screening endoscopy through the end of treatment
Other (non-biologic)	Cyclosporine (oral), thalidomide, tacrolimus, leflunomide, and any investigational agent	2 weeks prior to Day 1 through the end of treatment
Investigational biologics	Any investigational biologic agent	30 days prior to Day 1 (or at least 5 half-lives) through the end of treatment

*If subject has taken the concomitant medication within 5 half-lives prior to Day 1, but has an undetectable serum level on a commercially available assay assessed at screening, this is also acceptable for inclusion.

** Subjects who mistakenly use an antidiarrheal for a limited period of time (1 – 2 days) may be allowed to continue participation in the study following discussion and approval by the Medical Monitor and the Investigator.

If other prohibited concomitant medications, as shown in Table 2 are taken by a subject prior to study participation or during the study, the Investigator must contact the Medical Monitor.

Table 2: Other Prohibited Concomitant Medications

Drug Class	Agents Disallowed	Prohibited Period
Other biologics	Fecal Microbiota Transplant (FMT), antibody based or other systemic biologics, eg, denosumab, trastuzumab	Requires Medical Monitor consultation

5.2.3 Allowed Concomitant Therapy

Concomitant medications for UC (i.e., oral probiotics, aminosalicylates, thiopurines, and/or oral corticosteroids) must be at stable doses 2 weeks prior to the screening endoscopy; a subject must be willing to maintain stable doses of these medications [redacted] Oral prednisone or equivalent at doses ≤ 20 mg per day or budesonide ≤ 9 mg are permitted.

Low-dose aspirin for cardioprotection and/or temporary use of NSAID for minor ailments (other than for reasons related to the subject's underlying UC) may be used without prior consultation with the Medical Monitor.

The use of opioids related to the study procedure is allowed. Opioids used PRN should be assessed by the investigator on a case-by-case basis and upon consultation with the Medical Monitor.

5.2.3.1 Corticosteroid Tapering

A steroid taper should be initiated for responders at Week 12 of the IBT phase for subjects entering the CBT phase. For non-responders at Week 12 of the IBT phase, the steroid taper should be initiated at Week 24 of the OL phase only for subjects who have achieved a clinical response defined by the partial Mayo Score. The dose should be reduced at a rate starting at 2.5 mg per week up to 5 mg per week for prednisone (or equivalent taper if not prednisone) until the subject is no longer on steroids. Budesonide should be tapered by 3 mg every 2–3 weeks until the subject is no longer taking budesonide. For subjects undergoing steroid taper, steroids may be increased or restarted at doses up to and including their screening dose if return of symptoms is apparent. Subjects who are unable to steroid taper will be allowed to continue in the study. Subjects who need to increase their steroid dose beyond the maximum dose for allowed concomitant therapy use or increase their steroid treatment dose over their screening dose must be discontinued from the study.

5.3 Rescue Medications and Supportive Care

Sites will be staffed with medically trained personnel with appropriate access to full service acute-care hospitals to facilitate rapid institution of medical intervention.

See Appendix 7 for specific DILI guidance and close observation recommendation around potential Hy's Law cases.

5.4 Treatment Compliance

Study drug administration will be performed by qualified and designated site staff and documented in source documents and the eCRF.

6 STUDY ACTIVITIES

6.1 Schedule of Events

Adverse events and concomitant medications will be recorded from randomization through the safety reporting period (see Section 7.6.1.3). Adverse events that are the result of study protocol-specified intervention (defined in Section 7.6.1.1) as well as any concomitant medications given for treatment of these adverse events, should be recorded from the time of informed consent. Schedules of events (SOEs) are provided in Appendix 1. Descriptions of all study assessments are presented in Section 7.

On applicable visits, all PRO and quality of life-related assessments must be completed prior to other study procedures.

6.2 Screening Visit

Documented, signed, and dated informed consent must be obtained by the Investigator or his/her designee prior to the performance of any study related procedures, including washout of prohibited medications. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the subject and his or her legally acceptable representative, as applicable. A copy of the signed ICF must be given to the subject for their records.

After informed consent has been obtained, the subject has approximately 4 weeks (± 1 week) to complete all screening procedures. The subject's eligibility for the study will be evaluated during this period based on medical history, physical examination, laboratory values, Mayo Score diary data (SF and RB), and additional assessments, including screening endoscopy. Subjects who meet all of the inclusion and none of the exclusion criteria can be enrolled in the treatment period. For subjects eligible for this study, the ramdomization number is the same as the screening number.

Refer to Appendix 1 for all the procedures to be performed during the Screening Period.

6.2.1 Screen Failure

A screen failure is defined as a subject who has provided informed consent and fails to meet the inclusion and/or exclusion criteria. Subjects who fail screening will not be randomized into the study nor receive study drug.

6.2.2 Rescreening of Subjects

Subjects may be rescreened once after consultation with the Medical Monitor. In these cases, a new screening number must be assigned for each subject rescreened. Rescreening should include all screening procedures listed in the SOEs (see Table 3 and Table 4) unless noted otherwise and a new ICF must be signed to confirm ongoing consent for the study.

6.3 Initial Blinded Treatment Phase

6.3.1 Treatment Administration Visits

Eligible subjects will be randomized and receive their assigned SC dose of PT101 or placebo in a double-blind fashion starting on Day 1. Subjects will follow the schedule for dose administration and procedures for assessments as outlined in the SOEs (Table 3 and Table 4 in Appendix 1). The dose to be administered will be determined by the DRC and guided by the cohort progression criteria provided in Sections 3.1.1.4 and 9.3.4.

All safety, PK, and PD procedures are to be conducted prior to administration of study drug, unless otherwise specified. Subjects will be observed in clinic for 1 hour after administration of study drug.

6.3.2 Post-Dose Assessment Visits

Assessments will be performed post-dose to assess safety, PK, PD, biomarkers, and other outcomes. Subjects will follow the assessments as outlined in the SOEs (Appendix 1).

6.3.3 Early Termination Visit

Subjects who receive ≥ 1 dose of study drug should be encouraged to complete all study visits within the IBT phase. CCI [redacted] visit will be asked to return to the study site for ET visit approximately 28 days of the last dose of study drug administration

CCI [redacted]

6.3.4 End of Study Visit

For subjects who receive study drug and are not entering the CBT or OL phases CCI [redacted] The site will conduct a follow-up phone call approximately 48 hours after the Day 85 visit to confirm no AEs related to Day 85 study procedures had occurred. Additionally, a follow-up call approximately 90 days after the final dose of PT101 will be conducted to assess any changes in UC disease status. Subjects will be asked whether their UC is active, whether they have experienced a UC flare (defined as period of active symptoms), and whether they have started a new therapy for UC.

If a subject decides to withdraw his or her consent for further participation after receiving study drug but before EOS, he/she may do so without penalty. All efforts will be made to follow the subject for safety until EOS.

6.4 Continued Blinded Treatment and Open Label Phases

At Week 12 (Day 85), eligibility for continuation in the CBT or OL phase will be determined by clinical response status (responders versus non responders) from the modified Mayo Score (using the endoscopic subscore derived by the Investigator).

6.4.1 Continued Blinded Treatment Phase

Subjects who are eligible to enter the CBT phase as described in Section 3.1.2 will receive their first dose of blinded study drug (same treatment allocation as in the IBT phase) on Day 85 CCI [redacted] Assessments in this phase will primarily evaluate safety with exploratory efficacy assessments CCI [redacted] CCI [redacted] Subjects will have a safety follow-up visit approximately 28 days after their last dose of study drug. They will also receive a follow-up call approximately 90 days after the final dose of study drug to assess any changes in UC disease status. Subjects will be asked whether their UC is active, whether they have experienced a UC flare (defined as period of active symptoms), and whether they have started a new therapy for UC.

6.4.2 Open-Label Phase

Subjects who are eligible to enter the OL phase as described in Section 3.1.2 will receive their first dose of PT101 (there is no Placebo treatment arm in the Open-Label Phase) on Day 85 for CCI [redacted] Assessments in this phase will mainly assess safety and exploratory efficacy CCI [redacted] Subjects will have a safety follow-up visit approximately 28 days after their last dose of study drug. They will also receive a follow-up call approximately 90 days after the final dose of PT101 to assess any changes in UC disease status. Subjects will be asked whether their UC is active, whether they have experienced a UC flare (defined as period of active symptoms), and whether they have started a new therapy for UC.

6.5 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of PT101 in humans, and the PK, PD, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study subjects.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted per DRC recommendation based on newly available data.

- Repeat of or decrease in the dose of the study drug administered in any planned cohort
- Lengthening of the time period between CCI [redacted]

- Modification of the PK/PD sample processing and shipping details based on newly available data

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

Only subjects who meet all eligibility criteria specified in Section 4 will be enrolled in this study.

Subject medical history includes a thorough review of significant past medical history, current conditions, review of body systems, response to prior UC treatment, and any concomitant medications.

7.2 Response/Efficacy Assessments

7.2.1 Mayo Score

The Mayo Score is an instrument designed to measure disease activity in patients with UC. The Mayo Score ranges from 0 to 12 points and consists of the following 4 subscores, each graded from 0 to 3, with higher scores indicating more severe disease (see Appendix 3).

- Stool frequency (SF)
- Rectal bleeding (RB)
- Findings of flexible sigmoidoscopy
- Physician global assessment (PGA)

Calculation of the SF and RB subscores requires an assessment of the subject's bowel movement frequency and quantification of the amount of blood in the stool. The SF and RB Mayo subscores will be calculated based on the subject's Mayo Score diary data recorded in the week prior to the endoscopy (for modified Mayo Score) or prior to the visit (for partial Mayo Score) (see Section 7.2.1.1 for eDiary instructions and review).

The mucosal appearance during the sigmoidoscopic/colonoscopic portion of the endoscopic examination will be assessed for calculation of the Mayo endoscopic subscore based on the scoring system provided in Appendix 3. The endoscopic appearance will be read by both the Investigator and a central reader. Additional details are provided in the Central Imaging Management Solutions manual. Centrally read endoscopic subscores will be used for both IBT eligibility and the efficacy analyses. The Investigator-read endoscopic subscores will be used to assess eligibility for the OL and CBT phases.

The PGA subscore is assessed by the Investigator and is recorded at all study visits. The endoscopic subscore and the PGA must be performed by a physician qualified to perform

endoscopy. It is recommended that the same physician performs all such assessments for a particular subject throughout the study.

7.2.1.1 eDiary Instructions and Review

The SF and RB subscores are recorded daily in an eDiary. Subjects should be provided access to the eDiary and instructions for daily documentation of SF and RB. Additionally, all subjects will be provided with paper diary forms for cases where the subject doesn't have access to a suitable device for eDiary capture or as backup to the eDiary in case there is an issue with the subject's electronic device. Subjects should begin filling out the diary on the day of their initial screening visit and continue to fill it out on a daily basis throughout the remainder of the study. Subjects should be counseled about what is meant by normal SF: the average daily SF the subject experienced the last time the subject was in remission. If the subject has never been in remission, the normal SF is defined as the average daily SF before the initial onset of signs and symptoms of UC.

For the daily SF question, subjects should be counseled that a stool is defined as a visit to the toilet when they have either a bowel movement, pass blood only, pass mucus only, or pass blood and mucus. For the RB question, subjects should be counseled to select the category that describes their most severe RB over the last 24 hours. Subjects should be counseled to select "No Blood Seen" if they do not have a stool during a given day.

The modified Mayo Score will be used for the purposes of determining eligibility at screening and efficacy assessments at Week 12, the subscores for SF and RB will be calculated based on the data recorded in the diary for 3 consecutive days (excluding the bowel preparation day) during the week prior to the endoscopy. Thus, sites need to ensure subjects are entering eDiary (preferred) or paper diary forms data daily, especially prior to an endoscopy. Subjects must be instructed to document SF and RB on a daily basis and site personnel should be monitoring subject's compliance. For all subjects, the site will ensure that the SF and RB data are being entered in the ediary or paper diary forms by the subject by conducting a follow up phone call within 3 days before the endoscopy bowel preparation day at Screening and Week 12.

The partial Mayo Score will be assessed throughout the study and be used at Week 24 for the subjects in the OL phase to determine if the subject can start steroid tapering (if applicable). The subscore for SF and RB will be calculated based on the data recorded in the diary on 3 days (no need to be consecutive days) during the week prior to the corresponding visit where the partial Mayo Score is assessed.

7.2.1.2 Endoscopy

A colonoscopy or flexible sigmoidoscopy will be performed and recorded for central reader review at Screening and Week 12 (or upon ET as applicable).

Screening endoscopies will occur as follows:

- Only in subjects with a RB subscore ≥ 1, a SF subscore ≥ 1 and PGA ≥ 1 may proceed with screening endoscopy.

- Endoscopy (flexible sigmoidoscopy or colonoscopy) should be performed approximately 14 days prior to planned randomization to allow for Mayo endoscopic subscore calculation by the central reader to inform the modified Mayo Score utilized for eligibility (see inclusion criterion #3).

- Colonoscopy is required for:

    - Subjects > 50 years of age at screening if not performed within last 3 years

    - Subjects with extensive colitis ≥ 8 years, or disease limited to the left side of the colon for ≥ 10 years if not performed within 1 year before first administration of study drug

Week 12 endoscopies:

All subjects will have a flexible sigmoidoscopy at the end of the study or, if possible, at ET [redacted]

The Mayo endoscopic subscore will be provided to the Investigator or designated site staff by the vendor responsible for central reading. The value provided by the central reader will be used for calculation of the modified Mayo Score at screening and Week 12.

As SF and RB may be affected by bowel preparation for the endoscopy, the SF and RB subscores on the day prior to endoscopy, day of endoscopy, and day after endoscopy are not included in the calculation of the modified Mayo Score at screening and Week 12. For this reason, extended bowel preparation (> 24 hours prior to the procedure) is discouraged. Intestinal biopsies will be collected during endoscopy for efficacy assessments and exploratory biomarker analysis. At screening, up to 11 biopsies should be collected from the colon or sigmoid colon. At Week 12, up to 11 biopsies should be collected from the sigmoid colon. Please refer to the Lab Manual for specific collection instructions.

7.2.2 Modified Mayo Score and Partial Mayo Score

The modified Mayo Score is defined as the Mayo Score without the PGA and ranges from 0 to 9. The partial Mayo Score is defined as the Mayo Score without the endoscopy subscore and ranges from 0 to 9.

Endpoints based on the Mayo Scores are defined below:

- Clinical remission: modified Mayo Score (SF subscore ≤ 1 [with or without decrease], RB subscore of 0, and endoscopic subscore of ≤ 1 [where the definition of 1 does not include friability])

- Clinical response (based on the modified Mayo Score): decrease in modified Mayo Score of ≥ 2 and a relative ≥ 30% decrease from baseline, and a decrease of the Mayo RB subscore of at least 1 point or an absolute subscore for RB of 0 or 1

- Clinical response (based on the partial Mayo Score): decrease in partial Mayo Score of ≥ 2.

  Note: the clinical response based on the partial Mayo Score will be used in the decision to taper steroid (as applicable) at Week 24 for subjects in the OL phase.

- Endoscopic improvement: Mayo endoscopic subscore of less than or equal to 1

- Endoscopic remission: Mayo endoscopic subscore of 0

- Mucosal healing: Geboes index score < 2 and endoscopic remission (Mayo endoscopic subscore of 0)

- Symptomatic remission: SF subscore 0 or 1 with a decrease of ≥ 1 point from baseline, and RB subscore of 0

- Symptomatic response: ≥ 30% decrease from baseline in composite sum of SF and RB subscores

- UC-100: Composite UC-100 score (1 + 16 × Mayo SF subscore [0 to 3] + 6 × Mayo endoscopic subscore [0 to 3] + 1 × RHI score [0 to 33]) ranges from 1 (no disease activity) to 100 (severe disease activity)

7.2.3 Geboes Score and Robarts Histopathology Index

7.2.3.1 Geboes Score

The original Geboes score (GS) is the most commonly used colon mucosal histological score in the UC field. It is divided into 6 grades: architectural changes (Grade 0), chronic inflammatory infiltrate (Grade 1), lamina propria neutrophils and eosinophils (Grade 2), neutrophils in epithelium (Grade 3), crypt destruction (Grade 4) and erosions or ulcerations (Grade 5), and each grade of the score is divided in 4 subcategories (see Appendix 4). The Geboes score ranges from 0 to 5.4, with higher scores indicating more severe inflammation; typically, UC is defined as active histological inflammation with a Geboes score of ≥ 2B.1 (Ma, 2021).

7.2.3.2 Robarts Histopathology Index

The RHI is a recently validated instrument that measures histological disease activity in patients with UC (see Appendix 5). The RHI is divided into 4 categories: chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in epithelium, and erosion or ulceration (each ranging from 0–4). The RHI is comparable to, and often correlates with the Geboes score.

Endpoints based on the GS and RHI are defined below:

- Histologic remission: Geboes index score < 2B.1 or RHI score ≤ 3, with subscores of 0 for lamina propria neutrophils and 0 for neutrophils in epithelium

- Histologic response: change from baseline RHI ≥ 7 points
- Mucosal healing: Histologic remission (as defined by the Geboes or RHI score) and endoscopic remission (Mayo endoscopic subscore of 0)
- UC-100: Composite UC-100 score (1 + 16 × Mayo SF subscore [0 to 3] + 6 × Mayo endoscopic subscore [0 to 3] + 1 × RHI score [0 to 33]) ranges from 1 (no disease activity) to 100 (severe disease activity) (see Appendix 6)

7.3 Patient-Reported Outcomes and Quality of Life Measures

Paper questionnaires will be used to record the following patient-reported outcomes (PRO) and quality of life assessments during the study:

- IBDQ
- SF-36

PRO and quality of life measurements are collected and evaluated in a different manner than AEs; therefore, no attempt will be made to resolve any apparent discrepancies between AE and PRO data.

7.3.1 Inflammatory Bowel Disease Questionnaire

IBDQ is a psychometrically validated PRO instrument for measuring the disease-specific quality of life in patients with inflammatory bowel disease, including UC. The IBDQ comprises 32 items that are grouped into 4 dimensions: bowel function (loose stools, abdominal pain), emotional status (anger, depression, irritability), systemic symptoms (fatigue, altered sleep pattern) and social function (work attendance, need to cancel social events).

The 4 domains are scored as follows:

- Bowel symptoms: 10 to 70
- Systemic symptoms: 5 to 35
- Emotional function: 12 to 84
- Social function: 5 to 35

The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better quality of life. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points indicates a clinically meaningful improvement.

7.3.2 Short Form-36

The SF-36 is a widely used general health status questionnaire that assesses 8 domains of functional health and well-being: Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, Social Functioning, Mental Health, Role Limitations due to Emotional Problems, Vitality, and General Health Perceptions. Scales are scored from 0 to 100, with higher scores indicating a better health-related quality of life. A Physical Health component summary score and Mental Health component summary score are calculated from the 8 domain scores. The SF-36 is a psychometrically valid and reliable instrument. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.

7.4 Pharmacokinetic and Immunogenicity Assessments

Blood samples for PK and ADA analyses will be collected at baseline and at the timepoints specified in the SOE tables in Appendix 1.

PK parameters that will be assessed include C_{max}, T_{max}, $AUC_{0\text{-}t}$, C_{min}, $AUC_{0\text{-}inf}$, $t_{½}$, CL/F, and V_d/F. ADA to PT101 will be assessed using a standard 3-tier approach to measure binding antibody with a screening assay, ADA titer using a confirmatory assay, and neutralizing antibody to PT101 in subjects with confirmed positive titers.

7.5 Pharmacodynamics and Biomarker Assessments

Blood samples for PD and biomarker analyses will be collected at baseline and at the timepoints specified in the SOE tables in Appendix 1.

7.5.1 Pharmacodynamic Assessments

Whole blood will be collected for immunophenotyping (IPT) and receptor occupancy (RO) and analyzed by flow cytometry to enumerate immune cell subsets and assess CD25 (IL-2Rα) RO on Tregs.

7.5.2 Biomarker Assessments

Changes in additional PT101- and UC-associated exploratory biomarkers (e.g., proteomics) will be assessed in serum, blood, RNA, PBMCs, stool, and colonic tissue biopsy samples.

CRP will be assayed using a validated, high-sensitivity CRP assay. FC will be evaluated in stool samples using a validated method. Additional tests may also be performed on the stool samples for additional markers related to intestinal inflammation and treatment response.

Details on collecting, aliquoting, storing and shipping samples will be detailed in the Lab Manual.

7.5.2.1 Future Research

The Sponsor will also conduct future research on specimens for which consent was provided during this study. The objective of collecting/retaining specimens for future research is to explore and identify biomarkers that inform the scientific understanding of diseases (including UC) and/or their therapeutic treatments (including PT101).

If the subject provides documented informed consent for future research, the following specimens will be obtained as part of future research:

- Additional blood samples (for serum)
- Backup serum samples
- Backup blood samples
- Backup stool samples
- Leftover tissue samples

7.5.2.2 Genetic Analysis

Genetic analysis will be conducted on specimens for which consent was provided during the study. Genetic variation may impact a subject's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Samples collected may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study drug(s).

7.6 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, Events of Clinical Interest (ECIs), recording of concomitant medication, ECG, vital signs, physical examinations and laboratory tests.

Safety will be monitored over the course of the study by a DRC as described in Section 3.

7.6.1 Adverse Events

7.6.1.1 Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered

a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing Conditions eCRF:

- From the time of informed consent through the day prior to randomization, only those AEs that are the result of a study protocol-specified intervention must be recorded. A protocol-specified intervention AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.

- All medical conditions present or ongoing before randomization should be recorded as part of the subject's medical history.

- All AEs (regardless of relationship to study drug) should be recorded from randomization through the end of the safety reporting period (see Section 7.6.1.3). Complications that occur in association with any procedure should be recorded as AEs whether or not the procedure was protocol mandated.

- Changes in pre-existing medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.

- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, Version 5.0 (27 November 2017). The general categories for each grade are:

Grade	Severity	Alternate Description
1	Mild (apply event-specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal; local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Very severe, life-threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated
5	Death related to AE	Death related to AE

Abbreviations: AE=adverse event; ADL=activities of daily living; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AE severity and seriousness are assessed independently. ‘Severity’ characterizes the intensity of an AE. ‘Serious’ is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to study treatment should be evaluated by the Investigator using the criteria below. If the Investigator's opinion of not related to study drug for an SAE is given, an alternative cause of the event such as underlying disease(s), concomitant therapy, and other risk factors must be provided.

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug

Relationship of the Adverse Event to Study Procedure

The relationship of each AE to study procedure should be evaluated by the Investigator using the following criteria:

Related:	There is evidence to suggest there is a reasonable possibility of a causal relationship between the study procedure and the AE
Unrelated:	There is no reasonable possibility of a causal relationship between the study procedure and the AE

7.6.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the eCRF, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions eCRF:

- Description including onset and resolution dates
- Whether it met SAE criteria

- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

Recording Serious Adverse Events

For SAEs, record the event(s) on the eCRF with the seriousness criteria assessment.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and eCRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Pregnancy and Exposure During Breastfeeding

Female subjects who become pregnant must discontinue study drug. A determination regarding study drug discontinuation will be made by the Investigator and/or Sponsor for male subjects with a partner pregnancy after evaluating the risks and benefits of continuing with the study.

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 30 days after the last dose of study drug(s) including any pregnancies that occur in the partner of a male study subject. Only report pregnancies that occur in a male patient's partner if the estimated date of conception is after the male subject's first study drug dose. A completed Pregnancy Report Form by the Investigator (or designee) should be submitted to Alimentiv Safety within 24 hours after learning of the pregnancy. Suspicion that study drug may have interfered with the effectiveness of a contraceptive medication must also be recorded as an AE.

All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Although infant exposure during breastfeeding is not considered an AE, any infant exposure during breastfeeding by a subject (spontaneously reported to the investigator or their designee)

occurring during the study is reportable. The Sponsor should be notified within 24 hours of learning of the event.

Collection of data on the eCRF: All pregnancies and infant exposure during breastfeeding (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events eCRF.

Non-elective abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.6.1.1) should be reported as SAEs.

7.6.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from time of study drug randomization through the end of treatment visit or 28 days after the last study treatment, whichever is later. However, all AEs that are the result of a study protocol-specified intervention are to be recorded from the time of informed consent.

All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the Investigator should also be reported to the sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the patient dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

7.6.1.4 Serious Adverse Events Require Immediate Reporting

The Investigator (or designee) is required to complete the SAE page in the eCRF enabling transmission to Alimentiv Safety using the electronic data capture (EDC) system. In the event EDC transmission is not possible, (e.g., there are access or system problems), then the Investigator (or designee) must report the SAE to Alimentiv Clinical Safety by emailing or faxing a completed paper SAE form:

All SAEs must be reported to Alimentiv Clinical Safety group within 24 hours after the Investigator recognizes/classifies the event as a SAE.

The initial SAE report should include at a minimum: subject number, a narrative description of the event, and an assessment by the Investigator of the intensity of the event and relationship of the event to study drug. The initial SAE report received from the site should be as complete as possible. A complete follow-up SAE report must be submitted when information not available at the time of the initial report becomes available. The Sponsor (or designee) may request SAE follow-up information. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, as causality assessment is one of the criteria used when determining regulatory reporting requirements, it is particularly important that the Investigator always assess causality for every event before the initial transmission of the SAE data. The Investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.

The Investigator (or designee) is responsible for continuing to report to the Sponsor Clinical Safety any new or relevant follow-up information that he/she learns about the SAE.

The Investigator (or designee) is responsible for notifying their institutional review board/independent ethics committee (IRB/IEC) of SAEs that occur according to local regulations and guidelines.

Reports of pregnancy, exposure during breastfeeding, cancer, and ECIs (per Section 7.6.1.6), will be reported in the same timeframe as SAEs.

7.6.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 7.6.1.4).

The sponsor or Alimentiv will report all SAEs to regulatory authorities as required per local regulatory reporting requirements.

7.6.1.6 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

ECIs for this study include:

1. An overdose of Sponsor's product, as defined in Section 7.6.1.7

2. An elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in Appendix 7 and in the Investigator Study File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline

phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

3. Skin rash or pruritis being rated by the Investigator as Grade 3 in intensity

4. Dyspnea, all intensities

5. Significant eosinophilia defined as AEC > 5.0 giga/L confirmed on repeat measurement after at least 24 hours or eosinophil-associated organ injury.

7.6.1.7 Definition and Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

The Sponsor does not recommend specific treatment for an overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor based on the clinical evaluation of the subject.

7.6.2 Clinical Laboratory Tests

The following laboratory assessments will be performed by the central lab to evaluate safety at scheduled timepoints during the course of the study:

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, CRP, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, amylase, lipase, and uric acid.

- Hematology panel (complete blood count [CBC] with differential). Differential includes neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

- Coagulation parameters include prothrombin time/partial thromboplastin time/international normalized ratio (PT/PTT/INR)

- Creatinine clearance – the same method of assessment should be used at each timepoint

- Urinalysis

    - Standard urinalysis

    - Urine protein and creatinine for urine protein/creatinine ratio

7.6.3 Stool Sample for Enteric Pathogens Detection

Samples will be collected to test for enteric pathogens (e.g., Clostridium difficile toxin, pathogenic Escherichia coli, Salmonella species (spp), Shigella spp, Campylobacter spp, Yersinia spp), as well as ova and parasites. Bioculture or polymerase chain reaction (PCR) may be used.

A stool sample should also be collected at any time during the study for detection of pathogenic bacteria, ova, and parasites, and C. diff toxin assay when a subject becomes symptomatic, including worsening or return of disease activity.

Subjects who tested positive for enteric pathogens at screening and have been treated with complete resolution of the infection can be rescreened and randomized in the study (if eligible), at the discretion of the Medical Monitor (see Section 6.2.2). For these subjects, a stool sample will be collected at additional time-points over the course of the study as listed in the SOEs CCI [redacted]

7.6.4 HBV, HCV, HIV and TB Testing

Subjects with positive HCV antibody at screening must have further testing for HCV RNA. Subjects with HCV RNA ≥ lower limit of quantification (LLOQ) will not be eligible for the study. Subjects with positive HCV antibody but HCV RNA < LLOQ are eligible.

Subjects with positive HBVs Ag will be excluded from the study. Subjects with negative HBVsAg and positive HBVcAb must have further testing for HBV DNA. Subjects with HBV DNA ≥ LLOQ are not eligible for the study. Subjects with HBV DNA < LLOQ are eligible at the discretion of the investigator. Such subjects will undergo HBV DNA monitoring every 12 weeks while receiving study drug and if HBV DNA ≥ LLOQ they will be discontinued from the study.

Subjects who have HIV infection (positive antibody test) regardless of virologic status are excluded from the study.

All HBV, HCV and HIV testings will be performed by the local lab.

A TB assessment (QuantiFERON test or equivalent assay) performed by the central lab must be conducted at screening unless the subject has a history of active or latent TB that has been fully treated and the subject's eligibility has been confirmed by the Medical Monitor. Positive or negative TB assessment results must not be repeated. An indeterminate result can be repeated once and the second result (if positive or negative) will be considered final. Two sequential indeterminate results constitute a screen failure.

7.6.5 12-lead Electrocardiogram

Triplicate 12-lead ECGs will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SOEs using an ECG

machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT, and QTc intervals. The correction formula to be used for QTc is Fridericia.

Triplicate ECG measurements will be obtained at the screening visit and on Day 1. On Day 1 only, triplicate ECGs will be performed ~12 hours after study drug administration. The median of these measurements will be used to calculate change from baseline for safety evaluations (and for rechecks, if needed). Single measurements will be performed on Day 85 and ET visits.

At each time point when triplicate ECGs are required, 3 individual ECG tracings should be obtained at least 1 minute apart. The full set of triplicates should be completed in no more than 6 minutes.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Subjects may need to be shaved to ensure proper lead placement. Female subjects may need to remove interfering garments.

During an ECG, subjects should be in a quiet setting without distractions. Subjects should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving their arms or legs.

Screening ECG read results will be used as baseline ECG to evaluate subject eligibility and should be maintained in the subjects source documentation for this study. Any clinically significant changes from the baseline ECG should be recorded as AEs and evaluated further, as clinically warranted. Refer to Appendix 8 for evaluation and potentially significant findings.

If prolongation of the QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is < 500 msec.

If blood sample collection and/or measurement of vital signs is scheduled at the same timepoint as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood sample collection.

7.6.6 Vital Signs

Vital signs measures include HR, BP, respiratory rate, and temperature. Weight will also be measured.

Vital Sign Measurements (Heart Rate, Blood Pressure, Respiratory Rate, Temperature)

Subjects should be resting in a quiet setting without distractions in a semirecumbent position for at least 5 minutes before having vital sign measurements obtained. Supine or seated positions are also acceptable (per site standard procedures) as long as the position used is consistent across subjects at a given site. Vital signs will include HR, systolic and diastolic BP, respiratory rate, and body temperature at timepoints indicated in the SOEs. The correct size of the BP cuff and the correct positioning on the subject's arm is essential to increase the accuracy of BP measurements.

All HR and BP will be taken as a single measurement.

Body Temperature

Body temperature will be measured. The same method must be used for all measurements for each individual subject and should be the same for all subjects enrolled at a site.

7.6.7 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head (eyes, ears, nose, and throat), heart, lungs, neck, neurological, and skin.

An abbreviated or targeted interim physical examination may be done to assess areas with previously noted abnormalities and/or that are associated with any new complaints from the subject.

7.6.8 Pregnancy Testing

For WOCBP, a serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed at screening and before dosing. A negative pregnancy result is required before the subject may receive study drug. Additional pregnancy testing will be performed as specified in the SOEs in Appendix 1.

7.7 Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to PT101. Pharmacokinetic assessments are also frequently employed in clinical studies to help characterize dose-exposure-response relationships.

Standardized and internationally accepted criteria for the evaluation of UC will be used to assess disease activity in this study, including the Mayo Score, the Geboes score, the RHI, and UC-100 (Jairath, 2019; Jauregui-Amezaga, 2017; Magro, 2020; Mosli, 2017; Pai, 2019). The PRO and quality of life instruments used in this study are standardized questionnaires that have been widely used in clinical trials in multiple countries (Irvine, 1994; Ware and Sherbourne, 1992; Yalcin and Bump, 2003).

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with instructions for study compliance and eCRF completion will be provided. Prior to the enrollment of subjects at the site, the Sponsor or its designated clinical and medical personnel will review the following items with the Investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's Brochure/ package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The eCRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Subject coding and randomization (if applicable)
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Sponsor representative will review regulatory documentation, eCRFs, source documentation, and investigational product storage, preparation, and accountability. The eCRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study

subjects, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The Investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the Sponsor or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

The Sponsor will provide CRF Completion Guidelines for eCRF data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

The Investigator will permit the Sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect patient confidentiality are to be employed during monitoring. The eCRFs and related source documents will be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the eCRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified Investigators and appropriate study centers.
- Review of protocol procedures with the Investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- eCRFs will be reviewed for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers. Any discrepancies will be resolved with the Investigator or designees as appropriate.

8.5 Quality Assurance Procedures

The Sponsor or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Sponsor as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports. Data reported on the eCRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to an eCRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2 Investigator Record Retention

The Investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory/histopathology reports, inpatient or office records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study. If the Investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another Investigator or IRB/IEC. Notice of such transfer will be provided in writing to the Sponsor.

9 DATA ANALYSIS METHODS

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (e.g., adding baseline assessments to define a subgroup). The SAP will be finalized prior to DRC review of Cohort 1 data. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.1 Determination of Sample Size

A sample size of 10 subjects at each dose level (4:1 ratio: 8 subjects treated with PT101 and 2 administered placebo) was chosen so that there is a CCI to detect a ratio of 2 in the primary PD assessment of the mean change from baseline in the absolute number of peripheral Tregs as measured in whole blood CCI

This assumes a one-sided alpha level of 0.1 CCI CCI At least 30 subjects are expected to be evaluated at Week 12 (planned cohorts 1-3) and a total of approximately 60 subjects will be enrolled in the study.

9.2 Study Endpoint Definitions

See Section 7.2 for definitions of the efficacy/response endpoints.

9.3 Statistical and Analytical Plans

9.3.1 General Considerations

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. Continuous variables will be summarized by number of subjects and mean, standard deviation/standard error, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. Tests of statistical significance will be described in the SAP.

9.3.1.1 Subject Disposition

The number and percentage of subjects in study populations will be summarized by treatment group, separately for each stage. The subject disposition table will also include the number of subjects screened, randomized, and treated. No formal statistical comparisons will be performed.

Subjects who are screened but not randomized (screen failures) and the associated reasons for failure to randomize will be tabulated for all screened subjects. The number and percentage of subjects who complete the 12-week treatment period and of subjects who prematurely discontinue will be presented for each treatment group and pooled across treatment groups for the Safety Population. The reasons for premature discontinuation from treatment period as recorded in the eCRFs will be summarized.

9.3.1.2 Subject Characteristics

Demographic parameters (age, age group, sex, race, ethnicity, height, weight, body mass index) and other baseline characteristics will be summarized descriptively by treatment group for the intent-to-treat (ITT), full analysis set (FAS), per protocol (PP) analysis set, and safety analysis sets (SAF).

9.3.1.3 Protocol Deviations

Protocol deviations will be summarized by type in each treatment group. Both major and minor protocol deviations will be listed.

9.3.1.4 Prior and Concomitant Therapy

Prior medication is defined as any medication started before the date of study drug administration. A concomitant medication is defined as any medication taken on or after the date of study drug administration.

Prior and concomitant medications will be coded by drug name and therapeutic class using the World Health Organization (WHO) Drug Dictionary. Results will be tabulated by Anatomic

Therapeutic Class and preferred term. If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class.

9.3.1.5 Randomization and Blinding

Subjects will be randomized in a 4:1 ratio to a PT101 dose level/dosing regimen and placebo. The study will be conducted in a double-blind fashion, which will be described in the Clinical Trial Integrity Plan.

9.3.1.6 Adjustments for Covariates

Detailed methodology will be provided in the SAP.

9.3.1.7 Handling of Dropouts and Missing Data

Detailed methodology will be provided in the SAP.

9.3.1.8 Multiple Comparisons and Multiplicity

No multiplicity adjustments will be applied.

9.3.1.9 Data Transformations and Derivations

Time variables based on 2 dates (e.g., start date and end date) will be calculated as (end date – start date + 1 [in days]) unless otherwise specified in the SAP.

Baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of study drug unless otherwise specified in the SAP.

More detailed methodology will be provided in the SAP.

9.3.2 Analysis Sets

9.3.2.1 Intent-to-Treat Analysis Set

The ITT analysis set consists of all randomized subjects. Subjects will be included in the treatment group assigned at randomization regardless of the actual treatment received.

9.3.2.2 Full Analysis Set

The FAS consists of all randomized subjects who received any study drug (PT101 or placebo). Treatment groups will be determined using the actual treatment received, regardless of the randomization treatment assignment.

9.3.2.3 Per Protocol Analysis Set

The PP analysis set will consist of all subjects in the FAS who did not have any major protocol violations that might impact the efficacy analyses.

Exclusion of subjects from the PP analysis set will be determined in a final blinded data review meeting that will be held prior to unblinding the randomization list. Reasons for exclusion will be documented for each subject.

9.3.2.4 Safety Analysis Set

The SAF consists of all subjects who receive at least one dose of study drug. Treatment groups will be determined using the actual treatment received, regardless of the randomization treatment assignment. Safety analyses will be performed using the SAF.

Additional analysis sets of subjects may be defined in the SAP.

9.3.3 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.4 Safety and Efficacy Analyses

Progression from Cohort 1 to Cohort 2 per protocol will be based on DRC recommendations from all available unblinded safety and PK/PD data reviewed from Cohort 1 along with all unblinded safety data (all 8 subjects [PT101:PBO; 6:2] up to one week after CCI CCI CCI Recommendations from the DRC may also include modification to the study design, including but not limited to assessment of a lower dose or repeating a dose/dosing regimen, changes to subject safety monitoring assessments or addition of sampling timepoints. CCI CCI CCI DRC will review all safety and available PK/PD ons for the next cohort (Cohort 3) regarding study continuation, dose escalation per protocol or any modification to the study design. Moving sequentially from Cohort 1 through 3 will require demonstration of adequate safety, guided by the in-cohort stopping rules and the cohort progression criteria (see Section 3.1.1.4).

The safety of each dose level will be evaluated by examining the probability of experiencing a DLT (as defined in Section 3.1.1.3) based on a Bayesian Logistic Regression Model (BLRM) (Neuenschwander, 2008) and the incidence of TEAEs, TESAEs, treatment-related TEAEs, and treatment-related TESAEs.

A dose will be considered safe if the estimated probability (posterior median) of experiencing a DLT is ≤ 0.25. The MTD will be determined according to the following rules:

CCI

CCI The selected dose may not exceed the Escalation With Overdose Control (EWOC) threshold: the posterior probability of overdosing, either excessive or unacceptable toxicity ≤ 0.25.

The dose level(s) and dosing regimen with the best benefit/risk profile based on the totality of safety and efficacy data at Week 12 will inform selection for future clinical development.

For efficacy endpoints, to compare the proportion of subjects at a timepoint (i.e., Week 12), the Cochran-Mantel-Haenszel (CMH) method will be used and an exact 95% confidence interval will be estimated. CCI

CCI

For continuous data in terms of change from baseline to Week 12, analysis-of-covariance (ANCOVA) on last-observation-carried-forward (LOCF) will be used for analysis. For continuous data with repeated measures postrandomization, mixed-model-repeated measure (MMRM) will be used for analysis. Details on covariates will be specified in the SAP.

All analyses will be descriptive in nature, with point and 95% interval estimates, if necessary, provided for the following parameters of interest, separately for each available PT101 dose level/dosing regimen and placebo unless otherwise specified in the SAP:

- Mean change in total Mayo Scores, modified Mayo Score, RHI score, UC-100 score, and PROs (IBDQ, SF-36) at Week 12
- Mean change from baseline in partial Mayo Score, FC, and hs-CRP levels at assessed timepoints through Week 12
- Mean change from baseline in partial Mayo Score beyond Week 12

- Proportion of subjects achieving clinical remission, endoscopic improvement, clinical response, endoscopic remission, histologic remission, histologic response, mucosal healing at Week 12

- Proportion of subjects achieving symptomatic remission and symptomatic response at assessed timepoints through Week 12

9.3.5 Exploratory Efficacy Analyses

MMRM may be used to compare change from baseline in partial Mayo Score beyond Week 12 as well as change in PT101- and UC-associated biomarkers.

9.3.6 Pharmacokinetic and Immunogenicity Analyses

9.3.6.1 Pharmacokinetic Analyses

Serum concentrations of PT101 will be listed and summarized by treatment group using descriptive statistics (sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Concentration over time may also be plotted in semilogarithmic and linear formats.

ADA to PT101 will be assessed using a standard 3-tier approach to measure binding antibody with a screening assay, ADA titer using a confirmatory assay, and neutralizing antibody to PT101 in subjects with confirmed positive titers. Data will be listed and summarized by treatment group as detailed in the SAP.

9.3.6.2 Biomarker Analyses

Relationships of biomarker parameters (e.g., baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized. Details will be described separately in the SAP.

9.3.7 Safety Analyses

The safety analyses will be performed using the SAF. The safety parameters will include AEs and SAEs, vital sign measurements, ECG findings and clinical laboratory values. The primary safety analysis will include all data available for all subjects through Week 12.

9.3.7.1 Extent of Exposure

Duration of treatment will be summarized and listed. Duration of treatment, number of doses, and total dose will be summarized. Dose modifications will also be summarized.

9.3.7.2 Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths,

and AEs leading to study treatment discontinuation. Adverse events will be defined as treatment emergent if they are newly occurring or worsen following study treatment.

AEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA), preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 subject, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

9.3.7.3 Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.7.4 Clinical Laboratory Results

Laboratory values (e.g., chemistry, hematology, and urinalysis) may be presented graphically by visit. Summary statistics may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE and flagged when values are outside the normal reference range.

9.3.7.5 Other Safety Analyses

Vital Signs

Vital signs will be presented graphically for each vital sign by scheduled visit. Summary statistics and change from baseline and/or predose to postdose may be tabulated where appropriate.

ECG

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled ECG, and shifts from baseline may be tabulated.

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 (R1); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1 Informed Consent

The Investigator is responsible for presenting the risks and benefits of study participation to the patient in simple terms using the IRB/IEC approved informed consent document and for ensuring patients are re-consented when the informed consent document is updated during the study, if required. The Investigator will ensure that documented informed consent, including

optional genetic analysis and future research, is obtained from each subject, or legally acceptable representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from a legally acceptable representative for a subject who is unable to provide informed consent at study entry (if applicable), but the subject is later able to provide informed consent, the Investigator must obtain documented informed consent from the subject.

10.2 Ethical Review

The investigator will provide the Sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The Investigator will supply the following to the site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The Investigator must provide the following documentation to the Sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1 Investigator Information

The contact information and qualifications of the Principal Investigator and Subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2 Protocol Amendments and Study Termination

Any Investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The Investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The Sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or ET.

10.4 Study Documentation, Privacy and Records Retention

To protect the safety of subjects in the study and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and medical records in the subjects' files as original source documents for the study. If requested, the Investigator will provide the Sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the informed consent document for the study. eCRFs and other documents to be transferred to the Sponsor should be completed in strict accordance with the instructions provided by the Sponsor, including the instructions regarding the coding of subject identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

All study records containing subject details will identify the subject by initials (where permitted) and the assigned subject identification number. Subject information collected will comply with the applicable local laws and requirements for the protection of privacy of individually identifiable health information, such as the General Data Protection Regulation (GDPR) of the European Union.

10.5 Clinical Trial Agreement

Payments by the Sponsor to Investigators and institutions conducting the trial, requirements for Investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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APPENDIX 2: GUIDANCE ON CONTRACEPTION

ACCEPTABLE METHODS FOR HIGHLY EFFECTIVE BIRTH CONTROL
Male subjects, who are sexually active with a pregnant or breastfeeding woman, choose Option 1 or 2 Option 1: Male condom with spermicide and cervical cap Option 2: Male condom with spermicide and diaphragm
Female subjects who are of childbearing potential AND male subjects who are sexually active with women of childbearing potential[a], choose any TWO of the following methods: • Hormonal methods of contraception (excluding progestin-only pills) • Intrauterine device with failure rate < 1% • Tubal ligation • Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia) • A barrier method (male or female condom with spermicide, cervical cap with spermicide, diaphragm with spermicide

a A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological, physiological, or pharmacological causes.

UNACCEPTABLE METHODS OF CONTRACEPTION
• Abstinence (including periodic abstinence) • No method • Withdrawal • Rhythm • Any barrier method without spermicide • Spermicide only • Progestin-only pills • Concomitant use of female and male condoms

APPENDIX 3: MAYO SCORING SYSTEM

Stool frequency[a, d]:

0 = Normal number of bowel movements

1 = 1 to 2 bowel movements more than normal

2 = 3 to 4 bowel movements more than normal

3 = 5 or more bowel movements more than normal

Subscore, 0 to 3

Rectal bleeding[b, d]:

0 = No blood seen

1 = Streaks of blood with stool less than half the time

2 = Obvious blood with stool most of the time

3 = Blood alone passes

Subscore, 0 to 3

Findings on endoscopy:

0 = Normal or inactive disease

1 = Mild disease (erythema, decreased vascular pattern)

2 = Moderate disease (marked erythema, absent vascular pattern, any friability, erosions)

3 = Severe disease (spontaneous bleeding, ulceration)

Subscore, 0 to 3

Physician's global assessment[c]:

0 = Normal

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Subscore, 0 to 3

The Mayo Score ranges from 0 to 12, with higher scores indicating more severe disease

a Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency

b The daily bleeding score represents the most severe bleeding of the day

c The physician's global assessment acknowledges the 3 other criteria, the subject's recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status

d The modified Mayo Score calculated at the Screening and Week 12 visits must use the SF and RB Mayo subscores recorded on the eDiary (or paper diary) over the **3 consecutive days prior to the endoscopy** (excluding the bowel preparation day)

APPENDIX 4: ORIGINAL GEBOES SCORING SYSTEM

Grade 0: Architectural changes

0.0 No abnormality

0.1 Mild abnormality

0.2 Mild/moderate diffuse or multifocal abnormalities

0.3 Severe diffuse or multifocal abnormalities

Grade 1: Chronic inflammatory infiltrate

1.0 No increase

1.1 Mild but unequivocal increase

1.2 Moderate increase

1.3 Marked increase

Grade 2A: Eosinophils in lamina propria

2A.0 No increase

2A.1 Mild but unequivocal increase

2A.2 Moderate increase

2A.3 Marked increase

Grade 2B: Neutrophils in lamina propria

2B.0 No increase

2B.1 Mild but unequivocal increase

2B.2 Moderate increase

2B.3 Marked increase

Grade 3: Neutrophils in epithelium

3.0 None

3.1 < 5% crypts involved

3.2 < 50% crypts involved

3.3 > 50% crypts involved

Grade 4: Crypt destruction

4.0 None

4.1 Probable: local excess of neutrophils in part of the crypts

4.2 Probable: marked attenuation

4.3 Unequivocal crypt destruction

Grade 5: Erosions and ulcerations

5.0 No erosion, ulceration or granulation tissue

5.1 Recovering epithelium + adjacent inflammation

5.2 Probable erosion: focally stripped

5.3 Unequivocal erosion

5.4 Ulcer or granulation tissue

APPENDIX 5: ROBARTS HISTOPATHOLOGY INDEX

RHI =1 x chronic inflammatory infiltrate level (4 levels) + 2 x lamina propria neutrophils (4 levels) + 3 x neutrophils in epithelium (4 levels) + 5 x erosion or ulceration (4 levels after combining Geboes 5.2 and 5.2). The RHI ranges from 0 to 33.

Chronic Inflammatory Infiltrate Level

0 = no increase

1 = mild but unequivocal increase

2 = moderate increase

3 = marked increase

Lamina Propria Neutrophils

0 = none

1 = mild but unequivocal increase

2 = moderate increase

3 = marked increase

Neutrophils in Epithelium

0 = none

1 = < 5% crypts involved

2 = < 50% crypts involved

3 = > 50% crypts involved

Erosion or Ulceration

0 = no erosion, ulceration or granulation tissue

1 = recovering epithelium + adjacent inflammation

1 = probable erosion – focally stripped

2 = unequivocal erosion

3 = ulcer or granulation tissue

APPENDIX 6: COMPOSITE UC-100

Composite UC-100= (1 + 16 × Mayo Clinic stool frequency subscore [0 to 3] + 6 × Mayo Clinic endoscopic subscore [0 to 3] + 1 × RHI score [0 to 33])

The UC-100 ranges from 1 (no disease activity) to 100 (severe disease activity).

- Mayo Clinic stool frequency subscore (Appendix 3)
- Mayo Clinic endoscopic subscore (Appendix 3)
- RHI score (Appendix 5)

APPENDIX 7: DRUG-INDUCED LIVER INJURY GUIDANCE DOCUMENT

PURPOSE

The purpose of this appendix is to provide guidance regarding clinical follow-up and systematic data gathering and reporting on potential cases of drug induced liver injury (DILI) that meet specific agency-specified criteria ('Hy's Law' criteria as discussed below) as being predictive of a drug's ability to cause severe liver injury. The data collected will be used by the Sponsor or the Investigator to create narratives for regulatory agency reporting.

INTRODUCTION

Drug-induced hepatotoxicity is one of the most common causes of termination of drug development, a major reason for refusal of market authorization and for restricted use, and the single most important cause of the withdrawal of market authorization for products (Björnsson 2006). Thus, drug-induced hepatotoxicity is a major concern during the discovery, development to post-authorization phases of the product life cycle (excerpted from Premarket Evaluation of Hepatotoxicity of Health Products, Ministry of Public Health, Canada, April 2012).

As stated in the United States Food and Drug Administration (FDA) Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation; hepatocellular injury (usually detected by serum aminotransferase elevations [AT]) can be caused by drugs that rarely, if ever, cause severe DILI (e.g. aspirin, tacrine, statins, and heparin) as well as by drugs that do cause such injury.

The most specific predictor of a drug's potential for severe hepatotoxicity, is the occurrence of hepatocellular injury (AT elevation) accompanied by increased serum total bilirubin (TBL), not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K-dependent clotting factors, is another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e. AT elevation) accompanied by jaundice (i.e. TBL elevation) had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). This became known as "Hy's Law". This guidance describes the recommended process for monitoring and evaluation of subjects meeting the laboratory criteria for potential Hy's Law defined as:

- 1) an elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- 2) an elevated TBL lab value that is greater than or equal to two times (2X) ULN and

- 3) at the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,

It should be noted that **the guidance provided here specifically pertains to potential Hy's Law cases as defined above**. Due to the significant potential implications of a Hy's Law case for the health of study subjects as well as for the safety profile of the investigational agent or agents being evaluated, study investigators must follow these guidelines for evaluation of the study subject, and investigation for potential alternate etiologies.

It should also be noted that it is often appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that are suggestive of DILI but do not meet criteria for a potential Hy's Law case. In these situations, investigators should initiate appropriate evaluation and monitoring based on their judgment, using the guidelines below. They should communicate with the sponsor's medical monitor as soon as possible. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the sponsor medical monitor.

CLOSE OBSERVATION RECOMMENDATIONS

The following steps should be taken when a subject is observed to have an elevated AST or ALT lab value that is greater than or equal to 3X ULN and an elevated TBL lab value that is greater than or equal to 2X ULN and, at the same time, an ALP lab value that is less than 2X ULN, as a result of within-protocol-specific testing or unscheduled testing.

Treatment with PT101 should be stopped if the laboratory criteria for potential Hy's Law are met (Section 3.1.7 Individual Stopping Rules).

Initiate **close observation,** defined below, and continue performing **follow-up to resolution.**

Close observation is defined as follows:

- Repeat liver enzyme and serum bilirubin tests two (2) or three (3) times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the subject is asymptomatic.

- Obtain a detailed history of symptoms and prior or concurrent diseases. (See Section 4.1).

- Obtain additional pertinent history informing potential alternate etiologies for the liver enzyme and bilirubin elevations (see below).

- Complete Stage 1 workup for potential alternate etiologies for the liver enzyme and bilirubin elevations (see below).

- Consider gastroenterology or hepatology consultation.

Note: if the etiology of the observed laboratory abnormalities becomes clear in the course of evaluation, the evaluation may be abbreviated as appropriate and agreed upon by the study investigator and sponsor medical monitor.

EVALUATION OF POTENTIAL HY'S LAW CASES

When a subject meets criteria for being a potential Hy's Law case (as defined above), it is important to thoroughly assess the subject's history, hepatic risk factors, clinical condition and hepatic function until resolution (normal or baseline levels). This information is both critical for effect of evaluation and management of an active potential Hy's Law case, and for supporting optimal assessment of drug safety.

Accrued data pertinent to the evaluation of the potential Hy's Law case should be recorded in source documents and in appropriate CRFs.

Key elements of the evaluation to be addressed and documented in assessment

Consistent with regulatory guidance (see references) the following information must be gathered during evaluation of a potential Hy's Law case, even if the subject in question is known to be receiving control treatment. Information should be updated as data accrues throughout the evaluation.

1. Study drug treatment including the following:

a. Time and dates from start of drug administration to start of the illness (initial detection of pertinent laboratory abnormalities and/or physical symptoms or signs).

b. Time and date of interruption of drug administration

2. Narrative free text describing relevant medical history and the course of the illness.

This should include the following elements and should clearly address timeframe (including onset and duration of symptoms, signs, and relevant risk factors in medical history):

a. Pertinent history: Including history of present illness and potentially relevant past medical history including potential risk factors for liver disease of alternate etiologies (unrelated to study drug). See Table 7 and Table 8 below.

b. Pertinent physical examination findings. See Table 7 below.

c. Outcomes including treatment, recovery, hospitalization, liver transplant and death

Note: The history and physical examination elements noted in Table 7 and Table 8 should be specifically addressed as pertinent positive or negative findings

Table 7: Symptoms and signs to assess during evaluation of a potential Hy's Law case

Category	Examples of Signs and Symptoms
Blood/lymphatic	Susceptibility to bleeding
Circulatory	spider nevi, abdominal varicosities, edema
Digestive/hepatic	Anorexia/appetite loss, diarrhea, bloody or black stool, light-colored stools, nausea, vomiting, vomiting of blood, right upper quadrant abdominal pain, enlarged and tender liver, jaundice, enlarged spleen, ascites
Immune	Fever
Integumentary	Rash, pruritus
Muscular	Muscle aches and pains
Nervous	Changes in mental status or level of consciousness
Urinary	Dark urine
Miscellaneous	Fatigue, malaise, weight gain, other (identify):
General	Obesity (record weight and height)

Table 8: Medical history elements to assess in evaluation of a potential Hy's Law case.

Category	Examples of Confounding Variables
Subject medical history	Prior history of liver injury or disease, including but not limited to Gilbert's syndrome, autoimmune disorders, cancer, Wilson's disease, NASH, alcoholic or infectious hepatitis, biliary tract disease, hypoxic/ischaemic hepatopathy
Family history	Autoimmune disorder, cancer, Gilbert's syndrome, Wilson's disease
Substance use/abuse	Alcohol, illegal drugs, illegal intravenous (IV) drugs
Prior & Concomitant Medications: Review all non-study medications and therapies, including: over-the-counter (OTC), prescription. As appropriate, ask the subject to bring products/packaging to site and review contents.	History of recent of concomitant acetaminophen (APAP)/paracetamol use, excessive nonsteroidal anti-inflammatory drug (NSAID) intake, use of non-study drug or therapy that can cause liver damage or idiosyncratic adverse drug reactions History of prior exposure to the investigational drug or similar drugs that could potentially have predisposed to an immune/allergic reaction upon exposure in the study
Herbal and nutritional supplements	Herbal, complementary therapies, and nutritional supplements
Adulteration of products	Information on potential contamination or adulteration of food or other ingested products (such as nutritional supplements)
Chemical exposure	Occupational or in other situations
Potential exposure to infectious agents	Infectious hepatitis, transfusion, travel (last 3 years), tattoos, sexually transmitted diseases, new sexual partner, shared needles
Special Diet	Special diet started since randomization. Unusual foods (e.g. foraged mushrooms) or special diets. Consumption of seasonal foods.

Category	Examples of Confounding Variables
Other	Recent physical trauma, excessive exercise, or other prolonged physical exertion

3. All pertinent data including results of all evaluations for alternate etiologies. This should include all data, positive and negative, collected under Stage 1 and 2 evaluations (see below).

Note- laboratory data should be captured with laboratory normal ranges, and should include both protocol-scheduled laboratory evaluations as well as all unscheduled evaluations.

Data collected on multiple occasions over time should ideally be displayed in a chart or graph.

If applicable, request copies of hospital discharge summaries, consultation reports, pathology reports, special studies (e.g. imaging or biopsy), etc.

4. Summary assessment of evaluation for potential etiologies: This should include the investigator's summary impression regarding potential etiology of the observed liver function test abnormalities and status of the ongoing evaluation.

5. Medical status and treatment plan: This should include the investigator's summary impression regarding subject medical status and the treatment plan.

Evaluation for potential Hy's Law cases if there are no evident alternate etiologies

Note: If a clear etiology for the laboratory abnormalities has been confirmed, Stage 1 and 2 testing may not be required. In this case, consultation with the Sponsor medical monitor is required.

Stage 1 workup: should be performed within 48-72 hours:

- A detailed medical history and physical examination should be performed, including the elements noted in Table 7 and Table 8.
- Review aminotransferase values obtained prior to and during the study or administration of study medication.
- Consultation with a hepatologist/gastroenterologist should be strongly considered

Perform the following laboratory tests:

- Liver safety laboratories: ALT, AST, bilirubin (total and direct), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT)
- Prothrombin Time (PT) / international normalized ratio (INR)

- Creatine phosphokinase (CPK)
- Albumin
- Complete blood count including platelet count and white blood cell count with an automated differential. Specific attention should be paid to eosinophil count as hypereosinophilia may be associated with idiosyncratic drug reactions.
- Toxicology screen for drugs of abuse (including ethanol) and for acetaminophen/paracetamol level should also be sent. Investigators may order additional toxicology tests as clinically indicated.
- Viral hepatitis serologies (obtain appropriate consent prior to testing, if required locally)
    - A (IgG, IgM)
    - B (HepBs Ag, Hep Bs Ab, Hep Bc Ab)
    - C (RNA)
    - Cytomegalovirus (CMV): Viral PCR and serologies (IgG, IgM)
    - Epstein-Barr Virus (EBV): Viral PCR and serologies (IgG, IgM)
- Human Immunodeficiency Virus (HIV) testing (obtain appropriate consent prior to testing, if required locally)
- Appropriate samples should be collected and stored for potential viral PCR testing for the following viruses: hepatitis E, herpes simplex, varicella and parvovirus. **These samples should <u>not</u> be submitted for analysis unless testing for these pathogens is triggered under Stage 2 workup, or there is a specific suspicion.**
- Obtain a right upper quadrant ultrasound. If ultrasound is not available, MRI or CT scan may be used to image liver and biliary tract.

<u>Stage 2 workup</u>: Unless otherwise agreed upon by the study investigator and sponsor medical monitor, Stage 2 tests should be drawn within one (1) week of receiving the Stage 1 workup results and the results of Stage 1 evaluation are negative.

Notes:

• A specific test may be performed earlier if the investigator determines that the clinical presentation leads to a certain diagnosis.

• If no etiology for the liver safety test abnormalities has been identified and evaluation is progressing to Stage 2 workup, **<u>consultation with a</u>**

hepatologist/gastroenterologist must occur unless both the study investigator and sponsor medical monitor agree that there is a compelling reason that this is unnecessary.

Stage 2 workup should be guided by information accrued during Stage 1 workup as well as expert input from a hepatologist/gastroenterologist:

The following laboratory tests and evaluations may be considered, as appropriate, for evaluation of a potential Hy's Law case.

- **Serologies for the following infectious agents** (contain appropriate local consent):
    - Viral hepatitis D (if subject has hepatitis B)
    - Viral hepatitis E
    - Herpes simplex
    - Toxoplasmosis
    - Varicella
    - Parvovirus
- **Assessments for inherited liver diseases.** Ensure appropriate consent is obtained for any genetic testing.
    - Hemochromatosis
        - Iron Studies: serum ferritin, iron, total iron binding capacity
        - Genetic test if necessary to confirm a diagnosis. A genetic test will generally not be necessary if iron studies are normal.
    - Gilbert's disease: genetic testing if there is a suspicious history and total and direct bilirubin measurements do not support a clear diagnosis
    - Wilson's disease: ceruloplasmin and 24hr urinary copper
    - Alpha-1-antitrypsin deficiency: serum alpha-1-antitrypsin concentration and protease inhibitor (PI) typing
    - Cystic fibrosis: genetic testing

- **Tests for autoimmune hepatitis**
    - Antinuclear antibody (ANA)
    - Anti-smooth muscle antibodies
    - Anti-liver-kidney microsomal antibodies
    - Anti-soluble liver antigen antibodies
    - Anti-actin antibodies
- **Testing for primary biliary cirrhosis:** Anti-mitochondrial antibody (if ALP or TBL >ULN)
- Celiac disease screening including anti-tissue transglutaminase (TTG) antibody, IgA, and anti-endomysial (EMA) antibody if clinically indicated.
- Consider screening for cystic fibrosis if clinically indicated.

If laboratory tests or ultrasound evidence of biliary tract obstruction, consider obtaining ERCP or MRCP

CONTACTS

If you have any questions, please refer to your Sponsor contact list for the following Alimentiv or Pandion personnel:

- Clinical Research Associate or Subsidiary Monitor

- Medical Monitor

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- Drug-Related Hepatotoxicity, Victor J. Navarro and John R. Senior, N Engl J Med 2006;354:7314-9
- Drug-induced liver injury:Hy's rule revisited, Einar Björnsson MD, PhD, Clinical Pharmacology & Therapeutics, Vol. 79, Issue 6, June 2006.
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    - https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/hepatotoxicity-pre-market-evaluation.html

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- Zimmerman HJ 1978 *Hepatotoxicity, The Adverse Effects of Drugs and Other Chemicals on the Liver,* Drug-induced liver disease (Appleton-Centry-Crofts, New York), pp 351-5.
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APPENDIX 8: 12-LEAD ELECTROCARDIOGRAM ABNORMALITY CRITERIA

	Potentially Significant Findings Leading to Screen Failure	Potentially Significant Postrandomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	> 110 bpm	HR > 110 bpm and HR increase of ≥25 bpm from baseline, that is sustained for 90 minutes or longer
Sinus Bradycardia	< 40 bpm	HR < 40 bpm and HR decrease of ≥ 5 bpm from baseline
Sinus Pause/Arrest	> 2.0 seconds	> 2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR < 40 bpm	Junctional Rhythm with HR < 40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB

	Potentially Significant Findings Leading to Screen Failure	Potentially Significant Postrandomization Findings (clarification on action to take)
CONDUCTION		
1st Degree AV Block	PR ≥ 230 ms	PR ≥ 230 ms + Increase of > 15 ms; or PR Increase of > 25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS < 120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR < 120 ms	Delta Wave + PR < 120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥ 130 ms	QRS ≥ 130 ms + Increase of ≥ 10 ms
QTc (B or F)		
Male	QTc ≥ 470 ms	QTc ≥ 500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥ 480 ms	QTc ≥ 500 ms or Increase of ≥ 60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All

	Potentially Significant Findings Leading to Screen Failure	Potentially Significant Postrandomization Findings (clarification on action to take)
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fridericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.

Baseline is defined as Predose Day 1

APPENDIX 9: SPONSOR SIGNATURE PAGE

PANDION STATEMENT AND SIGNATURE

Pandion Therapeutics, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA (known as MSD outside the United States and Canada) 134 COOLIDGE AVE, 2nd FLOOR, WATERTOWN, MA 02472

STUDY ACKNOWLEDGEMENT

A Phase 1b, Randomized, Adaptive, Double-Blind, Placebo-Controlled, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of PT101 in Subjects with Active Ulcerative Colitis

This protocol has been approved by Pandion Therapeutics, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA (known as MSD outside the United States and Canada) . The following signature documents this approval:

PPD

Clinical Director

Signature

Date

APPENDIX 10: INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR STATEMENT

This study will be conducted in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

I have read the protocol, including all appendices, and I agree it contains all necessary details for me and my staff to conduct this study. I will conduct this study as outlined herein. I will provide study personnel under my supervision access to all materials provided by Pandion Therapeutics. I will ensure my staff are appropriately informed of their obligations.

_____	_____
Principal Investigator Name	Signature
_____	_____
Date	Site Number
_____	_____
Institution Name	Address of Institution

APPENDIX 11: DOCUMENT HISTORY

Version	Date
Original	12-Mar-2021
Amendment 1	11-May-2021
Amendment 4	17-Dec-2021
Amendment 8	13-May-2022


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