

CLINICAL STUDY PROTOCOL

NCT Number: NCT03259308

Study Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 302)

Study Number: SHP647-302

Protocol Version and Date:

Original Protocol: 06 Jul 2017
Amendment 1: 05 Sep 2018
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DRUG: SHP647

IND: 100,222

EUDRACT NO.: 2017-000572-28

SPONSOR:
Shire Human Genetic Therapies, Inc. ("Shire")
300 Shire Way, Lexington, MA 02421 USA

**PRINCIPAL/
COORDINATING
INVESTIGATOR:** [REDACTED], MD, PhD

**PROTOCOL
HISTORY:** Original Protocol: 06 Jul 2017

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PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature:	[REDACTED]	Date:	[REDACTED]
[REDACTED]			
MD/[REDACTED]			

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP647-302.

Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 302).

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]

Signature: _____ Date: _____

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Wilmington [REDACTED] or [REDACTED]

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
AE	adverse event
ADA	anti-drug antibodies
CI	confidence interval
CMH	Cochran-Mantel Haenszel
CNS	central nervous system
CRO	contract research organization
DMC	data monitoring committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EMA	European Medicines Agency
[REDACTED]	[REDACTED]
ET	Early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FWER	family-wise type I error rate
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
HRQL	health-related quality of life
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
IGRA	interferon gamma release assay
IRB	Institutional Review Board
IRT	interactive response technology
LTS	long-term safety extension
MAdCAM	mucosal addressin cell adhesion molecule

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[REDACTED]	[REDACTED]
PFS	prefilled syringe
PGA	physician global assessment
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
PML	progressive multifocal leukoencephalopathy
PRC	polymerase chain reaction
Q4W	once every 4 weeks
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SF-36	Short Form-36
TB	tuberculosis
TEAE	treatment-emergent AE
TNF	tumor necrosis factor
[REDACTED]	[REDACTED]
UC	ulcerative colitis
US	United States
[REDACTED]	[REDACTED]

STUDY SYNOPSIS

Protocol number: SHP647-302	Drug: SHP647
Title of the study: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 302)	
Number of subjects (total and for each treatment arm):	
A total of 825 subjects (330 subjects at 25 mg SHP647, 330 subjects at 75 mg SHP647, and 165 placebo subjects) are planned for enrollment into the study.	
Investigator(s): Multicenter study.	
Site(s) and Region(s):	
It is anticipated that the study will be conducted in at least 18 countries. Regions will include North America, Europe, the Middle East, and Africa, Latin America, and Asia-Pacific. Approximately 175 sites will be utilized.	
Study period (planned): 2017 to 2020	Clinical phase: 3
Objectives:	
Primary: To evaluate the efficacy of SHP647 in inducing remission, based on composite score of patient-reported symptoms and centrally read endoscopy, in subjects with moderate to severe ulcerative colitis (UC).	
Key Secondary:	
<ul style="list-style-type: none">• To evaluate the efficacy of SHP647 in achieving endoscopic remission, based on centrally read endoscopy.• To evaluate the efficacy of SHP647 in achieving clinical remission, based on composite score of patient-reported symptoms.• To evaluate the efficacy of SHP647 in inducing clinical response, based on composite score of patient-reported symptoms and centrally read endoscopy.• To evaluate the efficacy of SHP647 in achieving mucosal healing, based on endoscopic and histological assessment.	
Other Secondary:	
<ul style="list-style-type: none">• To evaluate the safety and tolerability of SHP647.• To evaluate the effect of SHP647 induction treatment on other clinical outcomes.• To evaluate the effect of SHP647 on abdominal pain, urgency, diarrhea, and absolute stool frequency and bleeding scores.• To evaluate the effect of SHP647 on health-related quality of life.• To evaluate the effect of SHP647 on incidence of hospitalizations and total inpatient days.	
Rationale: This study is designed to evaluate the efficacy of SHP647 in inducing remission in subjects with moderate to severe UC.	
SHP647 has been investigated in 2 completed dose-finding studies (A7281001 and A7281009) in subjects with moderate to severe UC; a third study (A7281010), an open-label long-term safety extension study, is ongoing. The Phase 1 study, A7281001, which investigated the safety, tolerance, pharmacokinetics, and pharmacodynamic properties of SHP647, supports further clinical development of SHP647 using subcutaneous (SC) administration. Therefore, SC doses of 25 mg or 75 mg of SHP647 or placebo on Day 1 (Week 0), Week 4, and Week 8 are recommended for the Phase 3 studies SHP647-301 and SHP647-302.	

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Investigational product, dose, and mode of administration:

The test product is SHP647, which will be provided as a sterile aqueous buffered solution for SC administration in a glass prefilled syringe (PFS) with a fixed needle. Each PFS contains 1 mL of SHP647 solution at an appropriate concentration to provide the intended dose of drug (25 or 75 mg). Additional information is provided in the current SHP647 investigator's brochure.

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain SHP647.

Methodology:

A total of 825 subjects (330 subjects at 25 mg SHP647, 330 subjects at 75 mg SHP647, and 165 placebo subjects) are planned for enrollment into the study. Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent form.

The study consists of a screening period up to 6 weeks and a 12-week treatment period. After the screening period, eligible subjects will be randomly assigned to receive 1 of 3 treatments (25 mg SHP647, 75 mg SHP647, or placebo) in a 2:2:1 ratio. Randomization will be stratified based upon the subject's status of prior anti-TNF (tumor necrosis factor) treatment (naïve or experienced) and glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline). Subjects will receive SC injections of SHP647 or placebo, using a PFS, on Week 0/Day 1 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 5). Subjects will undergo efficacy, [REDACTED] safety, and health outcome assessments at these visits.

Patient-reported UC signs and symptom data (including stool frequency, rectal bleeding severity and frequency, diarrhea frequency, urgency frequency, and abdominal pain/worst severity) will be collected using a daily electronic diary (e-diary) during the treatment period. The Mayo score is a measure of UC disease activity consisting of the following 4 subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician global assessment (PGA). The partial Mayo score consists of the Mayo score without the endoscopic subscores. The composite score is a recommended measure consisting of the Mayo score without the PGA subscore, and will be used for the primary efficacy endpoint. The Mayo scores and composite score will be based on subject daily e-diary entries.

At the end of the 12-week treatment period, eligible subjects will be offered the opportunity to participate in a double-blind maintenance study (SHP647-303; for subjects who achieve clinical response) or a long-term safety extension (LTS) study (SHP647-304; for subjects who do not achieve a clinical response). Subjects who withdraw early from the 12-week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

Inclusion and exclusion criteria:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must be between ≥ 16 and ≤ 80 years of age at the time of the signing of the informed consent/assent form.
NOTE: Subjects <18 years of age must weigh ≥ 40 kg and must have body mass index (BMI) ≥ 16.5 .
4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for ≥ 3 months before screening. The following must be available in each subject's source documentation:
 - A biopsy report to confirm the histological diagnosis.
 - A report documenting disease duration based upon prior colonoscopy.NOTE: If this documentation is not available at the time of screening, a colonoscopy with biopsy to confirm the diagnosis is required during the screening period.

5. Subjects must be willing to undergo a flexible sigmoidoscopy or colonoscopy (if preferred), including biopsy sample collection, during screening after all other inclusion criteria have been met.
6. Subjects must have moderate to severe active UC, defined as a total Mayo score of ≥ 6 , including a centrally read endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 at baseline (Visit 2).
7. Subjects must have evidence of UC extending proximal to the rectum (ie, not limited to proctitis).
8. Subjects must have had an inadequate response to, or lost response to, at least 1 conventional treatment such as mesalamine (5-aminosalicylic acid [5-ASA]), glucocorticoids, immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]), or anti-TNF.
9. Subjects receiving any treatment(s) for UC described in Section 5.2.1 of the protocol are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
10. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use acceptable contraception for the duration of the study.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subjects with indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of Crohn's disease.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for UC during the treatment period.
5. Subjects at risk for colorectal cancer must have a colonoscopy performed during the screening period with results available within 10 days before the baseline visit (Visit 2), unless the subject has had a colonoscopy

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within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year must be available in the source documents.

Subjects at risk for colorectal cancer include, but are not limited to:

- Subjects with extensive colitis for ≥ 8 years or disease limited to left side of colon (ie, distal to splenic flexure) for ≥ 10 years before screening, regardless of age.
 - Subjects ≥ 50 years of age at the time of signing of the informed consent form.
6. Subjects have had prior treatment with SHP647 (formerly PF-00547659).
 7. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
 8. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
 9. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).
 10. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
 11. Subjects have received parenteral or rectal glucocorticoids, or rectal 5-ASA, within 14 days before screening endoscopic procedure.
 12. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before baseline (Visit 2).
 13. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).
 14. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis [subjects with *C. difficile* infection at screening may be allowed re-test after treatment], evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
 15. Subjects with abnormal chest x-ray findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation.)
 16. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) who have not completed a generally accepted full course of treatment before randomization are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed.

Subjects who have no history of previously diagnosed active or latent tuberculosis are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥ 5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before randomization. If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

- An IGRA is strongly recommended for subjects with a prior Bacillus Calmette-Guérin (BCG) vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include Quantiferon TB Gold In-Tube Test.
- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent tuberculosis, a positive test on repeat will exclude the subject. Subjects with a history of active or latent tuberculosis infection must follow instructions for "Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless

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both of the following criteria are met" in this criterion.

- Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray, taken within the 3 months before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
 - A chest x-ray performed within 3 months prior to screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.
17. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
18. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on the targeted neurological assessment during the screening period.
19. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
20. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
- Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal (except disease under study), endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.
 - Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
 - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening.
 - History of significant cerebrovascular disease within 24 weeks before screening.
21. Subjects who have had significant trauma or major surgery within 4 weeks before the screening visit (Visit 1), or with any major elective surgery scheduled to occur during the study.
22. Subjects with evidence of or suspected liver disease, liver injury due to methotrexate or primary sclerosing cholangitis.
23. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). NOTE: if a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if the subject tests positive for antibody to Hepatitis B surface antigen (HBsAb also referred as anti-HBsAg) reflex testing.

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24. Subjects with positive hepatitis C antibody (HCVAb) with confirmation by HCV-ribonucleic acid (RNA) polymerase chain reaction (PCR) reflex testing.
25. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening. NOTE: Screening laboratory tests, if the results are considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results must be reviewed for eligibility prior to the screening endoscopy procedure.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥ 2.0 times the upper limit of normal (ULN).
 - Total bilirubin level ≥ 1.5 times the ULN (except in subjects with documented diagnosis of Gilbert's syndrome).
 - Hemoglobin level ≤ 80 g/L (8.0 g/dL).
 - Platelet count $\leq 100 \times 10^9/\text{L}$ ($100,000$ cells/ mm^3) or $\geq 1000 \times 10^9/\text{L}$ ($1,000,000$ cells/ mm^3).
 - White blood cell count $\leq 3.5 \times 10^9/\text{L}$ (3500 cells/ mm^3).
 - Absolute neutrophil count (ANC) < 2000 cells/ mm^3 .
 - Serum creatinine level $\geq 177 \mu\text{mol}/\text{L}$ (2 mg/dL) or estimated glomerular filtration rate (GFR) $< 40 \text{ ml/min}/1.73\text{m}^2$ based on the abbreviated MDRD.
26. Subjects with known infection with human immunodeficiency virus (HIV).
27. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse.
28. Subjects using medicinal marijuana (cannabis) or related products for recreational purposes who have a known dependency per the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Edition 5 (including urine drug screen and medical history). Exceptions are those subjects who are prescribed marijuana (by a physician) for medicinal use and where the product is sourced from a licensed pharmacy/provider. Such subjects must be using the product, in a stable regimen, for at least 3 months before screening.
29. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
30. Female subjects who are planning to become pregnant during the study period.
31. Male subjects who are planning to donate sperm must agree not to do so for the duration of the study and through 16 weeks after last dose of investigational product.
32. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: Up to 6 weeks
- Planned duration of treatment period: 12 weeks
- Planned duration of follow-up period: 16 weeks

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Endpoints and statistical analysis:

Analysis Sets:

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

The full analysis set (FAS) will consist of all subjects in the randomized set who have received at least 1 dose of investigational product.

The per-protocol (PP) set will consist of all subjects in the FAS who complete the Week 12 visit and who do not have predefined protocol deviations that may affect the primary efficacy endpoint.

The completer set will consist of all subjects in the FAS who have completed the final scheduled primary assessment for this study.

[REDACTED]

Primary Efficacy Endpoint: The primary efficacy endpoint is the proportion of subjects in remission at the Week 12 visit. Remission is defined as a composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy as follows:

- stool frequency subscore of 0 or 1 with at least a 1-point change from baseline
 - AND
- rectal bleeding subscore of 0
 - AND
- endoscopic subscore of 0 or 1 (modified, excludes friability).

The primary efficacy endpoint will be compared for each active treatment group (25 mg or 75 mg SHP647) to the placebo group using a Cochran-Mantel Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment and glucocorticoid use at baseline (Visit 2). Subjects with missing remission data at the Week 12 visit will be considered failures and counted as nonresponders. The endoscopy score will be based on centrally read results.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata, $j=1$ to m . The common treatment difference is a weighted average of the stratum-specific treatment differences.

The global family-wise type I error rate (FWER) for the statistical tests of the primary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz, et al 2009 will be utilized to propagate α from primary to key secondary endpoints and between the two SHP647 treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the primary endpoint (P) and alpha is propagated in a hierarchical manner to each of the 4 key secondary endpoints (K1-K4) within a pairwise treatment comparison.

Key Secondary Efficacy Endpoints:

- Proportion of subjects with endoscopic remission, as defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability), at the Week 12 visit.
- Proportion of subjects with clinical remission, as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at the Week 12 visit.
- Proportion of subjects with clinical response based on composite score at the Week 12 visit. Clinical response (composite) is defined as a decrease from baseline in the composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 .
- Proportion of subjects with mucosal healing based on endoscopic and histological assessment at the Week 12 visit. Mucosal healing is defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability) and centrally read Geboes score of ≤ 2 .

The key secondary endpoints will be analyzed using the same approach as described for the primary efficacy endpoint. Subjects with missing key secondary endpoint data at the Week 12 visit will be considered failures and counted as nonresponders.

Other Secondary Efficacy Endpoints:

- Proportion of subjects with remission, defined as a total Mayo score ≤ 2 with no individual subscore (stool frequency, rectal bleeding, endoscopy [modified, excludes friability], and physician's global assessment) exceeding 1, at the Week 12 visit.
- Proportion of subjects with clinical response based on total Mayo score at the Week 12 visit. Clinical response (Mayo) is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or an absolute subscore for rectal bleeding ≤ 1 .
- Proportion of subjects with partial Mayo score ≤ 2 with no individual subscore > 1 at the Week 4, 8, and 12 visits. The partial Mayo score does not include the endoscopy subscore.
- Proportion of subjects with clinical remission as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at Weeks 4 and 8.
- Proportion of subjects with endoscopic remission at the Week 12 visit with endoscopic subscore of 0.
- Proportion of subjects with clinical remission at the Week 4, 8, and 12 visits with both rectal bleeding and stool frequency subscores of 0.
- Proportion of subjects with deep remission at the Week 12 visit. Deep remission is defined as both endoscopic and rectal bleeding subscores of 0, and stool frequency subscore ≤ 1 and a centrally read Geboes score of ≤ 2 .
- Change from baseline at the Week 12 visit in abdominal pain, diarrhea and urgency item scores, absolute stool frequency, absolute rectal bleeding and total sign/symptom score based on subject daily e-diary entries (sum of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency).
- Change from baseline in IBDQ domain and total (absolute) scores (time frame: Week 0, Week 8, up to Week 12, or early termination).
- Change from baseline in Short Form-36 (SF-36), version 2, acute (physical and mental component summary scores and individual domain scores) to the Week 12/ET visit.
- Incidence of all-cause hospitalizations and total inpatient days.

Other secondary/exploratory endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis

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methods.

- Binary endpoints will be analyzed using the same approach as described for the primary endpoint. Subjects with missing binary endpoint data at a visit will be considered failures and counted as nonresponders.
- Continuous endpoints that are only measured at baseline and the Week 12 visit will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% confidence intervals (CIs) for least squares mean treatment differences will be provided.
- Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation (REML). The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

Safety Analyses:

All safety analyses will be performed using the safety set. Subjects will be analyzed according to the treatment they actually received.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

Antidrug antibody data will be summarized by treatment group and visit.

STUDY SCHEDULE

Table 1 Schedule of Assessments

Study Procedure	Screening ^a	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET ^b	Week 20 ^c	Week 28 ^c
Visit Number	1	2	3	4	5	6 (Part 1) ^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3		84 ±3	140 ±7
Informed consent/assent	X							
Eligibility assessment	X	X					X ^e	
Demographics and medical history ^f	X							
Complete physical examination ^g	X						X	X
Targeted physical examination ^g		X						
Targeted neurological assessment ^h	X						X	X
Vital signs ⁱ	X	X		X	X		X	X
Height	X							
Weight	X	X		X	X		X	X
12-lead ECG ⁱ	X	X					X	
Chest x-ray ^j	X							
Contraception check ^k	X	X	X	X	X		X	X
Laboratory Assessments								
Hematology	X ^l	X		X	X		X	X
Serum chemistry	X ^l	X		X	X		X	X
Urinalysis	X ^l	X		X	X		X	X
Stool microbiology ^m	X ^l							
HBsAg, HBcAb, HCV Ab ⁿ	X ^l							
FSH ^o	X ^l							
Serum β-hCG ^p	X ^l							
Urine β-hCG ^p		X		X	X		X	X
TB test (PPD or QuantiFERON TB Gold) ^q	X ^l							
JCV antibody banked sample ^r		X						
		X			X		X	
		X ^s			X ^s		X	
		X ^s			X ^s		X	
		X ^s			X ^s		X	
		X ^t	X ^t	X ^t	X ^t		X	

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Table 1 Schedule of Assessments

Study Procedure	Screening ^a	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET ^b	Week 20 ^c	Week 28 ^c
Visit Number	1	2	3	4	5	6 (Part 1) ^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3	84 ±3	140 ±7	196 ±7
ADA and NAb sampling		X ^s	X	X ^s	X ^s	X	X	X
Endoscopic Procedure								
Endoscopy (including biopsy) ^u	X ^u					X		
UC Assessments								
Total Mayo score		X ^v					X ^v	
Partial Mayo score				X	X			
Remission stool frequency and pre-UC stool frequency ^w	X							
PRO UC daily e-diary data instruction	X							
PRO UC daily e-diary data ^w	X	X	X	X	X	X	X	
Health Assessment^x								
IBDQ		X			X		X	
[REDACTED]		X			X		X	
Hospitalizations, inpatient days, [REDACTED] (HRUA)				X	X		X	X
[REDACTED]				X	X		X	
[REDACTED]		X		X	X		X	
[REDACTED]		X					X	
SF-36 v2, acute form		X			X		X	
[REDACTED]		X					X	
Treatment Procedures								
Randomization		X						
Administration of SHP647 or placebo ^y		X		X	X			
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample ^z	X			X	X			

Ab=antibody ADA=antidrug antibodies; β-hCG=beta-human chorionic gonadotropin; [REDACTED]; ECG=electrocardiogram; ED=emergency department;
 [REDACTED]; ET=early termination; FSH=follicle-stimulating hormone; GDH=glutamate dehydrogenase;
 HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HRUA=Healthcare Resource Utilization Assessment; HCV=hepatitis C virus; HCV RNA=hepatitis C
 virus ribonucleic acid; HEENT=head, eyes, ears, nose, and throat; IBDQ=Inflammatory Bowel Disease Questionnaire; JCV=John Cunningham virus; LTS=long-term safety
 extension; [REDACTED]; Nab=neutralizing antibody; PCR=polymerase chain reaction; PGA = physician's global assessment;

Table 1 Schedule of Assessments

Study Procedure	Screening^a	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET^b	Week 20^c	Week 28^c
Visit Number	1	2	3	4	5	6 (Part 1)^d	7	8
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3	84 ±3	140 ±7	196 ±7

PPD=purified protein derivative; PRO=patient-reported outcomes; SF-36 v2= short form-36 health survey, version 2; TB=tuberculosis; [REDACTED]; UC=ulcerative colitis; [REDACTED]

^a At least 2 visits will be necessary to complete the screening procedures, including endoscopy.

^b Subjects who withdraw early during the treatment period should return for the early termination (ET) visit and then enter into the safety follow-up period.

^c Participation in the safety follow-up period is not required if subject is entering the maintenance study (SHP647-303) or LTS (SHP647-304) at the completion of the Week 12 visit. For subjects participating in the 16-week safety follow-up period (not entering the maintenance study or LTS study), the Week 20 (Visit 7) visit will routinely be conducted by telephone; however, as an exception the visit can be performed as a study site visit if preferred. The Week 28 (Visit 8) visit will be at the study site.

^d Part 1 of Visit 6 should be scheduled preferably within 5 to 7 days before Part 2 visit; this will allow sufficient time for data from the centrally read endoscopy to be available at Part 2 of the visit.

^e The outcome of Visit 6, Part 2 is used to assess eligibility to enroll in the maintenance (SHP647-303) or LTS (SHP647-304) studies. Eligibility for SHP647-303 and SHP647-304 will be assessed under those respective protocols.

^f Medical history will include UC history, cardiac history, and smoking history.

^g Complete physical examination includes the review of the following body systems: general appearance, skin, HEENT, heart, lungs, confrontational visual fields (eyes), breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes. Targeted physical examination includes the review of the following body systems: skin, heart, lungs, confrontational visual fields (eyes), abdomen, and examination of body systems where there are symptom complaints by the subject.

^h Subjects will be evaluated to reveal any potential abnormalities in the following neurologic domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior. Subjects with any unexplained positive item at screening that is suggestive of PML should be excluded. See Section 7.2.3.3 for further details.

ⁱ Vital signs (including blood pressure, pulse, respiratory rate, and temperature) and 12-lead ECG should be performed before collection of blood samples for laboratory assessments and before endoscopic procedure.

^j A chest x-ray performed up to 12 weeks before screening (Visit 1) may be used if available; the official reading must be located in the subject's source documentation.

^k Contraception check should be performed for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential. See Section 4.4 for further details.

^l Screening laboratory test results, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results of repeated tests must be reviewed for eligibility prior to the screening endoscopy procedure.

^m The detection of *Clostridium difficile* by toxigenic stool culture (stool culture followed by detection of toxin) is considered the gold standard for the diagnosis of the colonization or infection with pathogenic *C. difficile*. Comparable sensitivity may be achieved by direct testing of stool via point-of-use rapid membrane enzyme immunoassay card for both *C. difficile* toxin A and B and GDH antigen on a card. Use of the card for point-of-care screening is encouraged where permitted by local regulation; any samples

Table 1 Schedule of Assessments

Study Procedure	Screening^a	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET^b	Week 20^c	Week 28^c
Visit Number	1	2	3	4	5	6 (Part 1)^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3		84 ±3	140 ±7
								196 ±7

showing a positive result with this method should be sent for toxigenic stool culture. Molecular techniques such as PCR for detection of toxin RNA are also acceptable alternatives. Refer to the laboratory manual for further guidance and instruction for *C. difficile* screening.

^a HCV RNA PCR if HCV Ab positive. If a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if the subject tests positive for antibody to Hepatitis B surface antigen (HBsAb also referred as anti-HBsAg) reflex testing.

^b For confirmation of postmenopausal status in females who have had 12 consecutive months of spontaneous amenorrhea and are ≥51 years of age.

^c For females of childbearing potential who are not surgically sterile, do not have confirmed ovarian failure, or do not meet the definition of postmenopausal as described in Section 4.4 and Section 7.2.3.7.

^d A documented negative PPD test within 12 weeks before baseline (Visit 2) is acceptable. Interferon gamma release assay official reading and method or test must be located in the source documentation.

^e A serum sample will be collected and banked. It may be analyzed if a subject shows neurologic symptoms suggestive of progressive multifocal leukoencephalopathy.

^f The sample must be collected before administration of investigational product.

^g The ■ sample must be collected before administration of investigational product.

^h Flexible sigmoidoscopy or colonoscopy (if preferred) at screening must be performed on all subjects after the majority of other eligibility criteria (eg, laboratory values) are met. Endoscopy must be performed during the screening period within 10 days before baseline (Visit 2), preferably within 5 to 7 days before the baseline visit, to obtain the centrally read endoscopic subscore. Biopsy samples will be collected for histological evaluation using the Geboes Score classification. Subjects at risk of colorectal cancer, as defined in exclusion criterion 5 (see Section 4.2), must have a colonoscopy performed at screening.

ⁱ Mayo score will be based on subject daily e-diary entries. The Mayo score at baseline will be calculated based on the stool frequency subscore and rectal bleeding subscore, reported by subjects in the PRO UC daily e-diary and PGA obtained at baseline and the centrally read endoscopic subscore for the endoscopy performed during the screening period. The Mayo score at the Week 12 visit will be calculated based on the stool frequency subscore and rectal bleeding subscore reported by subjects in the PRO UC daily e-diary and PGA and the centrally read endoscopic subscore for the endoscopy performed at Week 12, Visit 6 (Part 1). See Section 7.2.2.2 for further details.

^j PRO UC daily e-diary will be collected using a daily e-diary during the treatment period. Collection of the daily e-diary data must begin at least 10 days before the baseline visit (Visit 2). The subject should be provided with the handheld device to take home on their first visit. See Section 7.2.2.3 for further details. Compliance is assessed by site staff at each visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <23 out of 28 e-diary entries) when compared with the previous visit.

^k All health outcome or patient-reported questionnaires should be completed before completing any other visit assessments.

^l Interactive response technology will be used for randomization and dispensation of study treatment.

^m Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the visit at which testing will be done.

Note: See Section 7.2 for the order in which assessments should be performed. Timing of visits is relative to baseline (Visit 2).

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Ulcerative colitis (UC) is a chronic, relapsing disease marked by ulceration and inflammation of the colonic mucosa and submucosa. Initially it usually involves the rectum but may extend proximally to involve a portion of, or the entirety of, the colon. In the early stages, hemorrhagic and erythematous tissue is observed, progressing to mucosal ulceration with purulent exudates in severe cases. The ulceration pattern is continuous and may extend the entire length of the colon. Perforation of the bowel wall causing ileus and peritonitis can occur with transmural extension of the ulceration. Bloody diarrhea with or without mucus and lower abdominal pain with periods of remission and exacerbation are the most common symptoms.

The incidence of UC is estimated to be up to 24.3 cases per 100,000 persons per year in Europe and up to 19.2 cases per 100,000 persons per year in North America. No clear difference in incidence has been observed between men and women. Although UC can occur at any age, peak incidence has been observed in the second to fourth decades of life ([Molodecky et al., 2012](#)).

Ulcerative colitis is a lifelong condition with a serious effect on the quality of life. Current treatment primarily consists of symptomatic management with dietary modifications and opiates (loperamide), as well as disease modifying agents such as 5-aminosalicylic acid (5-ASA), systemic glucocorticoids, immunosuppressive agents (azathioprine/6-mercaptopurine, cyclosporine), and biologic therapy with anti-tumor necrosis factor (TNF) or anti-integrin agents. Despite recent advances, there is still an unmet need for an effective pharmacological treatment that will induce and maintain remission.

1.2 Product Background and Clinical Information

The selectivity of lymphocyte homing to specialized lymphoid tissue and mucosal sites of the gastrointestinal (GI) tract is influenced by the endothelial expression of mucosal addressin cell adhesion molecule (MAdCAM). MAdCAM is a member of the immunoglobulin super family of cell adhesion molecules and is mostly expressed on the cell surface of high endothelial venules of organized intestinal lymphoid tissue such as Peyer's patches and mesenteric lymph nodes ([Briskin et al., 1997; Liaskou et al., 2011; Shyjan et al., 1996](#)). MAdCAM plays a role in gut immune surveillance, and also appears to facilitate excessive lymphocyte infiltration under conditions of chronic GI inflammation. The $\alpha_4\beta_7$ integrin is the recognized ligand for MAdCAM, and expression of this ligand on populations of CD4 $^+$ and CD8 $^+$ T cells, as well as on subsets of B cells, distinguishes them as unique gut homing lymphocytes.

SHP647 (previously known as PF-00547659) is a fully human immunoglobulin G2 kappa (IgG_{2k}) monoclonal antibody that binds to human MAdCAM to reduce lymphocyte homing to the gut and GI inflammation. SHP647 binds MAdCAM-1 with high affinity and selectivity that prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM expressing sites in the high endothelial venules of the GI tract.

Always refer to the latest version of the SHP647 investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the pharmacokinetics, efficacy, and safety of SHP647.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

SHP647, a fully human IgG_{2k} antihuman MAdCAM monoclonal antibody, is under development for the treatment of UC. SHP647 prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM-expressing sites with high affinity and selectivity. Principal sites of MAdCAM expression on normal tissue include intestine, pancreas, stomach, esophagus, spleen, and to a lesser extent lung, liver, and bladder but not the central nervous system (CNS) ([Steffen et al., 1996](#)).

Although selective targeting of the MAdCAM receptors is a novel approach, the basic interference of lymphocyte homing by preventing the binding of these $\alpha_4\beta_7^+$ lymphocytes to the MAdCAM receptor and the resultant efficacy in UC is well established ([Feagan et al., 2013](#)). SHP647 is differentiated from other molecules used for the treatment of UC in that it blocks the interaction of $\alpha_4\beta_7^+$ lymphocytes to the MAdCAM receptor by selectively binding to MAdCAM in the gut (and related tissues) whereas other molecules only target the integrins on the infiltrating lymphocytes. Additionally, SHP647 does not bind to the vascular cell adhesion molecule; therefore, SHP647 is not expected to be an effective treatment for multiple sclerosis, or affect lymphocyte homing or surveillance in the CNS.

This study is designed to evaluate the efficacy of SHP647 in inducing remission in subjects with moderate to severe UC.

SHP647 has been investigated in 2 completed dose-finding studies (A7281001 and A7281009) in subjects with moderate to severe UC; a third study (A7281010), an open-label long-term safety extension study, is ongoing. Phase 1 study A7281001 evaluated both single (0.03-10.0 mg/kg intravenous [IV]; 3.0 mg/kg subcutaneous [SC]) and multiple doses (0.1-3.0 mg/kg IV; 0.3 and 1.0 mg/kg SC) of SHP647 in subjects with UC. Safety evaluation revealed a safety profile for SHP647 similar to that of placebo, with no pattern of adverse events (AEs) suggestive of increased risk of opportunistic infections or CNS effects, and no evidence of adverse effects on laboratory parameters, electrocardiograms (ECGs), vital signs, or neurological function. Events leading to withdrawal were due to exacerbations of the underlying UC.

Study A7281009 was a Phase 2b proof-of-concept (randomized, double-blind, placebo-controlled, parallel, dose-ranging) study designed to evaluate the efficacy, safety, and pharmacokinetics of SHP647 in subjects with moderate to severe UC. Treatment was assigned in a 1:1:1:1 ratio to dose levels of 7.5, 22.5, 75, or 225 mg SHP647 or placebo administered SC once every 4 weeks (Q4W at Weeks 0, 4, and 8). The primary endpoint of the study was the proportion of subjects in clinical remission at Week 12, with remission defined as a total Mayo score of ≤ 2 with no individual subscore > 1 (see [Appendix 2](#) for details of the Mayo score). More subjects were in clinical remission at Week 12 in SHP647-treated groups than in the placebo group, with statistical significance achieved for the 7.5, 22.5, and 75-mg doses ([Vermeire et al., 2017](#)). Based upon the total Mayo score with a centrally read endoscopic severity component, the increase in clinical remission rates over placebo at Week 12 for the 7.5, 22.5, and 75-mg doses were 8.0% (p=.043), 12.8% (p=.010), and 11.8% (p=.012). When the clinical remission rate at Week 12 was analyzed by stratum of previous anti-TNF exposure (experienced or naïve),

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a similar trend was observed across dose levels in both the anti-TNF experienced and anti-TNF naïve subjects. There was no evidence of an adverse safety signal, and there was no increase in the frequency of infections in MAdCAM-bearing tissues as evidenced by similar rates of nasopharyngitis among treatment arms.

Based on the efficacy and safety data in Study A7281009 and the systemic population pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation, clinical remission, clinical response and mucosal healing rates were higher in subjects with UC receiving doses of 22.5 and 75 mg Q4W than in those receiving doses of 7.5 mg and 225 mg Q4W. The induction responses were not demonstrated either at Week 4 or Week 8, but were observed at Week 12 regardless of dose level. No difference in the clinical responses between a 22.5-mg dose and a 25-mg dose is expected based on the current understanding of the mode of action of SHP647 and clinical observations to date. To better understand the exposure (dose)-response relationship in this population and understand individual patient exposure needs, the 25-mg and 75-mg doses (Q4W) will be tested in the Phase 3 program. Therefore, SC doses of 25 mg or 75 mg of SHP647 or placebo on Day 1 (Week 0), Week 4, and Week 8 are recommended for the 2 planned Phase 3 studies SHP647-301 and SHP647-302. The Phase 1 study, A7281001, which investigated the safety, tolerance, pharmacokinetics, and pharmacodynamic properties of SHP647, supports further clinical development of SHP647 using SC administration.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of SHP647 in inducing remission, based on composite score of patient-reported symptoms and centrally read endoscopy, in subjects with moderate to severe UC.

2.2.2 Secondary Objectives

2.2.2.1 Key Secondary Objective

The key secondary objectives are as follows:

- To evaluate the efficacy of SHP647 in achieving endoscopic remission, based on centrally read endoscopy.
- To evaluate the efficacy of SHP647 in achieving clinical remission, based on composite score of patient-reported symptoms.
- To evaluate the efficacy of SHP647 in inducing clinical response, based on composite score of patient-reported symptoms and centrally read endoscopy.
- To evaluate the efficacy of SHP647 in achieving mucosal healing, based on a centrally read endoscopic and histological assessment.

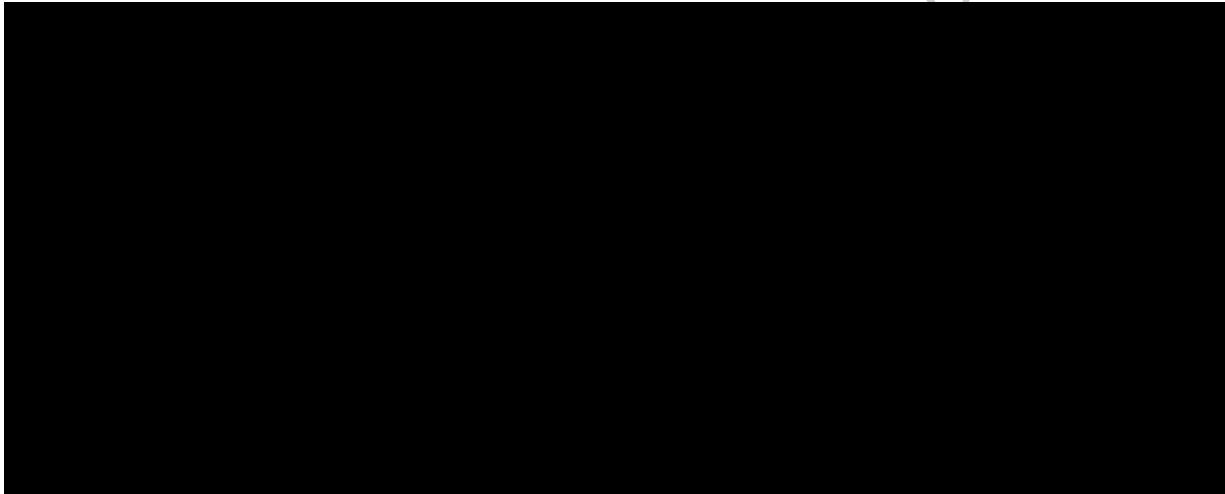
2.2.2.2 Other Secondary Objectives

The other secondary objectives are as follows:

- To evaluate the safety and tolerability of SHP647.
- To evaluate the effect of SHP647 induction treatment on other clinical outcomes.
- To evaluate the effect of SHP647 on abdominal pain, urgency, diarrhea, and absolute stool frequency and bleeding scores.
- To evaluate the effect of SHP647 on health-related quality of life (HRQL).
- To evaluate the effect of SHP647 on incidence of hospitalizations and total inpatient days.

2.2.3 Exploratory Objectives

The exploratory objectives of the study are as follows:



3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of SHP647 in inducing remission in subjects with moderate to severe UC.

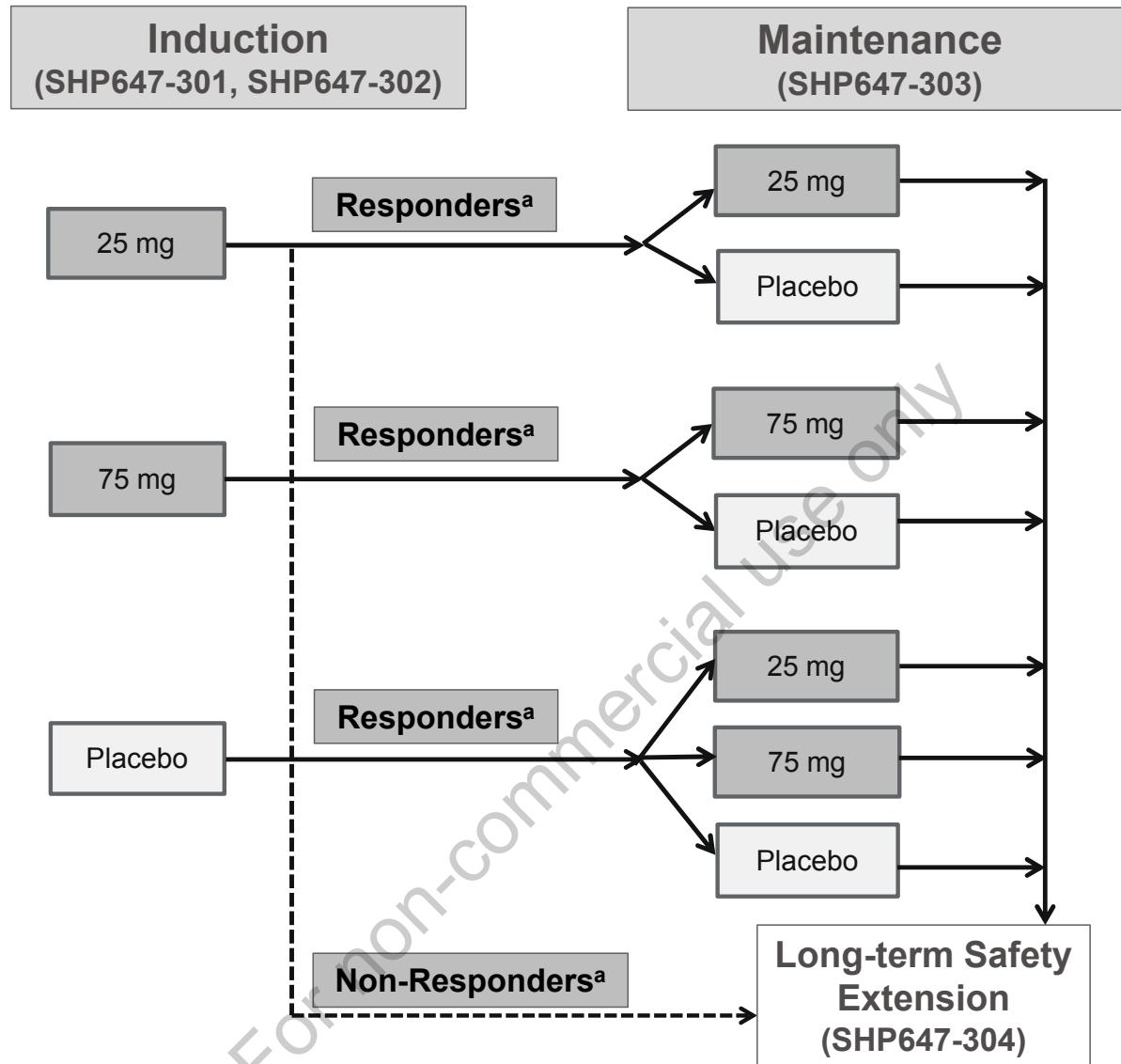
A total of 825 subjects (330 subjects at 25 mg SHP647, 330 subjects at 75 mg SHP647, and 165 placebo subjects) are planned for enrollment into the study ([Figure 1](#)). Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent form.

The study consists of a screening period up to 6 weeks and a 12-week treatment period. After the screening period, eligible subjects will be randomly assigned to receive 1 of 3 treatments (25 mg SHP647, 75 mg SHP647, or placebo) in a 2:2:1 ratio. Randomization will be stratified based upon the subject's status of prior anti-tumor necrosis factor (TNF) treatment (naïve or experienced) and glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline). Subjects will receive SC injections of SHP647 or placebo, using a prefilled syringe (PFS), on Week 0/Day 1 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 5). Subjects will undergo efficacy, [REDACTED], [REDACTED], safety, and health outcome assessments at these visits as detailed in [Table 1](#).

At the end of the 12-week treatment period, eligible subjects will be offered the opportunity to participate in a double-blind maintenance study (SHP647-303; for subjects who achieve clinical response) or a long-term safety extension (LTS) study (SHP647-304; for subjects who do not achieve a clinical response) as shown in [Figure 1](#). Subjects who withdraw early from the 12-week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

The overall study design is shown in [Figure 2](#).

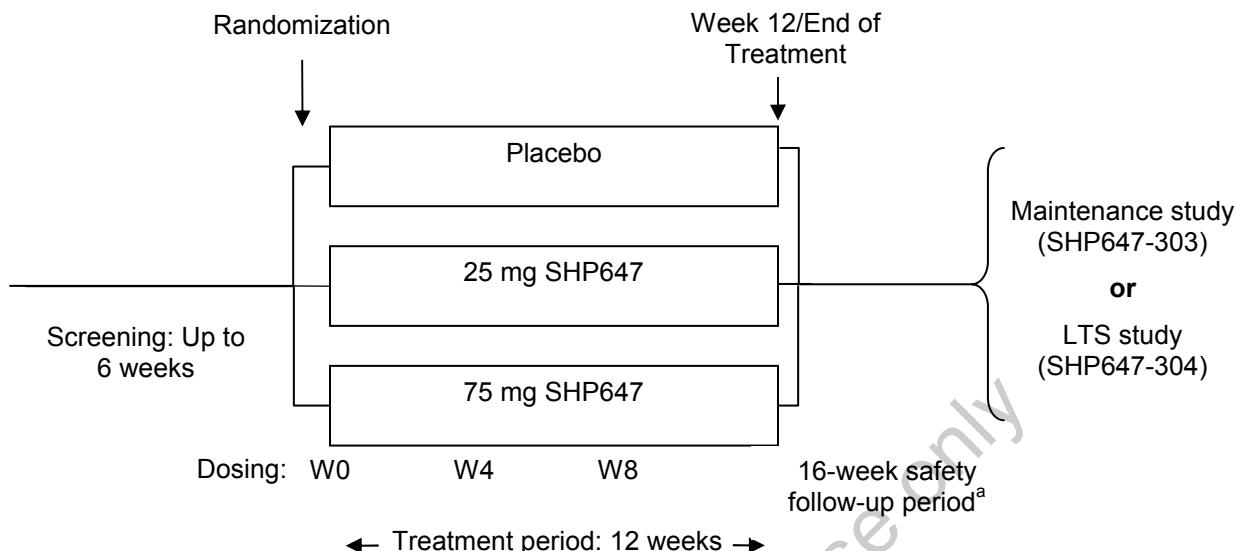
Figure 1 Overview of SHP647 Phase 3 Studies in Ulcerative Colitis



^a Clinical response is defined as:

1. A decrease from the induction study (SHP647-301 or SHP647-302) baseline in the composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1
OR
2. A decrease from the induction study (SHP647-301 or SHP647-302) baseline total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 .

Figure 2 Study Design Flow Chart



LTS=long-term safety extension; W=week

^a Subjects who withdraw early from the 12-week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period.

3.1.1 Rationale for Primary Endpoint

The Mayo score has historically been used as the primary endpoint for pivotal studies of agents intended to treat UC. Over the past decade, health authority thinking regarding efficacy endpoints for UC has evolved such that the traditional Mayo score is no longer recommended. Current regulatory guidance (FDA Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry [Draft], 2016; EMA Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis [Draft], 2016) includes a dual measurement of patient-reported signs and symptoms outcomes (stool frequency and rectal bleeding), and clinician-reported endoscopic outcomes (scoring any endoscopy with evidence of friability as a 2), including histology. Per agreement with health authorities, these 3 outcomes will be reported as a composite score.

Data will be collected to calculate the total Mayo score using both the traditional and modified endoscopy subscore as a sensitivity analysis and to estimate the impact of the modification on the primary endpoint. The clinical relevance of the traditional Mayo score is supported by its correlation with significant improvement in disease-specific HRQL as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) and in generic HRQL as measured by the Short Form-36 (SF-36) questionnaire.

3.1.2 Rationale for Key Secondary Endpoints

The first 2 key secondary endpoints are included to comply with EMA advice. European Medicines Agency would agree to the composite primary endpoint only if supported by a key secondary analysis, where the patient-reported symptoms and clinician-reported endoscopy are analyzed as “co-primary”.

The clinical response endpoint is based on the new composite score, and also represents 1 of the entry criteria for the maintenance study. This endpoint has not been previously tested.

Mucosal healing as a key secondary endpoint comprises both endoscopic and histologic components as recommended in the draft FDA and EMA guidance on UC (FDA Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry [Draft], 2016; EMA Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis [Draft], 2016).

The Geboes Score (see [Appendix 2](#)) will be used to evaluate histologic remission and to complement the endoscopic subscore in the assessment of mucosal healing.

3.2 Duration and Study Completion Definition

Each subject's final visit in this study may be at the end of the treatment period (Week 12) if continuing to Study SHP647-303 or SHP647-304, or at the end of the safety follow-up period (Week 28) if not continuing to either of these studies. In either case, the final visit will be in person at the site. A subject's maximum duration of participation is expected to be approximately 34 weeks: a screening period of up to 6 weeks, a treatment period of 12 weeks, and a safety follow-up period of 16 weeks (if applicable). It is expected that the study will be completed in approximately 3 years.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

It is anticipated that the study will be conducted in at least 18 countries. Regions will include North America, Europe, the Middle East, and Africa, Latin America, and Asia-Pacific. Approximately 175 sites will be utilized.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed. Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must be between ≥ 16 and ≤ 80 years of age at the time of the signing of the informed consent/assent form.

NOTE: Subjects <18 years of age must weigh ≥ 40 kg and must have body mass index (BMI) ≥ 16.5 .

4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for ≥ 3 months before screening. The following must be available in each subject's source documentation:
 - A biopsy report to confirm the histological diagnosis.
 - A report documenting disease duration based upon prior colonoscopy.

NOTE: If this documentation is not available at the time of screening, a colonoscopy with biopsy to confirm the diagnosis is required during the screening period.

5. Subjects must be willing to undergo a flexible sigmoidoscopy or colonoscopy (if preferred), including biopsy sample collection, during screening after all other inclusion criteria have been met.
6. Subjects must have moderate to severe active UC, defined as a total Mayo score of ≥ 6 , including a centrally read endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 at baseline (Visit 2).
7. Subjects must have evidence of UC extending proximal to the rectum (ie, not limited to proctitis).
8. Subjects must have had an inadequate response to, or lost response to, at least 1 conventional treatment such as mesalamine (5-ASA), glucocorticoids, immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]), or anti-TNF.
9. Subjects receiving any treatment(s) for UC described in Section 5.2.1 are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.

10. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use acceptable contraception (as described in Section 4.4) for the duration of the study.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Subjects with indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of Crohn's disease.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for UC during the treatment period.
5. Subjects at risk for colorectal cancer must have a colonoscopy ([Eaden and Mayberry, 2002](#)) performed during the screening period with results available within 10 days before the baseline visit (Visit 2), unless the subject has had a colonoscopy within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year must be available in the source documents.

Subjects at risk for colorectal cancer include, but are not limited to:

- Subjects with extensive colitis for ≥ 8 years or disease limited to left side of colon (ie, distal to splenic flexure) for ≥ 10 years before screening, regardless of age.
 - Subjects ≥ 50 years of age at the time of signing of the informed consent form.
6. Subjects have had prior treatment with SHP647 (formerly PF-00547659).
 7. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
 8. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
 9. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).
 10. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
 11. Subjects have received parenteral or rectal glucocorticoids, or rectal 5-ASA, within 14 days before screening endoscopic procedure.

12. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before baseline (Visit 2).
13. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).
14. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis [subjects with *C. difficile* infection at screening may be allowed re-test after treatment], evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
15. Subjects with abnormal chest x-ray findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation.)
16. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) who have not completed a generally accepted full course of treatment before randomization are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed.

Subjects who have no history of previously diagnosed active or latent tuberculosis are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥ 5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before randomization. If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

- An IGRA is strongly recommended for subjects with a prior Bacillus Calmette-Guérin (BCG) vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include Quantiferon TB Gold In-Tube Test.
- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent tuberculosis, a positive test on repeat will exclude the subject. Subjects with a history of active or latent tuberculosis infection must follow instructions for "Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met" in this criterion.
- Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray, taken within the 3 months before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
 - A chest x-ray performed within 3 months prior to screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.
17. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
18. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on the targeted neurological assessment during the screening period (see Section 7.2.3.3).
19. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
20. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
- Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI (except disease under study), endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.
 - Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
 - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening (Visit 1).
 - History of significant cerebrovascular disease within 24 weeks before screening (Visit 1).

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21. Subjects who have had significant trauma or major surgery within 4 weeks before the screening visit (Visit 1), or with any major elective surgery scheduled to occur during the study.
22. Subjects with evidence of or suspected liver disease, liver injury due to methotrexate or primary sclerosing cholangitis.
23. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). NOTE: if a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if the subject tests positive for antibody to Hepatitis B surface antigen (HBsAb also referred as anti-HBsAg) reflex testing.
24. Subjects with positive hepatitis C antibody (HCVAb) with confirmation by HCV-ribonucleic acid (RNA) polymerase chain reaction (PCR) reflex testing.
25. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening. NOTE: Screening laboratory tests, if the results are considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results must be reviewed for eligibility prior to the screening endoscopy procedure.
 - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥ 2.0 times the upper limit of normal (ULN).
 - Total bilirubin level ≥ 1.5 times the ULN (except in subjects with documented diagnosis of Gilbert's syndrome).
 - Hemoglobin level ≤ 80 g/L (8.0 g/dL).
 - Platelet count $\leq 100 \times 10^9/\text{L}$ ($100,000$ cells/ mm^3) or $\geq 1000 \times 10^9/\text{L}$ ($1,000,000$ cells/ mm^3).
 - White blood cell count $\leq 3.5 \times 10^9/\text{L}$ (3500 cells/ mm^3).
 - Absolute neutrophil count (ANC) < 2000 cells/ mm^3 .
 - Serum creatinine level $\geq 177 \mu\text{mol}/\text{L}$ (2 mg/dL) or estimated glomerular filtration rate (GFR) $< 40 \text{ ml/min}/1.73\text{m}^2$ based on the abbreviated MDRD.
26. Subjects with known infection with human immunodeficiency virus (HIV).
27. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse.
28. Subjects using medicinal marijuana (cannabis) or related products for recreational purposes, who have a known dependency per the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Edition 5 (including urine drug screen and medical history). Exceptions are those subjects who are prescribed marijuana (by a physician) for medicinal use and where the product is sourced from a licensed pharmacy/provider. Such subjects must be using the product, in a stable regimen, for at least 3 months before screening.
29. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or ECG abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study

results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

30. Female subjects who are planning to become pregnant during the study period.
31. Male subjects who are planning to donate sperm must agree not to do so for the duration of the study and through 16 weeks after last dose of investigational product.
32. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

4.3 Restrictions

Smoking can have an influence on the severity of UC disease symptoms. Subjects should inform the investigator of any changes to their smoking habits during the study; however, these data will not be captured in the electronic case report form (eCRF). Use of nicotine patches should be recorded as concomitant medication (see Section [5.2](#)).

For the purposes of this protocol, dietary supplements (such as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties) are considered to be concomitant medications (see Section [5.2](#)).

4.4 Reproductive Potential

The potential effects of SHP647 on embryofetal or postnatal development have not yet been assessed in animals or humans; these will be assessed in future studies. To minimize the risk of unintentional exposure of the embryo or fetus in the clinical study, all sexually active male and female subjects who, in the opinion of the investigator, are biologically capable of having children and with their partners are at risk of pregnancy, must agree to use an acceptable form of contraception, in accordance with the package instructions/leaflet, for the duration of the active treatment period and for at least 16 weeks after the last dose of investigational product.

True abstinence is considered to be a highly effective contraception (ie, a method that results in a failure rate of <1% per year) when it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to investigational product, and withdrawal are not acceptable methods of contraception.

During the screening visit, the investigator or designee in consultation with the subject will confirm the subject's childbearing potential status. For subjects of childbearing potential, it must be confirmed and documented that the subject has selected the most appropriate method of contraception from the permitted list of contraception methods. Subjects must affirm the consistent and correct use of at least 1 of the selected methods. Regular contraception check discussions will take place at the time points specified in [Table 1](#) (ie, at each site visit) and will be documented. In addition, the subject must be instructed to call the site immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

4.4.1 Contraceptive Methods for Female Study Subjects

Sexually active females of childbearing potential must be using an acceptable form of contraception, and must be advised to use acceptable contraceptives throughout the study period and for 16 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert.

Female subjects should be in one of the following categories:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥ 51 years of age); postmenopausal status should be confirmed by follicle-stimulating hormone (FSH) testing.
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks poststerilization or has medically confirmed ovarian failure.
- Females of childbearing potential with a negative serum pregnancy test result at screening and a negative urine pregnancy test result at baseline. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of highly effective contraception.

Acceptable methods of highly effective contraception (ie, methods that result in a failure rate of $<1\%$ per year) are:

- Combined (estrogen- and progestogen-containing) hormonal contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal) stabilized for at least 30 days before the screening visit (Visit 1)
- Progestogen-only hormonal contraception associated with inhibition of ovulation plus a barrier method
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Male sterilization/vasectomized partner with absence of sperm in the postvasectomy ejaculate
- True abstinence (see Section 4.4).

4.4.2 Contraceptive Methods for Male Study Subjects

Contraception is required for all sexually active male subjects, who with their partners, must agree to use 1 of the following acceptable methods of contraception throughout the study period and for 16 weeks following the last dose of investigational product:

- Male condom with spermicide; however if spermicide is not available in the country, additional contraception (ie, one of those listed below) must be used in addition to a condom

- Female condom with spermicide (use by female sexual partner); however, if spermicide is not available in the country, additional contraception (ie, one of those listed below) must be used in addition to a condom
- Sterile sexual partner
- Intrauterine device with spermicide (use by female sexual partner)
- Contraceptive sponge with spermicide (use by female sexual partner)
- Intravaginal system (eg, vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide) (use by female sexual partner)
- Oral, implantable, transdermal, or injectable hormonal contraceptive (use by female sexual partner) plus a barrier method.
- Male sterilization with absence of sperm in the postvasectomy ejaculate.

4.5 Withdrawal of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 12/ET (Visit 6) are to be performed. All subjects who discontinue treatment with investigational product should also undergo the protocol-specified 16-week safety follow-up period. In the event that subjects are unable to attend in person for the follow-up visits, all efforts should be made to collect information on AEs and concomitant medications. Comments (spontaneous or elicited) or complaints made by the subject must be recorded. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

Additional reasons a subject may be withdrawn from active treatment include but are not limited to:

- AEs
- Serious adverse events (SAEs)
- Protocol violations
- Failure to return for visits

A subject should be withdrawn from study treatment:

- If a new therapy is initiated for UC, or
- If a subject undergoes surgery for UC

Subjects who withdraw from active treatment due to an increase in disease symptoms may see nonstudy-related physicians for treatment, which may include treatments prohibited during the treatment periods of this study.

If a subject withdraws their consent, no further evaluation should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

4.5.2 Reasons for Withdrawal

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Other (if "Other" is selected, the investigator must specify the reason)
- Death
- Physician decision
- Pregnancy
- Screen failure
- Site terminated by sponsor.

4.5.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point before the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and that they return their electronic diary.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal remedies and vitamins) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the first dose of investigational product. Use of biologics for indications other than UC during the 90 days before screening must also be recorded.

Prior and concomitant UC-specific treatments from the previous 10 years will be recorded. The subject's entire history of biologic UC-specific treatments will be recorded.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the safety follow-up period, inclusive.

5.2.1 Permitted Treatment

Subjects must remain on stable doses of permitted UC treatments until completion of the Week 12 visit, unless decreases are required because of AEs. Stable doses of the following treatments for UC are permitted as concomitant medication:

- Oral 5-ASA or sulfasalazine, providing that the dose is stable for at least 2 weeks before baseline (Visit 2)
- Immunosuppressants (AZA, 6-MP, or MTX), providing that the dose is stable for at least 8 weeks before baseline (Visit 2).
- Oral glucocorticoids (prednisone or equivalent (see [Appendix 3](#)) up to a maximum of 20 mg/day or budesonide up to a maximum of 9 mg/day), providing that the dose is stable for at least 2 weeks before screening endoscopic procedure.

NOTE: Rectal 5-ASA and parenteral or rectal glucocorticoids are prohibited.

Subjects using medicinal marijuana (cannabis) under a physician's prescription, and who obtain the product from a licensed pharmacy or provider, should continue to use it under the same regimen for the duration of the study, unless otherwise instructed by the investigator or treating physician. Such subjects must be using the product, in a stable regimen, for at least 3 months before screening.

Routine nonlive vaccinations are allowed during the study.

Dietary and herbal supplements and probiotics are allowed in the study, provided they are being taken at stable doses at the time of the baseline visit (Visit 2) and for the duration of the study. They should be recorded as concomitant medications.

Use of nicotine patches should be recorded as concomitant medication.

5.2.2 Prohibited Treatment

Table 2 details the minimum required number of days before baseline (Visit 2) for common prior treatments that are excluded medications for this study.

Table 2 Common Excluded Treatments

Treatment	Permanently Excluded	Minimum Required Number of Days Before Baseline (Visit 2)			
		14	30	60	90
SHP647 (PF-00547659) in a previous study	X				
Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab)	X				
Parenteral and rectal glucocorticoids		X ^a			
Rectal 5-ASA		X ^a			
Investigational products			X ^b		
Live (attenuated) vaccine			X		
Anti-TNF treatment				X	
Biologics with immunomodulatory properties (other than anti-TNFs)					X

5-ASA=5-aminosalicylate; TNF=tumor necrosis factor.

^a The minimum required number of days before baseline (Visit 2) for rectal 5-ASA and parenteral or rectal glucocorticoids is defined as 14 days before screening endoscopic procedure (see Section 4.2, exclusion criterion 11).

^b Or 5 half-lives if longer.

Treatments not listed in Table 2 may be considered allowable; see Section 5.2.1 for further details.

No new nonpharmacological therapies that might affect bowel habit or GI function should be started during the study.

5.2.3 Rescue Therapy

Subjects must maintain their stable dose of background UC treatment, unless dose reduction or discontinuation are required due to associated AEs. If a subject requires initiation of a new therapy or increase in glucocorticoids for UC above the SHP647-301 or SHP647-302 baseline, the subject should be withdrawn from study treatment and enter the safety follow-up period, and appropriate treatment should be given at the discretion of the investigator.

Subjects who enter the safety follow-up period will no longer need to abstain from the medications that were prohibited during the baseline and treatment periods. High-dose glucocorticoids and other UC treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated during the safety follow-up period without prior discussion with the sponsor study physician or designee due to the long half-life of SHP647.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is SHP647, which will be provided as a sterile aqueous buffered solution for SC administration in a glass PFS with a fixed needle. Each PFS contains 1 mL of SHP647 solution at an appropriate concentration to provide the intended dose of drug (25 or 75 mg). Additional information is provided in the current SHP647 investigator's brochure.

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain SHP647.

6.1.1 Blinding the Treatment Assignment

The placebo syringes and solution will match the SHP647 syringes in appearance. The fill volume for all syringes will be the same.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive response technology (IRT) system will be used for screening and enrolling subjects, recording subject visits, randomization, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and emergency unblinding. Please refer to the Study Manual for additional details regarding the IRT system.

6.2.2 Allocation of Subjects to Treatment

This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule.

The total Mayo score will be calculated at baseline (Visit 2) before randomization. Endoscopic subscore based on the central reader's assessment will be used to determine eligibility. Subjects with a total Mayo score of ≥ 6 , including a centrally read endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 , and who fulfill all other eligibility criteria, will be randomized in a ratio of 2:2:1 via a computer-generated randomization schedule to receive SC injections of 25 mg SHP647, 75 mg SHP647, or placebo, respectively. The randomization will be performed centrally and stratified by status of prior anti-TNF therapy (2 strata: naïve versus experienced) and glucocorticoid use at baseline (2 strata: on glucocorticoids at baseline versus not on glucocorticoids at baseline).

To ensure that the allocation of subjects with prior anti-TNF therapy exposure is similar to that observed in Study A7281009, the percentage of subjects with prior anti-TNF therapy exposure will be capped at 60% of the sample population. There will be no cap on the number of anti-TNF naïve subjects randomized.

Subject numbers are assigned to all eligible subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number will be assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. Individual subject treatment will be automatically assigned by the IRT system.

Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

6.2.3 Dosing

Investigational product (SHP647 or placebo) will be administered subcutaneously by qualified site personnel Q4W (Weeks 0, 4, and 8). See Section [7.2](#) for the timing of dosing relative to other procedures.

Investigational product should be administered in the anterolateral right or left thighs. If there are clinical reasons why the drug cannot be administered in the leg, the drug may be administered in the deltoid area or abdomen with appropriate documentation. The location of the investigational product administration will be recorded.

After the first administration of investigational product, the subject must be observed by a member of the study staff for at least 30 minutes (the total duration should be determined at the discretion of the investigator). For subsequent administrations, observation of the subject is at the discretion of the investigator. Injection site and allergic reaction monitoring should be completed by a member of the study staff.

Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is dispensed by qualified staff members.

6.2.4 Unblinding the Treatment Assignment

Whenever possible, the investigator or subinvestigator should contact the Shire physician and/or assigned medical monitor before breaking the blind. It is understood that in an emergency situation it may not be possible to communicate with the study team before breaking the blind. The safety of the subject should be of primary concern. When the blinding code is broken the reasons must be fully documented.

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In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded on the IRT and the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. The IRT will notify the relevant personnel in the event of any code break. Code-break information is held by the pharmacist/designated person at the site.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

The sponsor will provide the investigator with packaged investigational product labeled in accordance with specific country regulatory requirements. All investigational product is labeled with a minimum of the following: protocol number, medication identification number, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements “For clinical trial use only” and/or “CAUTION: New Drug – Limited by Federal (or US) Law to Investigational Use”, and the sponsor’s name and address.

Additional labels may be applied in order to meet local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor’s prior written agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled containers: PFS with nominal fill volume of 1 mL. The PFS will be packaged in a labeled carton.

Changes to sponsor-supplied packaging before dosing may not occur without prior written agreement by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or delegated member of the study team. The pharmacist or delegated team member will enter the unique subject identifier on the investigational product labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that

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records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

The investigational product should be protected from light and should not be frozen. Do not shake.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented in the subject's source document and/or other investigational product record.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

With the written agreement of the sponsor, at the end of the study all unused stock may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational products must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, cartons) or at the individual count level for opened containers/packaging. The pharmacist or delegated team member will record details on the drug accountability form.

7. STUDY PROCEDURES

7.1 Study Schedule

The investigator may schedule visits (unscheduled visits) in addition to those listed on the schedule of activities ([Table 1](#)) in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

7.1.1 Screening Period

7.1.1.1 Screening Visit (Visit 1)

Subjects will be screened within 6 weeks before the baseline visit (Visit 2) to determine eligibility to participate in the study and to perform the other assessments and procedures specified in [Table 1](#). Each subject or subject's parent or legally authorized representative must participate in the informed consent process and provide written informed consent/assent before any assessments or procedures specified in the protocol are performed. Screening assessments may take place over more than 1 day (at least 2 visits will be necessary to complete the screening procedures, including endoscopy).

A screen failure is a subject who has given informed consent or assent, as applicable (and whose parents or legally authorized representatives have given informed consent, as applicable), failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria, and has not been randomized or administered investigational product.

A subject may be rescreened if their condition has changed and they may potentially be eligible. Subjects may be rescreened 1 time. NOTE: Screening laboratory tests, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results of repeated tests must be reviewed for eligibility prior to the screening endoscopy procedure.

Flexible sigmoidoscopy or colonoscopy (if preferred) must be performed on all subjects after the majority of other eligibility criteria (eg, laboratory values) are met. Endoscopy must be performed during the screening period within 10 days before baseline (Visit 2), preferably within 5 to 7 days before the baseline visit, to obtain the centrally read endoscopic subscore (see [Section 7.2.2.1](#)). Biopsy samples will be collected for histological evaluation using the Geboes Score classification. Subjects at risk of colorectal cancer, as defined in exclusion criterion 5 (see [Section 4.2](#)), must have a colonoscopy performed at screening.

If a subject has had the following procedures performed as a part of standard medical care within 12 weeks before screening (Visit 1), these procedures do not need to be repeated as a part of screening:

- Chest x-ray
- Documented negative PPD test or IGRA for TB

7.1.1.2 Baseline Visit (Visit 2; Week 0)

The baseline visit will take place on Day 1 (Week 0). The assessments and procedures specified in [Table 1](#) will be performed.

After eligibility has been reconfirmed and all baseline procedures and assessments have been completed, each subject will be randomized to 1 of the 3 treatment groups as described in Section [6.2.2](#) and the first dose of investigational product will be administered.

Results of the baseline laboratory tests are not required for investigational product administration but must be reviewed as soon as possible thereafter.

7.1.2 Treatment Period

7.1.2.1 Visit 3 (Week 2)

Visit 3 is scheduled to take place on Day 14 ± 3 days (Week 2). The assessments and procedures specified in [Table 1](#) will be performed.

7.1.2.2 Visits 4 and 5 (Weeks 4 and 8)

Visits 4 and 5 are scheduled to take place on Day 28 ± 3 days (Week 4) and Day 56 ± 3 days (Week 8), respectively. The assessments and procedures specified in [Table 1](#) will be performed.

7.1.2.3 Final On-treatment Visits: Visit 6, Parts 1 and 2 (Week 12/Early Termination)

The Week 12/ET visit (Visit 6) consists of 2 parts.

Part 1 of Visit 6 should be scheduled preferably within 5 to 7 days before Part 2; this will allow sufficient time for data from the centrally read endoscopy to be available at Part 2 of the visit. The Week 12/ET assessments and procedures that will take place during Part 1 are specified in [Table 1](#).

Part 2 of Visit 6 will take place on Day 84 ± 3 days. The Week 12/ET assessments and procedures that will take place during Part 2 are specified in [Table 1](#).

At Part 2 of Visit 6, after review of the Mayo score, health outcome assessments, and safety assessments, it will be determined whether the subject should enter the safety follow-up period of this study or enroll in the maintenance (SHP647-303) or LTS (SHP647-304) studies. Entry into the maintenance or LTS studies is dependent upon the subject's response and whether the subject agrees to participate.

The Week 12 assessments and procedures will also form the ET assessments for any subjects who are withdrawn early or discontinued from the study.

7.1.3 Follow-up Period: Visits 7 and 8 (Weeks 20 and 28)

Subjects who are withdrawn early from the study, or who do not enter either the maintenance or LTS studies, should enter the safety follow-up phase for safety monitoring. The safety follow-up

period for this protocol is 16 weeks from the last dose of investigational product administered to each subject.

During the safety follow-up period, the Week 20 visit (Visit 7) will take place on Day 140 ±7 days. This visit will routinely be conducted by telephone; however, as an exception the visit can be performed as a study site visit if preferred.

At the end of the safety follow-up period, there will be a visit at the site on Day 196 ±7 days, which will form the Week 28 visit (Visit 8). The assessments and procedures specified in [Table 1](#) will be performed, including querying for SAEs, AEs, and concomitant medications and procedures. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see [Section 8.1](#)).

Subjects who are proceeding to the maintenance or LTS studies will not enter the safety follow-up period.

7.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator, which may make it unfeasible to perform the tests and procedures. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject.

When timing of procedures and assessments coincide, the following order should be followed:

- Health outcome and patient-reported questionnaires
- Vital signs and ECG
- Blood sample collection
- Investigational product administration
- Endoscopy (generally performed at a separate visit; see [Section 7.2.2.1](#)).

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics will be recorded at the screening visit (Visit 1).

Each subject's stool frequency before symptoms of UC started or during remission will be recorded at the screening visit. The reference/normal stool frequency questions in [Appendix 2](#) will be asked and the responses documented.

7.2.2 Efficacy

The primary efficacy endpoint is the proportion of subjects in remission at the Week 12 visit. Remission is defined as a composite score of patient-reported symptoms using daily electronic diary (e-diary) and centrally read endoscopy as described in Section 9.8.1.

7.2.2.1 Endoscopy and Histology

Endoscopy will be performed at the time points specified in [Table 1](#) and will consist of either flexible sigmoidoscopy or colonoscopy (if preferred).

If it is necessary, bowel preparation should be conducted as per local routine. The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during endoscopy at baseline. The endoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's medical record.

During endoscopy, 2 biopsy samples will be collected from the most inflamed area of the sigmoid colon at Week 12/ET. Endoscopy and biopsy procedures will be defined in an endoscopy instructions manual and/or reference card(s), on which all sites will be trained. Endoscopy results will be reviewed by a central reader.

Biopsy samples will be centrally reviewed using the Geboes Score classification system (see [Appendix 2](#)) for the evaluation of histological disease severity in UC with higher numbers corresponding to more inflammation.

7.2.2.2 Mayo Score

The Mayo score is a measure of UC disease activity. Mayo scores (total or partial) will be recorded at the time points specified in [Table 1](#).

The total 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 2](#)):

- Stool frequency (0-3)
- Rectal bleeding (0-3)
- Findings of endoscopy (0-3)
- Physician global assessment (PGA, 0-3).

The partial Mayo score consists of the Mayo score without the endoscopic subscores and ranges from 0 to 9 points.

The composite score is a recommended measure consisting of the Mayo score without the PGA subscore and ranges from 0 to 9 points. The composite score will be used for the primary efficacy endpoint.

Calculation of the total and partial Mayo scores and composite score requires a self-assessment by the subject for stool frequency and the amount of blood in the stool. These data on stool frequency and rectal bleeding will be captured in the PRO-UC daily e-diary (see Section 7.2.2.3).

The Mayo stool frequency and rectal bleeding subscores will be calculated based on each subject's daily e-diary data recorded over the most recent 3 days (consecutive or nonconsecutive) prior to the visit excluding the following days: day of any bowel preparation, day of endoscopy, any days between day of bowel preparation and day of endoscopy, and the 2 days after the day of endoscopy.

The mucosal appearance during the sigmoidoscopic portion of the endoscopic examination will be assessed for the Mayo endoscopic subscore based on the scoring system provided in the protocol (see Appendix 2). The endoscopic appearance will be read by both the study site investigator and a central reader through video recorded during the procedure. Centrally read endoscopic subscores will be used for both eligibility and efficacy analyses.

The PGA 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). The endoscopic subscore and the PGA must be performed by a physician qualified to perform endoscopy, and it is recommended that the same physician performs all such assessments for a particular subject throughout the study.

7.2.2.3 Patient-reported Outcome – Ulcerative Colitis E-Diary

Patient-reported UC signs and symptom data will be collected using a daily e-diary during the treatment period. Collection of the daily e-diary data must begin at least 10 days before the baseline visit (Visit 2). Subjects will enter data on UC signs and symptoms items using an electronic handheld device that will be provided to subjects at the start of the study. Compliance is assessed by site staff at each visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <23 out of 28 e-diary entries) when compared with the previous visit.

Subjects will be asked to record the following signs and symptom data, as experienced over the previous 24 hours, in the e-diary:

- Stool frequency
- Rectal bleeding severity and frequency
- Diarrhea frequency
- Urgency frequency
- Abdominal pain worst severity

The full PRO-UC e-diary consists of 6 items. The first 2 items (stool frequency and rectal bleeding severity) will be used to determine the Mayo stool frequency and rectal bleeding subscores, which will be used to calculate the total and partial Mayo scores and the composite score. The PRO-UC e-diary is presented in Appendix 2.

7.2.3 Safety

7.2.3.1 Medical and Medication History

Medical history will be documented at screening (Visit 1), including UC history, cardiac history, and smoking history. Prior and concomitant medications and procedures will also be documented.

7.2.3.2 Physical Examination (Including Height and Weight)

Complete and targeted physical examinations will be performed at the time points specified in [Table 1](#). Complete physical examination includes the review of the following body systems: general appearance, skin, HEENT, heart, lungs, confrontational visual fields (eyes), breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes. Targeted physical examination includes the review of the following body systems: skin, heart, lungs, confrontational visual fields (eyes), abdomen, and examination of body systems where there are symptom complaints by the subject.

Weight will be measured at the time points specified in [Table 1](#). Height will be measured at screening (Visit 1) only.

Changes after the screening visit that are deemed clinically significant in the opinion of the investigator will be recorded as an AE.

7.2.3.3 Targeted Neurological Assessment

Targeted neurological assessments to monitor for the development of signs and/or symptoms of PML will be performed at the time points specified in [Table 1](#). Subjects will be evaluated to reveal any potential abnormalities in the following neurological domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior.

If any abnormalities are indicated, subjects will be further evaluated to help clarify any potential abnormal responses. Focus will be placed on possible alternative etiology (eg, fracture or stroke). If additional evaluation reveals an unexplained new abnormality, neurologic examination(s), targeted to the abnormal domain, will be performed by an investigator or qualified personnel.

Subjects with any unexplained positive neurological assessment item at screening should be excluded from enrollment in the study (exclusion criterion 18, [Section 4.2](#)).

A step-wise approach for the proposed neurological assessment plan is provided in [Table 3](#).

Table 3 Quarterly Neurological Assessments

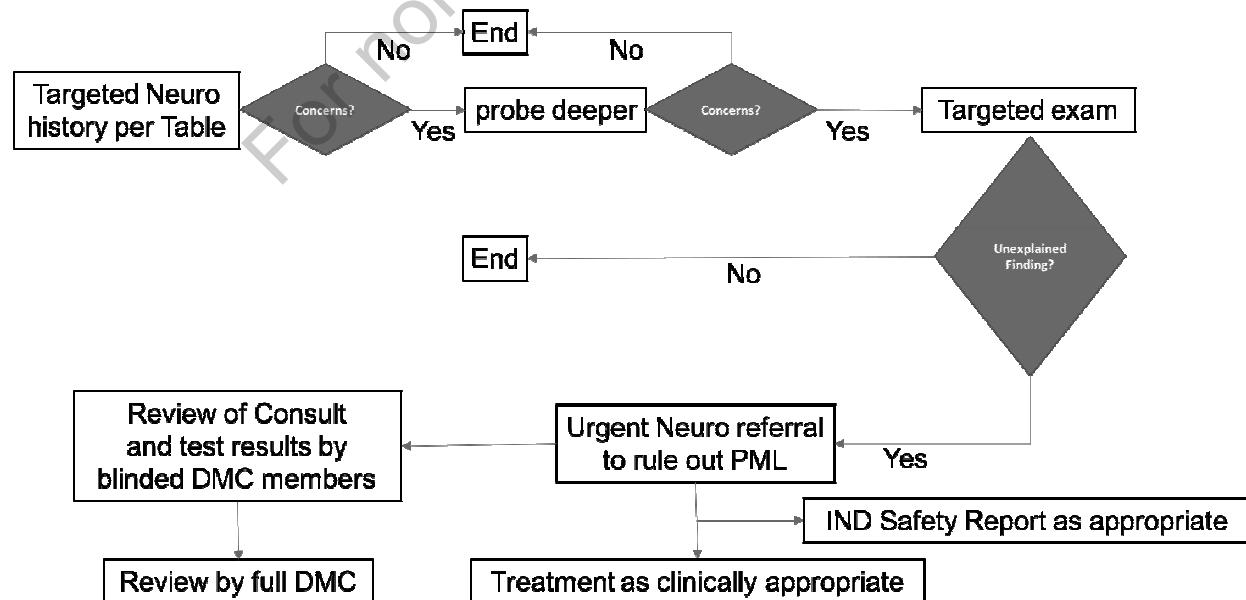
Domain	Step 1: Targeted Neurologic History	Step 2: If Abnormal Response
Vision	Diplopia or visual/visual field loss	Perform visual field assessment
Motor	Major motor weakness (eg, legs, arms)	Test leg strength (hopping, foot tapping), finger tapping, pronator drift and bilateral

Table 3 Quarterly Neurological Assessments

Domain	Step 1: Targeted Neurologic History	Step 2: If Abnormal Response
		muscle strength
Tactile sensation	Paresthesia, anesthesia in any domain (peripheral, central)	Pinprick test
Coordination/Cerebellar	Clumsiness, difficulty with walking, writing, or fine motor skills, etc.	Finger-nose, heel-shin, heel-toe walk, writing sample, draw a clock
Speech	Dysarthria, expressive aphasia	Naming objects, repeat multipart phrase, observe for dysarthria or aphasia
Verbal comprehension	Agnosia, receptive aphasia	Test to follow routine commands, eg, close eyes, touch finger to ear.
Cognition/Behavior	New onset of difficulties with memory or thinking, important changes in behavior	Recall 3 objects over 1 minute, serial 7 s, proverbs. Changes in activities of daily living over prior 6 months

Additionally, should there be any unexplained abnormal neurological findings, the subject is to be urgently referred to a neurologist. The sites will immediately inform the sponsor of any such occurrences. If the neurologist confirms the presence of PML, appropriate actions, including discontinuation of investigational product, will be taken. Suspected PML cases will be reviewed promptly by Data Monitoring Committee (DMC) members with PML expertise and presented at the next scheduled DMC meeting(s). If PML is diagnosed, the treatment code will be unblinded and there will be an urgent meeting of the DMC. A flow diagram of the quarterly assessments and actions is presented in [Figure 3](#). Any concerns from the DMC will be promptly communicated to the sponsor, investigator, and treating neurologist.

Figure 3 Flow Diagram for Quarterly Neurological Assessments



DMC=Data Monitoring Committee; IND=investigational new drug; neuro=neurological; PML=progressive multifocal leukoencephalopathy.

It is important to note that assessments based on neurological evaluations are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and data from neurological assessment collected from subjects. Investigators may determine if any finding on neurological testing constitutes an AE. Adverse event incidence rates will not be calculated from these neurological evaluation data but rather from the AE information recorded by the investigator.

7.2.3.4 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, “Have you had any health problems since your last visit?”). Adverse events are collected from the time informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3. (See Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.3.5 Vital Signs

Vital signs will be measured at the time points specified in Table 1. Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data. Vital signs include blood pressure, pulse, respiratory rate, and temperature. Vital signs should be recorded before laboratory blood collection and endoscopic procedures are performed.

Single measurements of sitting blood pressure will be recorded at each time point. Blood pressure should be determined by cuff with the subject’s arm supported at the level of the heart and recorded to the nearest mm Hg using the same method, the same arm (preferably the dominant arm), and the same position throughout the study.

Respiratory rate will be measured with the subject in a comfortable position. The observer should hold the extremity of the subject as a distraction for the subject (ie, pretending he/she is taking the subject’s radial pulse) and count the respiration for 1 minute.

Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used.

Any deviations from baseline (Visit 2) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE, unless documented in the subject’s medical history as a pre-existing medical condition.

7.2.3.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the central laboratory’s normal procedures. Reference ranges are to be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes.

The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Screening laboratory tests, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. The following clinical laboratory assessments will be performed at the time points specified in [Table 1](#):

Serum chemistry

- alkaline phosphatase
- aspartate aminotransferase
- alanine aminotransferase
- total bilirubin
- total protein
- albumin
- glucose
- blood urea nitrogen
- creatinine
- sodium
- potassium
- chloride
- calcium
- carbon dioxide

Hematology

- hemoglobin
- hematocrit
- mean corpuscular hemoglobin
- mean corpuscular hemoglobin concentration
- mean corpuscular volume
- erythrocyte (red blood cell) count
- leukocyte (white blood cell) count
- neutrophils
- lymphocytes
- monocytes
- eosinophils
- basophils
- platelet count

Virology

- hepatitis B surface antigen (HBsAg)
- hepatitis B core antibody (HBcAb)
- hepatitis B surface antibody (HBsAb also referred as anti-HBsAg) if HBsAg is negative and HBcAb is positive
- hepatitis C virus antibody (HCV Ab)
- HCV ribonucleic acid (RNA) polymerase chain reaction (PCR) if HCV Ab is positive

Urinalysis

- glucose
- protein
- specific gravity
- pH
- nitrite
- bilirubin
- ketones
- hemoglobin
- urobilinogen
- leukocyte esterase

Virology test results must be confirmed as negative before enrollment in the study; if a virology test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor, but will not be collected in the CRF database.

Stool microbiology will be performed at the screening visit (Visit 1). The detection of *Clostridium difficile* by toxigenic stool culture (stool culture followed by detection of toxin) is considered the gold standard for the diagnosis of the colonization or infection with pathogenic *C. difficile*. Comparable sensitivity may be achieved by direct testing of stool via point-of-use rapid membrane enzyme immunoassay card for both *C. difficile* toxin A and B and glutamate dehydrogenase antigen on a card. Use of the card for point-of-care screening is encouraged where permitted by local regulation; any samples showing a positive result with this method should be sent for toxigenic stool culture. Molecular techniques such as PCR for detection of toxin RNA are also acceptable alternatives. Refer to the laboratory manual for further guidance and instruction for *C. difficile* screening.

A tuberculosis (TB) test (purified protein derivative [PPD] or QuantiFERON TB Gold) will be performed at the screening visit (Visit 1). A documented negative PPD test within 12 weeks before baseline (Visit 2) is acceptable. The IGRA official reading and method or test must be located in the source documentation.

A serum sample will be collected and banked for John Cunningham virus antibody testing. It may be analyzed if a subject shows neurologic symptoms suggestive of PML.

All laboratory assessments should be performed at central laboratories, with the exception of the following assessments: stool microbiology (local or central laboratory) and TB test (PPD or QuantiFERON TB GOLD) (refer to laboratory manual for details).

7.2.3.7 Pregnancy Test and Follicle-stimulating Hormone Test

A beta-human chorionic gonadotropin (β -HCG) pregnancy test will be performed on all females of childbearing potential at the time points specified in [Table 1](#); if pregnancy is suspected; or on withdrawal of the subject from the study. A serum pregnancy test will be performed at the screening visit (Visit 1); all other pregnancy tests will be urine tests.

Pregnancy tests are not required for females of nonchildbearing potential who have undergone hysterectomy or bilateral oophorectomy, have medically confirmed ovarian failure, or are medically confirmed postmenopausal (cessation of regular menses for at least 12 consecutive

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months with no alternative pathological or physiological cause; postmenopausal status should be confirmed by FSH testing in females who have had 12 consecutive months of spontaneous amenorrhea and are 51 years of age or older).

7.2.3.8 Electrocardiogram

A 12-lead ECG will be recorded at the time points specified in [Table 1](#). When timing of measurements coincide, ECGs should be performed before laboratory blood collection and endoscopic procedure.

A central ECG reader will be used in this study. The eligibility of the subject is based on the assessment of the ECG by the investigator. If abnormal results are observed following assessment by the central reader, the investigator, in consultation with the appointed sponsor or contract research organization (CRO) medical monitor, reconfirms subject eligibility to continue.

7.2.3.9 Chest X-ray

A chest x-ray will be performed during screening (Visit 1). If a subject has had a chest x-ray performed as a part of standard medical care within 12 weeks before screening (Visit 1), it does not need to be repeated as a part of screening. The official reading must be located in the subject's source documentation.

7.2.3.10 Antidrug Antibodies

A blood sample for measurement of antidrug antibodies (ADA) and Nab will be collected at the time points specified in [Table 1](#). Blood samples must be collected before administration of investigational product.

7.2.4 Others

Term	Percentage
Climate change	100%
Global warming	~95%
Green energy	~85%
Sustainable development	~75%
Environmental protection	~65%
Recycling	~55%

7.2.4.3 Health-related Quality of Life Assessments

Each subject will complete the HRQL assessments at the site during the visits specified in [Table 1](#), using an electronic device. All health outcome and patient-reported questionnaires should be completed before any other assessments. The study site staff should check for completion of all PRO questionnaires.

It is important to note that patient-reported outcome (PRO) assessments are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and PRO data collected from subjects. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded by the investigator.

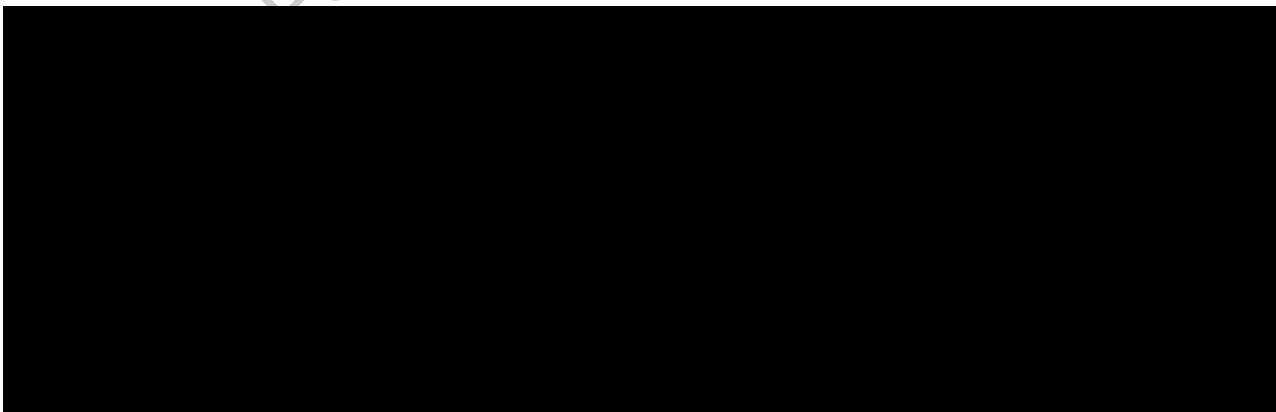
Inflammatory Bowel Disease Questionnaire

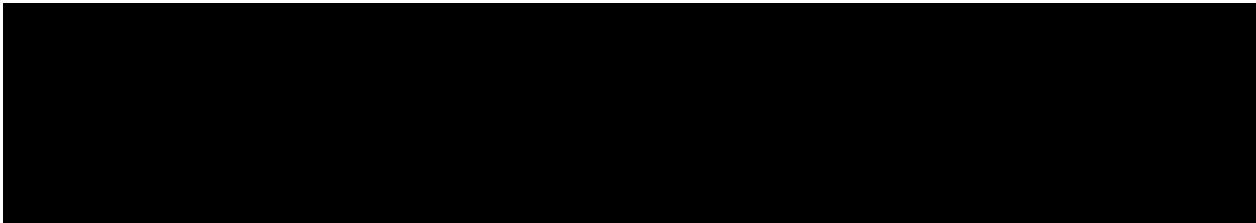
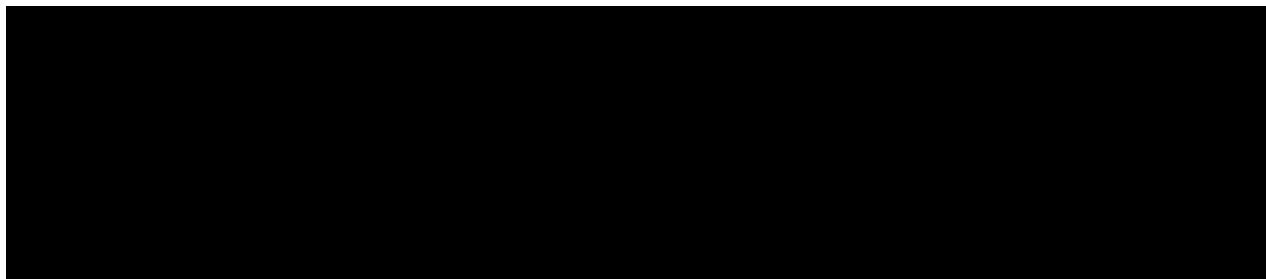
The IBDQ is a psychometrically validated PRO instrument for measuring the disease-specific HRQL in subjects with inflammatory bowel disease, including UC. The IBDQ consists of 32 items, which are grouped into 4 dimensions: bowel function, emotional status, systemic symptoms, and social function ([Irvine et al., 1994](#)). 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 HRQL. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement.

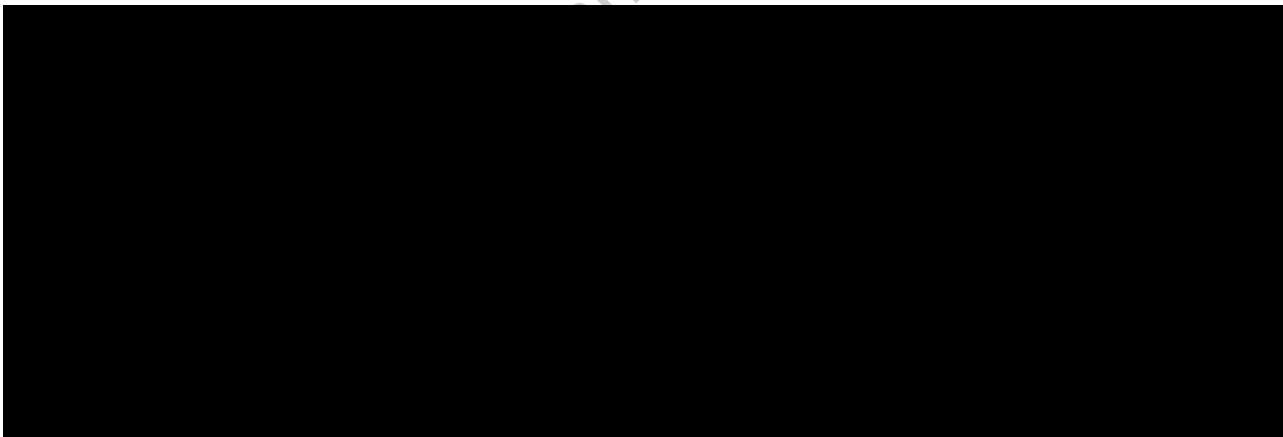
The IBDQ is presented in [Appendix 2](#).





Short Form-36 Health Survey, Acute Form

The SF-36 is a generic quality-of-life instrument that has been widely used to assess HRQL of subjects. Generic instruments are used in general populations to assess a wide range of domains applicable to a variety of health states, conditions, and diseases. The SF-36 consists of 36 items that are aggregated into 8 multi-item scales (physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional, and mental health), with scores ranging from 0 to 100 ([Ware and Sherbourne, 1992](#)). Higher scores indicate better HRQL.



7.2.4.4 Healthcare Resource Utilization Assessments

Hospitalizations, inpatient days, and [REDACTED] will be recorded at the time points specified in [Table 1](#). Ulcerative colitis-related and other surgeries will be collected from subjects during the treatment period.

7.2.5 Volume of Blood to Be Drawn from Each Subject

Table 4 Volume of Blood to Be Drawn from Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Hematology	1	6	6
Serum chemistry	6	6	36
HBsAg	2	1	2
HBcAb	2	1	2
HCV Ab	2	1	2
FSH	2	1	2
Serum β -hCG ^a	2	1	2
TB test (QuantiFERON TB Gold or PPD)	3	1	3
JCV antibody banked sample	3.5	1	3.5
[REDACTED]			
[REDACTED]	2.5	3	7.5
[REDACTED]	5	3	15
[REDACTED]	4	3	12
[REDACTED] [REDACTED]	3	5	15
ADA and NAb sampling	3	6	18
Total mL			126

Ab=antibody; ADA=antidrug antibodies; β -hCG=beta-human chorionic gonadotropin; [REDACTED]; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HCV=hepatitis C virus; JCV=John Cunningham virus; [REDACTED]; Nab=neutralizing antibody; PPD=purified protein derivative; TB=tuberculosis

^a β -hCG testing for female subjects only.

^b If a catheter is used, the first mL is to be discarded; then take 4 mL into appropriate tube for [REDACTED]. A total of 5 mL of blood drawn has been used in determination of sample volume.

The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 126 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured in the subject's source document. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the subject's source document.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia before dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded in the subject's source document).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as “not related.” Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.” The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study in the eCRF. Outcomes are as follows:

- Fatal
- Not recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown.

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section [7.1.3](#).

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to Shire Global Pharmacovigilance using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine beta human chorionic gonadotropin (β -hCG) test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional administration of investigational product at a dose interval that is less than 2 weeks between doses
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

There is no specific antidote for overdose with SHP647. Treatment should be symptomatic and supportive.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is Section 6.8 of the SHP647 investigator's brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to Shire Global Pharmacovigilance and the CRO/Shire medical monitor within 24 hours of the first awareness of

the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or email the form to Shire Global Pharmacovigilance. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A **serious adverse event (SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death.
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an ED or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3 and must be reported to Shire Global Pharmacovigilance and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to Shire Global Pharmacovigilance within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject’s death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject’s death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject’s death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as “dose not changed” or “not applicable” (if the subject never received investigational product). The investigational product action of “withdrawn” should not be selected solely as a result of the subject’s death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor or the CRO is responsible for notifying the relevant regulatory authorities, US central Institutional Review Boards (IRBs), and European Union (EU) central Ethics Committees (ECs) of related, unexpected SAEs.

In addition the CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP647 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol in the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered in the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, antibodies to investigational product, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, before unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed. The SAP will be finalized before unblinding to preserve the integrity of the statistical analysis and study conclusions.

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC, USA).

Unless otherwise specified, summary tabulations will be presented by treatment group. All data listings will be sorted by treatment group, site, and subject number, and will include the subject's age, sex, and race.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis or adaptive design in this study.

An external DMC will be established to review the overall safety of the study subjects on an ongoing basis.

The DMC will be responsible for the ongoing monitoring of safety of subjects enrolled in the study according to the DMC charter. Recommendations made by the DMC to alter the conduct of the study or to amend the protocol will be forwarded to Shire for review and for a final decision. Shire or its designee will notify investigative sites and regulatory authorities as appropriate, of DMC recommendations (which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints).

Further details regarding the DMC can be found in the DMC charter, which will be available before the administration of investigational product to any subject. Analyses of the data for DMC review will be conducted according to the DMC charter and DMC SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not applicable.

9.6 Sample Size Calculation and Power Considerations

Graphical methods are used to control the global family-wise type I error rate (FWER) at the .05 level (2-sided) for the comparisons of the 2 SHP647 treatment groups with the placebo group. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the primary endpoint. Therefore, the power analysis and sample size estimation was calculated based on the chi-square test of proportions using nQuery Advisor Version 7.0 for an individual SHP647 dose compared with placebo.

Assuming a .025 (2-sided) significance level for each pairwise treatment comparison, approximately 1375 subjects will be screened to randomize 825 subjects (2:2:1 allocation ratio: 330 subjects in the 25 mg SHP647 treatment group, 330 subjects in the 75 mg SHP647 treatment group, and 165 subjects in the placebo group) which would yield an approximately 93% power to detect individual pairwise treatment difference in the primary efficacy endpoint, remission at Week 12, of 11% (5% placebo versus 16% SHP647). Expected remission rates at Week 12 are

based on observed rates from the A7281009 study and placebo remission rates from literature ([Feagan et al., 2013](#); [Sandborn et al., 2017](#)). No adjustment for missing data is required in these sample size calculations as subjects with missing data for clinical remission at Week 12 are imputed as failures and the above rates account for these subjects.

With the sample size of 825, [Table 5](#) provides the power for detecting a treatment difference between a SHP647 treatment group and the placebo group for the key secondary endpoints.

Table 5 Power to Detect the Corresponding Treatment Effect for Key Secondary Endpoints

Key Secondary Endpoint at Week 12	SHP647 Assumption	Placebo Assumption	Power
Endoscopic remission	24%	8%	0.99
Clinical remission	30%	16%	0.89
Clinical response by composite score	50%	35%	0.82
Mucosal healing	15%	5%	0.88

9.7 Study Population

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

The full analysis set (FAS) will consist of all subjects in the randomized set who have received at least 1 dose of investigational product.

The per-protocol (PP) set will consist of all subjects in the FAS who complete the Week 12 visit and who do not have predefined protocol deviations that may affect the primary efficacy endpoint.

The completer set will consist of all subjects in the FAS who have completed the final scheduled primary assessment for this study.



9.8 Efficacy Analyses

Unless otherwise specified, all efficacy analyses will be based on the FAS and subjects will be analyzed according to their randomized treatment, regardless of the treatment they actually received.

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects in remission at the Week 12 visit. Remission is defined as a composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy as follows:

- stool frequency subscore of 0 or 1 with at least a 1-point change from baseline
AND
- rectal bleeding subscore of 0
AND
- endoscopic subscore of 0 or 1 (modified, excludes friability)

The primary efficacy endpoint will be compared for each active treatment group (25 mg or 75 mg SHP647) to the placebo group using a Cochran-Mantel Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment and glucocorticoid use at baseline (Visit 2). Subjects with missing remission data at the Week 12 visit will be considered failures and counted as nonresponders. The endoscopy score will be based on centrally read results.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata, $j=1$ to m . The common treatment difference is a weighted average of the stratum-specific treatment differences.

The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% confidence interval (CI) using the method of Yan and Su (2010) and CMH p-value will be presented for each active treatment group to placebo comparison.

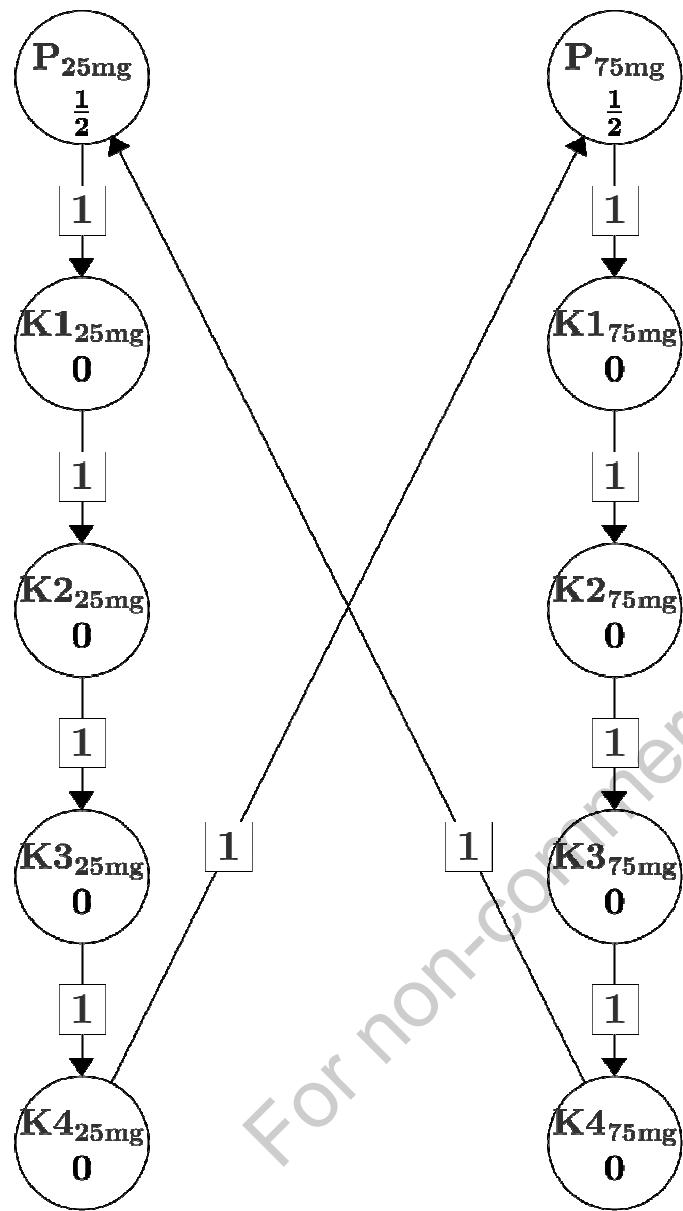
Sensitivity analyses which explore the impact of missing data on the primary efficacy endpoint will be conducted. These analyses may compare imputations of the missing values which favor placebo (eg, worst case) and/or imputations which favor active treatment (eg, best case). In addition, imputation methods based on informative missingness and other missing data mechanisms may be performed. Additional sensitivity analyses will also be conducted using the per-protocol set and the completer set. Additional analyses may be developed in the SAP. All sensitivity analyses will be described in the SAP.

Prespecified subgroup analyses are planned for the primary endpoint including, but not limited to gender, prior anti-TNF treatment, glucocorticoid use at baseline, randomization stratum, and other important subjects. A full list of important subgroups will be described within the SAP. Within subgroups, efficacy endpoints will be compared for each active treatment group (25 mg SHP647 and 75 mg SHP647) with the placebo group using a Chi-square test. Subjects with missing remission data at the Week 12 visit will be considered failures and counted as nonresponders. The endoscopy subscore will be based on centrally read results. The estimate of the treatment difference, along with the corresponding Newcombe (hybrid-score) 95% CI and Chi-square test p-value, will be presented.

Adjustments for Multiplicity

The global FWER for the statistical tests of the primary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al (2009) will be utilized to propagate α from primary to key secondary endpoints and between the two SHP647 treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the primary endpoint (P) and alpha is propagated in a hierarchical manner to each of the 4 key secondary endpoints (K1-K4) within a pairwise treatment comparison. A graphical visualization of the α propagation is presented in [Figure 4](#).

Figure 4 Visualization of Alpha Propagation



Only p-values that are significant according to this graphical approach are inferential and statistically significant. All other p-values are descriptive.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoints are as follows:

- Proportion of subjects with endoscopic remission, as defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability), at the Week 12 visit.
- Proportion of subjects with clinical remission, as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at the Week 12 visit.
- Proportion of subjects with clinical response based on composite score at the Week 12 visit. Clinical response (composite) is defined as a decrease from baseline in the composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 .
- Proportion of subjects with mucosal healing based on endoscopic and histological assessment at the Week 12 visit. Mucosal healing is defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability) and centrally read Geboes score of ≤ 2 .

Similar to the primary endpoint, the 4 key secondary endpoints will all be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

The key secondary endpoints will be analyzed using the same approach as described for the primary efficacy endpoint. Subjects with missing key secondary endpoint data at the Week 12 visit will be considered failures and counted as nonresponders.

In addition, the sensitivity analyses and prespecified subgroup analyses described for the primary endpoint will be repeated for the key secondary endpoints.

9.8.2.2 Other Secondary Efficacy Endpoints

The other secondary endpoints are as follows:

- Proportion of subjects with remission, defined as a total Mayo score ≤ 2 with no individual subscore (stool frequency, rectal bleeding, endoscopy [modified, excludes friability], and physician's global assessment) exceeding 1, at the Week 12 visit.
- Proportion of subjects with clinical response based on total Mayo score at the Week 12 visit. Clinical response (Mayo) is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 .

- Proportion of subjects with partial Mayo score ≤ 2 with no individual subscore > 1 at the Week 4, 8, and 12 visits. The partial Mayo score does not include the endoscopy subscore.
- Proportion of subjects with clinical remission as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at Weeks 4 and 8.
- Proportion of subjects with endoscopic remission at the Week 12 visit with endoscopic subscore of 0.
- Proportion of subjects with clinical remission at the Week 4, 8, and 12 visits with both rectal bleeding and stool frequency subscores of 0.
- Proportion of subjects with deep remission at the Week 12 visit. Deep remission is defined as both endoscopic and rectal bleeding subscores of 0, and stool frequency subscore ≤ 1 and a centrally read Geboes score of ≤ 2 .
- Change from baseline at the Week 12 visit in abdominal pain, urgency and diarrhea item scores, absolute stool frequency, absolute rectal bleeding and total sign/symptom score based on subject daily e-diary entries (sum of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency).
- Change from baseline in IBDQ domain and total (absolute) scores (time frame: Week 0, Week 8, up to Week 12, or early termination).
- Change from baseline in SF-36, version 2, acute (physical and mental component summary scores and individual domain scores) to the Week 12/ET visit.
- Incidence of all-cause hospitalizations and total inpatient days.

Other secondary/exploratory endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods.

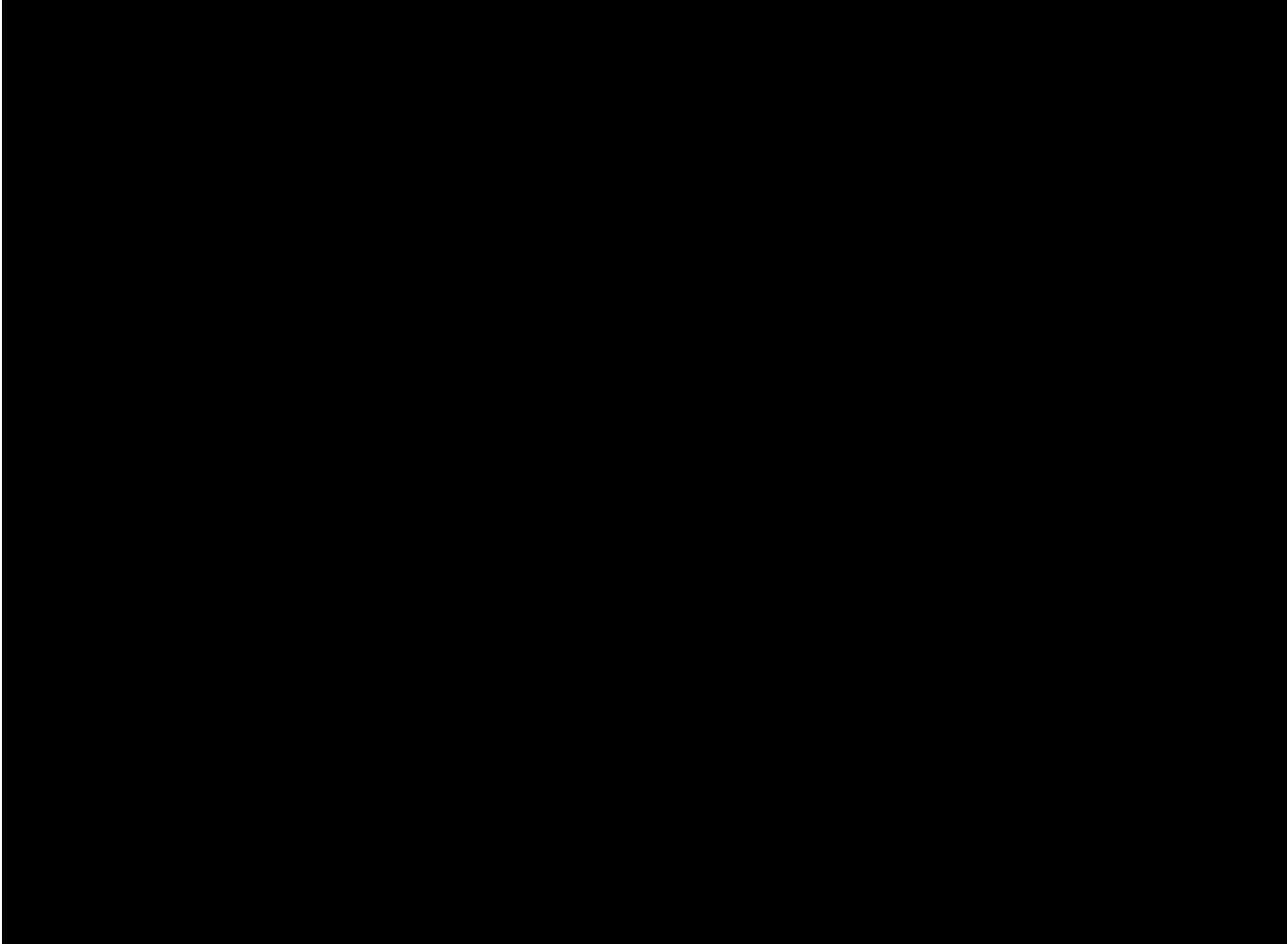
- Binary endpoints will be analyzed using the same approach as described for the primary endpoint. Subjects with missing binary endpoint data at a visit will be considered failures and counted as nonresponders.
- Continuous endpoints that are only measured at baseline and the Week 12 visit will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences will be provided.
- Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation (REML). The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means,

treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

Full details of the analysis of other secondary efficacy endpoints will be included in the SAP.

9.8.3 Exploratory Efficacy Endpoints

The exploratory endpoints are as follows:



Exploratory efficacy endpoints will be summarized with descriptive statistics and presented by treatment group. Exploratory efficacy endpoints will be analyzed using the same approach described as for the other secondary endpoints. See Section 9.8.2.2 for an overview of the planned analyses. Full details for the analysis of exploratory efficacy endpoints will be included in the SAP.

9.9 Safety Analyses

All safety analyses will be performed using the safety set. Subjects will be analyzed according to the treatment they actually received.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities.

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Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by SOC, by preferred term, and by treatment group.

Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

Antidrug antibody data will be summarized by treatment group and visit.

Further details of safety analyses will be described in the SAP.

9.10 Other Analyses

ANSWER **ANSWER** **ANSWER** **ANSWER** **ANSWER**

Digitized by srujanika@gmail.com

ANSWER

A horizontal bar chart consisting of four bars of varying lengths. The first three bars are extremely long, while the fourth bar is much shorter, indicating a significant difference in magnitude between the categories represented by the first three and the fourth.

[REDACTED]

ANSWER The answer is (A). The first two digits of the number 1234567890 are 12.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place before the start of the study. An insurance certificate is supplied to the CRO and investigator as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will upload the clinical study report to the EudraCT database and will also provide a summary of the clinical study report to the CRO for submission to the competent authority of the countries concerned as required by local regulatory requirement(s). This requirement will be

fulfilled within 1 year for nonpediatric studies as per guidance. The ECs will be provided with a copy of the same summary as locally required.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site before commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's or subject's legally authorized representative's consent and/or assent, as applicable, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any coinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor or designee. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded in eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic CRFs must be completed by the investigator or designee as stated in the site delegation log.

All data in the eCRF will have a separate source (eg, paper or ePRO); no data will be recorded directly in the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject e-diary, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The clinical research associate/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data

(eg, subject's medical file, appointment books, original laboratory reports, x-rays etc). Nonstudy site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and/or assent from all study subjects before any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor before

the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) before study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved before site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Before implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor or designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP647; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records

and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish before release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days before submission for publication. If requested in writing by Shire, the institution and principal

investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	06 Jul 2017	Global

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Appendix 2 Scales and Assessments

The following scales/assessments will be used in the study and are provided in this appendix:

- Stool frequency screening questions

- Mayo scoring system

- Geboes score grading system

- PRO-UC diary

- IBDQ



- SF-36



For questionnaires, language-specific validated versions will be used only.

Stool Frequency Screening Questions

1. Think back to before you ever had symptoms of UC. How many bowel movements did you typically have in a 24-hour period before ever having symptoms of UC?

Number of bowel movements in a 24-hour period before ever having symptoms of UC:

2. Remission of ulcerative colitis (UC) is defined as a time when your symptoms have gone away, you're feeling well, and/or your UC is no longer impacting your regular daily activities. Have you ever experienced a remission of UC?

Yes

No

If YES,

When you are in remission how many bowel movements do you typically have in a 24-hour period? Remember that remission is a time when your symptoms have gone away, you're feeling well, and/or your UC is no longer impacting you regular daily activities.

Number of bowel movements in a 24-hour period when in remission:

Mayo Scoring System for Assessment of Ulcerative Colitis Activity

Stool frequency^a

0 = Normal number of stools for this subject

1 = 1 to 2 stools more than normal

2 = 3 to 4 stools more than normal

3 = 5 or more stools more than normal

Subscore, 0 to 3

Rectal bleeding^b

0 = No blood seen

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

2 = Obvious blood (more than just streaks) or streaks of 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, lack of 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 total 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 three other criteria, the subject's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status.

Source: [Schroeder et al., 1987](#).

Geboes Score Grading System

Grade 0 – Structural (architectural change)	
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1 – Chronic inflammatory infiltrate	
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2A – Lamina propria eosinophils	
Subgrades	
2A.0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
Grade 2B – Lamina propria neutrophils	
Subgrades	
2B.0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3 – Neutrophils in epithelium	
Subgrades	
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4 – Crypt destruction	
Subgrades	
4.0	None
4.1	Probable – local excess of neutrophils in part of crypt
4.2	Probable – marked attenuation
4.3	Unequivocal crypt destruction
Grade 5 – Erosion or ulceration	
Subgrades	
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

Source: [Geboes et al., 2000](#)

Patient-reported Outcomes – Ulcerative Colitis (PRO-UC) Diary Version 1

Item #	Item
1.	Please indicate how often you had a bowel movement over the past 24 hours. A bowel movement is defined as a trip to the toilet and passing stool (liquid, soft, or solid), passing blood only, passing blood and mucus, or passing mucus only. Enter number of bowel movements passed:
2.	Please rate your worst experience of rectal bleeding over the past 24 hours. No blood seen Streaks of blood with stool less than half of the time Obvious blood (more than just streaks) or streaks of blood with stool most of the time Blood alone passes
3.	You indicated you had X bowel movements in the past 24 hours. Of these, how many had blood, either in the stool, in the toilet bowl, or on the toilet paper? Enter the number of bowel movements with blood:
4.	You indicated you had X bowel movements in the past 24 hours. Of these, how many were loose or watery? Enter number of loose or watery bowel movements:
5.	You indicated you had X bowel movements in the past 24 hours. How many of those involved urgency (having to suddenly rush to the toilet to make it on time)? Enter number of bowel movements with urgency:
6.	Please rate your worst abdominal pain over the past 24 hours. 0-10 numeric rating scale, with 0 anchor at “No pain” and 10 at “Worst Imaginable Pain”

Inflammatory Bowel Disease Questionnaire (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks.

You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from:
 1. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
 2. EXTREMELY FREQUENT
 3. VERY FREQUENT
 4. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 5. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 6. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 7. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from:
 1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from:

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

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

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

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

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

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

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

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

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

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

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

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

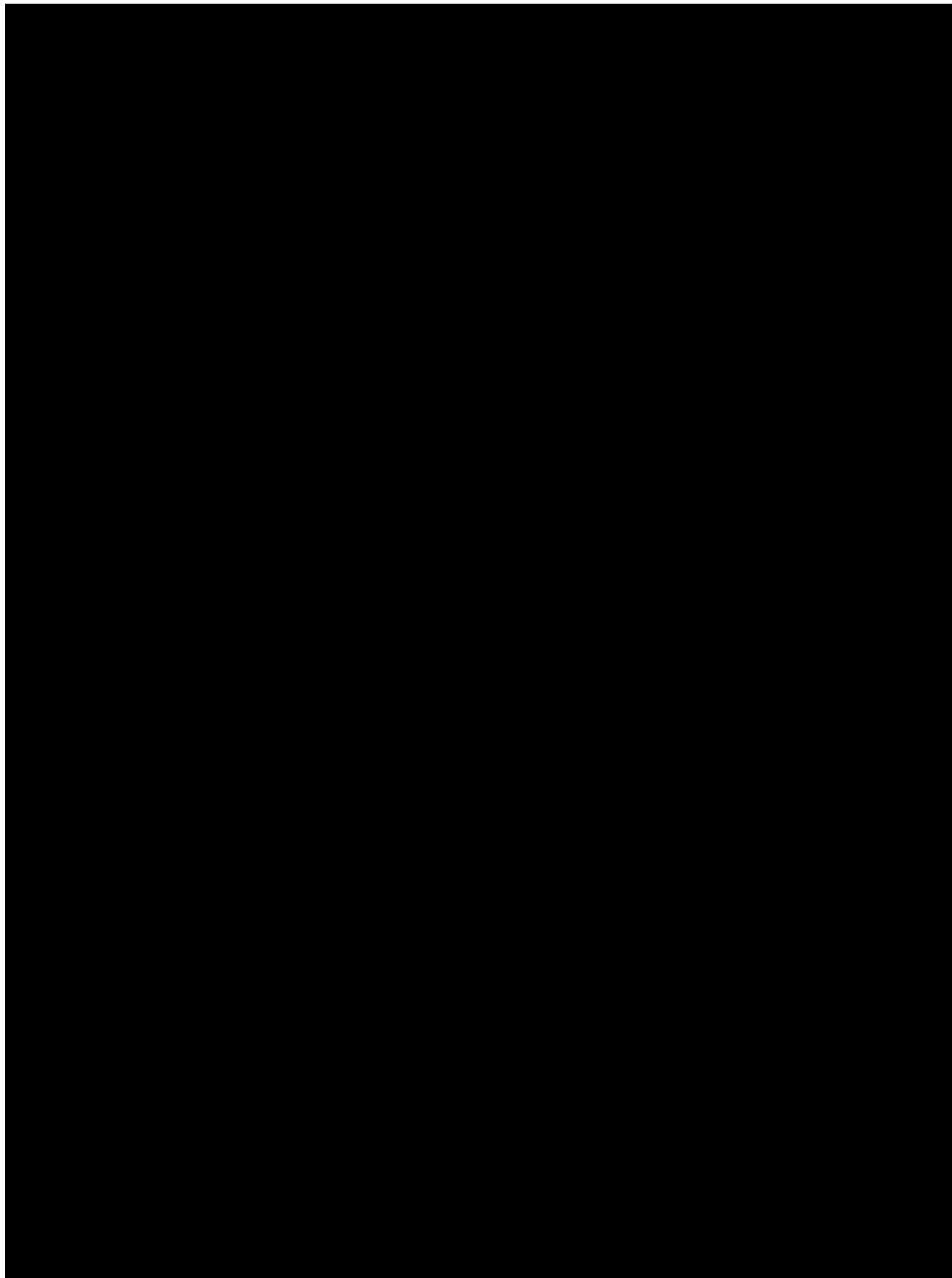
1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

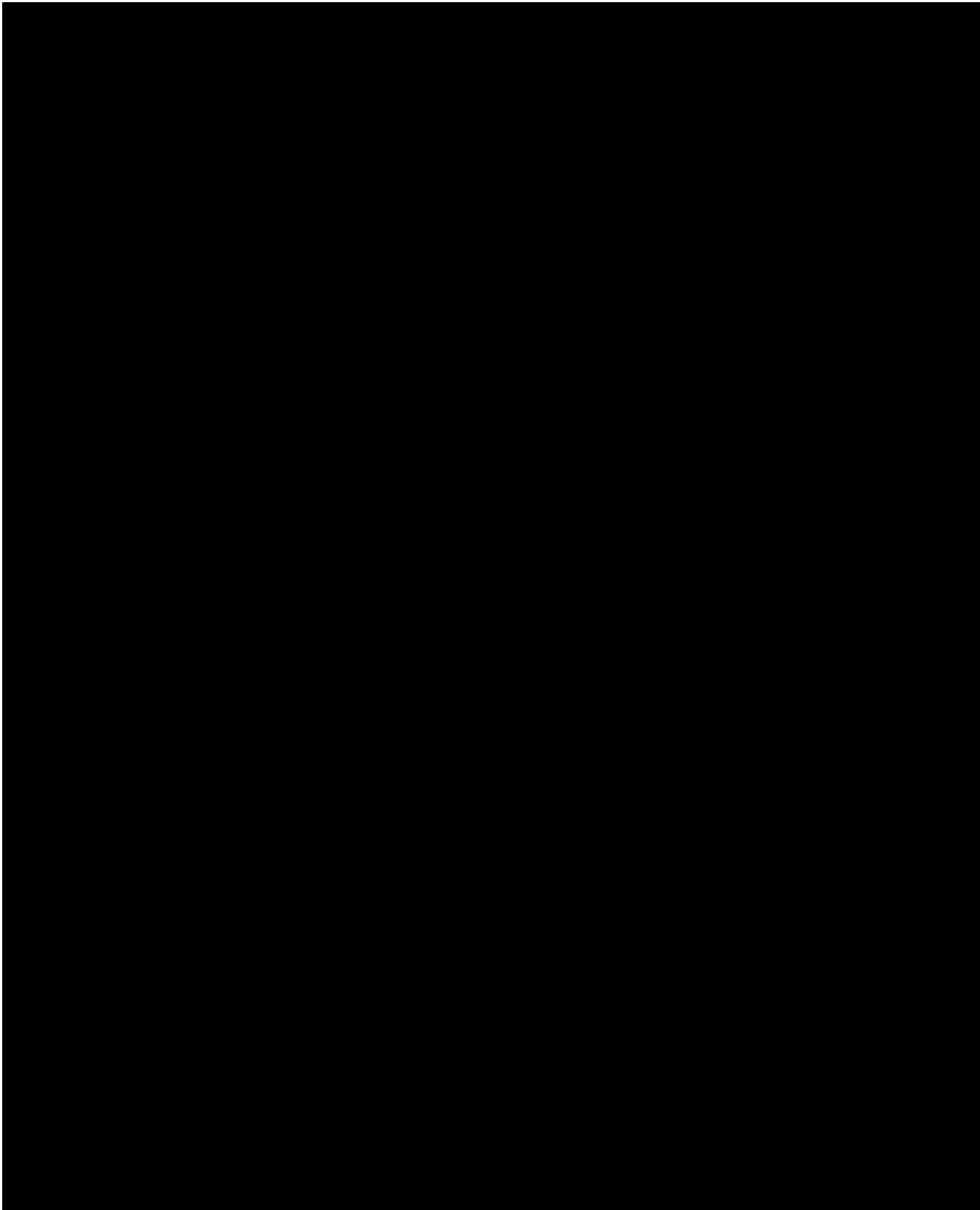
31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from:

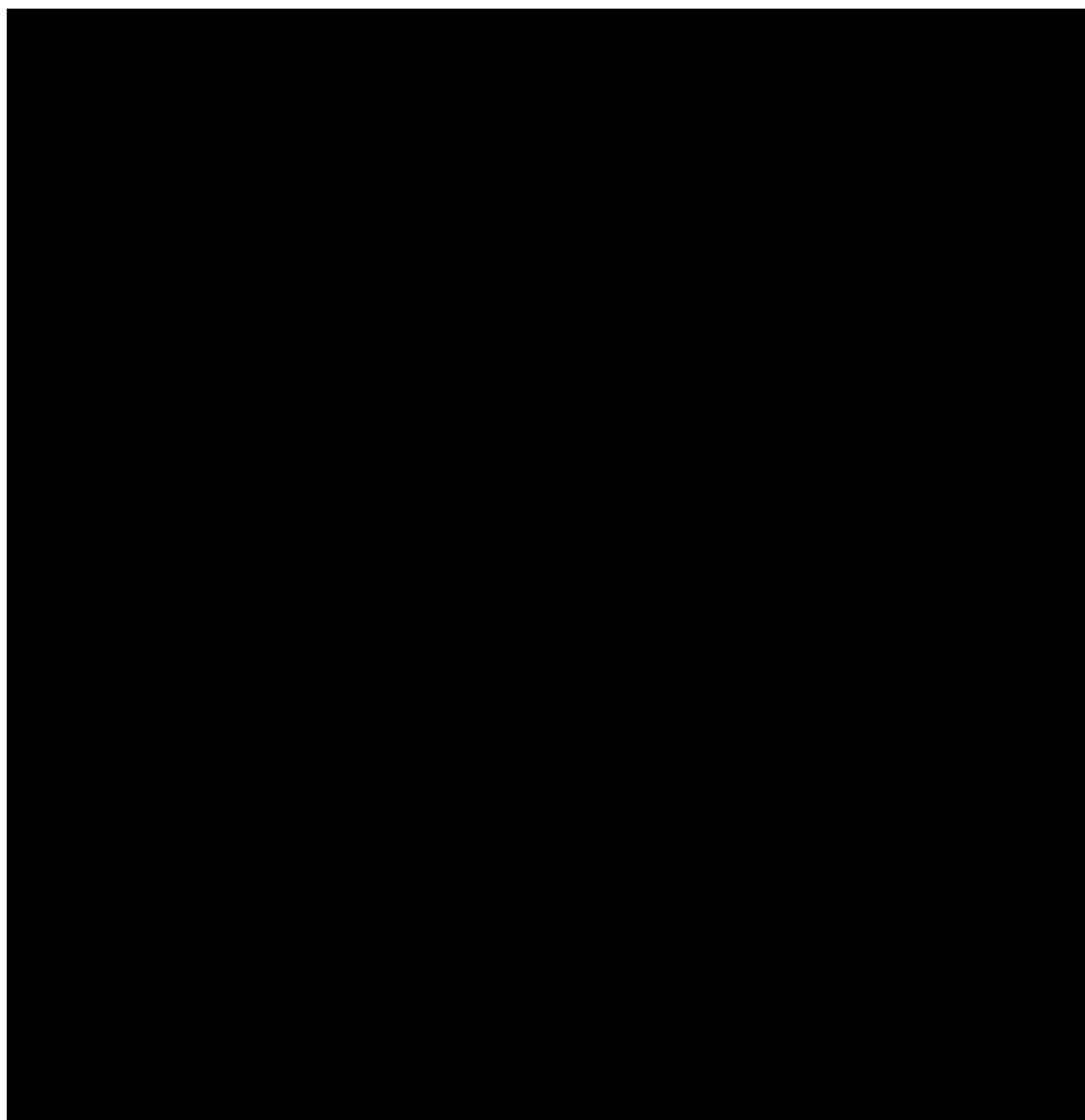
1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

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

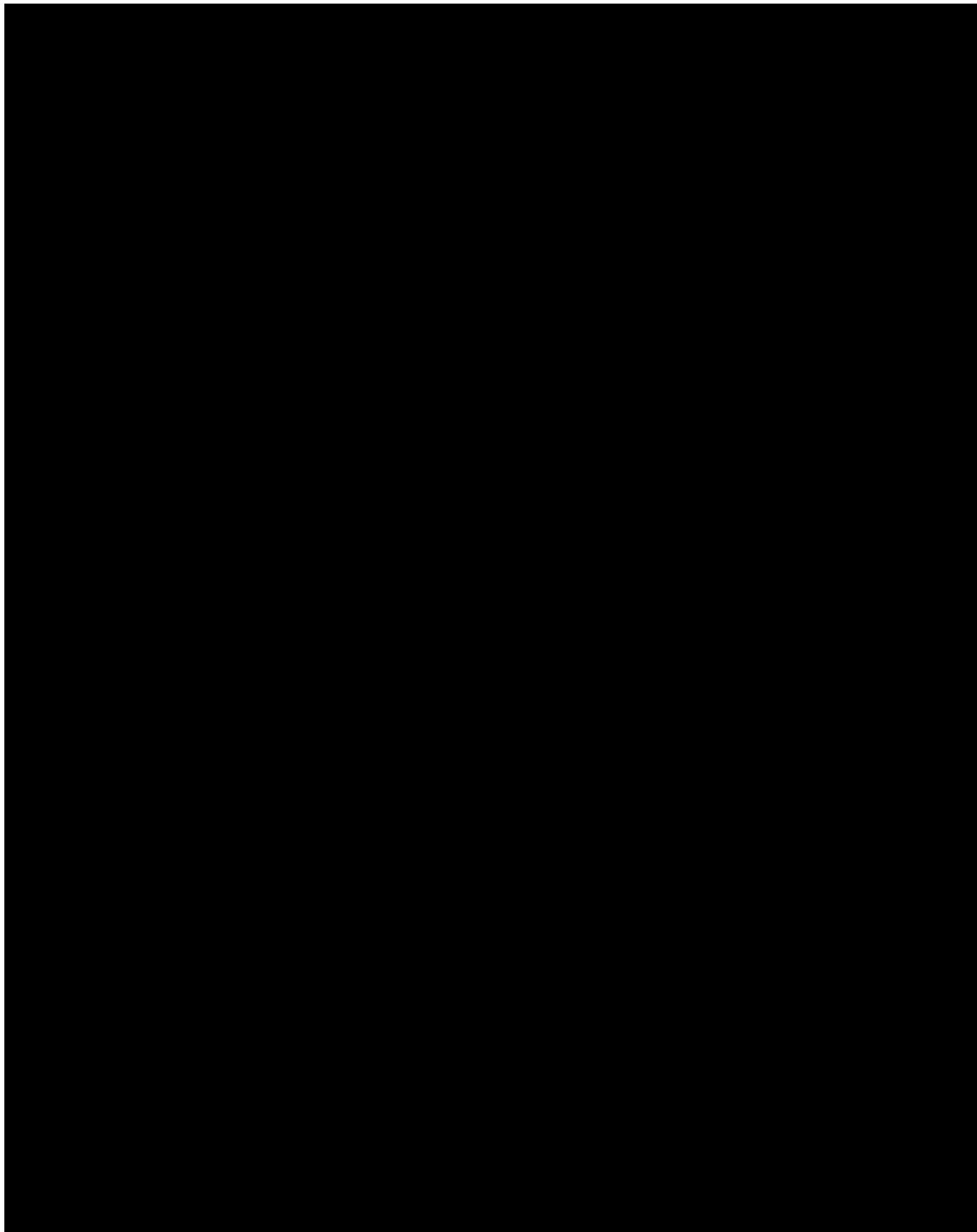
1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2. GENERALLY DISSATISFIED, UNHAPPY
3. SOMEWHAT DISSATISFIED, UNHAPPY
4. GENERALLY SATISFIED, PLEASED
5. SATISFIED MOST OF THE TIME, HAPPY
6. VERY SATISFIED MOST OF THE TIME, HAPPY
7. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

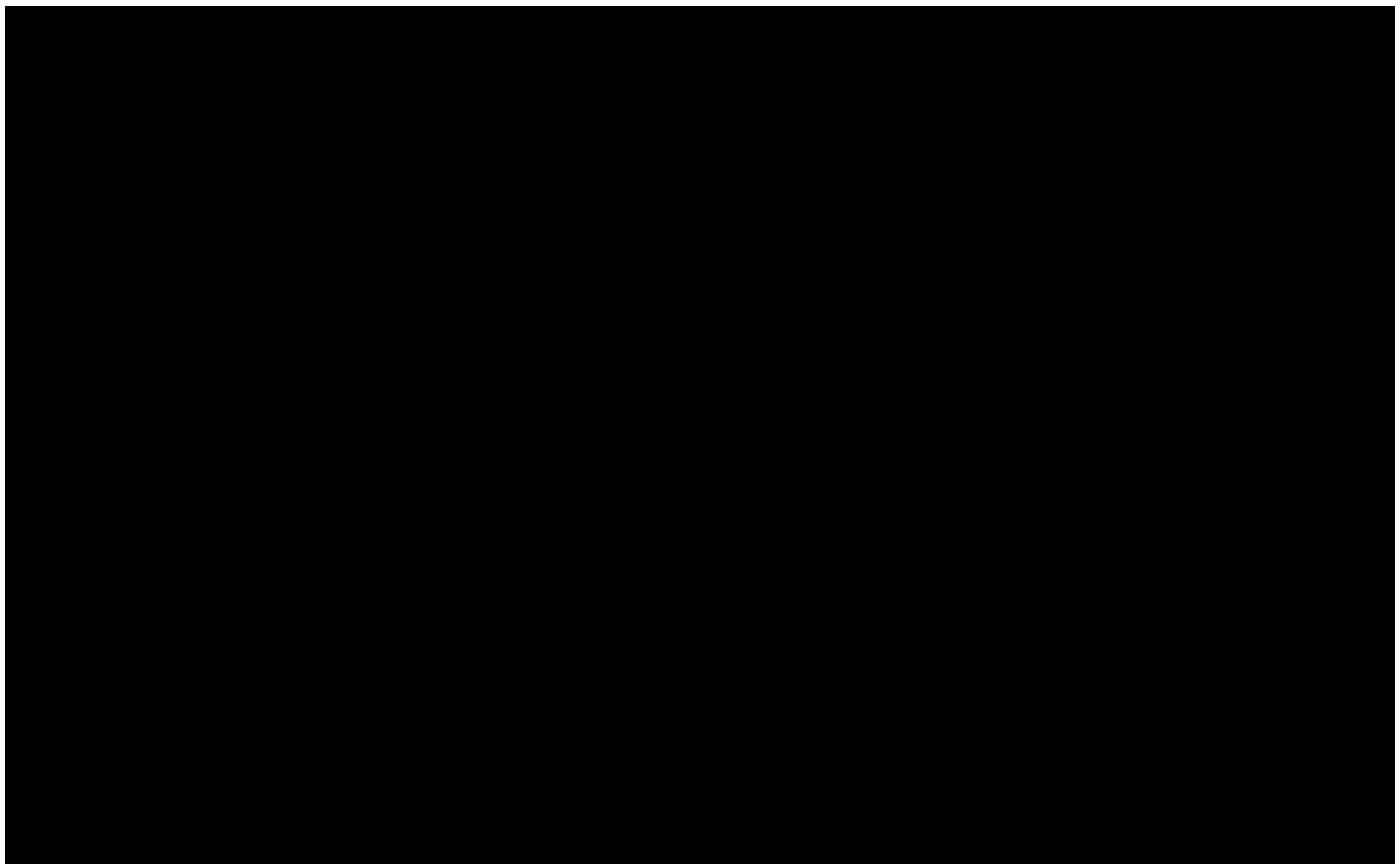






For





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Short Form-36 Health Survey, Acute Form

For non-commercial use only

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an in the one box that best describes your answer.

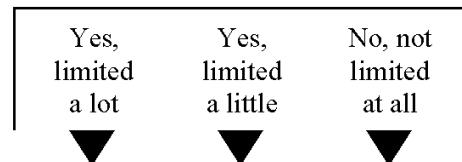
1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
<input type="checkbox"/>				
1	2	3	4	5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?



- a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports 1 2 3
- b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf 1 2 3
- c Lifting or carrying groceries 1 2 3
- d Climbing several flights of stairs 1 2 3
- e Climbing one flight of stairs 1 2 3
- f Bending, kneeling, or stooping 1 2 3
- g Walking more than a mile 1 2 3
- h Walking several hundred yards 1 2 3
- i Walking one hundred yards 1 2 3
- j Bathing or dressing yourself 1 2 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

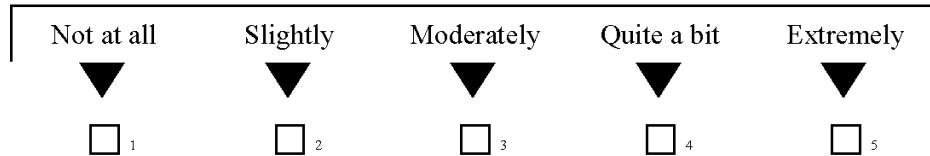
- a Cut down on the amount of time you spent on work or other activities 1..... 2..... 3..... 4..... 5
- b Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c Were limited in the kind of work or other activities 1..... 2..... 3..... 4..... 5
- d Had difficulty performing the work or other activities (for example, it took extra effort) 1..... 2..... 3..... 4..... 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

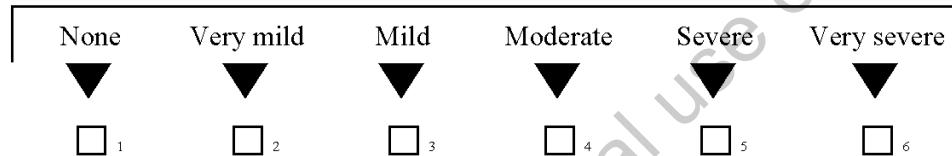
All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Cut down on the amount of time you spent on work or other activities 1..... 2..... 3..... 4..... 5
- b Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c Did work or other activities less carefully than usual 1..... 2..... 3..... 4..... 5

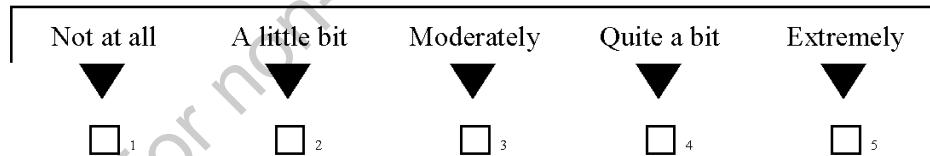
6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much bodily pain have you had during the past week?



8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...

All of the time	Most of the time	Some of the time	A little of the time	None of the time

- a Did you feel full of life? 1..... 2..... 3..... 4..... 5
- b Have you been very nervous?..... 1..... 2..... 3..... 4..... 5
- c Have you felt so down in the dumps that nothing could cheer you up?..... 1..... 2..... 3..... 4..... 5
- d Have you felt calm and peaceful?..... 1..... 2..... 3..... 4..... 5
- e Did you have a lot of energy?..... 1..... 2..... 3..... 4..... 5
- f Have you felt downhearted and depressed?..... 1..... 2..... 3..... 4..... 5
- g Did you feel worn out?..... 1..... 2..... 3..... 4..... 5
- h Have you been happy?..... 1..... 2..... 3..... 4..... 5
- i Did you feel tired? 1..... 2..... 3..... 4..... 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

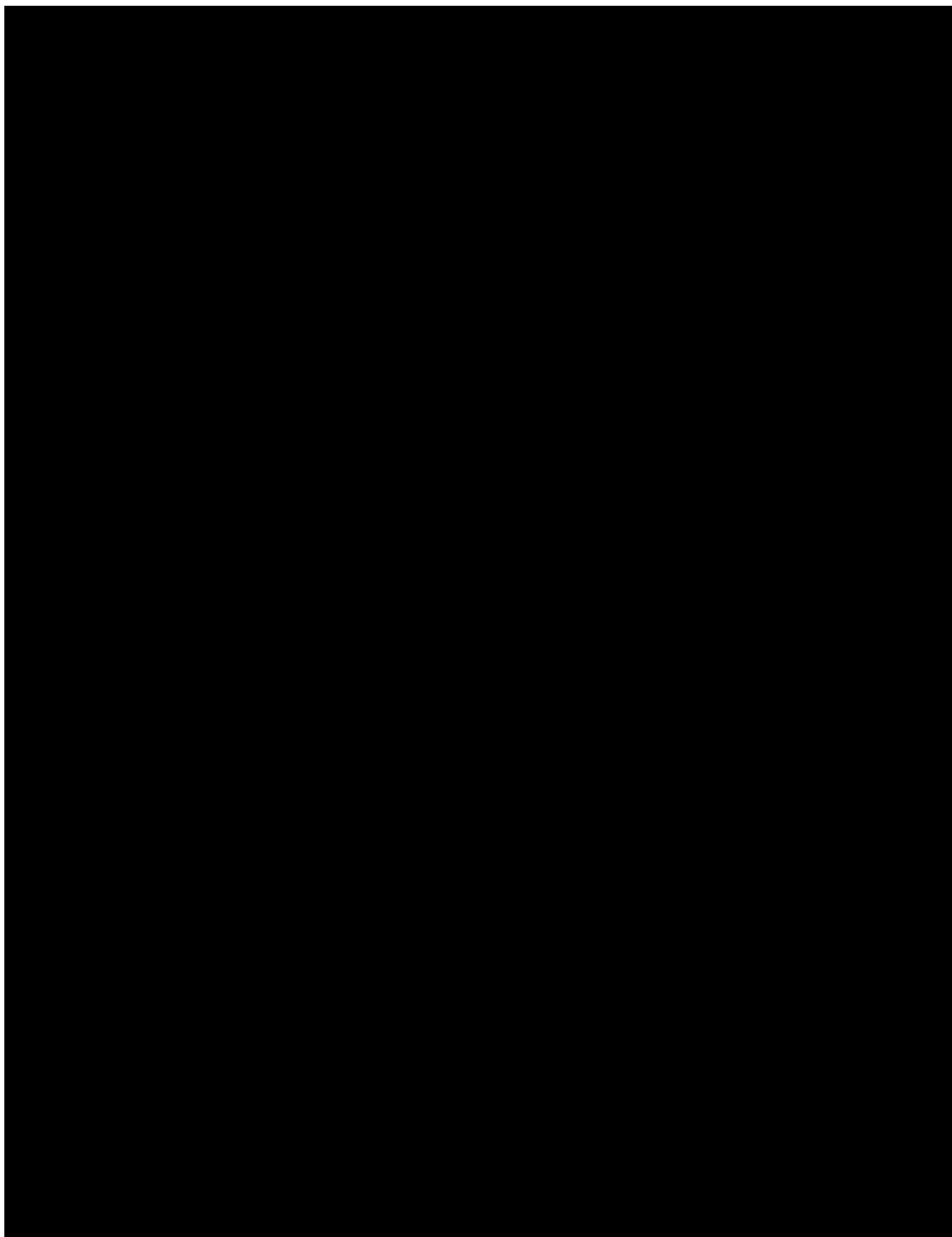
All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

11. How TRUE or FALSE is each of the following statements for you?

Definitely true	Mostly true	Don't know	Mostly false	Definitely false
▼	▼	▼	▼	▼

- a I seem to get sick a little easier than other people 1..... 2..... 3 4..... 5
- b I am as healthy as anybody I know 1..... 2..... 3 4..... 5
- c I expect my health to get worse..... 1..... 2..... 3 4..... 5
- d My health is excellent..... 1..... 2..... 3 4..... 5

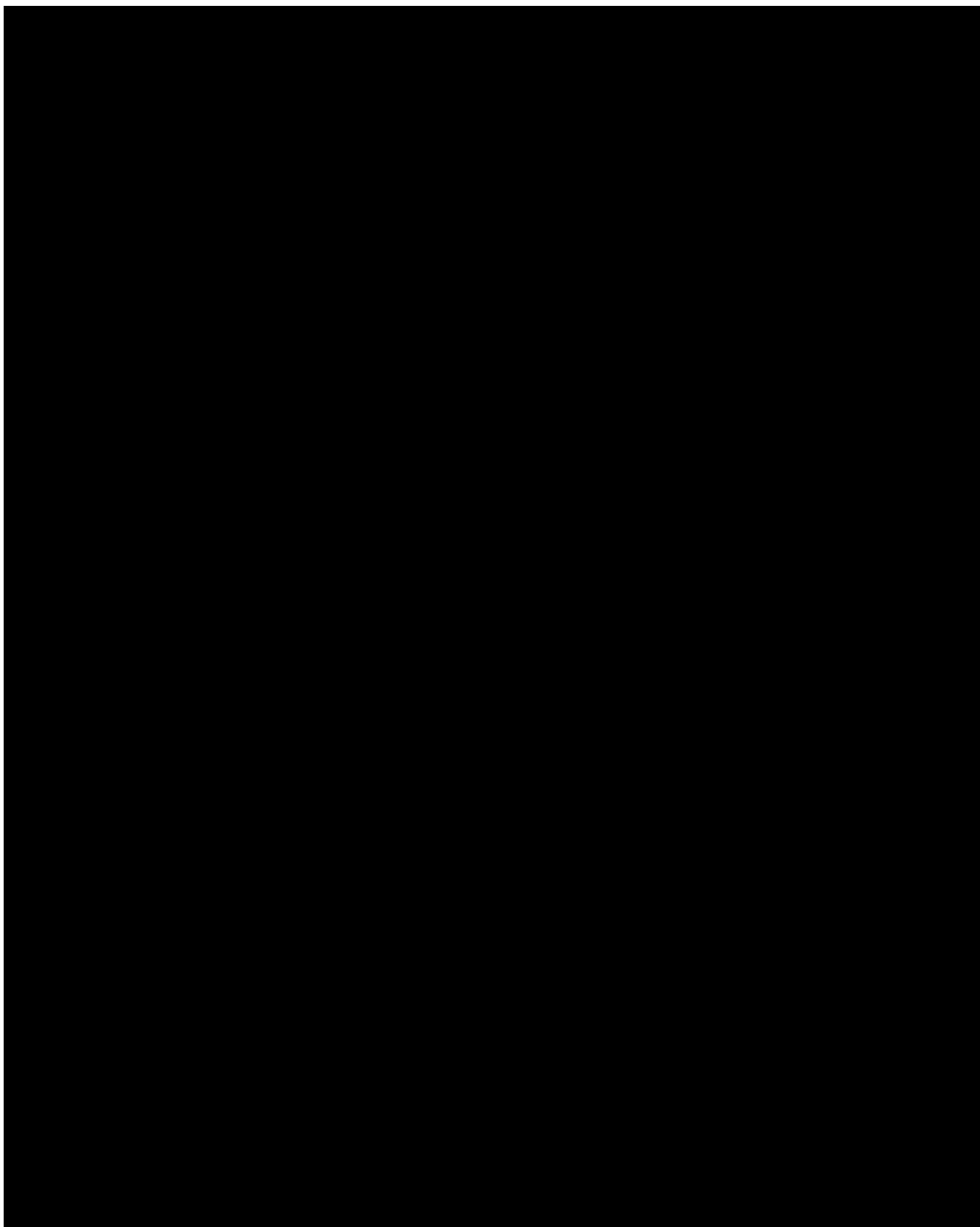
Thank you for completing these questions!

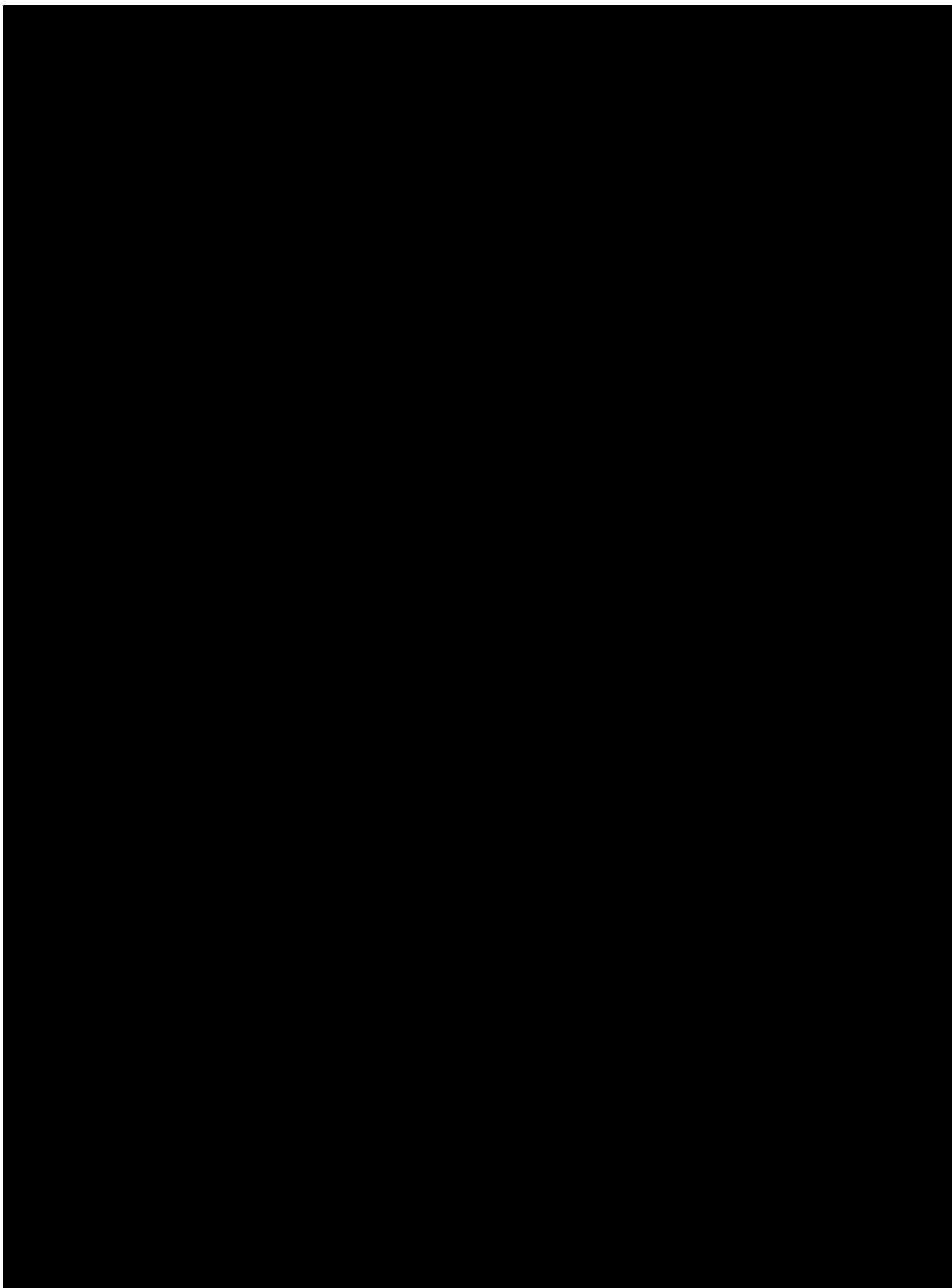


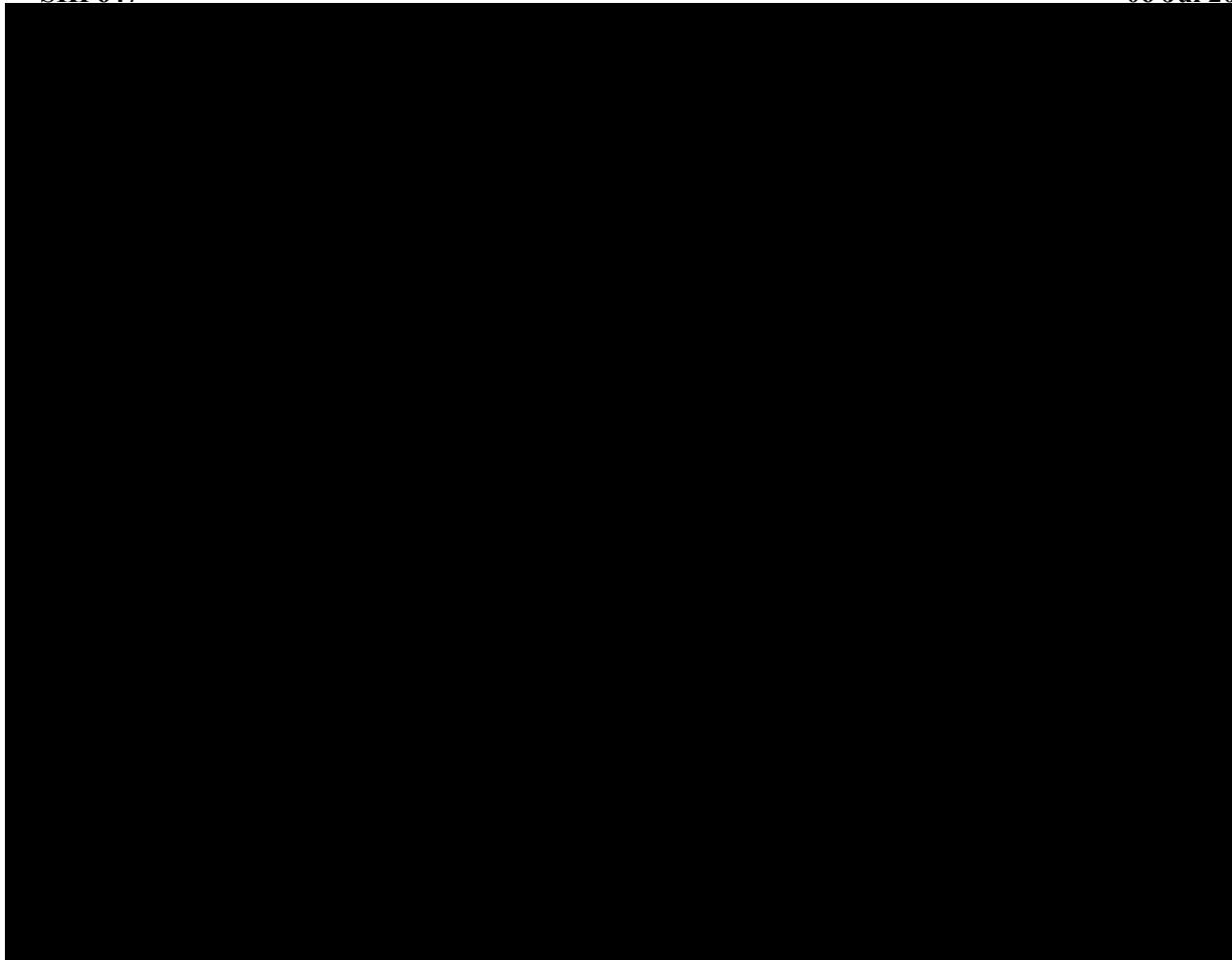
**Shire
Protocol SHP647-302
SHP647**

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06 Jul 2017**







For non-co-

Appendix 3 Glucocorticoid Equivalent Doses

Glucocorticoid	Equivalent Dose (mg)
<i>Short Acting:</i>	
Cortisone	25
Hydrocortisone	20
<i>Intermediate Acting:</i>	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
<i>Long Acting:</i>	
Betamethasone	0.6
Dexamethasone	0.75

Reference: [Lacy et al., 2001-2002](#)



PROTOCOL: SHP647-302

TITLE: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 302)

DRUG: SHP647

IND: 100,222

EUDRACT NO.: 2017-000572-28

SPONSOR:

Shire Human Genetic Therapies, Inc. ("Shire")
300 Shire Way, Lexington, MA 02421 USA

**PRINCIPAL/
COORDINATING
INVESTIGATOR:** [REDACTED], MD, PhD

**PROTOCOL
HISTORY:** Protocol Amendment 1: 05 Sep 2018
Original Protocol: 06 Jul 2017

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PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature:	[REDACTED]	Date:	11-SEP-2018
[REDACTED] MD, [REDACTED]			

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP647-302.

Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 302).

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ Date: _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Emergency Contact Information Section 8.2.2, Reporting Procedures	Replaced “Shire Global Pharmacovigilance” with “the Shire Global Drug Safety Department.” Updated the global fax number and email address for serious adverse event reporting.	To provide updated emergency contact information. The email address was updated in accordance with SHP647-302 Protocol Administrative Change Memo #4, dated 03 May 2018.
Product Quality Complaints	Updated the email address for reporting of product complaints that originate in the European Union and Rest of World. The email address now is the same for all regions.	To provide updated information for reporting of product complaints.
Study Synopsis , Site(s) and Region(s) Section 3.3, Sites and Regions	Revised the anticipated number of study sites from 175 to 210.	To provide a revised projection for the number of study sites expected to participate.
Study Synopsis , Objectives, Other Secondary Section 2.2.2.2, Other Secondary Objectives Section 2.2.3 , Exploratory Objectives	Added text to clarify the endpoints associated with the other secondary objectives based on “other clinical outcomes” and [REDACTED]	To clarify the measures that support those objectives.
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #1 to indicate that subjects with non-steroidal anti-inflammatory drug-induced colitis will be excluded.	To further define the exclusion of subjects with colitis.
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Added exclusion criterion #10: “Subjects have received any nonbiologic treatment with immunomodulatory properties (other than their current background UC treatment) within 30 days before baseline (Visit 2).”	To indicate exclusion of subjects with prior nonbiologic treatment with immunomodulatory properties within the specified timeframe.
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria Section 5.2.2 , Prohibited Treatments	Added exclusion criterion #13: “Subjects have received leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange within 30 days before baseline (Visit 2).”	To indicated exclusion of subjects with prior apheresis or plasma exchange within the specified timeframe.
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #16 (now #18) to clarify that subjects with a history of <i>Mycobacterium tuberculosis</i> (TB) infection will be excluded.	To further define the exclusion of subjects with any history of positive TB.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria Section 7.2.3.6, Clinical Laboratory Evaluations	Revised the name of interferon gamma release assay (IGRA) from “QuantiFERON TB Gold In-Tube Test” to “QuantiFERON TB Gold Plus In-Tube Test.”	To reflect a change in assay for detection of TB.
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #22 (now #24) to indicate that subjects with cirrhosis with or without decompensation will be excluded.	To further define the exclusion of subjects with compromised liver function.
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Moved exclusion of subjects with primary sclerosing cholangitis from exclusion criterion #22 to new criterion #25.	To further define the exclusion of subjects with compromised liver function.
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #24 (now #26) to indicate that subjects with negative HBsAg but positive HBcAb may be eligible if no presence of HBV DNA is confirmed.	To clarify that subjects with positive HBcAb, without HBV DNA, may be eligible for the study.
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #25 (now #27) to indicate that subjects with chronic hepatitis C (HCV) without evidence of HCV RNA within 12 weeks of baseline may be considered eligible.	To clarify that subjects with chronic HCV, without HCV RNA, may be eligible for the study.
Study Synopsis , Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #26 (now #28) to indicate that subjects meeting the following lab criteria would be excluded: <ul style="list-style-type: none">• ALT or AST $\geq 3 \times$ ULN• Total bilirubin level ≥ 1.5 times the ULN (> 2 times the ULN if subject has a known documented history of Gilbert's syndrome) Added a note to exclusion criterion #26 (now #28) to specify that, if platelet count is $< 150,000$ cells/mm ³ , a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.	To align criteria with FDA guidelines.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Study Synopsis , Inclusion and exclusion criteria Section 4.2 , Exclusion Criteria	Updated exclusion criterion #28 (now #30) to include exclusion of subjects with abuse of medicinal marijuana. Deleted former exclusion criterion #28 related to medicinal marijuana dependency.	To indicate that subjects with medicinal marijuana abuse would be excluded.
Study Synopsis , Inclusion and exclusion criteria Section 4.2 , Exclusion Criteria	Updated exclusion criterion #31 (now #33) to indicate the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including male subjects are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and for 16 weeks after last dose of investigational product.	To specify the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including sperm banking or donation for male subjects and egg donation or harvest for female subjects.
Study Synopsis , Endpoints and statistical analysis, Analysis Sets Section 9.7 , Study Population	[REDACTED]	For clarity and consistency of how these are defined across the Phase 3 protocols.
Study Synopsis , Endpoints and statistical analysis, Analysis Sets Section 9.8.1 , Primary Efficacy Endpoint Section 9.8.2 , Secondary Efficacy Endpoints Section 9.8.3 , Exploratory Efficacy Endpoints	Removed “subjects with” and “proportion of subjects with” from the efficacy endpoints where applicable.	To describe the endpoints correctly.
Study Synopsis , Safety Analyses Section 9.9 , Safety Analyses	Added further details on planned summary presentations for the safety analyses. Clarified definition of TEAE.	For clarity.
Section 1.3 , Benefit and Risk Assessment	Added new section describing risk and benefits of SHP647 treatment.	To provide updated risk and benefit information for SHP647.
Schedule of Assessments, footnote “m” Section 7.2.3.6 , Clinical Laboratory Evaluations	Updated SOA footnote “m” and added text in Section 7.2.3.6 to clarify that diagnosis of <i>C. difficile</i> infection should be made using the central laboratory. Added diagnostic algorithms and relevant related to <i>C. difficile</i> testing and diagnosis.	To provide appropriate guidance regarding laboratory testing for <i>C. difficile</i> infection.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Schedule of Assessments, footnote “o”	Added new row to SOA and footnote ‘o’ to indicate HIV tests may be performed at local laboratories (per local requirements) if documentation of a negative HIV test within 6 months of screening is unavailable.	To clarify the timing of acceptable documentation of HIV status.
Schedule of Assessments, footnote “v” Section 2.2.3, Exploratory Objectives Section 7.1.1.1, Screening Visit (Visit 1) Section 7.2.2.1, Endoscopy and Histology Section 9.8.3, Exploratory Efficacy Endpoints Appendix 2 , Scales and Assessments	[REDACTED]	[REDACTED]
Section 3.1, Study Design and Flow Chart	Updated Figure 2 to show more clearly the possible paths for subjects following completion of the 12-week treatment period, ie either entering the maintenance study SHP647-303, entering the LTS study SHP647-304, or entering the 16-week safety follow-up period in this induction study.	To provide clarity regarding the flow of subjects following completion of the 12-week treatment period in this study.
Section 4.4, Reproductive Potential	Made edits to clarify the appropriate methods of contraception for female and male subjects of reproductive potential.	To clarify language regarding appropriate contraceptive methods for subjects of reproductive potential.
Section 4.5.1, Subject Withdrawal Criteria	Added pregnancy to the list of reasons a subject may be withdrawn from study treatment.	For clarity and consistency with language in Section 8.1.6.
Section 5.2.2, Prohibited Treatments	Updated Table 2 to add nonbiologics with immunomodulatory properties as prohibited medications.	To include nonbiologics with immunomodulatory properties as prohibited medications.
Section 6.2.2, Allocation of Subjects to Treatment	Added language to place a cap on the Japan-specific sample population with prior anti-TNF exposure at 60%.	To ensure comparability to the rest of the global population, which has the same cap on prior anti-TNF therapy exposure.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Section 7.1.3 , Follow-up Period: Visits 7 and 8 (Weeks 20 and 28)	<p>Revised text to clarify that the 16-week safety follow-up period is timed relative to the End of Treatment visit, not to the subject's last dose of investigational product.</p>	<p>To accurately reflect the timing for the start of the safety follow-up period and align with the Schedule of Assessments.</p> <p>This change was made with SHP647-302 Protocol Administrative Change Memo #1 (dated 08 Aug 2017).</p>
Section 7.2 , Study Evaluations and Procedures	<p>Added statement that blood and tissue samples may be stored for up to the duration allowed by local regulations, but for no longer than 25 years.</p> <p>Revised from "blood sample collection" to "laboratory sample collection" to clarify that this includes other sample collection, eg urine.</p> <p>Moved investigational product administration to the last bullet point in the ordering of procedures.</p>	<p>To provide clarity regarding the length of time that blood and tissue samples may be stored. This change was made with SHP647-302 Protocol Administrative Change Memo #2 (dated 07 Sep 2017).</p> <p>To improve clarity.</p> <p>To improve clarity.</p>
Section 7.2.2.2 , Mayo score	Removed language stating that endoscopic appearance would be read locally; it is to be centrally read only.	To clarify that endoscopic appearance will be read centrally, not locally.
Section 7.2.3.5 , Vital Signs	Removed language that specified measuring body temperature orally with a digital thermometer or by using tympanic temperature.	To clarify how body temperature should be obtained.
Section 7.2.3.6 , Clinical Laboratory Evaluations	Added information on laboratory testing for <i>C. difficile</i> infection, including diagnostic algorithms.	To provide appropriate guidance regarding laboratory testing for <i>C. difficile</i> infection.
Section 7.2.5 , Volume of Blood to be Drawn for Each Subject	<p>Made corrections to the blood sample volumes for hematology, serum chemistry, and serum CRP, and the approximate total blood volume in Table 4 (Volume of Blood to be Drawn for Each Subject) and in the paragraph thereafter.</p> <p>Added sample collections/blood volumes for HIV and HBV DNA.</p> <p>Updated the blood sample volumes and approximate total blood volume to reflect these changes.</p>	To reflect accurately the blood sample volumes for hematology, serum chemistry, and serum CRP, and reflect addition of HIV and HBV DNA testing.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Section 8.1.8, Unexpected Adverse Event	Added definitions of unexpected adverse event and suspected unexpected serious adverse reaction.	To define unexpected adverse event and suspected unexpected serious adverse reaction.
Section 8.1.9, Suspected Unexpected Serious Adverse Reaction		
Section 8.2.7, Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting	Added text to clarify that “related, unexpected SAEs” refers to “SUSARs.”	To clarify that “related, unexpected SAEs” refers to “SUSARs.”
Section 8.2.8, Safety Monitoring Rules	Added new section describing safety monitoring and stopping algorithms for elevated hepatic blood tests.	To provide appropriate guidance on patients who have been enrolled with elevated liver function test values or who experience and increase in liver function test(s) during the study.
Section 10, Sponsor’s and Investigator’s Responsibilities	Added a statement that compliance with the noted regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.	To clarify that the study is conducted in accordance with the ethical principles in the Declaration of Helsinki.
Section 10.1.1, Good Clinical Practice Compliance	Added language to clarify that the sponsor will ensure that local regulatory requirements are met during the study, including annual safety reporting, ie, Development Safety Update Reports.	To clarify language regarding regulatory reporting requirements.
Appendix 2, Mayo Scoring System for Assessment of Ulcerative Colitis Activity	Added a footnote (“c”) to the Mayo Scoring System for Assessment of Ulcerative Colitis Activity to clarify that the “findings on endoscopy” scoring represents the modified endoscopy subscore and that data will be collected to calculate the total Mayo score using both the modified endoscopy subscore and traditional endoscopy subscore, which will be used as a sensitivity analysis and to estimate the impact of the modification on the primary endpoint.	To provide clarity regarding Mayo Scoring System and use of the modified and traditional endoscopy scores. This change was described in SHP647-302 Protocol Administrative Change Memo #2 (dated 07 Sep 2017).
Appendix 2, Scales and Assessments	[REDACTED]	[REDACTED]

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Appendix 4 , Determination of Failure or Intolerance to Prior Treatment for Ulcerative Colitis	Added new appendix section, “Determination of Failure or intolerance to Prior Treatment for Ulcerative Colitis” to provide guidance as related to inclusion criterion #8 in which subjects meeting these criteria on prior conventional treatments (eg, sulfasalazine, mesalamine, glucocorticoids, immunosuppressants, or anti-TNF) may be eligible for this study.	To provide additional granularity regarding the eligibility of subjects who demonstrated inadequate response, loss of response, or intolerance on conventional treatment.
Appendix 5 , Guidance for Treatment of Increased Gastrointestinal Symptoms	Added new Appendix 5, “Guidance for Treatment of Increased Gastrointestinal Symptoms related to diagnosis and treatment of <i>C. difficile</i> infection.”	To provide updated treatment guidance for subjects diagnosed with <i>C. difficile</i> infection.
Throughout protocol	Minor changes to wording.	To improve clarity, consistency, and remove redundancy of text.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or email the Shire “Clinical Study Serious Adverse Event and Non-serious AE as Required by the Protocol Form” within 24 hours to the Shire Global Drug Safety Department. The fax number and email address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor using the details below.

Fax
[REDACTED] (Global)

Email
[REDACTED]

For protocol- or safety-related issues, the investigator must contact the medical monitor via the appropriate regional safety hotline (24 hours):

North America:

PPD 24 Hour Safety Hotline: RTP [REDACTED]; Wilmington [REDACTED]

PPD 24 Hour Safety Hotline Fax: RTP [REDACTED] or [REDACTED];
Wilmington [REDACTED] or [REDACTED]

Latin America:

PPD 24 Hour Safety Hotline: [REDACTED]

PPD 24 Hour Safety Hotline Fax: [REDACTED]

Europe, the Middle East, and Africa; and Asia-Pacific:

PPD 24 Hour Safety Hotline: [REDACTED]

PPD 24 Hour Safety Hotline Fax: [REDACTED]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	Email Address
North and South America, the European Union, and Rest of World	[REDACTED]

Telephone number (provided for reference if needed):

Shire, Lexington, MA (USA)
[REDACTED]

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CI	confidence interval
CMH	Cochran-Mantel Haenszel
CNS	central nervous system
CRO	contract research organization
DMC	data monitoring committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EMA	European Medicines Agency
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FWER	family-wise type I error rate
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HRQL	health-related quality of life
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
IGRA	interferon gamma release assay
IRB	Institutional Review Board

IRT	interactive response technology
LTS	long-term safety extension
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
PFS	prefilled syringe
PGA	physician global assessment
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
PRC	polymerase chain reaction
PRO	patient-reported outcome
Q4W	once every 4 weeks
REML	restricted maximum likelihood estimation
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SF-36	Short Form-36
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent AE
TNF	tumor necrosis factor
[REDACTED]	[REDACTED]
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
[REDACTED]	[REDACTED]

STUDY SYNOPSIS

Protocol number: SHP647-302	Drug: SHP647
Title of the study: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 302)	
Number of subjects (total and for each treatment arm):	
A total of 825 subjects (330 subjects at 25 mg SHP647, 330 subjects at 75 mg SHP647, and 165 placebo subjects) are planned for enrollment into the study.	
Investigator(s): Multicenter study.	
Site(s) and Region(s):	
It is anticipated that the study will be conducted in at least 18 countries. Regions will include North America, Europe, the Middle East, and Africa, Latin America, and Asia-Pacific. Approximately 210 sites will be utilized.	
Study period (planned): 2017 to 2020	Clinical phase: 3
Objectives:	
Primary: To evaluate the efficacy of SHP647 in inducing remission, based on composite score of patient-reported symptoms and centrally read endoscopy, in subjects with moderate to severe ulcerative colitis (UC).	
Key Secondary:	
<ul style="list-style-type: none">• To evaluate the efficacy of SHP647 in achieving endoscopic remission, based on centrally read endoscopy.• To evaluate the efficacy of SHP647 in achieving clinical remission, based on composite score of patient-reported symptoms.• To evaluate the efficacy of SHP647 in inducing clinical response, based on composite score of patient-reported symptoms and centrally read endoscopy.• To evaluate the efficacy of SHP647 in achieving mucosal healing, based on endoscopic and histological assessment using the Geboes Score grading system.	
Other Secondary:	
<ul style="list-style-type: none">• To evaluate the safety and tolerability of SHP647.• To evaluate the effect of SHP647 induction treatment on other clinical and endoscopic outcomes (including Mayo-based remission and clinical response, partial Mayo score over time, clinical remission over time, endoscopic remission, and deep remission).• To evaluate the effect of SHP647 on abdominal pain, urgency, diarrhea, and absolute stool frequency and bleeding scores.• To evaluate the effect of SHP647 on health-related quality of life (as measured by the Inflammatory Bowel Disease Questionnaire [IBDQ] and the Short Form-36 Health Survey [SF-36]).• To evaluate the effect of SHP647 on incidence of hospitalizations and total inpatient days.	
Rationale:	
This study is designed to evaluate the efficacy and safety of SHP647 in inducing remission in subjects with moderate to severe UC.	
SHP647 has been investigated in 2 completed dose-finding studies (A7281001 and A7281009) in subjects with moderate to severe UC; a third study (A7281010), an open-label long-term safety extension study, is ongoing. The Phase 1 study, A7281001, which investigateded the safety, tolerance, pharmacokinetics, and pharmacodynamic properties of SHP647, supports further clinical development of SHP647 using subcutaneous (SC) administration. SC doses of 25 mg or 75 mg of SHP647 or placebo on Day 1 (Week 0), Week 4, and Week 8 are recommended for the Phase 3 studies SHP647-301 and SHP647-302.	

Investigational product, dose, and mode of administration:

The test product is SHP647, which will be provided as a sterile aqueous buffered solution for SC administration in a glass prefilled syringe (PFS) with a fixed needle. Each PFS contains 1 mL of SHP647 solution for injection at an appropriate concentration to provide the intended dose of drug (25 or 75 mg). Additional information is provided in the current SHP647 investigator's brochure.

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain SHP647.

Methodology:

A total of 825 subjects (330 subjects at 25 mg SHP647, 330 subjects at 75 mg SHP647, and 165 placebo subjects) are planned for enrollment into the study. Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent form.

The study consists of a screening period up to 6 weeks and a 12-week treatment period. After the screening period, eligible subjects will be randomly assigned to receive 1 of 3 treatments (25 mg SHP647, 75 mg SHP647, or placebo) in a 2:2:1 ratio. Randomization will be stratified based upon the subject's status of prior anti-TNF (tumor necrosis factor) treatment (naïve or experienced) and glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline). Subjects will receive SC injections of SHP647 or placebo, using a PFS, on Week 0/Day 1 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 5). Subjects will undergo efficacy, [REDACTED], [REDACTED] safety, and health outcome assessments at these visits.

Patient-reported UC signs and symptom data (including stool frequency, rectal bleeding severity and frequency, diarrhea frequency, urgency frequency, and abdominal pain worst severity) will be collected using a daily electronic diary (e-diary) during the treatment period. The Mayo score is a measure of UC disease activity consisting of the following 4 subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician global assessment (PGA). The partial Mayo score consists of the Mayo score without the endoscopic subscores. The composite score is a recommended measure consisting of the Mayo score without the PGA subscore, and will be used for the primary efficacy endpoint. The Mayo scores and composite score will be based on subject daily e-diary entries.

At the end of the 12-week treatment period, eligible subjects will be offered the opportunity to participate in a double-blind maintenance study (SHP647-303; for subjects who achieve clinical response) or a long-term safety extension (LTS) study (SHP647-304; for subjects who do not achieve a clinical response). Subjects who withdraw early from the 12-week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

Inclusion and exclusion criteria:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must be between ≥ 16 and ≤ 80 years of age at the time of the signing of the informed consent/assent form.

NOTE: Subjects <18 years of age must weigh ≥ 40 kg and must have body mass index (BMI) ≥ 16.5 .

4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for ≥ 3 months before screening. The following must be available in each subject's source documentation:
 - A biopsy report to confirm the histological diagnosis.

- A report documenting disease duration based upon prior colonoscopy.

NOTE: If this documentation is not available at the time of screening, a colonoscopy with biopsy to confirm the diagnosis is required during the screening period.

5. Subjects must be willing to undergo a flexible sigmoidoscopy or colonoscopy (if preferred), including biopsy sample collection, during screening after all other inclusion criteria have been met.
6. Subjects must have moderate to severe active UC, defined as a total Mayo score of ≥ 6 , including a centrally read endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 at baseline (Visit 2).
7. Subjects must have evidence of UC extending proximal to the rectum (ie, not limited to proctitis).
8. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as mesalamine (5-aminosalicylic acid [5-ASA]), glucocorticoids, immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]), or anti-TNF (refer to Appendix 4 for guidance).
9. Subjects receiving any treatment(s) for UC described in Section 5.2.1 of the protocol are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
10. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception for the duration of the study.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subjects with indeterminate colitis, microscopic colitis, non-steroidal anti-inflammatory drug-induced colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of Crohn's disease.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for UC during the treatment period.
5. Subjects at risk for colorectal cancer must have a colonoscopy performed during the screening period with results available within 10 days before the baseline visit (Visit 2), unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidence of dysplasia and colon cancer must be available in the source documents.

Subjects at risk for colorectal cancer include, but are not limited to:

- Subjects with extensive colitis for ≥ 8 years or disease limited to left side of colon (ie, distal to splenic flexure) for ≥ 10 years before screening, regardless of age.
 - Subjects ≥ 50 years of age at the time of signing of the informed consent form.
6. Subjects have had prior treatment with SHP647 (formerly PF-00547659).
 7. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
 8. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
 9. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).

10. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than their current background UC treatment) within 30 days before baseline (Visit 2).
11. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
12. Subjects have received parenteral or rectal glucocorticoids, or rectal 5-ASA, within 14 days before screening endoscopic procedure.
13. Subjects have received leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange within 30 days before baseline (Visit 2).
14. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before baseline (Visit 2).
15. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).
16. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis [subjects with *C. difficile* infection at screening may be allowed re-test after treatment], evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
17. Subjects with abnormal chest x-ray findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation.)
18. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) or subjects with this history who have not completed a generally accepted full course of treatment before randomization are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed.

Subjects who have no history of previously diagnosed active or latent tuberculosis are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥ 5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before randomization. If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

- An IGRA is strongly recommended for subjects with a prior Bacillus Calmette-Guérin (BCG) vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON TB Gold Plus In-Tube Test.
- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent tuberculosis, a positive test on repeat will exclude the subject. Subjects with a history of active or latent tuberculosis infection must follow instructions for "Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met" in this criterion.
- Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray, taken within the 3 months before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
 - A chest x-ray performed within 3 months prior to screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.
19. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
20. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on the targeted neurological assessment during the screening period.
21. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
22. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
- Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal (except disease under study), endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.
 - Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
 - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening.
 - History of significant cerebrovascular disease within 24 weeks before screening.
23. Subjects who have had significant trauma or major surgery within 4 weeks before the screening visit (Visit 1), or with any major elective surgery scheduled to occur during the study.
24. Subjects with evidence of cirrhosis with or without decompensation.
25. Subjects with primary sclerosing cholangitis.
26. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). NOTE: if a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if no presence of HBV DNA is confirmed by HBV DNA PCR reflex testing performed in the central laboratory.
27. Subjects with chronic hepatitis C (HCV) (positive HCVAb and HCVRNA). Note: Subjects who are HCVAb positive without evidence of HCVRNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCVRNA at least 12 weeks prior to baseline]).
28. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening. NOTE: Screening laboratory tests, if the results are considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results must be reviewed for eligibility prior to the screening endoscopy procedure.

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels $\geq 3.0 \times$ the upper limit of normal (ULN).
 - Total bilirubin level $\geq 1.5 \times$ ULN or $> 2.0 \times$ ULN if the subject has a known documented history of Gilbert's syndrome).
 - Hemoglobin level ≤ 80 g/L (8.0 g/dL).
 - Platelet count $\leq 100 \times 10^9/\text{L}$ (100,000 cells/mm³) or $\geq 1000 \times 10^9/\text{L}$ (1,000,000 cells/mm³).*
 - White blood cell count $\leq 3.5 \times 10^9/\text{L}$ (3500 cells/mm³).
 - Absolute neutrophil count (ANC) $< 2 \times 10^9/\text{L}$ (2000 cells/mm³).
 - Serum creatinine level $> 1.5 \times$ ULN or estimated glomerular filtration rate $< 30 \text{ mL/min}/1.73 \text{ m}^2$ based on the abbreviated Modification of Diet in Renal Disease Study Equation.
*Note: If platelet count is $< 150,000$ cells/mm³, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.
29. Subjects with known HIV infection based on documented history, with positive serological test, or positive HIV serologic test at screening, tested at the site's local laboratory in accordance with country requirements, or tested at the central laboratory. Note: A documented negative HIV test within 6 months of screening is acceptable and does not need to be repeated.
30. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse or dependency of any kind, including abuse of medicinal marijuana (cannabis).
31. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
32. Female subjects who are planning to become pregnant during the study period.
33. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm, and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
34. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: Up to 6 weeks
- Planned duration of treatment period: 12 weeks
- Planned duration of follow-up period: 16 weeks

Endpoints and statistical analysis:

Analysis Sets:

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

The full analysis set (FAS) will consist of all subjects in the randomized set who have received at least 1 dose of investigational product.

The per-protocol (PP) set will consist of all subjects in the FAS who do not have predefined protocol deviations that may affect the primary efficacy endpoint.

The completer set will consist of all subjects in the FAS who have completed the final scheduled primary assessment for this study.

[REDACTED]

[REDACTED]

Primary Efficacy Endpoint: The primary efficacy endpoint is remission at the Week 12 visit. Remission is defined as a composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy as follows:

- stool frequency subscore of 0 or 1 with at least a 1-point change from baseline
 - AND
- rectal bleeding subscore of 0
 - AND
- endoscopic subscore of 0 or 1 (modified, excludes friability).

The primary efficacy endpoint will be compared for each active treatment group (25 mg or 75 mg SHP647) to the placebo group using a Cochran-Mantel Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment and glucocorticoid use at baseline (Visit 2). Subjects with missing remission data at the Week 12 visit will be considered failures and counted as nonresponders. The endoscopy score will be based on centrally read results.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata, $j=1$ to m . The common treatment difference is a weighted average of the stratum-specific treatment differences.

The global family-wise type I error rate (FWER) for the statistical tests of the primary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz, et al 2009 will be utilized to propagate α from primary to key secondary endpoints and between the two SHP647 treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the primary endpoint (P) and alpha is propagated in a hierarchical manner to each of the 4 key secondary endpoints (K1-K4) within a pairwise treatment comparison.

Key Secondary Efficacy Endpoints:

- Endoscopic remission, as defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability), at the Week 12 visit.
- Clinical remission, as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at the Week 12 visit.
- Clinical response based on composite score at the Week 12 visit. Clinical response (composite) is defined as a decrease from baseline in the composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 .
- Mucosal healing based on endoscopic and histological assessment at the Week 12 visit. Mucosal healing is defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability) and centrally read Geboes score of ≤ 2 .

The key secondary endpoints will be analyzed using the same approach as described for the primary efficacy endpoint. Subjects with missing key secondary endpoint data at the Week 12 visit will be considered failures and counted as nonresponders.

Other Secondary Efficacy Endpoints:

- Remission, defined as a total Mayo score ≤ 2 with no individual subscore (stool frequency, rectal bleeding, endoscopy [modified, excludes friability], and physician's global assessment) exceeding 1, at the Week 12 visit.
- Clinical response based on total Mayo score at the Week 12 visit. Clinical response (Mayo) is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or an absolute subscore for rectal bleeding ≤ 1 .
- Partial Mayo score ≤ 2 with no individual subscore > 1 at the Week 4, 8, and 12 visits. The partial Mayo score does not include the endoscopy subscore.
- Clinical remission as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at Weeks 4 and 8.
- Endoscopic remission at the Week 12 visit with endoscopic subscore of 0.
- Clinical remission at the Week 4, 8, and 12 visits with both rectal bleeding and stool frequency subscores of 0.
- Deep remission at the Week 12 visit. Deep remission is defined as both endoscopic and rectal bleeding subscores of 0, and stool frequency subscore ≤ 1 and a centrally read Geboes score of ≤ 2 .
- Change from baseline at the Week 12 visit in abdominal pain, diarrhea and urgency item scores, absolute stool frequency, absolute rectal bleeding and total sign/symptom score based on subject daily e-diary entries (sum of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency).
- Change from baseline in IBDQ domain and total (absolute) scores (time frame: Week 0, Week 8, up to Week 12, or early termination).
- Change from baseline in Short Form-36 (SF-36), version 2, acute (physical and mental component summary scores and individual domain scores) to the Week 12/ET visit.
- Incidence of all-cause hospitalizations and total inpatient days.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods.

- Binary endpoints will be analyzed using the same approach as described for the primary endpoint. Subjects with missing binary endpoint data at a visit will be considered failures and counted as nonresponders.
- Continuous endpoints that are only measured at baseline and the Week 12 visit will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% confidence intervals (CIs) for least squares mean treatment differences will be provided.
- Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation (REML). The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

Safety Analyses:

All safety analyses will be performed using the safety set. Subjects will be analyzed according to the treatment they actually received.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, serious AEs, and deaths will be similarly summarized or listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

Antidrug antibody data will be summarized by treatment group and visit.

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STUDY SCHEDULE

Table 1: Schedule of Assessments

Study Procedure	Screening^a	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET^b	Week 20^c	Week 28^c
Visit Number	1	2	3	4	5	6 (Part 1)^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3		84 ±3	140 ±7
Informed consent/assent	X							
Eligibility assessment	X	X					X ^e	
Demographics and medical history ^f	X							
Complete physical examination ^g	X						X	X
Targeted physical examination ^g		X						
Targeted neurological assessment ^h	X						X	X
Vital signs ⁱ	X	X		X	X		X	X
Height	X							
Weight	X	X		X	X		X	X
12-lead ECG ⁱ	X	X					X	
Chest x-ray ^j	X							
Contraception check ^k	X	X	X	X	X		X	X
Laboratory Assessments								
Hematology	X ^l	X		X	X		X	X
Serum chemistry	X ^l	X		X	X		X	X
Urinalysis	X ^l	X		X	X		X	X
Stool microbiology ^m	X ^l							
HBsAg, HBcAb, HCV Ab ⁿ	X ^l							
HIV testing per local regulation ^o	X							
FSH ^p	X ^l							
Serum β-hCG ^q	X ^l							
Urine β-hCG ^q		X		X	X		X	X
TB test (PPD or QuantiFERON TB Gold Plus) ^r		X ^l						
JCV antibody banked sample ^s		X						
[REDACTED]		X		X			X	
[REDACTED]		X ^l		X ^l			X	
[REDACTED]		X ^l		X ^l			X	
[REDACTED]		X ^l		X ^l			X	

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Study Procedure	Screening^a	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET^b	Week 20^c	Week 28^c
Visit Number	1	2	3	4	5	6 (Part 1)^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3	84 ±3	140 ±7	196 ±7
ADA and NAb sampling		X ^u	X ^u	X ^u	X ^u		X	
Endoscopic Procedure								
Endoscopy (including biopsy) ^v		X ^v				X		
UC Assessments								
Total Mayo score		X ^w					X ^w	
Partial Mayo score				X	X			
Remission stool frequency and pre-UC stool frequency	X							
PRO UC daily e-diary data instruction	X							
PRO UC daily e-diary data ^x	X	X	X	X	X	X	X	
Health Assessment^y								
IBDQ		X			X		X	
		X			X		X	
Hospitalizations, inpatient days, (HRUA)				X	X		X	
				X	X		X	
		X		X	X		X	
		X					X	
SF-36 v2, acute form		X			X		X	
		X					X	
Treatment Procedures								
Randomization ^z		X						
Administration of SHP647 or placebo ^z		X		X	X			
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample ^{aa}	X			X	X			

Ab=antibody ADA=antidrug antibodies; β-hCG=beta-human chorionic gonadotropin; [REDACTED]; ECG=electrocardiogram; ED=emergency department; [REDACTED]; ET=early termination; FSH=follicle-stimulating hormone; GDH=glutamate dehydrogenase; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HRUA=Healthcare Resource Utilization Assessment; HCV=hepatitis C virus; HCV RNA=hepatitis C virus ribonucleic acid; HEENT=head, eyes, ears, nose, and throat; IBDQ=Inflammatory Bowel Disease Questionnaire; JCV=John Cunningham virus;

Table 1: Schedule of Assessments

Study Procedure	Screening^a	Baseline	Treatment					Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET^b		Week 20^c	Week 28^c
Visit Number	1	2	3	4	5	6 (Part 1)^d	6 (Part 2)	7	8
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3		84 ±3	140 ±7	196 ±7

LTS=long-term safety extension; [REDACTED]; Nab=neutralizing antibody; PCR=polymerase chain reaction; PGA=physician's global assessment; [REDACTED]; [REDACTED]; PML=progressive multifocal leukoencephalopathy; PPD=purified protein derivative; PRO=patient-reported outcomes; SF-36 v2=short form-36 health survey, version 2; TB=tuberculosis; [REDACTED]; UC=ulcerative colitis; [REDACTED].

^a At least 2 visits will be necessary to complete the screening procedures, including endoscopy.

^b Subjects who withdraw early during the treatment period should return for the early termination (ET) visit and then enter into the safety follow-up period.

^c Participation in the safety follow-up period is not required if subject is entering the maintenance study (SHP647-303) or LTS (SHP647-304) at the completion of the Week 12 visit. For subjects participating in the 16-week safety follow-up period (not entering the maintenance study or LTS study), the Week 20 (Visit 7) visit will routinely be conducted by telephone; however, as an exception the visit can be performed as a study site visit if preferred. The Week 28 (Visit 8) visit will be at the study site.

^d Part 1 of Visit 6 should be scheduled preferably within 5 to 7 days before Part 2 visit; this will allow sufficient time for data from the centrally read endoscopy to be available at Part 2 of the visit.

^e The outcome of Visit 6, Part 2 is used to assess eligibility to enroll in the maintenance (SHP647-303) or LTS (SHP647-304) studies. Eligibility for SHP647-303 and SHP647-304 will be assessed under those respective protocols.

^f Medical history will include UC history, cardiac history, and smoking history.

^g Complete physical examination includes the review of the following body systems: general appearance, skin, HEENT, heart, lungs, confrontational visual fields (eyes), breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes. Targeted physical examination includes the review of the following body systems: skin, heart, lungs, confrontational visual fields (eyes), abdomen, and examination of body systems where there are symptom complaints by the subject.

^h Subjects will be evaluated to reveal any potential abnormalities in the following neurologic domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior. Subjects with any unexplained positive item at screening that is suggestive of PML should be excluded. See Section 7.2.3.3 for further details.

ⁱ Vital signs (including blood pressure, pulse, respiratory rate, and temperature) and 12-lead ECG should be performed before collection of blood samples for laboratory assessments and before endoscopic procedure.

^j A chest x-ray performed up to 12 weeks before screening (Visit 1) may be used if available; the official reading must be located in the subject's source documentation.

^k Contraception check should be performed for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential. See Section 4.4 for further details.

^l Screening laboratory test results, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results of repeated tests must be reviewed for eligibility prior to the screening endoscopy procedure.

^m Diagnosis of *C. difficile* infection should be made using the central laboratory. If for any reason the central laboratory is not available, refer to Appendix 5 for guidance regarding alternate diagnostic algorithms.

Table 1: Schedule of Assessments

Study Procedure	Screening^a	Baseline	Treatment					Follow-up		
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET^b		Week 20^c	Week 28^c	
Visit Number	1	2	3	4	5	6 (Part 1)^d	6 (Part 2)	7	8	
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3			84 ±3	140 ±7	196 ±7

^a Subjects who test negative for HBsAg but positive for HBcAb without HBV DNA may be considered eligible. For subjects who test positive for HBcAb and negative for HBsAg, a blood sample should be taken for HBV DNA. Blood for HBV DNA reflex testing is collected for required subjects only. If HBV DNA is positive, these subjects will not be eligible.

^b Documentation of a negative HIV test result within 6 months prior to screening will be accepted.

^c For confirmation of postmenopausal status in females who have had 12 consecutive months of spontaneous amenorrhea and are ≥51 years of age.

^d For females of childbearing potential who are not surgically sterile, do not have confirmed ovarian failure, or do not meet the definition of postmenopausal as described in Section 4.4 and Section 7.2.3.7.

^e A documented negative PPD test within 12 weeks before baseline (Visit 2) is acceptable. Interferon gamma release assay official reading and method or test must be located in the source documentation.

^f A serum sample will be collected and banked. It may be analyzed if a subject shows neurologic symptoms suggestive of progressive multifocal leukoencephalopathy.

^g The sample must be collected before administration of investigational product.

^h The [] sample must be collected before administration of investigational product.

ⁱ Flexible sigmoidoscopy or colonoscopy (if preferred) at screening must be performed on all subjects after the majority of other eligibility criteria (eg, laboratory values) are met. Endoscopy must be performed during the screening period within 10 days before baseline (Visit 2), preferably within 5 to 7 days before the baseline visit, to obtain the centrally read endoscopic subscore. Biopsy samples will be collected for histological evaluation using the Geboes Score classification for the key secondary efficacy endpoint and []. Subjects at risk of colorectal cancer, as defined in exclusion criterion 5 (see Section 4.2), must have a colonoscopy performed at screening, unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidence of dysplasia and colon cancer must be available in the source documents.

^j Mayo score will be based on subject daily e-diary entries. The Mayo score at baseline will be calculated based on the stool frequency subscore and rectal bleeding subscore, reported by subjects in the PRO UC daily e-diary and PGA obtained at baseline and the centrally read endoscopic subscore for the endoscopy performed during the screening period. The Mayo score at the Week 12 visit will be calculated based on the stool frequency subscore and rectal bleeding subscore reported by subjects in the PRO UC daily e-diary and PGA and the centrally read endoscopic subscore for the endoscopy performed at Week 12, Visit 6 (Part 1). See Section 7.2.2.2 for further details.

^k PRO UC daily e-diary will be collected using a daily e-diary during the treatment period. Collection of the daily e-diary data must begin at least 10 days before the baseline visit (Visit 2). The subject should be provided with the handheld device to take home on their first visit. See Section 7.2.2.3 for further details. Compliance is assessed by site staff at each visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <23 out of 28 e-diary entries) when compared with the previous visit.

^l All health outcome or patient-reported questionnaires should be completed before completing any other visit assessments.

^m Interactive response technology will be used for randomization and dispensation of study treatment.

Table 1: Schedule of Assessments

Study Procedure	Screening ^a	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET ^b	Week 20 ^c	Week 28 ^c
Visit Number	1	2	3	4	5	6 (Part 1) ^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3		84 ±3	140 ±7

^{aa} Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the visit at which testing will be done.

Note: See Section 7.2 for the order in which assessments should be performed. Timing of visits is relative to baseline (Visit 2).

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Ulcerative colitis (UC) is a chronic, relapsing disease marked by ulceration and inflammation of the colonic mucosa and submucosa. Initially it usually involves the rectum but may extend proximally to involve a portion of, or the entirety of, the colon. In the early stages, hemorrhagic and erythematous tissue is observed, progressing to mucosal ulceration with purulent exudates in severe cases. The ulceration pattern is continuous and may extend the entire length of the colon. Perforation of the bowel wall causing ileus and peritonitis can occur with transmural extension of the ulceration. Bloody diarrhea with or without mucus and lower abdominal pain with periods of remission and exacerbation are the most common symptoms.

The incidence of UC is estimated to be up to 24.3 cases per 100,000 persons per year in Europe and up to 19.2 cases per 100,000 persons per year in North America. No clear difference in incidence has been observed between men and women. Although UC can occur at any age, peak incidence has been observed in the second to fourth decades of life ([Molodecky et al. 2012](#)). Ulcerative colitis is a lifelong condition with a serious effect on the quality of life. Current treatment primarily consists of symptomatic management with dietary modifications and opiate antidiarrheal drugs (loperamide), as well as disease modifying agents such as 5-aminosalicylic acid (5-ASA), systemic glucocorticoids, immunosuppressive agents (azathioprine/6-mercaptopurine, cyclosporine), and biologic therapy with anti-tumor necrosis factor (TNF) or anti-integrin agents. Despite recent advances, there is still an unmet need for an effective pharmacological treatment that will induce and maintain remission.

1.2 Product Background and Clinical Information

The selectivity of lymphocyte homing to specialized lymphoid tissue and mucosal sites of the gastrointestinal (GI) tract is influenced by the endothelial expression of mucosal addressin cell adhesion molecule (MAdCAM). MAdCAM is a member of the immunoglobulin super family of cell adhesion molecules and is mostly expressed on the cell surface of high endothelial venules of organized intestinal lymphoid tissue such as Peyer's patches and mesenteric lymph nodes ([Briskin et al. 1997](#); [Shyjan et al. 1996](#); [Liaskou et al. 2011](#)). MAdCAM plays a role in gut immune surveillance, and also appears to facilitate excessive lymphocyte infiltration under conditions of chronic GI inflammation. The $\alpha_4\beta_7$ integrin is the recognized ligand for MAdCAM, and expression of this ligand on populations of CD4 $^{+}$ and CD8 $^{+}$ T cells, as well as on subsets of B cells, distinguishes them as unique gut homing lymphocytes.

SHP647 (previously known as PF-00547659) is a fully human immunoglobulin G2 kappa (IgG_{2k}) monoclonal antibody that binds to human MAdCAM to reduce lymphocyte homing to the gut and GI inflammation. SHP647 binds MAdCAM-1 with high affinity and selectivity that prevents the binding of $\alpha_4\beta_7^{+}$ lymphocytes to MAdCAM expressing sites in the high endothelial venules of the GI tract.

1.3 Benefit/Risk Assessment

SHP647 has been evaluated in Phase 1 and 2 clinical studies in subjects with UC and CD. In UC study A7281009, induction with SHP647 at doses of 7.5 mg, 22.5 mg, or 75 mg every 4 weeks resulted in statistically significantly higher proportions of subjects in remission at Week 12 based on total Mayo score (both local and central read) when compared with placebo treatment. In CD study A7281006, induction with SHP647 did not meet the primary endpoint; no statistically significant differences were observed between the active treatment arms and the placebo arm in CDAI-70 response rate at Week 8 or Week 12. Post hoc analyses suggested evidence of drug effect in subjects with more inflammation at baseline, as indicated by higher serum concentrations of CRP or Simple Endoscopic Score for CD (SES-CD).

In UC induction study A7281009, decreases in fecal calprotectin were observed in all groups, including placebo; however, there were no statistically significant differences in the decrease in fecal calprotectin between any dose level of SHP647 and placebo. Decreases in hsCRP were also observed in all 4 treatment groups; however, other than the 75 mg dose group at Week 12, no statistically significant differences were observed in active treatment vs placebo. In the induction Study A7281006 in subjects with CD, compared to placebo, nominally statistically significant decreases in fecal calprotectin were observed in the 75 mg group at Week 8 and in the 22.5 mg and 75 mg groups at Week 12. Generally, decreases from baseline in hsCRP were observed in all 4 treatment groups over the 12-week induction period. Compared to placebo, nominally statistically significant decreases in hsCRP were observed in all 3 active treatment groups (22.5 mg, 75 mg, and 225 mg) at Week 12. There was no evidence of a dose response for either of these parameters. A nominally statistically significant increase was observed in circulating $\beta7^+$ central memory T lymphocytes at Weeks 8 and 12, consistent with the predicted mechanism of action.

The most common SAEs across all studies were CD and UC. In Study A7281006, the randomized, placebo-controlled induction study in CD, TEAEs were most commonly reported within the GI disorders system organ class (SOC) followed by the infections and infestations SOC. The most common all-causality TEAEs were CD (worsening and progression of underlying disease), followed by pyrexia, headache, and arthralgia, all of which had similar incidences in the placebo treatment group compared with the active treatment groups. In Study A7281009, the randomized, placebo-controlled induction study in UC, TEAEs were most commonly reported within the GI disorders SOC followed by the infections and infestations SOC. The most common all-causality TEAE was headache, followed by abdominal pain, nasopharyngitis, UC (worsening and progression of underlying disease), and nausea, all with similar incidence between placebo- and drug-treated subjects.

The long-term, open-label safety studies (Studies A7281007 and A7281010) were not placebo-controlled, but permitted exposure to the investigational product at doses of 75 mg or 225 mg every 4 weeks for 18 and 36 months, respectively. In Study A7281007, the most common all-causality TEAE was CD (worsening or progression), arthralgia, nasopharyngitis, and abdominal pain. In Study A7281010, the most common all-causality TEAEs have been UC (worsening or progression), arthralgia, and nasopharyngitis.

SHP647 appears to be generally well tolerated, with the majority of TEAEs distributed at similar frequencies among treatment arms with only peripheral edema, gastroenteritis, and arthralgia more frequently reported in SHP647- than placebo-treated subjects in the pooled induction studies. In the placebo-controlled induction studies, nasopharyngitis was not reported more frequently in SHP647- than placebo-treated subjects, but occurred at relatively high frequency during long-term safety studies. SHP647 does not appear to be associated with impaired CNS immune surveillance. No case of PML or myocarditis has been reported. SHP647, in doses of 7.5 mg, 22.5 mg, and 75 mg, appears to increase the rate of remission in subjects with UC, and may have an effect in patients with CD who have greater evidence of inflammation based on biomarker or endoscopic data.

Always refer to the latest version of the SHP647 investigator's brochure for the overall benefit/risk assessment and the most accurate and current information regarding the pharmacokinetics, efficacy, and safety of SHP647.

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2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

SHP647, a fully human IgG_{2k} antihuman MAdCAM monoclonal antibody, is under development for the treatment of UC. SHP647 prevents the binding of α₄β₇⁺ lymphocytes to MAdCAM-expressing sites with high affinity and selectivity. Principal sites of MAdCAM expression on normal tissue include intestine, pancreas, stomach, esophagus, spleen, and to a lesser extent lung, liver, and bladder but not the central nervous system (CNS) ([Steffen et al. 1996](#)).

Although selective targeting of the MAdCAM receptors is a novel approach, the basic interference of lymphocyte homing by preventing the binding of these α₄β₇⁺ lymphocytes to the MAdCAM receptor and the resultant efficacy in UC is well established ([Feagan et al. 2013](#)). SHP647 is differentiated from other molecules used for the treatment of UC in that it blocks the interaction of α₄β₇⁺ lymphocytes to the MAdCAM receptor by selectively binding to MAdCAM in the gut (and related tissues) whereas other molecules only target the integrins on the infiltrating lymphocytes. Additionally, SHP647 does not bind to the vascular cell adhesion molecule; therefore, SHP647 is not expected to be an effective treatment for multiple sclerosis, or affect lymphocyte homing or surveillance in the CNS.

This study is designed to evaluate the efficacy of SHP647 in inducing remission in subjects with moderate to severe UC.

SHP647 has been investigated in 2 completed dose-finding studies (A7281001 and A7281009) in subjects with moderate to severe UC; a third study (A7281010), an open-label long-term safety extension study, is ongoing. Phase 1 study A7281001 evaluated both single (0.03-10.0 mg/kg intravenous [IV]; 3.0 mg/kg subcutaneous [SC]) and multiple doses (0.1-3.0 mg/kg IV; 0.3 and 1.0 mg/kg SC) of SHP647 in subjects with UC. Safety evaluation revealed a safety profile for SHP647 similar to that of placebo, with no pattern of adverse events (AEs) suggestive of increased risk of opportunistic infections or CNS effects, and no evidence of adverse effects on laboratory parameters, electrocardiograms (ECGs), vital signs, or neurological function. Events leading to withdrawal were due to exacerbations of the underlying UC.

Study A7281009 was a Phase 2b proof-of-concept (randomized, double-blind, placebo-controlled, parallel, dose-ranging) study designed to evaluate the efficacy, safety, and pharmacokinetics of SHP647 in subjects with moderate to severe UC. Treatment was assigned in a 1:1:1:1 ratio to dose levels of 7.5, 22.5, 75, or 225 mg SHP647 or placebo administered SC once every 4 weeks (Q4W at Weeks 0, 4, and 8). The primary endpoint of the study was the proportion of subjects in clinical remission at Week 12, with remission defined as a total Mayo score of ≤2 with no individual subscore >1 (see [Appendix 2](#) for details of the Mayo score). More subjects were in clinical remission at Week 12 in SHP647-treated groups than in the placebo group, with statistical significance achieved for the 7.5, 22.5, and 75-mg doses ([Vermeire et al. 2017](#)). Based upon the total Mayo score with a centrally read endoscopic severity component, the increase in clinical remission rates over placebo at Week 12 for the 7.5, 22.5, and 75-mg doses were 8.0% (p=.043), 12.8% (p=.010), and 11.8% (p=.012).

When the clinical remission rate at Week 12 was analyzed by stratum of previous anti-TNF exposure (experienced or naïve), a similar trend was observed across dose levels in both the anti-TNF experienced and anti-TNF naïve subjects. There was no evidence of an adverse safety signal, and there was no increase in the frequency of infections in MAdCAM-bearing tissues as evidenced by similar rates of nasopharyngitis among treatment arms.

Based on the efficacy and safety data in Study A7281009 and the systemic population pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation, clinical remission, clinical response and mucosal healing rates were higher in subjects with UC receiving doses of 22.5 and 75 mg Q4W than in those receiving doses of 7.5 mg and 225 mg Q4W. The induction responses were not demonstrated either at Week 4 or Week 8, but were observed at Week 12 regardless of dose level. No difference in the clinical responses between a 22.5-mg dose and a 25-mg dose is expected based on the current understanding of the mode of action of SHP647 and clinical observations to date. To better understand the exposure (dose)-response relationship in this population and understand individual patient exposure needs, the 25-mg and 75-mg doses (Q4W) will be tested in the Phase 3 program. Therefore, SC doses of 25 mg or 75 mg of SHP647 or placebo on Day 1 (Week 0), Week 4, and Week 8 are recommended for the 2 planned Phase 3 studies SHP647-301 and SHP647-302. The Phase 1 study, A7281001, which investigated the safety, tolerance, pharmacokinetics, and pharmacodynamic properties of SHP647, supports further clinical development of SHP647 using SC administration.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of SHP647 in inducing remission, based on composite score of patient-reported symptoms and centrally read endoscopy, in subjects with moderate to severe UC.

2.2.2 Secondary Objectives

2.2.2.1 Key Secondary Objectives

The key secondary objectives are as follows:

- To evaluate the efficacy of SHP647 in achieving endoscopic remission, based on centrally read endoscopy.
- To evaluate the efficacy of SHP647 in achieving clinical remission, based on composite score of patient-reported symptoms.
- To evaluate the efficacy of SHP647 in inducing clinical response, based on composite score of patient-reported symptoms and centrally read endoscopy.
- To evaluate the efficacy of SHP647 in achieving mucosal healing, based on a centrally read endoscopic and histological assessment using the Geboes Score grading system.

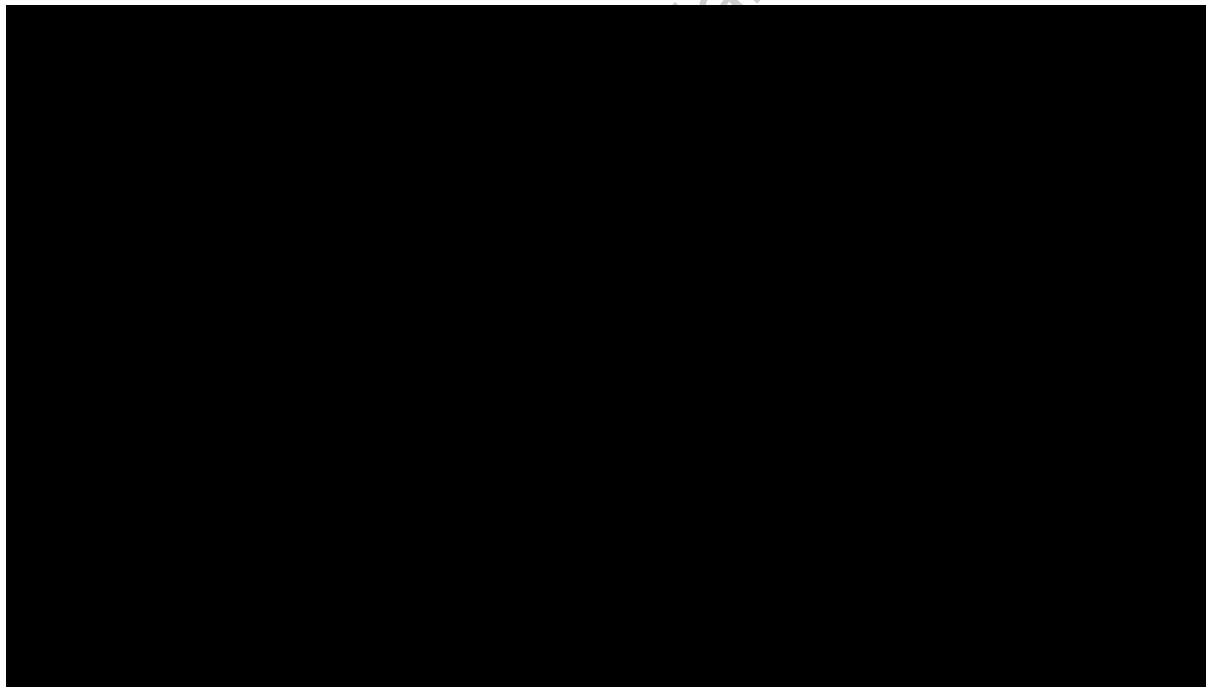
2.2.2.2 Other Secondary Objectives

The other secondary objectives are as follows:

- To evaluate the safety and tolerability of SHP647.
- To evaluate the effect of SHP647 induction treatment on other clinical and endoscopic outcomes (including Mayo-based remission and clinical response, partial Mayo score over time, clinical remission over time, endoscopic remission, and deep remission)
- To evaluate the effect of SHP647 on abdominal pain, urgency, diarrhea, and absolute stool frequency and bleeding scores.
- To evaluate the effect of SHP647 on health-related quality of life (HRQL) (as measured by the Inflammatory Bowel Disease Questionnaire [IBDQ] and the Short Form-36 Health Survey [SF-36]).
- To evaluate the effect of SHP647 on incidence of hospitalizations and total inpatient days.

2.2.3 Exploratory Objectives

The exploratory objectives of the study are as follows:



3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of SHP647 in inducing remission in subjects with moderate to severe UC.

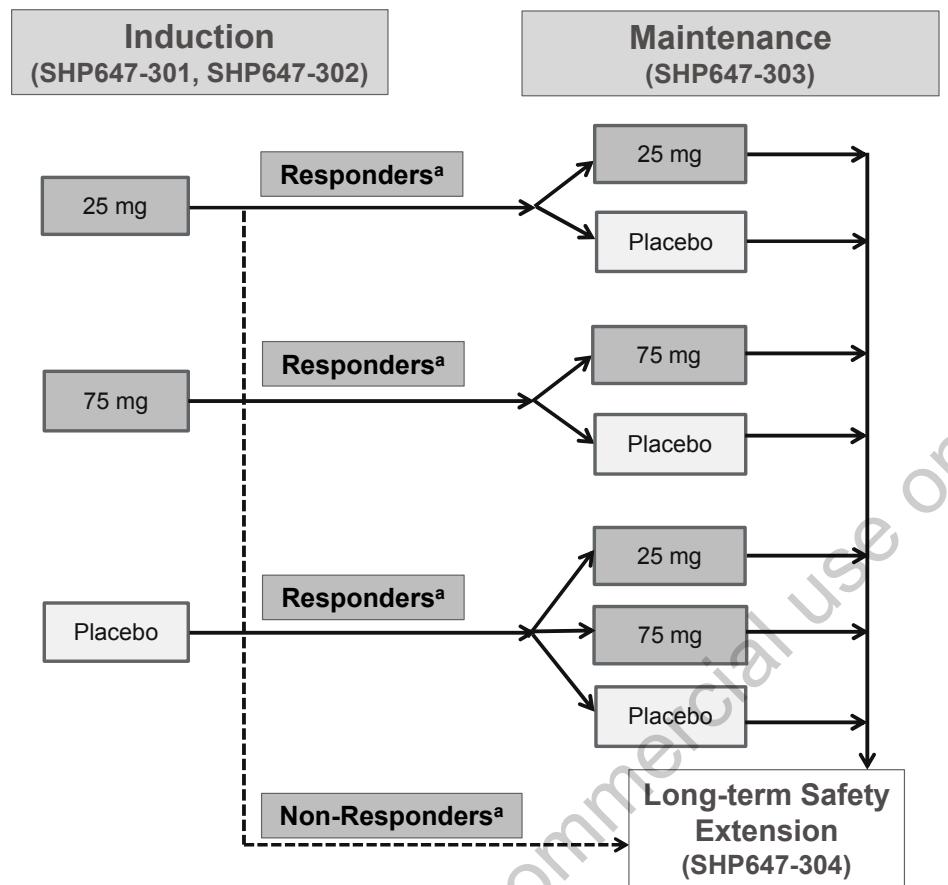
A total of 825 subjects (330 subjects at 25 mg SHP647, 330 subjects at 75 mg SHP647, and 165 placebo subjects) are planned for enrollment into the study ([Figure 1](#)). Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent form.

The study consists of a screening period up to 6 weeks and a 12-week treatment period. After the screening period, eligible subjects will be randomly assigned to receive 1 of 3 treatments (25 mg SHP647, 75 mg SHP647, or placebo) in a 2:2:1 ratio. Randomization will be stratified based upon the subject's status of prior anti-tumor necrosis factor (TNF) treatment (naïve or experienced) and glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline). Subjects will receive SC injections of SHP647 or placebo, using a prefilled syringe (PFS), on Week 0/Day 1 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 5). Subjects will undergo efficacy, [REDACTED], [REDACTED], safety, and health outcome assessments at these visits as detailed in [Table 1](#).

At the end of the 12-week treatment period, eligible subjects will be offered the opportunity to participate in a double-blind maintenance study (SHP647-303; for subjects who achieve clinical response) or a long-term safety extension (LTS) study (SHP647-304; for subjects who do not achieve a clinical response) as shown in [Figure 1](#). Subjects who withdraw early from the 12-week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

The overall study design is shown in [Figure 2](#).

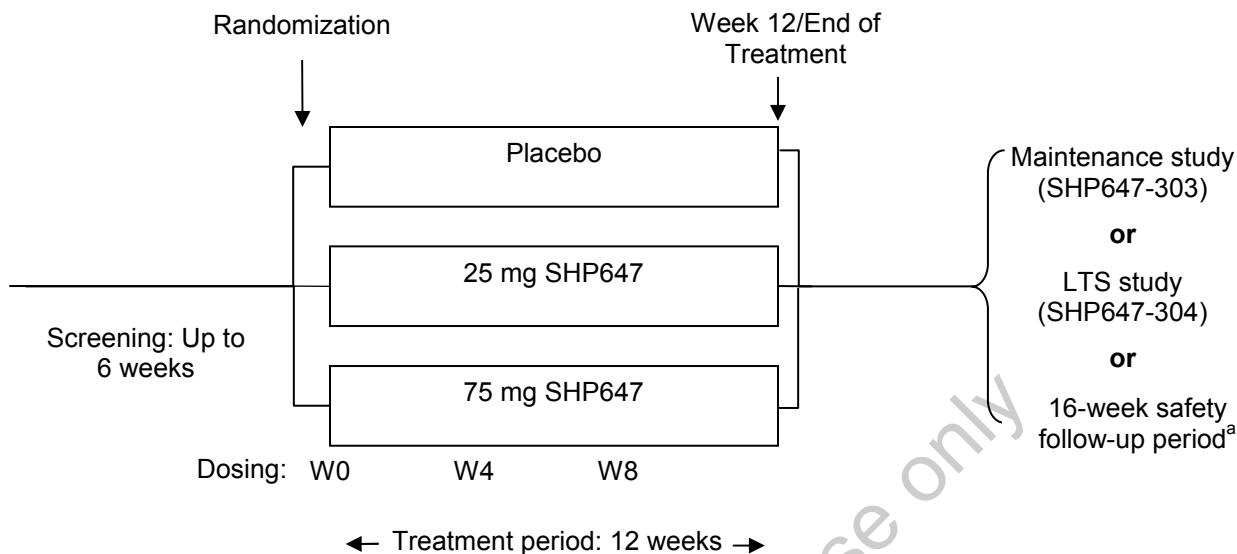
Figure 1: Overview of SHP647 Phase 3 Studies in Ulcerative Colitis



^a Clinical response is defined as:

1. A decrease from the induction study (SHP647-301 or SHP647-302) baseline in the composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 OR
2. A decrease from the induction study (SHP647-301 or SHP647-302) baseline total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 .

Figure 2: Study Design Flow Chart



LTS=long-term safety extension; W=week.

^a Subjects who withdraw early from the 12-week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period.

3.1.1 Rationale for Primary Endpoint

The Mayo score has historically been used as the primary endpoint for pivotal studies of agents intended to treat UC. Over the past decade, health authority thinking regarding efficacy endpoints for UC has evolved such that the traditional Mayo score is no longer recommended. Current regulatory guidance (FDA Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry [Draft], 2016; EMA Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis [Draft], 2016) includes a dual measurement of patient-reported signs and symptoms outcomes (stool frequency and rectal bleeding), and clinician-reported endoscopic outcomes (scoring any endoscopy with evidence of friability as a 2), including histology. Per agreement with health authorities, these 3 outcomes will be reported as a composite score.

Data will be collected to calculate the total Mayo score using both the traditional and modified endoscopy subscore as a sensitivity analysis and to estimate the impact of the modification on the primary endpoint. The clinical relevance of the traditional Mayo score is supported by its correlation with significant improvement in disease-specific HRQL as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) and in generic HRQL as measured by the Short Form-36 (SF-36) questionnaire.

3.1.2 Rationale for Key Secondary Endpoints:

The first 2 key secondary endpoints are included to comply with EMA advice. European Medicines Agency would agree to the composite primary endpoint only if supported by a key secondary analysis, where the patient-reported symptoms and clinician-reported endoscopy are analyzed as “co-primary”.

The clinical response endpoint is based on the new composite score, and also represents 1 of the entry criteria for the maintenance study. This endpoint has not been previously tested.

Mucosal healing as a key secondary endpoint comprises both endoscopic and histologic components as recommended in the draft FDA and EMA guidance on UC (FDA Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry [Draft], 2016; EMA Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis [Draft], 2016).

The Geboes Score (see [Appendix 2](#)) will be used to evaluate histologic remission and to complement the endoscopic subscore in the assessment of mucosal healing for the key secondary endpoint.

3.2 Duration and Study Completion Definition

Each subject's final visit in this study may be at the end of the treatment period (Week 12) if continuing to Study SHP647-303 or SHP647-304, or at the end of the safety follow-up period (Week 28) if not continuing to either of these studies. In either case, the final visit will be in person at the site. A subject's maximum duration of participation is expected to be approximately 34 weeks: a screening period of up to 6 weeks, a treatment period of 12 weeks, and a safety follow-up period of 16 weeks (if applicable). It is expected that the study will be completed in approximately 3 years.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

It is anticipated that the study will be conducted in at least 18 countries. Regions will include North America, Europe, the Middle East, and Africa, Latin America, and Asia-Pacific. Approximately 210 sites will be utilized.

4 STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed. Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must be between ≥ 16 and ≤ 80 years of age at the time of the signing of the informed consent/assent form.

NOTE: Subjects <18 years of age must weigh ≥ 40 kg and must have body mass index (BMI) ≥ 16.5 .

4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for ≥ 3 months before screening. The following must be available in each subject's source documentation:

- A biopsy report to confirm the histological diagnosis.
- A report documenting disease duration based upon prior colonoscopy.

NOTE: If this documentation is not available at the time of screening, a colonoscopy with biopsy to confirm the diagnosis is required during the screening period.

5. Subjects must be willing to undergo a flexible sigmoidoscopy or colonoscopy (if preferred), including biopsy sample collection, during screening after all other inclusion criteria have been met.
6. Subjects must have moderate to severe active UC, defined as a total Mayo score of ≥ 6 , including a centrally read endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 at baseline (Visit 2).
7. Subjects must have evidence of UC extending proximal to the rectum (ie, not limited to proctitis).
8. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as mesalamine (5-ASA), glucocorticoids, immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]), or anti-TNF (refer to [Appendix 4](#) for guidance).

9. Subjects receiving any treatment(s) for UC described in Section 5.2.1 are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
10. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception (as described in Section 4.4) for the duration of the study.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Subjects with indeterminate colitis, microscopic colitis, non-steroidal anti-inflammatory drug-induced colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of Crohn's disease.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for UC during the treatment period.
5. Subjects at risk for colorectal cancer must have a colonoscopy ([Eaden and Mayberry 2002](#)) performed during the screening period with results available within 10 days before the baseline visit (Visit 2), unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidence of dysplasia and colon cancer must be available in the source documents.

Subjects at risk for colorectal cancer include, but are not limited to:

- Subjects with extensive colitis for ≥ 8 years or disease limited to left side of colon (ie, distal to splenic flexure) for ≥ 10 years before screening, regardless of age.
 - Subjects ≥ 50 years of age at the time of signing of the informed consent form.
6. Subjects have had prior treatment with SHP647 (formerly PF-00547659).
 7. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
 8. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
 9. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).
 10. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than their current background UC treatment) within 30 days before baseline (Visit 2).

11. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
12. Subjects have received parenteral or rectal glucocorticoids, or rectal 5-ASA, within 14 days before screening endoscopic procedure.
13. Subjects have received leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange within 30 days before baseline (Visit 2).
14. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before baseline (Visit 2).
15. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).
16. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis [subjects with *C. difficile* infection at screening may be allowed re-test after treatment], evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
17. Subjects with abnormal chest x-ray findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation.)
18. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) or subjects with this history who have not completed a generally accepted full course of treatment before randomization are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed.

Subjects who have no history of previously diagnosed active or latent tuberculosis are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥ 5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before randomization. If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

- An IGRA is strongly recommended for subjects with a prior Bacillus Calmette-Guérin (BCG) vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON TB Gold Plus In-Tube Test.
- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent tuberculosis, a positive test on repeat will exclude the subject.

Subjects with a history of active or latent tuberculosis infection must follow instructions for “Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met” in this criterion.

- Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray, taken within the 3 months before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
 - A chest x-ray performed within 3 months prior to screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.
19. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
20. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on the targeted neurological assessment during the screening period (see Section 7.2.3.3).
21. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
22. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
- Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI (except disease under study), endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.

- Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
 - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening (Visit 1).
 - History of significant cerebrovascular disease within 24 weeks before screening (Visit 1).
23. Subjects who have had significant trauma or major surgery within 4 weeks before the screening visit (Visit 1), or with any major elective surgery scheduled to occur during the study.
24. Subjects with evidence of cirrhosis with or without decompensation.
25. Subjects with primary sclerosing cholangitis.
26. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). NOTE: if a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if no presence of HBV DNA is confirmed by HBV DNA PCR reflex testing performed in the central laboratory.
27. Subjects with chronic hepatitis C (HCV) (positive HCVAb and HCVRNA). Note: Subjects who are HCVAb positive without evidence of HCVRNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCVRNA at least 12 weeks prior to baseline]).
28. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening. NOTE: Screening laboratory tests, if the results are considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results must be reviewed for eligibility prior to the screening endoscopy procedure.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels $\geq 3.0 \times$ the upper limit of normal (ULN).
 - Total bilirubin level $\geq 1.5 \times$ ULN or $>2.0 \times$ ULN if the subject has a known documented history of Gilbert's syndrome.
 - Hemoglobin level ≤ 80 g/L (8.0 g/dL).
 - Platelet count $\leq 100 \times 10^9$ /L (100,000 cells/mm³) or $\geq 1000 \times 10^9$ /L (1,000,000 cells/mm³).*
 - White blood cell count $\leq 3.5 \times 10^9$ /L (3500 cells/mm³).
 - Absolute neutrophil count (ANC) $< 2 \times 10^9$ /L (2000 cells/mm³).
 - Serum creatinine level $> 1.5 \times$ ULN or estimated glomerular filtration rate < 30 mL/min/1.73m² based on the abbreviated Modification of Diet in Renal Disease Study Equation.

*Note: If platelet count is $< 150,000$ cells/mm³, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.

29. Subjects with known human immunodeficiency (HIV) infection based on documented history, with positive serological test, or positive HIV serologic test at screening, tested at the site's local laboratory in accordance with country requirements or tested at the central laboratory. Note: A documented negative HIV test within 6 months of screening is acceptable and does not need to be repeated.
30. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse or dependency of any kind, including abuse of medical marijuana (cannabis).
31. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
32. Female subjects who are planning to become pregnant during the study period.
33. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
34. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

4.3 Restrictions

- Smoking can have an influence on the severity of UC disease symptoms. Subjects should inform the investigator of any changes to their smoking habits during the study; however, these data will not be captured in the electronic case report form (eCRF). Use of nicotine patches should be recorded as concomitant medication (see Section 5.2).
- For the purposes of this protocol, dietary supplements (such as vitamins, minerals, purified food substances, and herbs with pharmaceutical properties) are considered to be concomitant medications (see Section 5.2).

4.4 Reproductive Potential

The potential effects of SHP647 on embryofetal or postnatal development have not yet been assessed in animals or humans; these will be assessed in future studies. To minimize the risk of unintentional exposure of the embryo or fetus in the clinical study, all sexually active male and female subjects who, in the opinion of the investigator, are biologically capable of having children and with their partners are at risk of pregnancy, must agree to use an appropriate form of contraception, in accordance with the package instructions/leaflet, for the duration of the active treatment period and for at least 16 weeks after the last dose of investigational product.

True abstinence is considered to be a highly effective contraception (ie, a method that results in a failure rate of <1% per year) when it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to investigational product, and withdrawal are not appropriate methods of contraception.

During the screening visit, the investigator or designee in consultation with the subject will confirm the subject's childbearing potential status. For subjects of childbearing potential, it must be confirmed and documented that the subject has selected the most appropriate method of contraception from the permitted list of contraception methods. Subjects must affirm the consistent and correct use of at least 1 of these selected methods. Regular contraception check discussions will take place at the time points specified in [Table 1](#) (ie, at each site visit) and will be documented. In addition, the subject must be instructed to call the site immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

4.4.1 Contraceptive Methods for Female Study Subjects

Sexually active females of childbearing potential must already be using an established highly effective form of contraception, and must be advised to use appropriate contraceptives throughout the study period and for 16 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert.

Female subjects should be in one of the following categories:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥51 years of age); postmenopausal status should be confirmed by follicle-stimulating hormone (FSH) testing.
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks poststerilization or has medically confirmed ovarian failure.
- Females of childbearing potential with a negative serum pregnancy test result at screening and a negative urine pregnancy test result at baseline (Visit 2). Females of childbearing potential must agree to practice true abstinence (refrain from sexual activity that could result in pregnancy) or agree to use appropriate methods of highly effective contraception.

Highly effective contraception (ie, methods that result in a failure rate of <1% per year when used consistently and correctly) are:

- Combined (estrogen- and progestogen-containing) hormonal contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal) stabilized for at least 30 days before the screening visit (Visit 1)
- Progestogen-only hormonal contraception associated with inhibition of ovulation plus a barrier method
- Intrauterine device

- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization/vasectomized partner with documented absence of sperm in the postvasectomy ejaculate
- True abstinence (see Section 4.4).

4.4.2 Contraceptive Methods for Male Study Subjects

Contraception is required for all sexually active male subjects, who with their female sexual partners, must agree to use 1 of the following appropriate methods of contraception throughout the study period and for 16 weeks following the last dose of investigational product.

Appropriate methods of contraception for male subjects are:

- Male condom with spermicide; however, if spermicide is not available in the country, additional contraception (ie, one of those listed below) must be used in addition to a male condom
- Male sterilization with documented absence of sperm in the postvasectomy ejaculate.

Appropriate methods for female sexual partners of male subjects are (unless the female sexual partner is sterile [surgically or documented nonsurgical sterility]):

- Use of a highly effective method of contraception listed in Section 4.4.1 OR an acceptable method of contraception (failure rate of >1% per year):
 - Female condom with spermicide (use by female sexual partner); however, if spermicide is not available in the country, additional contraception (ie, one of those listed below) must be used in addition to a female condom
 - Intrauterine device with spermicide
 - Contraceptive sponge with spermicide
 - Intravaginal system (eg, vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide).

4.5 Withdrawal of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 12/ET (Visit 6) are to be performed. All subjects who discontinue treatment with investigational product should also undergo the protocol-specified 16-week safety follow-up period. In the event that subjects are unable to attend in person for the follow-up visits, all efforts should be made to collect information on AEs and concomitant medications.

Comments (spontaneous or elicited) or complaints made by the subject must be recorded. The reason for termination and date of stopping investigational product must be recorded.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

Additional reasons a subject may be withdrawn from study treatment include but are not limited to:

- AEs
- Serious adverse events (SAEs)
- Pregnancy
- Protocol violations
- Failure to return for visits.

A subject should be withdrawn from study treatment:

- If a new therapy is initiated for UC, or
- If a subject undergoes surgery for UC.

Subjects who withdraw from study treatment due to an increase in disease symptoms may see nonstudy-related physicians for treatment, which may include treatments prohibited during the treatment periods of this study.

If a subject withdraws their consent, no further evaluation should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

4.5.2 Reasons for Withdrawal

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Other (if "Other" is selected, the investigator must specify the reason)
- Death

- Physician decision
- Pregnancy
- Screen failure
- Site terminated by sponsor.

4.5.3 Subjects “Lost to Follow-up” Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point before the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and that they return their electronic diary.

5 PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal remedies and vitamins) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the first dose of investigational product. Use of biologics for indications other than UC during the 90 days before screening must also be recorded.

Prior and concomitant UC-specific treatments from the previous 10 years will be recorded. The subject's entire history of biologic UC-specific treatments will be recorded.

Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or 5-ASA, glucocorticoids, immunosuppressants (AZA, 6-MP, or MTX), or anti-TNF agents. Please refer to [Appendix 4](#) for guidance on defining prior treatment failure and intolerance to prior treatment for UC.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the safety follow-up period, inclusive.

5.2.1 Permitted Treatment

Subjects must remain on stable doses of permitted UC treatments until completion of the Week 12 visit, unless decreases are required because of AEs. Stable doses of the following treatments for UC are permitted as concomitant medication:

- Oral 5-ASA or sulfasalazine, providing that the dose is stable for at least 2 weeks before baseline (Visit 2)
- Immunosuppressants (AZA, 6-MP, or MTX), providing that the dose is stable for at least 8 weeks before baseline (Visit 2).
- Oral glucocorticoids (prednisone or equivalent [see [Appendix 3](#)]) up to a maximum of 20 mg/day or budesonide up to a maximum of 9 mg/day), providing that the dose is stable for at least 2 weeks before screening endoscopic procedure.

NOTE: Rectal 5-ASA and parenteral or rectal glucocorticoids are prohibited from within 14 days before screening endoscopic procedure.

Subjects using medicinal marijuana (cannabis) under a physician's prescription, and who obtain the product from a licensed pharmacy or provider, should continue to use it under the same regimen for the duration of the study, unless otherwise instructed by the investigator or treating physician. Such subjects must be using the product, in a stable regimen, for at least 3 months before screening.

Routine nonlive vaccinations are allowed during the study.

Dietary and herbal supplements and probiotics are allowed in the study, provided they are being taken at stable doses at the time of the baseline visit (Visit 2) and for the duration of the study. They should be recorded as concomitant medications.

Use of nicotine patches should be recorded as concomitant medication.

5.2.2 Prohibited Treatment

Table 2 details the minimum required number of days before baseline (Visit 2) for common prior treatments that are excluded medications for this study.

Table 2: Common Excluded Treatments

Treatment	Permanently Excluded	Minimum Required Number of Days Before Baseline (Visit 2)			
		14	30	60	90
SHP647 (PF-00547659) in a previous study	X				
Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab)	X				
Parenteral and rectal glucocorticoids		X ^a			
Rectal 5-ASA		X ^a			
Investigational products			X ^b		
Live (attenuated) vaccine			X		
Nonbiologics with immunomodulatory properties (other than their current background UC treatment)			X		
Anti-TNF treatment				X	
Leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange			X		
Biologics with immunomodulatory properties (other than anti-TNFs) including biosimilars					X

5-ASA=5-aminosalicylate; TNF=tumor necrosis factor.

^a The minimum required number of days before baseline (Visit 2) for rectal 5-ASA and parenteral or rectal glucocorticoids is defined as 14 days before screening endoscopic procedure (see Section 4.2, exclusion criterion 11).

^b Or 5 half-lives if longer.

Treatments not listed in Table 2 may be considered allowable; see Section 5.2.1 for further details.

No new nonpharmacological therapies that might affect bowel habit or GI function should be started during the study.

5.2.3 Rescue Therapy

Subjects must maintain their stable dose of background UC treatment, unless dose reduction or discontinuation is required due to associated AEs. If a subject requires initiation of a new therapy or increase in glucocorticoids for UC above the SHP647-301 or SHP647-302 baseline, the subject should be withdrawn from study treatment and enter the safety follow-up period, and appropriate treatment should be given at the discretion of the investigator.

Subjects who enter the safety follow-up period will no longer need to abstain from the medications that were prohibited during the baseline and treatment periods. High-dose glucocorticoids and other UC treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated during the safety follow-up period without prior discussion with the sponsor study physician or designee due to the long half-life of SHP647.

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6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is SHP647, which will be provided as a sterile aqueous buffered solution for SC administration in a glass PFS with a fixed needle. Each PFS contains 1 mL of SHP647 solution for injection at an appropriate concentration to provide the intended dose of drug (25 or 75 mg). Additional information is provided in the current SHP647 investigator's brochure.

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain SHP647.

6.1.1 Blinding the Treatment Assignment

The placebo syringes and solution will match the SHP647 syringes in appearance. The fill volume for all syringes will be the same.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive response technology (IRT) system will be used for screening and enrolling subjects, recording subject visits, randomization, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and emergency unblinding. Please refer to the Study Manual for additional details regarding the IRT system.

6.2.2 Allocation of Subjects to Treatment

This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule.

The total Mayo score will be calculated at baseline (Visit 2) before randomization. Endoscopic subscore based on the central reader's assessment will be used to determine eligibility. Subjects with a total Mayo score of ≥ 6 , including a centrally read endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 , and who fulfill all other eligibility criteria, will be randomized in a ratio of 2:2:1 via a computer-generated randomization schedule to receive SC injections of 25 mg SHP647, 75 mg SHP647, or placebo, respectively. The randomization will be performed centrally and stratified by status of prior anti-TNF therapy (2 strata: naïve versus experienced) and glucocorticoid use at baseline (2 strata: on glucocorticoids at baseline versus not on glucocorticoids at baseline).

To ensure that the allocation of subjects with prior anti-TNF therapy exposure is similar to that observed in Study A7281009, the percentage of subjects with prior anti-TNF therapy exposure will be capped at 60% of the sample population. Additionally, in Japan only, enrollment of Japanese subjects with prior anti-TNF therapy exposure will be capped at 60%, to ensure comparability to the rest of the global study population. There will be no cap on the number of anti-TNF naïve subjects randomized.

Subject numbers are assigned to all eligible subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number will be assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. Individual subject treatment will be automatically assigned by the IRT system.

Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

6.2.3 Dosing

Investigational product (SHP647 or placebo) will be administered subcutaneously by qualified site personnel Q4W (Weeks 0, 4, and 8). See Section [7.2](#) for the timing of dosing relative to other procedures.

Investigational product should be administered in the anterolateral right or left thigh. If there are clinical reasons why the investigational product cannot be administered in the thigh, the investigational product may be administered in the deltoid area or abdomen with appropriate documentation. The location of the investigational product administration will be recorded.

After the first administration of investigational product, the subject must be observed by a member of the study staff for at least 30 minutes (the total duration should be determined at the discretion of the investigator). For subsequent administrations, observation of the subject is at the discretion of the investigator. Injection site and allergic reaction monitoring should be completed by a member of the study staff.

Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is dispensed by qualified staff members.

6.2.4 Unblinding the Treatment Assignment

Whenever possible, the investigator or subinvestigator should contact the Shire physician and/or assigned medical monitor before breaking the blind. It is understood that in an emergency situation it may not be possible to communicate with the study team before breaking the blind. The safety of the subject should be of primary concern. When the blinding code is broken the reasons must be fully documented.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded on the IRT and the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. The IRT will notify the relevant personnel in the event of any code break. Code-break information is held by the pharmacist/designated person at the site.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

The sponsor will provide the investigator with packaged investigational product labeled in accordance with specific country regulatory requirements. All investigational product is labeled with a minimum of the following: protocol number, medication identification number, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements “For clinical trial use only” and/or “CAUTION: New Drug – Limited by Federal (or US) Law to Investigational Use”, and the sponsor’s name and address.

Additional labels may be applied in order to meet local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name.

Additional labels may not be added without the sponsor’s prior written agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled containers: PFS with nominal fill volume of 1 mL. The PFS will be packaged in a labeled carton.

Changes to sponsor-supplied packaging before dosing may not occur without prior written agreement by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or delegated member of the study team. The pharmacist or delegated team member will enter the unique subject identifier on the investigational product labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range.

The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

The investigational product should be protected from light and should not be frozen. Do not shake.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented in the subject's source document and/or other investigational product record.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

With the written agreement of the sponsor, at the end of the study all unused stock may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational products must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, cartons) or at the individual count level for opened containers/packaging. The pharmacist or delegated team member will record details on the drug accountability form.

7 STUDY PROCEDURES

7.1 Study Schedule

The investigator may schedule visits (unscheduled visits) in addition to those listed on the schedule of activities ([Table 1](#)) in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

7.1.1 Screening Period

7.1.1.1 Screening Visit (Visit 1)

Subjects will be screened within 6 weeks before the baseline visit (Visit 2) to determine eligibility to participate in the study and to perform the other assessments and procedures specified in [Table 1](#). Each subject or subject's parent or legally authorized representative must participate in the informed consent process and provide written informed consent/assent before any assessments or procedures specified in the protocol are performed. Screening assessments may take place over more than 1 day (at least 2 visits will be necessary to complete the screening procedures, including endoscopy).

A screen failure is a subject who has given informed consent or assent, as applicable (and whose parents or legally authorized representatives have given informed consent, as applicable), failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria, and has not been randomized or administered investigational product.

A subject may be rescreened if their condition has changed and they may potentially be eligible. Subjects may be rescreened 1 time. NOTE: Screening laboratory tests, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results of repeated tests must be reviewed for eligibility prior to the screening endoscopy procedure.

Flexible sigmoidoscopy or colonoscopy (if preferred) must be performed on all subjects after the majority of other eligibility criteria (eg, laboratory values) are met. Endoscopy must be performed during the screening period within 10 days before baseline (Visit 2), preferably within 5 to 7 days before the baseline visit, to obtain the centrally read endoscopic subscore (see [Section 7.2.2.1](#)). Biopsy samples will be collected for histological evaluation using the Geboes Score classification and [REDACTED]. Subjects at risk of colorectal cancer, as defined in exclusion criterion 5 (see [Section 4.2](#)), must have a colonoscopy performed at screening, unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no presence of dysplasia and colon cancer must be available in the source documents.

If a subject has had the following procedures performed as a part of standard medical care within 12 weeks before screening (Visit 1), these procedures do not need to be repeated as a part of screening:

- Chest x-ray
- Documented negative PPD test or IGRA for TB.

7.1.1.2 Baseline Visit (Visit 2; Week 0)

The baseline visit will take place on Day 1 (Week 0). The assessments and procedures specified in [Table 1](#) will be performed.

After eligibility has been reconfirmed and all baseline procedures and assessments have been completed, each subject will be randomized to 1 of the 3 treatment groups as described in Section [6.2.2](#) and the first dose of investigational product will be administered.

Results of the baseline laboratory tests are not required for investigational product administration but must be reviewed as soon as possible thereafter.

7.1.2 Treatment Period

7.1.2.1 Visit 3 (Week 2)

Visit 3 is scheduled to take place on Day 14 ± 3 days (Week 2). The assessments and procedures specified in [Table 1](#) will be performed.

7.1.2.2 Visits 4 and 5 (Weeks 4 and 8)

Visits 4 and 5 are scheduled to take place on Day 28 ± 3 days (Week 4) and Day 56 ± 3 days (Week 8), respectively. The assessments and procedures specified in [Table 1](#) will be performed.

7.1.2.3 Final On-treatment Visits: Visit 6, Parts 1 and 2 (Week 12/Early Termination)

The Week 12/ET visit (Visit 6) consists of 2 parts.

Part 1 of Visit 6 should be scheduled preferably within 5 to 7 days before Part 2; this will allow sufficient time for data from the centrally read endoscopy to be available at Part 2 of the visit. The Week 12/ET assessments and procedures that will take place during Part 1 are specified in [Table 1](#).

Part 2 of Visit 6 will take place on Day 84 ± 3 days. The Week 12/ET assessments and procedures that will take place during Part 2 are specified in [Table 1](#).

At Part 2 of Visit 6, after review of the Mayo score, health outcome assessments, and safety assessments, it will be determined whether the subject should enter the safety follow-up period of this study or enroll in the maintenance (SHP647-303) or LTS (SHP647-304) studies. Entry into the maintenance or LTS studies is dependent upon the subject's response and whether the subject agrees to participate.

The Week 12 assessments and procedures will also form the ET assessments for any subjects who are withdrawn early or discontinued from the study.

7.1.3 Follow-up Period: Visits 7 and 8 (Weeks 20 and 28)

Subjects who are withdrawn early from the study, or who do not enter either the maintenance or LTS studies, should enter the 16-week safety follow-up phase for safety monitoring.

During the safety follow-up period, the Week 20 visit (Visit 7) will take place on Day 140 ±7 days or 8 weeks ±7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study. This visit will routinely be conducted by telephone; however, as an exception the visit can be performed as a study site visit if preferred.

At the end of the safety follow-up period, there will be a visit at the site on Day 196 ±7 days, or 16 weeks ±7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study, which will form the Week 28 visit (Visit 8). The assessments and procedures specified in [Table 1](#) will be performed, including querying for SAEs, AEs, and concomitant medications and procedures. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section [8.1](#)).

Subjects who are proceeding to the maintenance or LTS studies will not enter the safety follow-up period.

7.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator, which may make it unfeasible to perform the tests and procedures. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject.

When timing of procedures and assessments coincide, the following order should be followed:

- Health outcome and patient-reported questionnaires
- Vital signs and ECG
- Laboratory sample collection
- Endoscopy (generally performed at a separate visit; see Section [7.2.2.1](#)).
- Investigational product administration

Note: Blood and tissue samples may be stored for up to the duration allowed by local regulations, but for no longer than 25 years.

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics will be recorded at the screening visit (Visit 1).

Each subject's stool frequency before symptoms of UC started or during remission will be recorded at the screening visit. The reference/normal stool frequency questions in [Appendix 2](#) will be asked and the responses documented.

7.2.2 Efficacy

The primary efficacy endpoint is remission at the Week 12 visit. Remission is defined as a composite score of patient-reported symptoms using daily electronic diary (e-diary) and centrally read endoscopy as described in Section 9.8.1.

7.2.2.1 Endoscopy and Histology

Endoscopy will be performed at the time points specified in [Table 1](#) and will consist of either flexible sigmoidoscopy or colonoscopy (if preferred).

If it is necessary, bowel preparation should be conducted as per local routine. The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during endoscopy at baseline. The endoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's medical record.

During endoscopy, 2 biopsy samples will be collected from the most inflamed area of the sigmoid colon at screening and Week 12/ET. Endoscopy and biopsy procedures will be defined in an endoscopy instructions manual and/or reference card(s), on which all sites will be trained. Endoscopy results will be reviewed by a central reader.

Biopsy samples will be centrally reviewed using the Geboes Score classification system and [REDACTED] (see [Appendix 2](#)) for the evaluation of histological disease severity in UC with higher numbers corresponding to more inflammation. The Geboes score will be used for the key secondary efficacy evaluation and [REDACTED].

Subjects at risk for colorectal cancer (see exclusion criterion number 5) must have a colonoscopy performed during the screening period with results available within 10 days before the baseline visit (Visit 2), unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidence of dysplasia and colon cancer must be available in the source documents.

7.2.2.2 Mayo Score

The Mayo score is a measure of UC disease activity. Mayo scores (total or partial) will be recorded at the time points specified in [Table 1](#).

The total 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 2](#)):

- Stool frequency (0-3)
- Rectal bleeding (0-3)
- Findings of endoscopy (0-3)
- Physician global assessment (PGA, 0-3).

The partial Mayo score consists of the Mayo score without the endoscopic subscores and ranges from 0 to 9 points.

The composite score is a recommended measure consisting of the Mayo score without the PGA subscore and ranges from 0 to 9 points. The composite score will be used for the primary efficacy endpoint.

Calculation of the total and partial Mayo scores and composite score requires a self-assessment by the subject for stool frequency and the amount of blood in the stool. These data on stool frequency and rectal bleeding will be captured in the PRO-UC daily e-diary (see Section 7.2.2.3).

The Mayo stool frequency and rectal bleeding subscores will be calculated based on each subject's daily e-diary data recorded over the most recent 3 days (consecutive or nonconsecutive) of the last 10 days prior to the visit excluding the following days: day of any bowel preparation, day of endoscopy, any days between day of bowel preparation and day of endoscopy, and the 2 days after the day of endoscopy.

The mucosal appearance during the sigmoidoscopic portion of the endoscopic examination will be assessed for the Mayo endoscopic subscore based on the scoring system provided in the protocol (see Appendix 2). The endoscopic appearance will be read by a central reader through video recorded during the procedure. Centrally read endoscopic subscores will be used for both eligibility and efficacy analyses.

The PGA 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). The endoscopic subscore and the PGA must be performed by a physician qualified to perform endoscopy, and it is recommended that the same physician performs all such assessments for a particular subject throughout the study.

7.2.2.3 Patient-reported Outcome – Ulcerative Colitis E-Diary

Patient-reported UC signs and symptom data will be collected using a daily e-diary starting during the screening period. Collection of the daily e-diary data must begin at least 10 days before the baseline visit (Visit 2). Subjects will enter data on UC signs and symptoms items using an electronic handheld device that will be provided to subjects at the start of the study. Compliance is assessed by site staff at each visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <23 out of 28 e-diary entries) when compared with the previous visit.

Subjects will be asked to record the following signs and symptom data, as experienced over the previous 24 hours, in the e-diary:

- Stool frequency
- Rectal bleeding severity and frequency
- Diarrhea frequency
- Urgency frequency
- Abdominal pain worst severity.

The full PRO-UC e-diary consists of 6 items. The first 2 items (stool frequency and rectal bleeding severity) will be used to determine the Mayo stool frequency and rectal bleeding subscores, which will be used to calculate the total and partial Mayo scores and the composite score. The PRO-UC e-diary is presented in [Appendix 2](#).

7.2.3 Safety

7.2.3.1 Medical and Medication History

Medical history will be documented at screening (Visit 1), including UC history, cardiac history, and smoking history. Prior and concomitant medications and procedures will also be documented.

7.2.3.2 Physical Examination (Including Height and Weight)

Complete and targeted physical examinations will be performed at the time points specified in [Table 1](#). Complete physical examination includes the review of the following body systems: general appearance, skin, HEENT, heart, lungs, confrontational visual fields (eyes), breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes. Targeted physical examination includes the review of the following body systems: skin, heart, lungs, confrontational visual fields (eyes), abdomen, and examination of body systems where there are symptom complaints by the subject.

Weight will be measured at the time points specified in [Table 1](#). Height will be measured at screening (Visit 1) only.

Changes after the screening visit that are deemed clinically significant in the opinion of the investigator will be recorded as an AE.

7.2.3.3 Targeted Neurological Assessment

Targeted neurological assessments to monitor the development of signs and/or symptoms of PML will be performed at the time points specified in [Table 1](#). Subjects will be evaluated to reveal any potential abnormalities in the following neurological domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior.

If any abnormalities are indicated, subjects will be further evaluated to help clarify any potential abnormal responses. Focus will be placed on possible alternative etiology (eg, fracture or stroke). If additional evaluation reveals an unexplained new abnormality, neurologic examination(s), targeted to the abnormal domain, will be performed by an investigator or qualified personnel.

Subjects with any unexplained positive neurological assessment item at screening should be excluded from enrollment in the study (exclusion criterion 18, Section [4.2](#)).

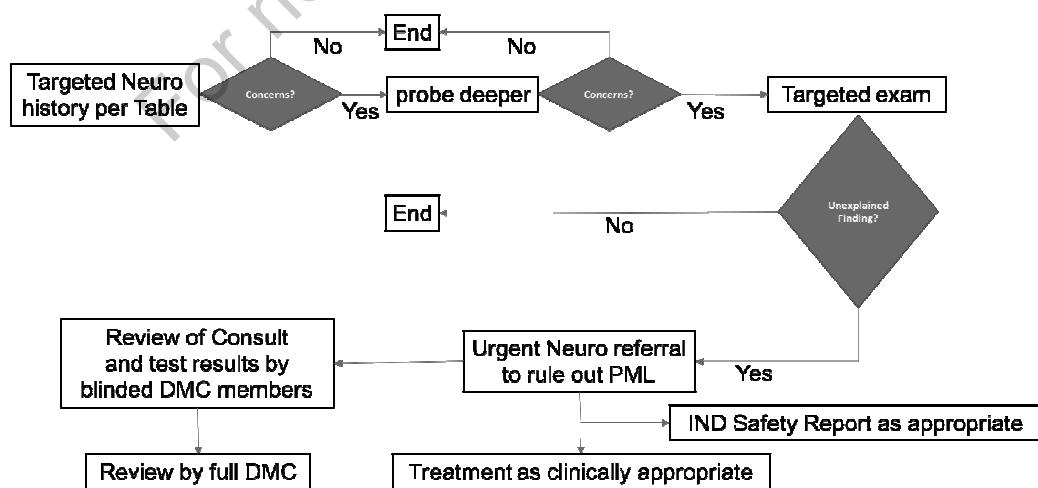
A step-wise approach for the proposed neurological assessment plan is provided in [Table 3](#).

Table 3: Quarterly Neurological Assessments

Domain	Step 1: Targeted Neurologic History	Step 2: If Abnormal Response
Vision	Diplopia or visual/visual field loss	Perform visual field assessment
Motor	Major motor weakness (eg, legs, arms)	Test leg strength (hopping, foot tapping), finger tapping, pronator drift and bilateral muscle strength
Tactile sensation	Paresthesia, anesthesia in any domain (peripheral, central)	Pinprick test
Coordination/Cerebellar	Clumsiness, difficulty with walking, writing, or fine motor skills, etc.	Finger-nose, heel-shin, heel-toe walk, writing sample, draw a clock
Speech	Dysarthria, expressive aphasia	Naming objects, repeat multipart phrase, observe for dysarthria or aphasia
Verbal comprehension	Agnosia, receptive aphasia	Test to follow routine commands, eg, close eyes, touch finger to ear.
Cognition/Behavior	New onset of difficulties with memory or thinking, important changes in behavior	Recall 3 objects over 1 minute, serial 7 s, proverbs. Changes in activities of daily living over prior 6 months

Additionally, should there be any unexplained abnormal neurological findings, the subject is to be urgently referred to a neurologist. The sites will immediately inform the sponsor of any such occurrences. If the neurologist confirms the presence of PML, appropriate actions, including discontinuation of investigational product, will be taken. Suspected PML cases will be reviewed promptly by Data Monitoring Committee (DMC) members with PML expertise and presented at the next scheduled DMC meeting(s). If PML is diagnosed, the treatment code will be unblinded and there will be an urgent meeting of the DMC. A flow diagram of the quarterly assessments and actions is presented in [Figure 3](#). Any concerns from the DMC will be promptly communicated to the sponsor, investigator, and treating neurologist.

Figure 3: Flow Diagram for Quarterly Neurological Assessments



DMC=Data Monitoring Committee; IND=investigational new drug; neuro=neurological; PML=progressive multifocal leukoencephalopathy.

It is important to note that assessments based on neurological evaluations are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and data from neurological assessment collected from subjects. Investigators may determine if any finding on neurological testing constitutes an AE. Adverse event incidence rates will not be calculated from these neurological evaluation data but rather from the AE information recorded by the investigator.

7.2.3.4 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, “Have you had any health problems since your last visit?”). Adverse events are collected from the time informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3. (See Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.3.5 Vital Signs

Vital signs will be measured at the time points specified in Table 1. Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data. Vital signs include blood pressure, pulse, respiratory rate, and temperature. Vital signs should be recorded before laboratory blood collection and endoscopic procedures are performed.

Single measurements of sitting blood pressure will be recorded at each time point. Blood pressure should be determined by cuff with the subject’s arm supported at the level of the heart and recorded to the nearest mm Hg using the same method, the same arm (preferably the dominant arm), and the same position throughout the study.

Respiratory rate will be measured with the subject in a comfortable position. The observer should hold the extremity of the subject as a distraction for the subject (ie, pretending he/she is taking the subject’s radial pulse) and count the respiration for 1 minute.

Body temperature should be taken using a thermometer and reported in degrees Celsius or Fahrenheit.

Any deviations from baseline (Visit 2) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE, unless documented in the subject’s medical history as a pre-existing medical condition.

7.2.3.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the central laboratory’s normal procedures. Reference ranges are to be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant.

Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Screening laboratory tests, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. The following clinical laboratory assessments will be performed at the time points specified in [Table 1](#):

Serum chemistry

alkaline phosphatase	blood urea nitrogen
aspartate aminotransferase	creatinine
alanine aminotransferase	sodium
total bilirubin	potassium
total protein	chloride
albumin	calcium
glucose	carbon dioxide

Hematology

hemoglobin	neutrophils
hematocrit	lymphocytes
mean corpuscular hemoglobin	monocytes
mean corpuscular hemoglobin concentration	eosinophils
mean corpuscular volume	basophils
erythrocyte (red blood cell) count	platelet count
leukocyte (white blood cell) count	

Virology

hepatitis B surface antigen (HBsAg)	hepatitis C virus antibody (HCV Ab)
hepatitis B core antibody (HBcAb)	HCV ribonucleic acid (RNA) polymerase chain reaction (PCR) if HCV Ab is positive
hepatitis B DNA if HBsAg is negative and HBcAb is positive	HIV

Urinalysis

glucose	bilirubin
protein	ketones
specific gravity	hemoglobin
pH	urobilinogen
nitrite	leukocyte esterase

Virology test results must be confirmed as negative before enrollment in the study; if a virology test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor, but will not be collected in the CRF database.

Stool microbiology will be performed at the screening visit (Visit 1). Diagnosis of *C. difficile* infection should be made using the central laboratory. If, for any reason, the central laboratory is not available, please refer to [Appendix 5](#) for guidance regarding diagnostic algorithms.

A tuberculosis (TB) test (purified protein derivative [PPD] or QuantiFERON TB Gold Plus) will be performed at the screening visit (Visit 1). A documented negative PPD test within 12 weeks before baseline (Visit 2) is acceptable. The IGRA official reading and method or test must be located in the source documentation.

A serum sample will be collected and banked for John Cunningham virus antibody testing. It may be analyzed if a subject shows neurologic symptoms suggestive of PML.

All laboratory assessments should be performed at central laboratories, with the exception of the following assessments: stool microbiology (local or central laboratory) and TB test (PPD or QuantiFERON TB Gold Plus) (refer to laboratory manual for details).

7.2.3.7 Pregnancy Test and Follicle-stimulating Hormone Test

A beta-human chorionic gonadotropin (β -HCG) pregnancy test will be performed on all females of childbearing potential at the time points specified in [Table 1](#); if pregnancy is suspected; or on withdrawal of the subject from the study. A serum pregnancy test will be performed at the screening visit (Visit 1); all other pregnancy tests will be urine tests.

Pregnancy tests are not required for females of nonchildbearing potential who have undergone hysterectomy or bilateral oophorectomy, have medically confirmed ovarian failure, or are medically confirmed postmenopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; postmenopausal status should be confirmed by FSH testing in females who have had 12 consecutive months of spontaneous amenorrhea and are 51 years of age or older).

7.2.3.8 Electrocardiogram

A 12-lead ECG will be recorded at the time points specified in [Table 1](#). When timing of measurements coincide, ECGs should be performed before laboratory blood collection and endoscopic procedure.

A central ECG reader will be used in this study. The eligibility of the subject is based on the assessment of the ECG by the investigator. If abnormal results are observed following assessment by the central reader, the investigator, in consultation with the appointed sponsor or contract research organization (CRO) medical monitor, reconfirms subject eligibility to continue.

7.2.3.9 Chest X-ray

A chest x-ray will be performed during screening (Visit 1). If a subject has had a chest x-ray performed as a part of standard medical care within 12 weeks before screening (Visit 1), it does not need to be repeated as a part of screening. The official reading must be located in the subject's source documentation.

7.2.3.10 Antidrug Antibodies

A blood sample for measurement of antidrug antibodies (ADA) and Nab will be collected at the time points specified in [Table 1](#). Blood samples must be collected before administration of investigational product.

7.2.4 Others

Term	Percentage (%)
Smartphone	95
Cloud computing	92
Big data	88
Machine learning	85
Blockchain	82
Artificial intelligence	78
Robotics	75
Quantum computing	72
Cloud robotics	20

7.2.4.3 Health-related Quality of Life Assessments

Each subject will complete the HRQL assessments at the site during the visits specified in **Table 1**, using an electronic device. All health outcome and patient-reported questionnaires should be completed before any other assessments. The study site staff should check for completion of all PRO questionnaires.

It is important to note that patient-reported outcome (PRO) assessments are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and PRO data collected from subjects. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded by the investigator.

Inflammatory Bowel Disease Questionnaire

The IBDQ is a psychometrically validated PRO instrument for measuring the disease-specific HRQL in subjects with inflammatory bowel disease, including UC. The IBDQ consists of 32 items, which are grouped into 4 dimensions: bowel function, emotional status, systemic symptoms, and social function ([Irvine et al. 1994](#)). 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 HRQL. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement.

The IBDQ is presented in [Appendix 2](#).



Short Form-36 Health Survey, Acute Form

The SF-36 is a generic quality-of-life instrument that has been widely used to assess HRQL of subjects. Generic instruments are used in general populations to assess a wide range of domains applicable to a variety of health states, conditions, and diseases. The SF-36 consists of 36 items that are aggregated into 8 multi-item scales (physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional, and mental health), with scores ranging from 0 to 100 ([Ware and Sherbourne 1992](#)). Higher scores indicate better HRQL.

7.2.4.4 Healthcare Resource Utilization Assessments

Hospitalizations, inpatient days, and [REDACTED] will be recorded at the time points specified in [Table 1](#). Ulcerative colitis-related and other surgeries will be collected from subjects during the treatment period.

7.2.5 Volume of Blood to Be Drawn from Each Subject

Table 4: Volume of Blood to Be Drawn from Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Hematology	2	6	12
Serum chemistry	4	6	24
HBsAg	2	1	2
HBcAb	2	1	2
HCV Ab	2	1	2
HBV DNA	6	1	6
HIV	2	1	2
FSH	2	1	2
Serum β-hCG ^a	2	1	2
TB test (QuantiFERON TB Gold Plus or PPD)	4	1	4
JCV antibody banked sample	3.5	1	3.5

Table 4: Volume of Blood to Be Drawn from Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
[REDACTED]			
[REDACTED]	2	3	6
[REDACTED]	5	3	15
[REDACTED]	4	3	12
[REDACTED]	3	5	15
ADA and NAb sampling	3	6	18
Total mL			127.5

Ab=antibody; ADA=antidrug antibodies; β -hCG=beta-human chorionic gonadotropin; [REDACTED]; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HBV DNA=hepatitis B virus deoxyribonucleic acid; HCV=hepatitis C virus; HIV=human immunodeficiency virus; JCV=John Cunningham virus; [REDACTED]; Nab=neutralizing antibody; PPD=purified protein derivative; TB=tuberculosis.

^a β -hCG testing for female subjects only.

^b If a catheter is used, the first mL is to be discarded; then take 4 mL into appropriate tube for [REDACTED]. A total of 5 mL of blood drawn has been used in determination of sample volume.

The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 127.5 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured in the subject's source document. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the subject's source document.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia before dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded in the subject's source document).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as “not related.” Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.” The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study in the eCRF. Outcomes are as follows:

- Fatal
- Not recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown.

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value.

When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section [7.1.3](#).

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the [emergency contact information](#) section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire “Clinical Study Serious Adverse Event and Non-serious AE as Required by the Protocol Form.” Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire “Clinical Study Serious Adverse Event and Non-serious AE as Required by the Protocol Form” as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine beta human chorionic gonadotropin (β -hCG) test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section [8.2](#). Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional administration of investigational product at a dose interval that is less than 2 weeks between doses
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

There is no specific antidote for overdose with SHP647. Treatment should be symptomatic and supportive.

8.1.8 Unexpected Adverse Event

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the reference safety information (RSI).

“Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

8.1.9 Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is Section 6.8 of the SHP647 investigator's brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire "Clinical Study Serious Adverse Event and Non-serious AE as Required by the Protocol Form" and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or email the form to the Shire Global Drug Safety Department. A copy of the Shire "Clinical Study Serious Adverse Event and Non-serious AE as Required by the Protocol Form" (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the **emergency contact information** section of the protocol.

8.2.3 Serious Adverse Event Definition

A **serious adverse event (SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).

- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an ED or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject’s death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject’s death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject’s death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as “dose not changed” or “not applicable” (if the subject never received investigational product). The investigational product action of “withdrawn” should not be selected solely as a result of the subject’s death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor or the CRO is responsible for notifying the relevant regulatory authorities, US central Institutional Review Boards (IRBs), and European Union (EU) central Ethics Committees (ECs) of related, unexpected SAEs (ie, SUSARs).

In addition the CRO is responsible for notifying active sites of all related, unexpected SAEs (ie, SUSARs) occurring during all interventional studies across the SHP647 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.2.8 Safety Monitoring for Potential Cases of Drug-induced Liver Injury

The following safety monitoring and stopping criteria are provided for elevated hepatic blood tests based on normal and elevated baseline ALT and total bilirubin levels.

Abnormal values in ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities per [Table 5](#) should be evaluated further to definitively determine the etiology of the abnormal laboratory values. The measurement(s) should be reconfirmed with another blood draw preferably within 48 to 72 hours of the initial finding of potential concern. Please refer to lab manual for further instructions.

Guidance for Dosing Interruption: Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

Table 5: Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
Normal baseline ALT \geq 5x ULN Elevated baseline^a: ALT \geq 3x baseline <i>or</i> \geq 300 U/L (whichever occurs first)	Normal <u>Patients with Gilbert's syndrome or hemolysis:</u> No change in baseline TBL	None	Repeat ALT, AST, ALP, TBL, in 2-5 days. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation. ^c
Normal baseline ALT \geq 8x ULN Elevated baseline^a: ALT \geq 5x baseline or \geq 500 U/L (whichever occurs first)	Normal <u>Patients with Gilbert's syndrome or hemolysis:</u> No change in baseline TBL	None	Interrupt study drug. ^b Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation. ^c
Normal baseline ALT \geq 3x ULN Elevated baseline^a: ALT \geq 2x baseline or \geq 300 U/L (whichever occurs first)	TBL \geq 2mg/dL increased over baseline <i>or</i> <u>Patients with Gilbert's syndrome or hemolysis:</u> Doubling of baseline direct bilirubin	None	Interrupt study drug. ^b Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation. ^c

Table 5: Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
Normal baseline ALT \geq 5x ULN Elevated baseline^a: ALT \geq 2x baseline or \geq 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain or Immunologic symptoms Rash Eosinophilia > 5%	Interrupt study drug. ^b Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation. ^c

ALT=alanine aminotransferase; AST=aspartate aminotransferase; TBL=total bilirubin, ALP=alkaline phosphatase; ULN=upper limit of normal.

^a Elevated baseline ALT defined as ALT \geq 1.5 \times ULN

^b Confirmatory repeat liver-related blood tests should be performed within 2-3 days before the investigational product (IP) is interrupted.

^c If HBV DNA positive, antivirals would need to be started ASAP.

Source: Adapted from [Chalasani and Regev 2016](#).

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol in the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered in the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, antibodies to investigational product, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, before unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed. The SAP will be finalized before unblinding to preserve the integrity of the statistical analysis and study conclusions.

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC, USA).

Unless otherwise specified, summary tabulations will be presented by treatment group. All data listings will be sorted by treatment group, site, and subject number, and will include the subject's age, sex, and race.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis or adaptive design in this study.

An external DMC will be established to review the overall safety of the study subjects on an ongoing basis.

The DMC will be responsible for the ongoing monitoring of safety of subjects enrolled in the study according to the DMC charter. Recommendations made by the DMC to alter the conduct of the study or to amend the protocol will be forwarded to Shire for review and for a final decision. Shire or its designee will notify investigative sites and regulatory authorities as appropriate, of DMC recommendations (which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints).

Further details regarding the DMC can be found in the DMC charter, which will be available before the administration of investigational product to any subject. Analyses of the data for DMC review will be conducted according to the DMC charter and DMC SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not applicable.

9.6 Sample Size Calculation and Power Considerations

Graphical methods are used to control the global family-wise type I error rate (FWER) at the .05 level (2-sided) for the comparisons of the 2 SHP647 treatment groups with the placebo group. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the primary endpoint. Therefore, the power analysis and sample size estimation was calculated based on the chi-square test of proportions using nQuery Advisor Version 7.0 (Statistical Solutions Ltd, Cork, Ireland) for an individual SHP647 dose compared with placebo.

Power calculations are made based on assuming a .025 (2-sided) significance level for each pairwise treatment comparison. Approximately 1375 subjects will be screened to randomize 825 subjects (2:2:1 allocation ratio: 330 subjects in the 25 mg SHP647 treatment group, 330 subjects in the 75 mg SHP647 treatment group, and 165 subjects in the placebo group) which would yield an approximately 93% power to detect individual pairwise treatment difference in the primary efficacy endpoint, remission at Week 12, of 11% (5% placebo versus 16% SHP647). Expected remission rates at Week 12 are based on observed rates from the A7281009 study and placebo remission rates from literature ([Feagan et al. 2013](#); [Sandborn et al. 2017](#)).

No adjustment for missing data is required in these sample size calculations as subjects with missing data for remission at Week 12 are imputed as failures and the above rates account for these subjects.

With the sample size of 825, [Table 6](#) provides the power for detecting a treatment difference between a SHP647 treatment group and the placebo group for the key secondary endpoints.

Table 6: Power to Detect the Corresponding Treatment Effect for Key Secondary Endpoints

Key Secondary Endpoint at Week 12	SHP647 Premise	Placebo Premise	Power
Endoscopic remission	24%	8%	0.99
Clinical remission	30%	16%	0.89
Clinical response by composite score	50%	35%	0.82
Mucosal healing	15%	5%	0.88

9.7 Study Population

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

The full analysis set (FAS) will consist of all subjects in the randomized set who have received at least 1 dose of investigational product.

The per-protocol (PP) set will consist of all subjects in the FAS who do not have predefined protocol deviations that may affect the primary efficacy endpoint.

The completer set will consist of all subjects in the FAS who have completed the final scheduled primary assessment for this study.



9.8 Efficacy Analyses

Unless otherwise specified, all efficacy analyses will be based on the FAS and subjects will be analyzed according to their randomized treatment, regardless of the treatment they actually received.

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is remission at the Week 12 visit. Remission is defined as a composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy as follows:

- stool frequency subscore of 0 or 1 with at least a 1-point change from baseline

AND

- rectal bleeding subscore of 0

AND

- endoscopic subscore of 0 or 1 (modified, excludes friability).

The primary efficacy endpoint will be compared for each active treatment group (25 mg or 75 mg SHP647) to the placebo group using a Cochran-Mantel Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment and glucocorticoid use at baseline (Visit 2). Subjects with missing remission data at the Week 12 visit will be considered failures and counted as nonresponders. The endoscopy score will be based on centrally read results.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata, $j=1$ to m . The common treatment difference is a weighted average of the stratum-specific treatment differences.

The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% confidence interval (CI) using the method of Yan and Su (2010) and CMH p-value will be presented for each active treatment group to placebo comparison.

Sensitivity analyses which explore the impact of missing data on the primary efficacy endpoint will be conducted. These analyses may compare imputations of the missing values which favor placebo (eg, worst case) and/or imputations which favor active treatment (eg, best case). In addition, imputation methods based on informative missingness and other missing data mechanisms may be performed. Additional sensitivity analyses will also be conducted using the per-protocol set and the completer set. Additional analyses may be developed in the SAP. All sensitivity analyses will be described in the SAP.

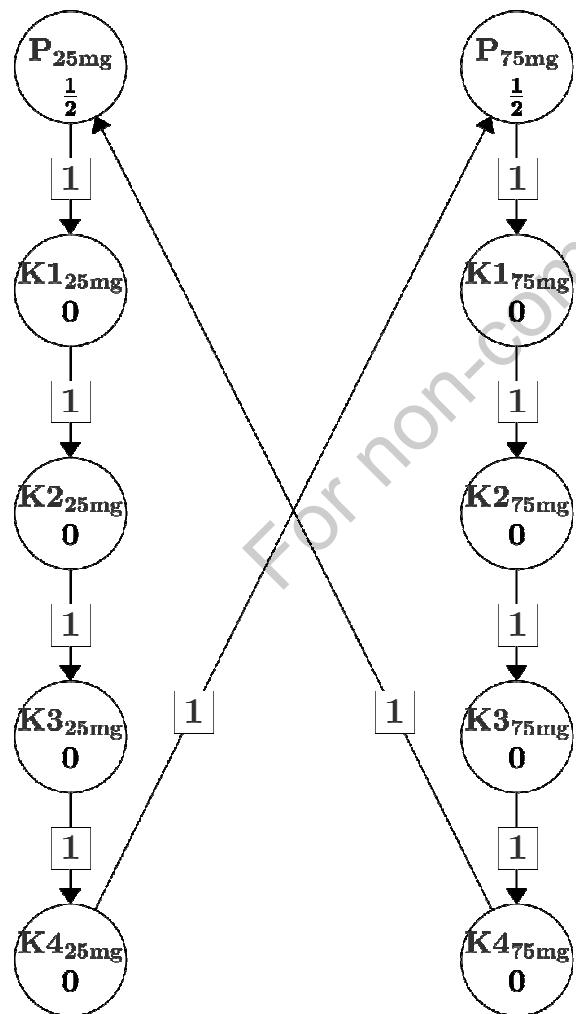
Prespecified subgroup analyses are planned for the primary endpoint including, but not limited to gender, prior anti-TNF treatment, glucocorticoid use at baseline, region, age group, randomization stratum, and other important subgroups. A full list of important subgroups will be described within the SAP. Within subgroups, efficacy endpoints will be compared for each active treatment group (25 mg SHP647 and 75 mg SHP647) with the placebo group using a Chi-square test.

Subjects with missing remission data at the Week 12 visit will be considered failures and counted as nonresponders. The endoscopy subscore will be based on centrally read results. The estimate of the treatment difference, along with the corresponding Newcombe (hybrid-score) 95% CI and Chi-square test p-value, will be presented.

Adjustments for Multiplicity

The global FWER for the statistical tests of the primary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al (2009) will be utilized to propagate α from primary to key secondary endpoints and between the two SHP647 treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the primary endpoint (P) and alpha is propagated in a hierarchical manner to each of the 4 key secondary endpoints (K1-K4) within a pairwise treatment comparison. A graphical visualization of the α propagation is presented in [Figure 4](#).

Figure 4: Visualization of Alpha Propagation



Only p-values that are significant according to this graphical approach are inferential and statistically significant. All other p-values are descriptive.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoints are as follows:

- Endoscopic remission, as defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability), at the Week 12 visit.
- Clinical remission, as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at the Week 12 visit.
- Clinical response based on composite score at the Week 12 visit. Clinical response (composite) is defined as a decrease from baseline in the composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 .
- Mucosal healing based on endoscopic and histological assessment at the Week 12 visit. Mucosal healing is defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability) and centrally read Geboes score of ≤ 2 .

Similar to the primary endpoint, the 4 key secondary endpoints will all be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

The key secondary endpoints will be analyzed using the same approach as described for the primary efficacy endpoint. Subjects with missing key secondary endpoint data at the Week 12 visit will be considered failures and counted as nonresponders.

In addition, the sensitivity analyses and prespecified subgroup analyses described for the primary endpoint will be repeated for the key secondary endpoints.

9.8.2.2 Other Secondary Efficacy Endpoints

The other secondary endpoints are as follows:

- Remission, defined as a total Mayo score ≤ 2 with no individual subscore (stool frequency, rectal bleeding, endoscopy [modified, excludes friability], and physician's global assessment) exceeding 1, at the Week 12 visit.
- Clinical response based on total Mayo score at the Week 12 visit. Clinical response (Mayo) is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 .

- Partial Mayo score ≤ 2 with no individual subscore > 1 at the Week 4, 8, and 12 visits. The partial Mayo score does not include the endoscopy subscore.
- Clinical remission as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at Weeks 4 and 8.
- Endoscopic remission at the Week 12 visit with endoscopic subscore of 0.
- Clinical remission at the Week 4, 8, and 12 visits with both rectal bleeding and stool frequency subscores of 0.
- Deep remission at the Week 12 visit. Deep remission is defined as both endoscopic and rectal bleeding subscores of 0, and stool frequency subscore ≤ 1 and a centrally read Geboes score of ≤ 2 .
- Change from baseline at the Week 12 visit in abdominal pain, urgency and diarrhea item scores, absolute stool frequency, absolute rectal bleeding and total sign/symptom score based on subject daily e-diary entries (sum of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency).
- Change from baseline in IBDQ domain and total (absolute) scores (time frame: Week 0, Week 8, up to Week 12, or early termination).
- Change from baseline in SF-36, version 2, acute (physical and mental component summary scores and individual domain scores) to the Week 12/ET visit.
- Incidence of all-cause hospitalizations and total inpatient days.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods.

Binary endpoints will be analyzed using the same approach as described for the primary endpoint. Subjects with missing binary endpoint data at a visit will be considered failures and counted as nonresponders.

Continuous endpoints that are only measured at baseline and the Week 12 visit will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences will be provided.

Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation (REML). The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

Full details of the analysis of other secondary efficacy endpoints will be included in the SAP.

9.8.3 Exploratory Efficacy Endpoints

The exploratory endpoints are as follows:



Exploratory efficacy endpoints will be summarized with descriptive statistics and presented by treatment group. Exploratory efficacy endpoints will be analyzed using the same approach described as for the other secondary endpoints. See Section 9.8.2.2 for an overview of the planned analyses. Full details for the analysis of exploratory efficacy endpoints will be included in the SAP.

9.9 Safety Analyses

All safety analyses will be performed using the safety set. Subjects will be analyzed according to the treatment they actually received.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities.

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Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by SOC, by preferred term, and by treatment group.

Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, serious AEs, and deaths will be similarly summarized or listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

Antidrug antibody data will be summarized by treatment group and visit.

Further details of safety analyses will be described in the SAP.

9.10 Other Analyses

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10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before and during the study (including annual safety reporting, ie, Development Safety Update Reports). The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place before the start of the study. An insurance certificate is supplied to the CRO and investigator as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will upload the clinical study report to the EudraCT database and will also provide a summary of the clinical study report to the CRO for submission to the competent authority of the countries concerned as required by local regulatory requirement(s). This requirement will be fulfilled within 1 year for nonpediatric studies as per guidance. The ECs will be provided with a copy of the same summary as locally required.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site before commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's or subject's legally authorized representative's consent and/or assent, as applicable, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any coinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor or designee. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded in eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic CRFs must be completed by the investigator or designee as stated in the site delegation log.

All data in the eCRF will have a separate source (eg, paper or ePRO); no data will be recorded directly in the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject e-diary, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The clinical research associate/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, x-rays etc). Nonstudy site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and/or assent from all study subjects before any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities.

A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor before the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) before study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved before site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Before implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor or designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP647; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish before release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days before submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12 APPENDICES

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APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Protocol Amendment 1	05 Sep 2018	Global
Original Protocol	06 Jul 2017	Global

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APPENDIX 2 SCALES AND ASSESSMENTS

The following scales/assessments will be used in the study and are provided in this appendix:

- Stool frequency screening questions
- Mayo scoring system
- Geboes score grading system
- [REDACTED]
- PRO-UC diary
- IBDQ
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- SF-36
- [REDACTED]

For questionnaires, language-specific validated versions will be used only.

Stool Frequency Screening Questions

1. Think back to before you ever had symptoms of UC. How many bowel movements did you typically have in a 24-hour period before ever having symptoms of UC?

Number of bowel movements in a 24-hour period before ever having symptoms of UC:

2. Remission of ulcerative colitis (UC) is defined as a time when your symptoms have gone away, you're feeling well, and/or your UC is no longer impacting your regular daily activities. Have you ever experienced a remission of UC?

- Yes
- No

If YES,

When you are in remission how many bowel movements do you typically have in a 24-hour period? Remember that remission is a time when your symptoms have gone away, you're feeling well, and/or your UC is no longer impacting you regular daily activities.

Number of bowel movements in a 24-hour period when in remission:

Mayo Scoring System for Assessment of Ulcerative Colitis Activity

Stool frequency^a

- 0 = Normal number of stools for this subject
1 = 1 to 2 stools more than normal
2 = 3 to 4 stools more than normal
3 = 5 or more stools more than normal
Subscore, 0 to 3

Rectal bleeding^b

- 0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood (more than just streaks) or streaks of blood with stool most of the time
3 = Blood alone passes
Subscore, 0 to 3

Findings on endoscopy^c

- 0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern)
2 = Moderate disease (marked erythema, lack of vascular pattern, any friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Subscore, 0 to 3

Physician's global assessment^d:

- 0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Subscore, 0 to 3

The total 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 Findings on endoscopy scoring represents the modified endoscopy subscore (value of 1 does not include friability).

NOTE: Data will be collected to calculate the total Mayo score using both the modified endoscopy subscore and traditional endoscopy subscore (value of 1 including mild friability) as a sensitivity analysis and to estimate the impact of the modification on the primary endpoint.

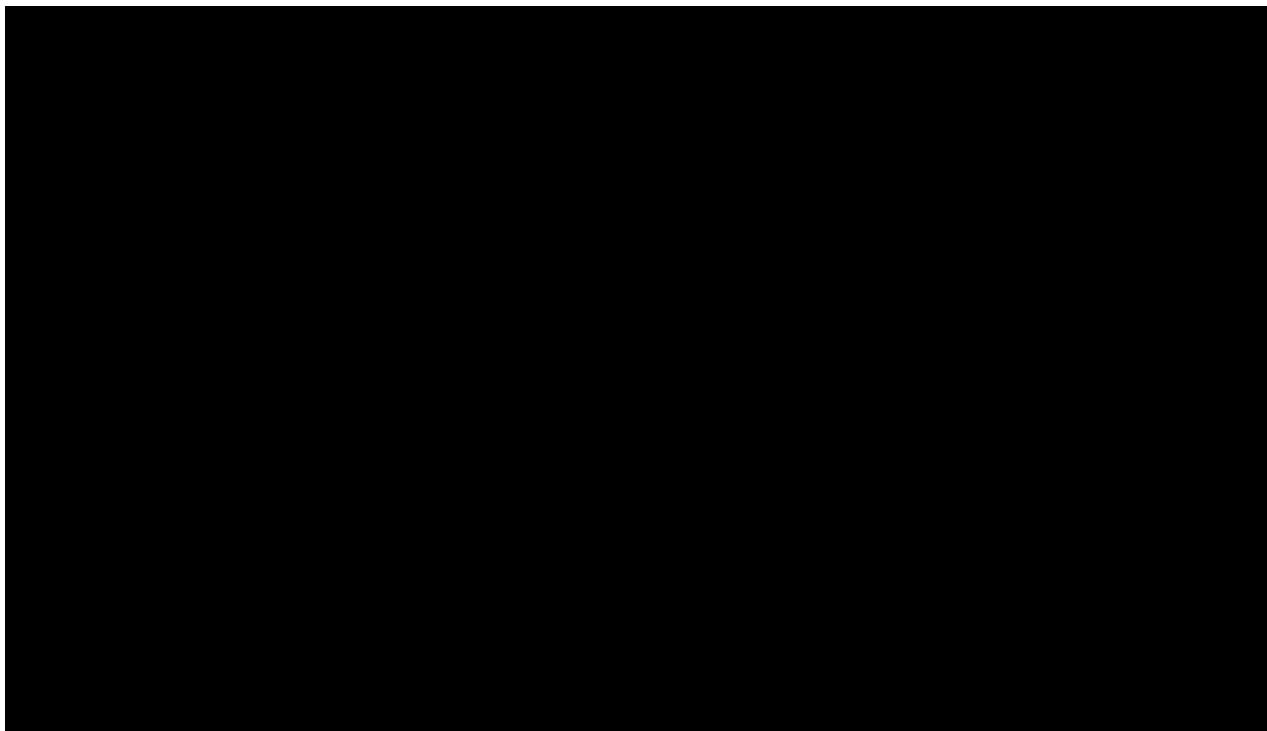
^d The physician's global assessment acknowledges the three other criteria, the subject's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status.

Source: [Schroeder et al. 1987](#)

Geboes Score Grading System

Grade 0 – Structural (architectural change)	
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1 – Chronic inflammatory infiltrate	
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2A – Lamina propria eosinophils	
Subgrades	
2A.0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
Grade 2B – Lamina propria neutrophils	
Subgrades	
2B.0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3 – Neutrophils in epithelium	
Subgrades	
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4 – Crypt destruction	
Subgrades	
4.0	None
4.1	Probable – local excess of neutrophils in part of crypt
4.2	Probable – marked attenuation
4.3	Unequivocal crypt destruction
Grade 5 – Erosion or ulceration	
Subgrades	
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

Source: [Geboes et al. 2000](#)



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Patient-reported Outcomes – Ulcerative Colitis (PRO-UC) Diary Version 1

Item #	Item
1.	<p>Please indicate how often you had a bowel movement over the past 24 hours. A bowel movement is defined as a trip to the toilet and passing stool (liquid, soft, or solid), passing blood only, passing blood and mucus, or passing mucus only.</p> <p>Enter number of bowel movements passed:</p>
2.	<p>Please rate your worst experience of rectal bleeding over the past 24 hours.</p> <ul style="list-style-type: none">• No blood seen• Streaks of blood with stool less than half of the time• Obvious blood (more than just streaks) or streaks of blood with stool most of the time• Blood alone passes
3.	<p>You indicated you had X bowel movements in the past 24 hours. Of these, how many had blood, either in the stool, in the toilet bowl, or on the toilet paper?</p> <p>Enter the number of bowel movements with blood:</p>
4.	<p>You indicated you had X bowel movements in the past 24 hours. Of these, how many were loose or watery?</p> <p>Enter number of loose or watery bowel movements:</p>
5.	<p>You indicated you had X bowel movements in the past 24 hours. How many of those involved urgency (having to suddenly rush to the toilet to make it on time)?</p> <p>Enter number of bowel movements with urgency:</p>
6.	<p>Please rate your worst abdominal pain over the past 24 hours.</p> <ul style="list-style-type: none">• 0-10 numeric rating scale, with 0 anchor at “No pain” and 10 at “Worst Imaginable Pain”

Inflammatory Bowel Disease Questionnaire (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks.

You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from:
 1. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
 2. EXTREMELY FREQUENT
 3. VERY FREQUENT
 4. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 5. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 6. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 7. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from:
 1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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

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

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

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

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

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

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

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

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

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

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

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

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:
1. A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
 2. A LOT OF DIFFICULTY
 3. A FAIR BIT OF DIFFICULTY
 4. SOME DIFFICULTY
 5. A LITTLE DIFFICULTY
 6. HARDLY ANY DIFFICULTY
 7. NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES
13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from:

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

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

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

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

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

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

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

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

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

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

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

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

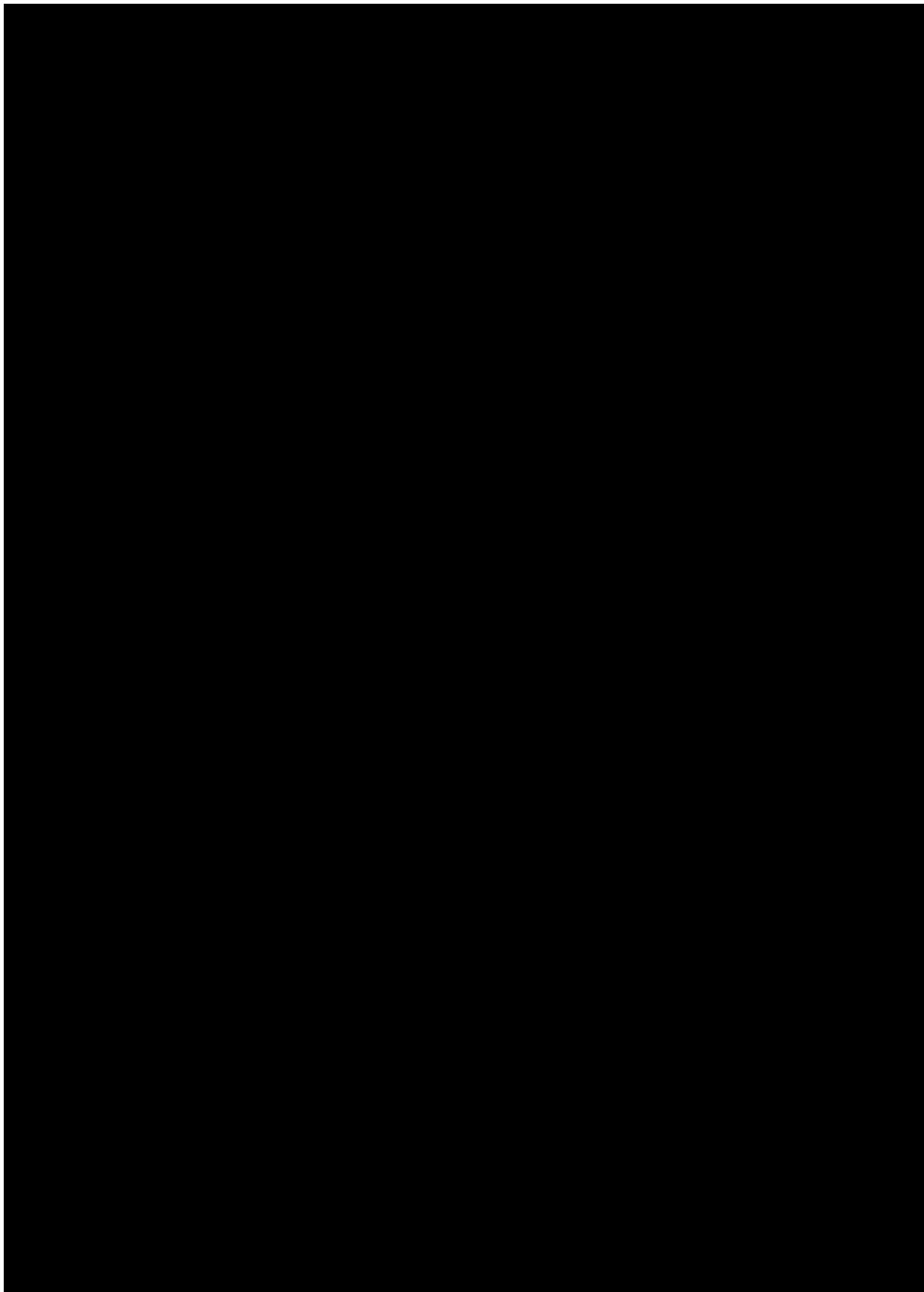
1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

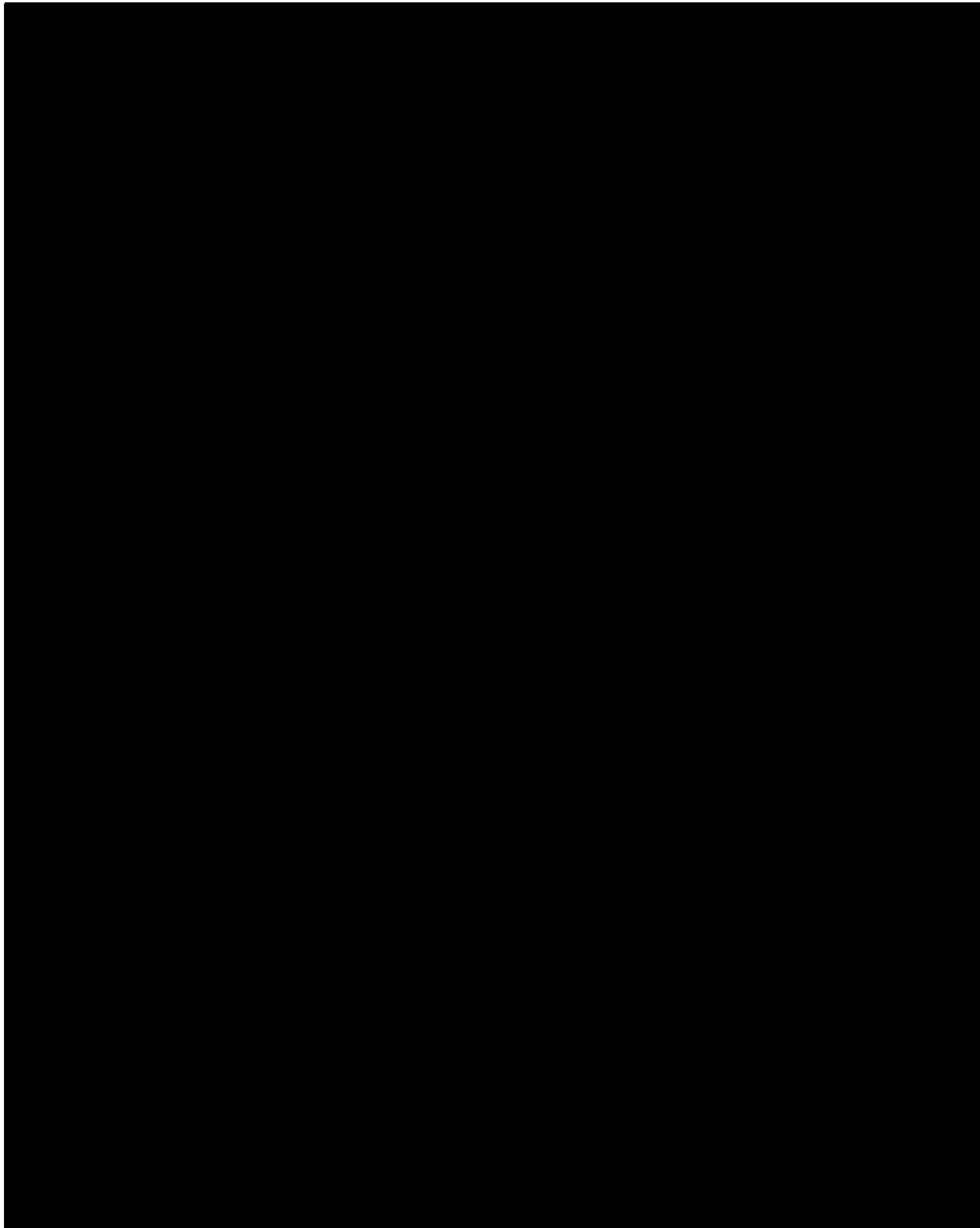
31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from:

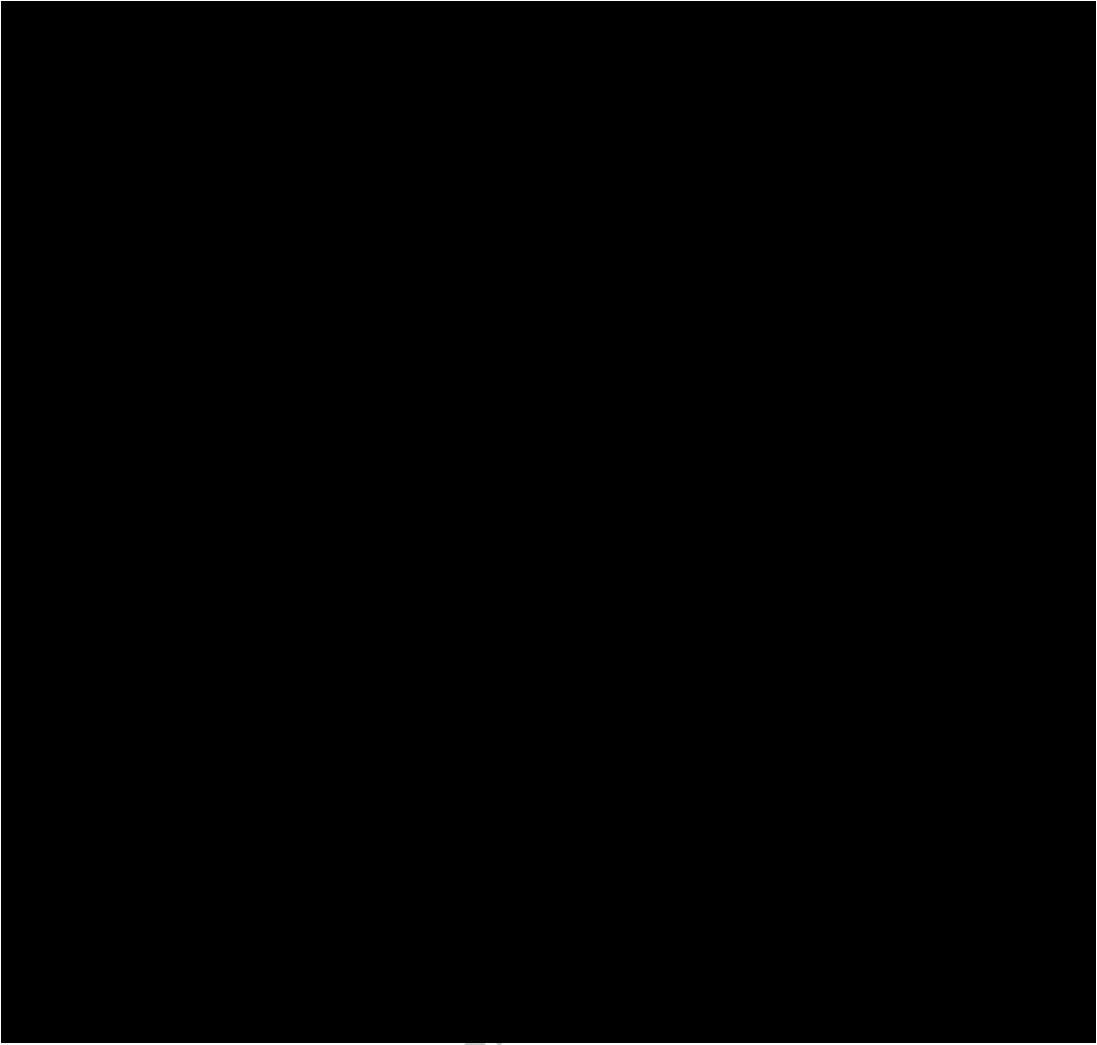
1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

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

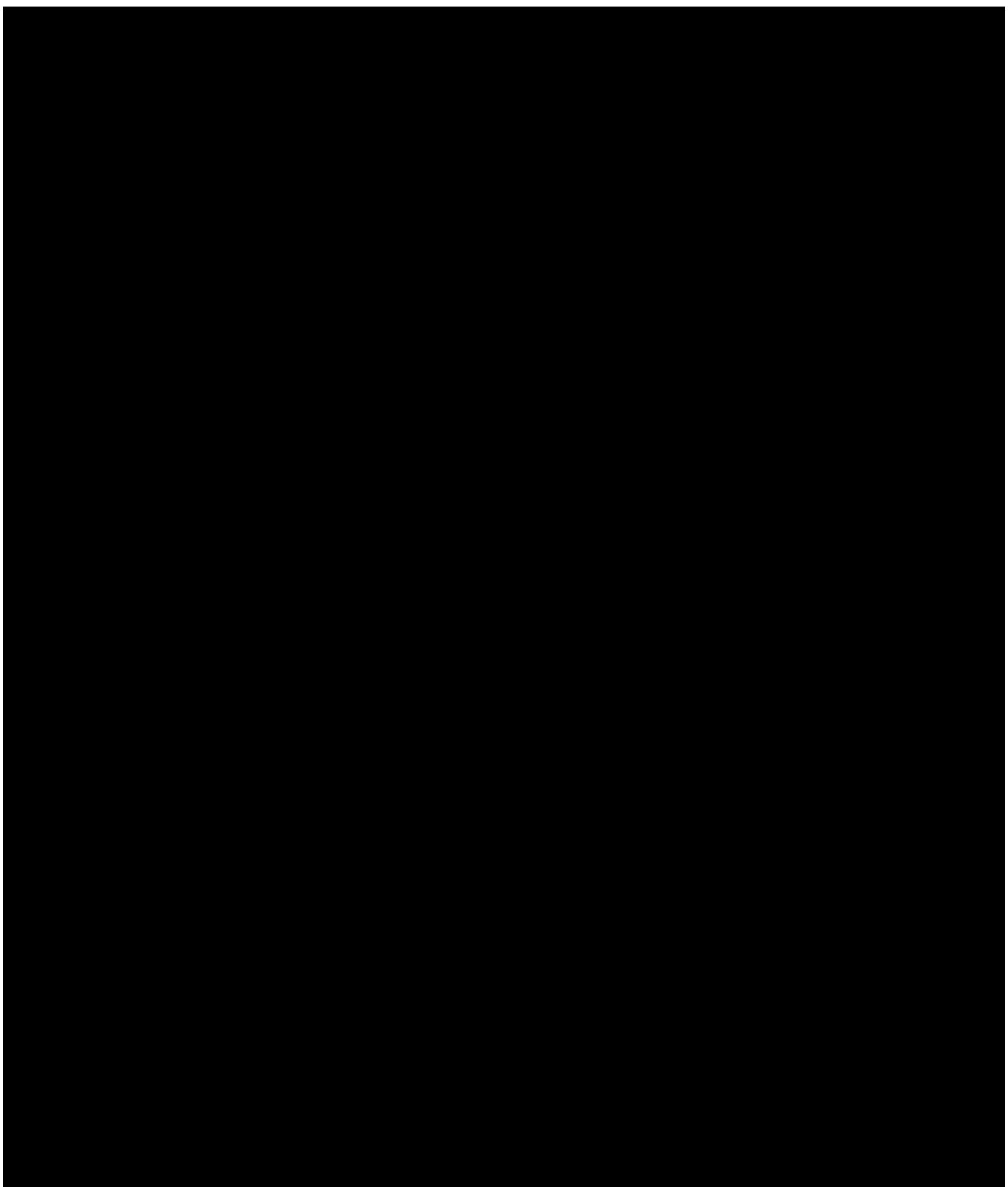
1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2. GENERALLY DISSATISFIED, UNHAPPY
3. SOMEWHAT DISSATISFIED, UNHAPPY
4. GENERALLY SATISFIED, PLEASED
5. SATISFIED MOST OF THE TIME, HAPPY
6. VERY SATISFIED MOST OF THE TIME, HAPPY
7. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

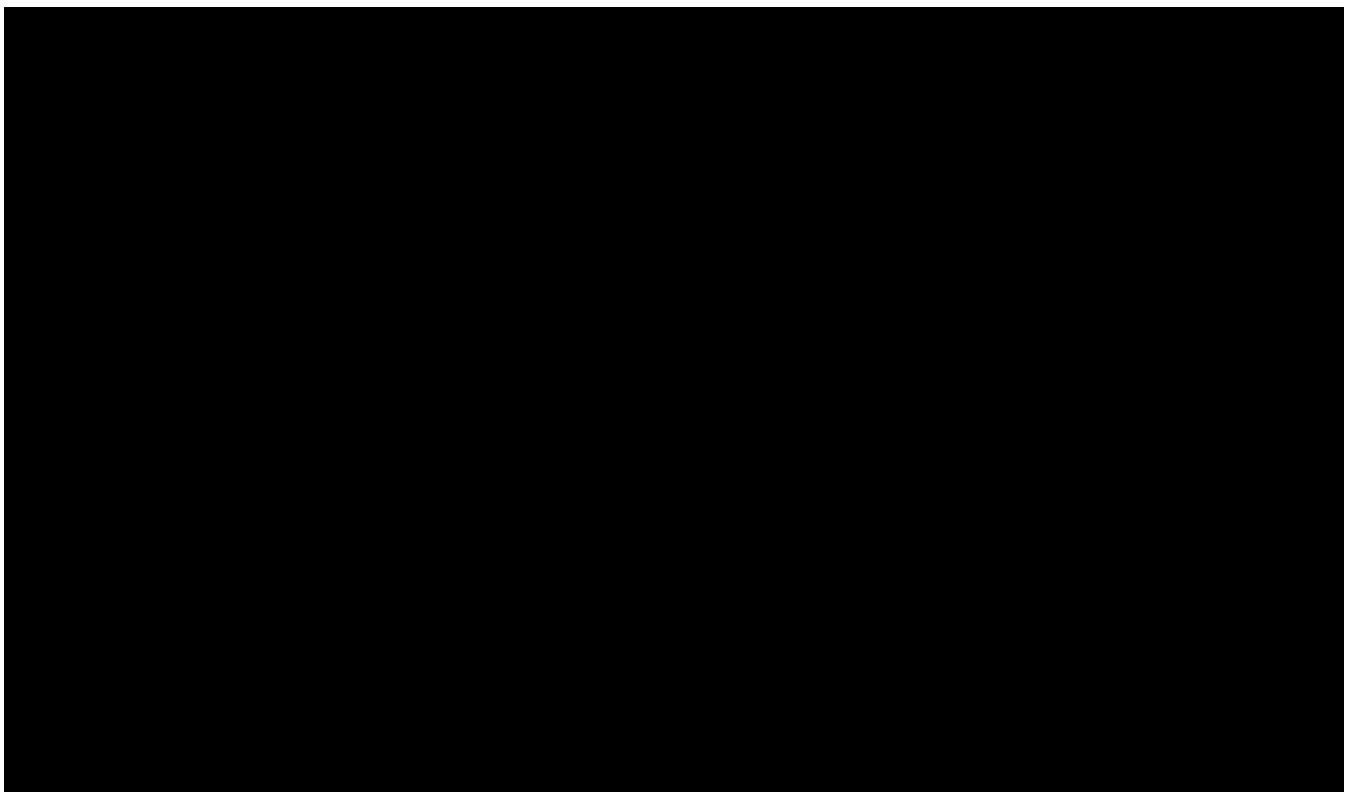






For non





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Short Form-36 Health Survey, Acute Form

For non-commercial use only

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an in the one box that best describes your answer.

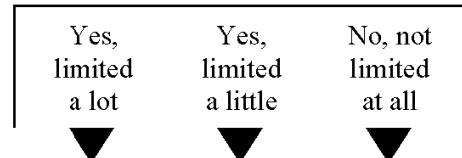
1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?



- a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports 1 2 3
- b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf 1 2 3
- c. Lifting or carrying groceries 1 2 3
- d. Climbing several flights of stairs 1 2 3
- e. Climbing one flight of stairs 1 2 3
- f. Bending, kneeling, or stooping 1 2 3
- g. Walking more than a mile 1 2 3
- h. Walking several hundred yards 1 2 3
- i. Walking one hundred yards 1 2 3
- j. Bathing or dressing yourself 1 2 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

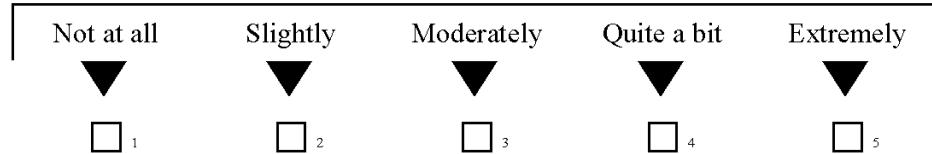
- a Cut down on the amount of time you spent on work or other activities 1..... 2..... 3..... 4..... 5
- b Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c Were limited in the kind of work or other activities 1..... 2..... 3..... 4..... 5
- d Had difficulty performing the work or other activities (for example, it took extra effort) 1..... 2..... 3..... 4..... 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

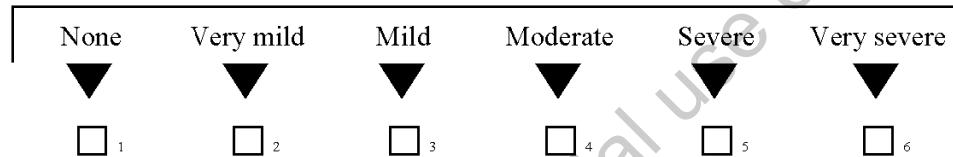
All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Cut down on the amount of time you spent on work or other activities 1..... 2..... 3..... 4..... 5
- b Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c Did work or other activities less carefully than usual 1..... 2..... 3..... 4..... 5

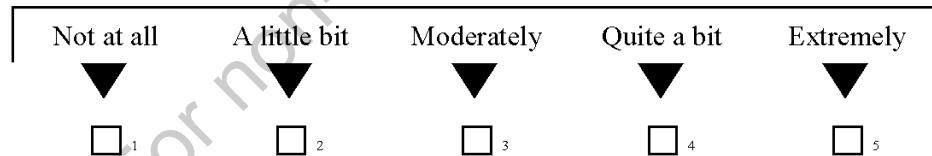
6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much bodily pain have you had during the past week?



8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Did you feel full of life? 1 2 3 4 5
- b Have you been very nervous? 1 2 3 4 5
- c Have you felt so down in the dumps that nothing could cheer you up? 1 2 3 4 5
- d Have you felt calm and peaceful? 1 2 3 4 5
- e Did you have a lot of energy? 1 2 3 4 5
- f Have you felt downhearted and depressed? 1 2 3 4 5
- g Did you feel worn out? 1 2 3 4 5
- h Have you been happy? 1 2 3 4 5
- i Did you feel tired? 1 2 3 4 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

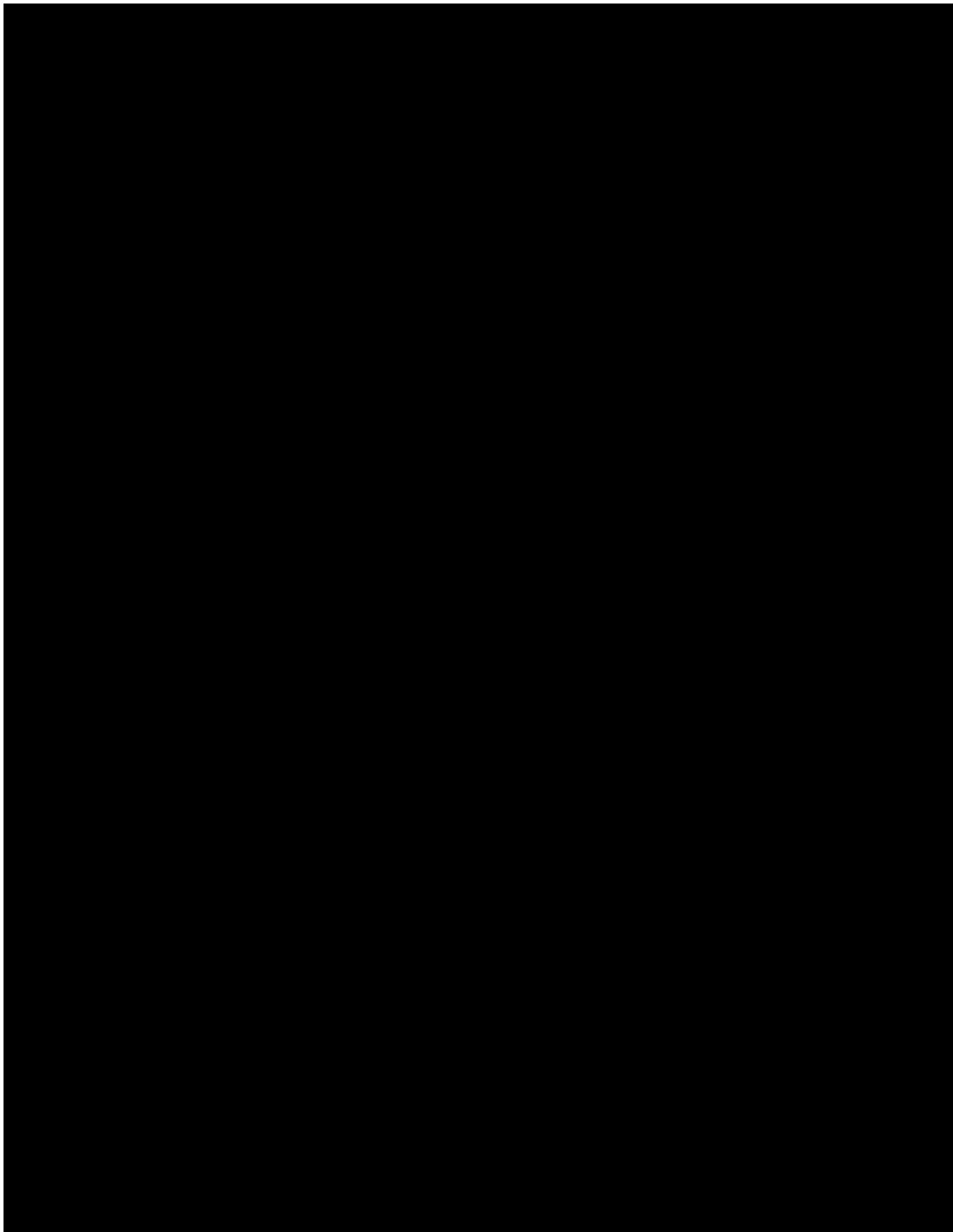
All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

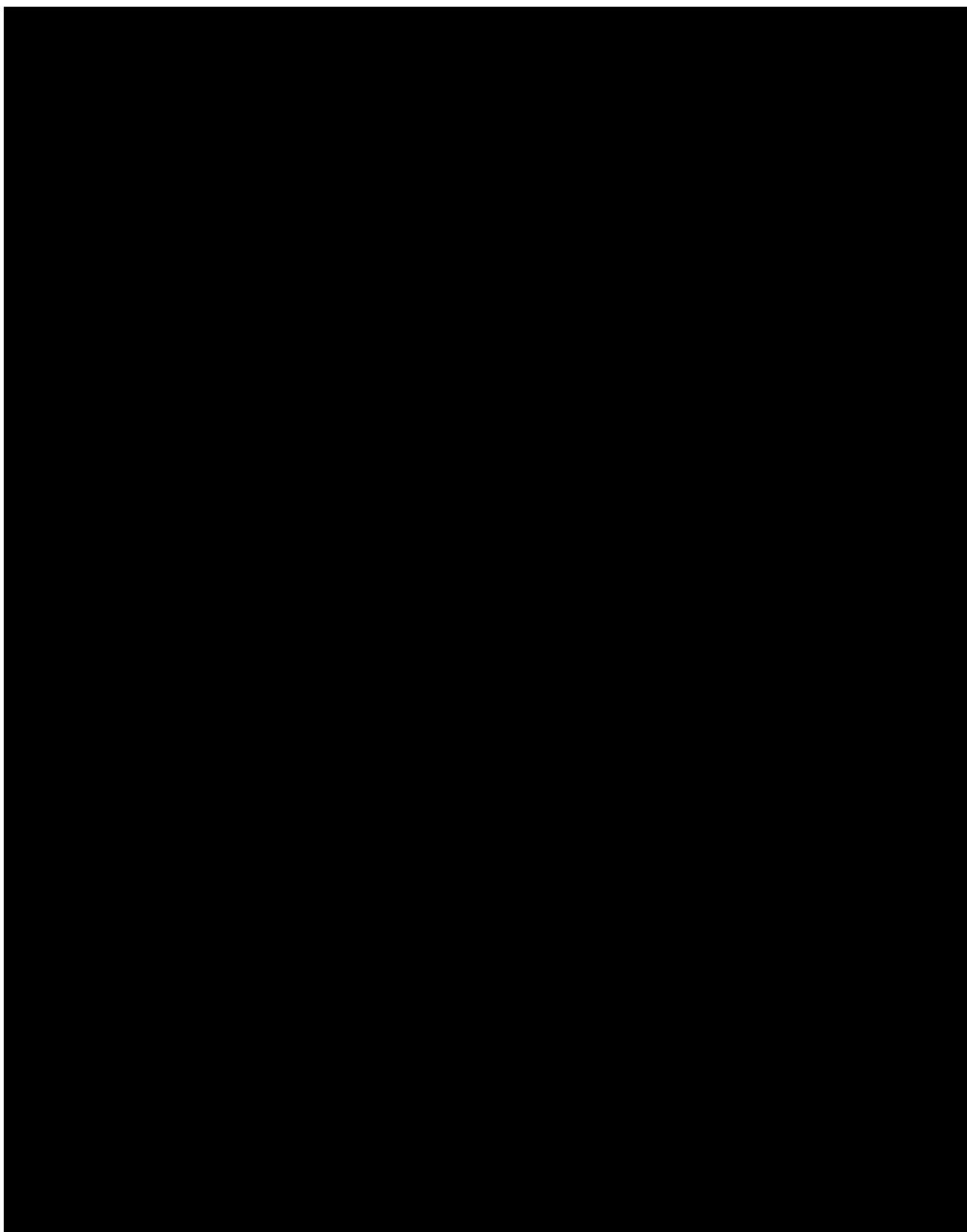
11. How TRUE or FALSE is each of the following statements for you?

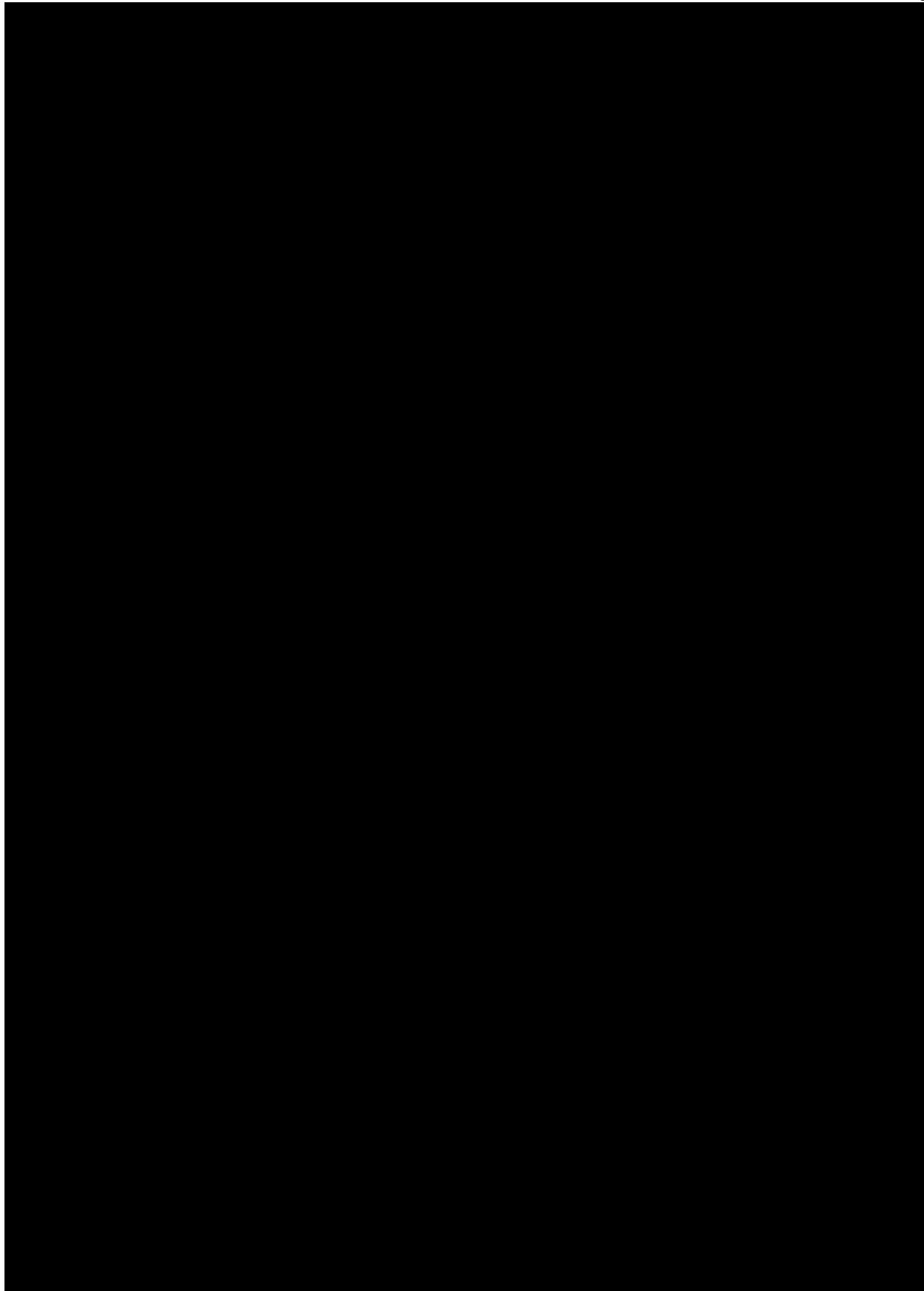
Definitely true	Mostly true	Don't know	Mostly false	Definitely false

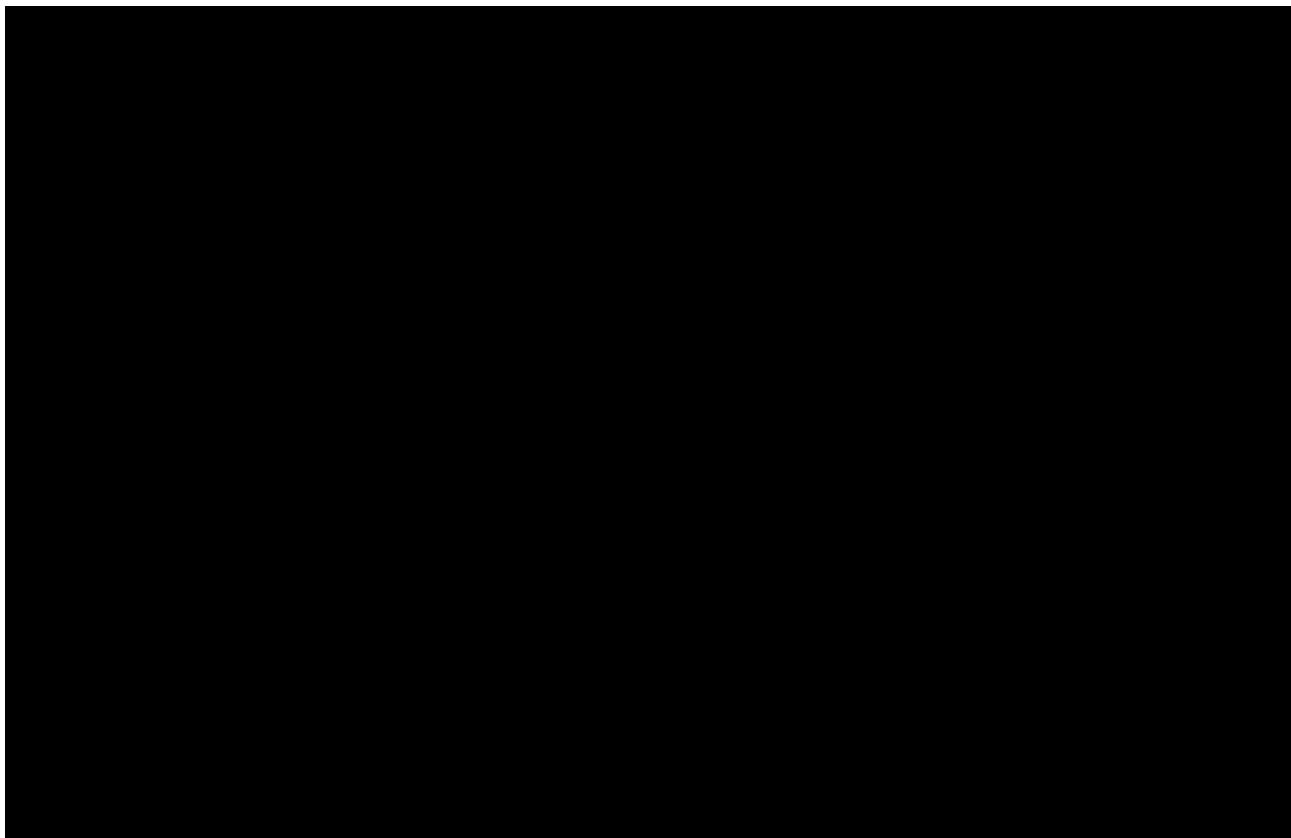
- a I seem to get sick a little easier than other people 1 2 3 4 5
- b I am as healthy as anybody I know 1 2 3 4 5
- c I expect my health to get worse 1 2 3 4 5
- d My health is excellent 1 2 3 4 5

Thank you for completing these questions!









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APPENDIX 3 GLUCOCORTICOID EQUIVALENT DOSES

Glucocorticoid	Equivalent Dose (mg)
<i>Short Acting:</i>	
Cortisone	25
Hydrocortisone	20
<i>Intermediate Acting:</i>	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
<i>Long Acting:</i>	
Betamethasone	0.6
Dexamethasone	0.75

Reference: [Lacy et al. 2001-2002](#)

APPENDIX 4 DETERMINATION OF FAILURE OR INTOLERANCE TO PRIOR TREATMENT FOR ULCERATIVE COLITIS

The information below should serve as guidance. Local therapeutic standards and investigator judgment should be considered.

AMINOSALICYLATES

Mesalamine (5-ASA)

Inadequate response to or loss of response: defined as persistent signs and symptoms of active disease despite treatment with mesalamine for at least 8 weeks at daily doses of 4.8 g/day.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to mesalamine treatment.

As guidance, the US package insert of mesalamine lists the following AEs. Please check the respective latest label of your country as well ([Lialda® 2018](#)):

Renal Impairment including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure.

Acute intolerance syndrome includes cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash.

Hypersensitivity Reactions including cardiac hypersensitivity reactions (myocarditis and pericarditis)

Hepatic Impairment: hepatic failure in patients with pre-existing liver disease

Photosensitivity in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema

Other treatment related adverse events: headache, flatulence, abnormal liver function test, alopecia, pruritus, tachycardia, hypertension, hypotension, acne, prurigo, rash, urticaria, abdominal distention, colitis, diarrhea, pancreatitis, rectal polyp, vomiting, decreased platelet count, arthralgia, back pain, somnolence, tremor, pharyngolaryngeal pain, asthenia, face edema, fatigue, pyrexia, ear pain. Based on postmarketing experience when it is not always possible to reliably establish a causal relationship to drug exposure: lupus-like syndrome, drug fever, pericarditis, pericardial effusion, myocarditis, pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer, jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, Kawasaki-like syndrome including changes in liver enzymes, agranulocytosis, aplastic anemia, anaphylactic reaction, angioedema, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), myalgia, lupus-like syndrome, peripheral neuropathy, Guillain-Barre syndrome, transverse myelitis, intracranial hypertension, interstitial nephritis, nephrogenic diabetes insipidus, interstitial lung disease, hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis), psoriasis, pyoderma gangrenosum, erythema nodosum, photosensitivity, oligospermia.

Sulfasalazine (SSZ)

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite treatment with at least one 8-week induction regimen at daily dose at 4g/day.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to sulfasalazine treatment.

As guidance, the US package insert of sulfasalazine lists the following AEs. Please check the respective latest label of your country as well ([Azulfidine® 2016](#)):

Hypersensitivity reactions: erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, drug rash with eosinophilia and systemic symptoms (DRESS), anaphylaxis, serum sickness syndrome, interstitial lung disease, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, lupus erythematosus-like syndrome, hepatitis and hepatic necrosis with or without immune complexes, fulminant hepatitis, sometimes leading to liver transplantation, parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection, and alopecia.

Blood dyscrasias: agranulocytosis, leukopenia, myelodysplastic syndrome, aplastic anemia, megaloblastic (macrocytic) anemia, hemolytic anemia, cyanosis, methemoglobinemia, Heinz body anemia, hypoprothrombinemia, and thrombocytopenia.

Gastrointestinal reactions: hepatitis, hepatic failure, pancreatitis, bloody diarrhea, impaired folic acid absorption, impaired digoxin absorption, stomatitis, diarrhea, abdominal pains, and neutropenic enterocolitis.

Central nervous system reactions: transverse myelitis, convulsions, meningitis, transient lesions of the posterior spinal column, cauda equina syndrome, Guillain-Barre syndrome, peripheral neuropathy, mental depression, vertigo, hearing loss, insomnia, ataxia, hallucinations, tinnitus, and drowsiness.

Renal reactions: toxic nephrosis with oliguria and anuria, nephritis, nephrotic syndrome, urinary tract infections, hematuria, crystalluria, proteinuria, and hemolytic-uremic syndrome.

Other reactions: urine discoloration and skin discoloration, Goiter production, diuresis and hypoglycemia, oligospermia. Based on postmarketing experience when it is not always possible to reliably establish a causal relationship to drug exposure: elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure, folate deficiency, nephrolithiasis, oropharyngeal pain, angioedema.

In addition anorexia, headache, nausea, vomiting, gastric distress, pruritus, urticaria, rash, fever, sore throat, fever, pallor, purpura.

GLUCOCORTICOIDS

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or intravenously for 1 week OR two failed attempts to taper corticosteroids to below a dose equivalent to 10 mg prednisone (oral) daily.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to glucocorticoid treatment.

As guidance, the US package insert of Medrol® lists the followings AEs. Please check the respective latest label of your country as well ([Medrol® 2018](#)):

Fluid and Electrolyte Disturbances: sodium retention, congestive heart failure, hypertension, fluid retention, potassium loss, and hypokalemic alkalosis

Musculoskeletal: muscle weakness, loss of muscle mass, steroid myopathy, osteoporosis, tendon rupture, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, and pathologic fracture of long bones.

Gastrointestinal: peptic ulcer with or without perforation and hemorrhage, pancreatitis, abdominal distention, and ulcerative esophagitis,

Dermatologic: impaired wound healing, petechiae and ecchymoses, thin fragile skin, facial erythema, and increased sweating

Neurological: increased intracranial pressure with papilledema (pseudo-tumor cerebri), convulsions, vertigo, and headache

Psychic derangements: euphoria, insomnia, mood swings, personality changes, severe depression, psychotic manifestations, aggravated existing emotional instability or psychotic tendencies.

Endocrine: Cushingoid state, secondary adrenocortical and pituitary unresponsiveness, menstrual irregularities, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements of insulin or oral hypoglycemic agents in diabetics

Ophthalmic: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, and secondary ocular infections.

Metabolic: negative nitrogen balance due to protein catabolism

Other: urticaria and other allergic, anaphylactic or hypersensitivity reactions.

IMMUNOSUPPRESSANTS

Azathioprine (AZA)

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite a history of AZA use for at least 12 weeks at daily doses ≥ 1.5 mg/kg, including its use as adjunctive therapy or steroid-sparing therapy.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related AZA treatment.

As guidance, the US package insert of an AZA product lists the following AEs. Please check the respective latest label of your country as well ([Imuran® 2014](#)):

Gastrointestinal hypersensitivity reaction characterized by severe nausea, vomiting and potentially with diarrhea, rash, fever, malaise, myalgia, elevations in liver enzymes, and occasionally, hypotension.

Hypersensitivity pancreatitis.

Hepatotoxicity that may be associated with anorexia, diarrhea, jaundice and ascites.

Cytopenias: leukopenia, thrombocytopenia, anemias including macrocytic anemia, and/or pancytopenia, bone marrow suppression, and myelotoxicity.

Serious infections (bacterial, viral, fungal, protozoal, and opportunistic infections, including reactivation of latent infections) secondary to treatment

Other: skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea, negative nitrogen balance, reversible interstitial pneumonitis, hepatosplenic T-cell lymphoma and Sweet's Syndrome (acute febrile neutrophilic dermatosis).

Mercaptopurine (6-MP)

Inadequate response or loss of response defined as persistent signs and symptoms of active disease despite a history of 6-MP use for at least 12 weeks at daily doses ≥ 0.75 mg/kg, including its use as adjunctive therapy or steroid-sparing therapy.

Intolerance defined as documented treatment discontinuation for AEs suspected to be related to 6-MP treatment.

As guidance, the US package insert of a 6-MP product lists the following AEs. Please check the respective latest label of your country as well ([Purinethol® 2011](#)):

Myelosuppression: anemia, leukopenia, and thrombocytopenia

Embryo-Fetal Toxicity

Treatment Related Malignancies

Renal: hyperuricemia and/or hyperuricosuria

Gastrointestinal: including hepatotoxicity: elevated transaminases, elevated bilirubin, ascites potentially intestinal ulceration, oral lesions, nausea, vomiting, anorexia, diarrhea and sprue-like symptoms, pancreatitis

Miscellaneous: skin rashes, hyperpigmentation, alopecia, drug fever, oligospermia

Methotrexate (MTX)

Inadequate response or loss of response: defined as failure to respond to at least one 8-week regimen of or maintain remission at doses of at least 15 mg/week, given by the intramuscular or subcutaneous route.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to MTX treatment.

As guidance, the US package insert of a MTX product lists the following AEs. Please check the respective latest label of your country as well ([Methotrexate® 2018](#)):

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders: anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia, lymphadenopathy and lymphoproliferative disorders, hypogammaglobulinemia

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus)

Central Nervous System: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions, cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy

Hepatobiliary: acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity decrease in serum albumin, and liver enzyme elevations

Infection: opportunistic infections e.g. *Pneumocystis carinii* pneumonia, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, *H. simplex* hepatitis, and disseminated *H. simplex*

Musculoskeletal System: stress fracture

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology

Pulmonary System: respiratory fibrosis, respiratory failure, interstitial pneumonitis, chronic interstitial obstructive pulmonary disease

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects

Other: nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis, anaphylactoid reactions

ANTI-TNF AGENTS

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite at least one 4 week induction regimen with the following minimum doses of:

- infliximab (5 mg/kg IV, 2 doses at least 2 weeks apart) or
- adalimumab (one 80 mg SC dose followed by one 40 mg dose at least 2 weeks apart) or
- golimumab (one 200 mg SC dose followed by 100 mg dose at least 2 weeks apart)

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to Anti-TNF agents.

As guidance, the US package insert of a Humira lists the following AEs. Please check the respective latest labels for the other Anti-TNF agents and the labels of your country as well ([Humira® 2017](#)):

Anaphylaxis or serious allergic reactions: generalized rash and flushing, hypersensitivity reactions including angioneurotic edema

Development of neutralizing autoantibodies

Body As A Whole: Pain in extremity, pelvic pain, surgery, thorax pain

Cardiovascular System: Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, heart failure

Gastrointestinal: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, vomiting, nausea, abdominal pain, hepatic reactions including acute liver failure, hepatic necrosis

Lupus-like syndrome

Endocrine System: Parathyroid disorder

Hemic and Lymphatic System: Cytopenias, pancytopenia, Agranulocytosis, polycythemia

Infections: tuberculosis (new and reactivation of latent tuberculosis) and opportunistic infections pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma

Nervous System: Confusion, paresthesia, subdural hematoma, tremor

Respiratory System: upper respiratory infection, sinusitis, flu syndrome, asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion

Special Senses: Cataract

Thrombosis: Thrombosis leg

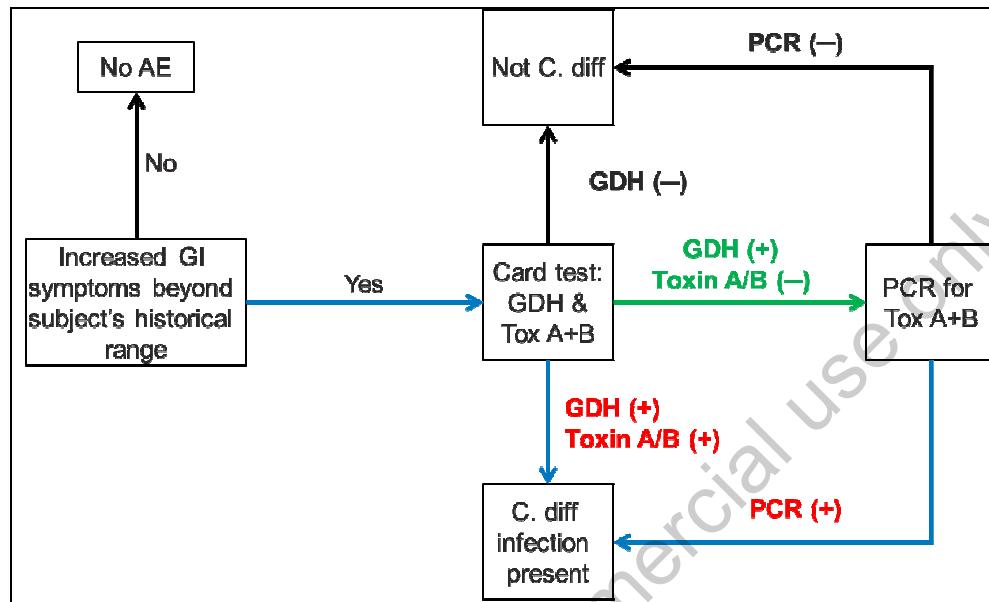
Urogenital System: Cystitis, kidney calculus, menstrual disorder

Other: headache, rash, injection site reaction, infusion-related reactions such as fever or chills, cardiopulmonary reactions such as chest pain, hypotension, hypertension, or dyspnea and/or pruritus or urticaria, back pain, urinary tract infection, hypertension

APPENDIX 5 GUIDANCE FOR DIAGNOSIS AND TREATMENT OF INCREASED GASTROINTESTINAL SYMPTOMS

If, for any reason, the central laboratory is not available, the preferred diagnostic algorithm is to use the Alere Quik Chek card test ([Figure A1](#)).

Figure A1 Algorithm for *C. difficile* Diagnosis Using the Quick Check Card Test



If the Alere Quik Chek card test is not available, then a diagnosis may be established by following either of the algorithms shown in [Figure A2](#) (using PCR for toxin), [Figure A3](#) using toxigenic culture or [Figure A4](#) (using toxigenic culture, followed by PCR). The rationale for the method in [Figure A3](#) is that the majority of PCR tests are expected to be negative for toxin, thus obviating the need for the test at the central laboratory. The expected turnaround time at the central laboratory for a GDH card test is expected to be shorter than that for stool culture for *C. difficile* at the local laboratory. The details of the sensitivity and specificity of these tests were reported by Khanna ([Khanna et al. 2017](#)).

When medically reasonable, treatment decisions should be deferred until an etiology has been determined. When this is not feasible, management of symptoms should be dictated by the clinical situation.

Figure A2 Alternative 1 for *C. difficile* Testing Using Local Laboratory When No Alere Quick Chek Card Test is Available

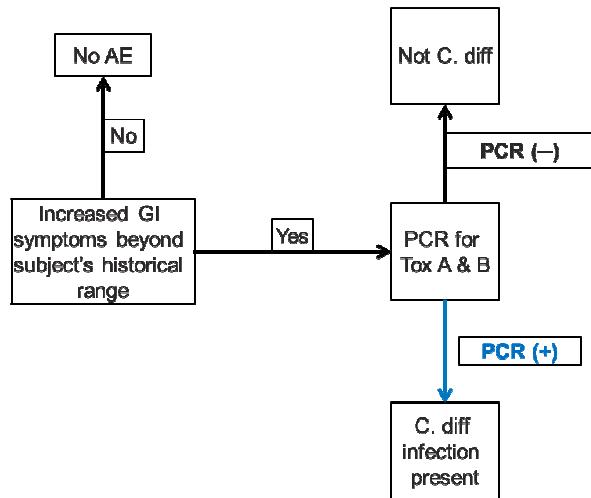


Figure A3 Alternative 2 for *C. difficile* Testing Using Local Laboratory When No Card Test is Available

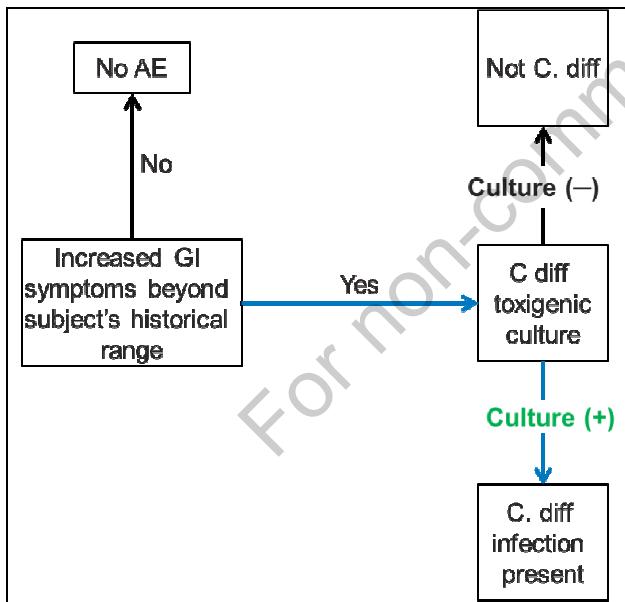
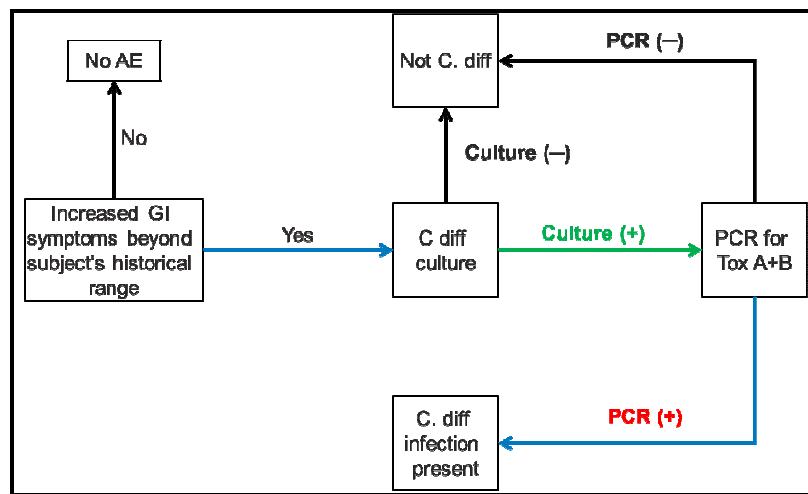


Figure A4 Alternative 3 for *C. difficile* Testing Using Local Laboratory When No Alere Quick Chek Card Test is Available



Treatment

When medically reasonable, treatment decisions should be deferred until an etiology has been determined. When this is not feasible, management of symptoms should be dictated by the clinical situation. **If management requires a prohibited treatment (eg, intravenous glucocorticoids for induction or maintenance studies) the subject should be withdrawn from treatment.**

If treatment has been deferred, once an etiology is determined (eg, *C. difficile*, disease exacerbation, *Campylobacter*), appropriate treatment should be promptly implemented without waiting for a scheduled visit. If the etiology is determined to be *C. difficile*, treatment guidelines conforming to the current IDSA recommendations for *C. difficile* infection ([McDonald et al. 2018](#)) or the recent expert review on *C. difficile* infection in IBD ([Khanna et al. 2017](#)) should be consulted.

If *C. difficile* infection was identified, clinical improvement should be noted within about 5 days after the start of treatment. If improvement does not occur, the etiology is most likely an IBD flare secondary to *C. difficile* and treatment failure assessment should proceed per the protocol. Another possible explanation is primary failure of *C. difficile* therapy which is unlikely.

If an infectious etiology other than *C. difficile* is identified, it should be managed as appropriate, with reference to current clinical guidelines ([Shane et al. 2017](#)).

If any infectious etiology is determined, the site should contact the medical monitor to make him or her aware of the diagnosis and to discuss treatment and ongoing study participation.



PROTOCOL: SHP647-302

TITLE: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 302)

DRUG: Ontamalimab (SHP647)

IND: 100,222

EUDRACT NO.: 2017-000572-28

SPONSOR: Shire Human Genetic Therapies, Inc. (“Shire”)
300 Shire Way, Lexington, MA 02421 USA

**PRINCIPAL/
COORDINATING
INVESTIGATOR:** [REDACTED], MD, PhD

**PROTOCOL
HISTORY:** Protocol Amendment 2: 11 Nov 2019
Protocol Amendment 1: 05 Sep 2018
Original Protocol: 06 Jul 2017

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PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature:	[REDACTED]	Date:	11 NOV 2019
[REDACTED]		MD,	[REDACTED]

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP647-302.

Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 302).

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]

Signature: _____ Date: _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Region/Country/Site Specific
2	11 Nov 2019	Global
Section(s) Affected by Change	Description of Change	Rationale
Product Quality Complaints	Updated language regarding reporting of product quality complaints.	To align product quality complaints language with current Shire template.
Study Synopsis, Number of Subjects (total and for each treatment arm), Methodology Section 3.1, Study Design and Flow Chart	Updated sample size projections.	To reflect a decrease in the sample size in this study due to a reduced number of subjects required to rollover to the SHP647-303 study to meet targeted power levels.
Section 9.6, Sample Size Calculation and Power Considerations	Updated sample size projections and power considerations.	
Study Synopsis, Rationale Section 2.1, Rationale for the Study	Revised to describe Study A7281010 as a completed study.	To reflect that Study A7281010 has been completed.
Study Synopsis, Inclusion Criteria Section 4.1, Inclusion Criteria Section 4.4, Reproductive Potential	Added the term 'highly effective methods for female and medically appropriate methods for male study subjects' to inclusion criterion #10 in parentheses after the term 'appropriate contraception'. Also added after the terms 'appropriate form of contraception' and 'appropriate method of contraception' in Section 4.4.	To clarify what is meant by appropriate contraception methods.
Study Synopsis, Exclusion Criteria Table 1, Schedule of Assessments footnote 'r' Section 4.2, Exclusion Criteria Section 7.2.3.6, Clinical Laboratory Evaluations	Language in exclusion criterion #18, changed from '12 weeks before randomization' to '12 weeks before screening'. Language in the footnote and section 7.2.3.6 revised to '12 weeks before baseline' to '12 weeks before screening'.	For consistency with other sections.
Study Synopsis, Exclusion Criteria Section 4.2, Exclusion Criteria	Language in exclusion criterion #18, changed from '3 months before and during screening visit' and '3 months prior to screening visit' to '12 weeks before and during screening visit'.	For consistency with other sections.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Region/Country/Site Specific
2	11 Nov 2019	Global
Section(s) Affected by Change	Description of Change	Rationale
Study Synopsis , Analysis Sets Section 9.7 , Study Population	[REDACTED]	[REDACTED]
Study Synopsis , Other Secondary Efficacy Endpoints Section 9.8.2.2 , Other Secondary Efficacy Endpoints	For the endpoint “change from baseline at the Week 12 visit in abdominal pain, diarrhea, and urgency item scores, absolute stool frequency, absolute rectal bleeding and total sign/symptom score based on subject daily e-diary entries (sum of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency)”, revised the text in parentheses to read “(average of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency)”.	To correctly describe the scoring of patient-reported ulcerative colitis (UC) sign and symptom data.
Study Synopsis , Safety Analyses Section 9.9 , Safety Analyses	Added that adverse events of special interest will be summarized by treatment group.	To include analysis of adverse events of special interest.
Table 1 , Schedule of Assessments footnote ‘d’ Section 7.1.2.3 , Final On-treatment Visits: Visit 6, Parts 1 and 2 (Week 12/Early Termination)	Revised to extend the window between the colonoscopy procedure at Visit 6 (Part 1) and Visit 6 (Part 2) to 10 days, although 5 to 7 days is preferable.	To allow sufficient time for data from the centrally read endoscopy to be available at Part 2 of Visit 6.
Table 1 , Schedule of Assessments footnote ‘r’	Added interferon-gamma release assay along with purified protein derivative test.	For consistency with other sections.
Table 1 , Schedule of Assessments footnote ‘m’ Section 7.2.3.6 , Clinical Laboratory Evaluations Section 7.2.3.12 , Evaluation of Increased Gastrointestinal Symptoms	Added new subsection to Section 7.2.3 and language to describe the evaluation of increased gastrointestinal symptoms.	To clarify that infectious etiology must be evaluated when a subject experiences an increase in gastrointestinal symptoms.
Table 1 , Schedule of Assessments footnote ‘aa’ Section 7.2.3.11 , Monitoring for Type I and Type III Immune Reactions	Added new row to Table 1 , new subsection to Section 7.2.3 , and language to describe the monitoring for hypersensitivity.	To address Food and Drug Administration (FDA) recommendation to evaluate the risk of hypersensitivity reactions in the Phase 3 studies and aid in the collection of relevant safety data.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Region/Country/Site Specific
2	11 Nov 2019	Global
Section(s) Affected by Change	Description of Change	Rationale
Section 4.4, Reproductive Potential	Updated text to reflect results of an enhanced pre- and postnatal development (ePPND) toxicity study in nonhuman primates.	<p>Updated information to reflect preliminary results from an ePPND toxicity study of ontamalimab in nonhuman primates, which indicated that, at the dose levels tested (30 and 60 mg/kg), infant losses were increased in ontamalimab-exposed animals when compared both to control animals in the study and to the historical control animal data from the testing facility.</p> <p>The relevance of this finding to humans is unknown but cannot be excluded.</p> <p>Results of the ePPND study were reported in the ontamalimab Investigator's Brochure Edition 8.0.</p>
Section 4.4.1, Contraceptive Methods for Female Study Subjects	Added text to specify that contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the clinical study.	To align with guidance document "Recommendations related to contraception and pregnancy testing in clinical trials" of Clinical Trial Facilitation Group.
Section 4.5.1, Subject Withdrawal Criteria	The term 'protocol violations' has been changed to 'protocol deviations'.	For consistency with Section 4.5.2 (Reasons for Withdrawal).
Section 5.2.1, Permitted Treatment	Added that oral beclomethasone up to a maximum of 5 mg/day is permitted (providing that the dose is stable for at least 2 weeks before screening endoscopic procedure).	To reflect that beclomethasone is a topically active oral glucocorticoid used in certain regions as standard of care for UC.
Section 7.2.3.3, Targeted Neurological Assessment	Revised wording from 'exclusion criterion 18' to 'exclusion criterion 20' to reflect the correct criterion.	For clarity regarding exclusion criteria.
Table 3, Quarterly Neurological Assessments	Column heading changed from 'targeted neurological history' to 'interim neurologic history and targeted neurologic examination'.	To align with language of newly proposed electronic case report form.
Section 7.2.4.3, Health-related Quality of Life Assessments	Changed the term 'dimensions' to 'domains'.	For consistency.
Section 7.2.5, Volume of Blood to Be Drawn from Each Subject	Increased [REDACTED] sample volume from 3 mL to 5 mL.	To correct the sample volume needed for the [REDACTED].

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Region/Country/Site Specific
2	11 Nov 2019	Global
Section(s) Affected by Change	Description of Change	Rationale
Section 8.1.3, Adverse Events of Special Interest	Added new subsection to describe classification of hypersensitivity as an adverse event of special interest.	To address FDA recommendation to evaluate the risk of hypersensitivity reactions in the Phase 3 studies and aid in the collection of relevant safety data.
Section 8.1.7, Pregnancy	Added text to specify that in cases of pregnancy, where the outcome is a live birth, the vital status and clinical condition of the infant should be obtained and documented at 1 year postpartum.	To extend the timeframe for follow-up of pregnancy outcomes for female study participants or partners of male study participants in response to preliminary findings of the ePPND study.
Section 9.5, Planned Interim Analysis, Adaptive Design, Data Monitoring Committee, and Hypersensitivity Adjudication Committee	Added text to specify that external hypersensitivity adjudication committee will be established to review data from subjects who experience a suspected Type I or Type III hypersensitivity reaction.	To address FDA recommendation to evaluate the risk of hypersensitivity reactions in the Phase 3 studies and aid in the collection of relevant safety data.
Section 9.8.3, Exploratory Efficacy Endpoints	[REDACTED]	[REDACTED].
Section 10.1.5, Study Suspension, Termination, and Completion	To clarify that the end-of-study declaration may be made by the sponsor or alternatively its representatives.	Added for clarity.
Appendix 2, Scales and Assessments	Added instructions before the start of questions for Treatment Satisfaction Questionnaire for Medication.	For consistency with other ontamalimab Phase 3 protocols.
Appendix 4, Determination of Failure or Intolerance to Prior Treatment for Ulcerative Colitis	Added guidance for the determination of failure or intolerance to prior tofacitinib treatment.	To include tofacitinib, as it is a common prior treatment for UC.
Throughout protocol	‘SHP647’ was updated to ‘ontamalimab’ throughout the protocol.	To reflect that ontamalimab is the international nonproprietary name for SHP647.
Throughout protocol	Minor changes to wording and editorial changes.	To improve clarity, consistency, and remove redundancy of text.

See [Appendix 1](#) for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or email the Shire “Clinical Study Serious Adverse Event and Nonserious AE as Required by the Protocol Form” within 24 hours to the Shire Global Drug Safety Department. The fax number and email address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor using the details below.

Fax [REDACTED] (Global)

Email [REDACTED]

For protocol- or safety-related issues, the investigator must contact the medical monitor via the appropriate regional safety hotline (24 hours):

North America:

PPD 24 Hour Safety Hotline: RTP [REDACTED]; Wilmington [REDACTED]

PPD 24 Hour Safety Hotline Fax: RTP [REDACTED] or [REDACTED];
Wilmington [REDACTED] or [REDACTED]

Latin America:

PPD 24 Hour Safety Hotline: [REDACTED]

PPD 24 Hour Safety Hotline Fax: [REDACTED]

Europe, the Middle East, and Africa; and Asia-Pacific:

PPD 24 Hour Safety Hotline: [REDACTED]

PPD 24 Hour Safety Hotline Fax: [REDACTED]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or nonmedical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Shire licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that a product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	<ul style="list-style-type: none">• Capsule fill empty or overage• Bottle/vial fill shortage or overage• Capsule/tablet damaged/broken• Syringe/vial cracked/broken	<ul style="list-style-type: none">• Syringe leakage• Missing components• Product discoloration• Device malfunction
Labeling	<ul style="list-style-type: none">• Label missing• Leaflet or Instructions For Use (IFU) missing• Label illegible	<ul style="list-style-type: none">• Incomplete, inaccurate, or misleading labeling• Lot number or serial number missing
Packaging	<ul style="list-style-type: none">• Damaged packaging (eg, secondary, primary, bag/pouch)• Tampered seals• Inadequate or faulty closure	<ul style="list-style-type: none">• Missing components within package
Foreign material	<ul style="list-style-type: none">• Contaminated product• Particulate in bottle/vial• Particulate in packaging	

Please report the product quality complaint using the “Product Complaint Data Collection Form” via the email address:

[REDACTED]

Telephone number (provided for reference if needed):

Shire, Lexington, MA (USA)

[REDACTED]

For instructions on reporting adverse events related to product complaints, see Section 8.2.2.

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
β-hCG	beta-human chorionic gonadotropin
CD	Crohn's disease
CI	confidence interval
CMH	Cochran-Mantel Haenszel
CNS	central nervous system
CRO	contract research organization
CRP	C-reactive protein
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
ED	emergency department
e-diary	electronic diary
EMA	European Medicines Agency
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FWER	family-wise Type I error rate
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	hepatitis B core antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
IgG _{2κ}	immunoglobulin G2 kappa
IGRA	interferon gamma release assay
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LTS	long-term safety extension
██████████	██████████
MTX	methotrexate
NAb	neutralizing antibody
PCR	polymerase chain reaction
████	████
PFS	prefilled syringe
PGA	physician global assessment
████	████
████	████
PML	progressive multifocal leukoencephalopathy
PP	per-protocol
PPD	purified protein derivative
PRO	patient-reported outcome
Q4W	once every 4 weeks
RSI	reference safety information
SAE	serious adverse event

SAP	statistical analysis plan
SC	subcutaneous
SF-36	Short Form-36 Health Survey
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
[REDACTED]	[REDACTED]
UC	ulcerative colitis
ULN	upper limit of normal
VAS	visual analog scale
[REDACTED]	[REDACTED]

STUDY SYNOPSIS

Protocol number: SHP647-302	Drug: Ontamalimab (SHP647)
Title of the study: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 302)	
Number of subjects (total and for each treatment arm):	
A total of 740 subjects (296 subjects at 25 mg ontamalimab, 296 subjects at 75 mg ontamalimab, and 148 subjects on placebo) are planned for enrollment into the study.	
Investigator(s): Multicenter study.	
Site(s) and Region(s):	
It is anticipated that the study will be conducted in at least 18 countries. Regions will include North America Europe, the Middle East, and Africa, Latin America, and Asia-Pacific. Approximately 210 sites will be utilized.	
Study period (planned): 2017 to 2020	Clinical phase: 3
Objectives:	
Primary: To evaluate the efficacy of ontamalimab in inducing remission, based on composite score of patient-reported symptoms and centrally read endoscopy, in subjects with moderate to severe ulcerative colitis (UC).	
Key Secondary:	
<ul style="list-style-type: none">• To evaluate the efficacy of ontamalimab in achieving endoscopic remission, based on centrally read endoscopy• To evaluate the efficacy of ontamalimab in achieving clinical remission, based on composite score of patient-reported symptoms• To evaluate the efficacy of ontamalimab in inducing clinical response, based on composite score of patient-reported symptoms and centrally read endoscopy• To evaluate the efficacy of ontamalimab in achieving mucosal healing, based on endoscopic and histological assessment using the Geboes Score grading system.	
Other Secondary:	
<ul style="list-style-type: none">• To evaluate the safety and tolerability of ontamalimab• To evaluate the effect of ontamalimab induction treatment on other clinical and endoscopic outcomes (including Mayo-based remission and clinical response, partial Mayo score over time, clinical remission over time, endoscopic remission, and deep remission)• To evaluate the effect of ontamalimab on abdominal pain, urgency, diarrhea, and absolute stool frequency and bleeding scores• To evaluate the effect of ontamalimab on health-related quality of life (as measured by the Inflammatory Bowel Disease Questionnaire [IBDQ] and the Short Form-36 Health Survey [SF-36])• To evaluate the effect of ontamalimab on incidence of hospitalizations and total inpatient days.	
Rationale:	
This study is designed to evaluate the efficacy and safety of ontamalimab in inducing remission in subjects with moderate to severe UC.	
Ontamalimab has been investigated in subjects with moderate to severe UC in 3 completed studies: 2 dose-finding studies (A7281001 and A7281009) and an open-label, long-term safety extension (LTS) study (A7281010), which was ongoing at the time of the original protocol and has since completed. The Phase 1 study, A7281001, which investigated the safety, tolerance, pharmacokinetics (PK), and pharmacodynamic (PD) properties of ontamalimab, supports further clinical development of ontamalimab using subcutaneous (SC) administration. Subcutaneous doses of 25 mg or 75 mg of ontamalimab or placebo on Day 1 (Week 0), Week 4, and Week 8 are recommended for the Phase 3 studies SHP647-301 and SHP647-302.	

Investigational product, dose, and mode of administration:

The test product is ontamalimab, which will be provided as a sterile aqueous buffered solution for SC administration in a glass prefilled syringe (PFS) with a fixed needle. Each PFS contains 1 mL of ontamalimab solution for injection at an appropriate concentration to provide the intended dose of drug (25 or 75 mg). Additional information is provided in the current ontamalimab investigator's brochure.

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain ontamalimab.

Methodology:

A total of 740 subjects (296 subjects at 25 mg ontamalimab, 296 subjects at 75 mg ontamalimab, and 148 subjects on placebo) are planned for enrollment into the study. Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent form.

The study consists of a screening period up to 6 weeks and a 12-week treatment period. After the screening period, eligible subjects will be randomly assigned to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo) in a 2:2:1 ratio. Randomization will be stratified based upon the subject's status of prior anti-tumor necrosis factor (TNF) treatment (naïve or experienced) and glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline). Subjects will receive SC injections of ontamalimab or placebo, using a PFS, on Week 0/Day 1 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 5). Subjects will undergo efficacy, [REDACTED] safety, and health outcome assessments at these visits.

Patient-reported UC signs and symptom data (including stool frequency, rectal bleeding severity and frequency, diarrhea frequency, urgency frequency, and abdominal pain worst severity) will be collected using a daily electronic diary (e-diary) during the treatment period. The Mayo score is a measure of UC disease activity consisting of the following 4 subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician global assessment (PGA). The partial Mayo score consists of the Mayo score without the endoscopic subscores. The composite score is a recommended measure consisting of the Mayo score without the PGA subscore, and will be used for the primary efficacy endpoint. The Mayo scores and composite score will be based on subject daily e-diary entries.

At the end of the 12-week treatment period, eligible subjects will be offered the opportunity to participate in a double-blind maintenance study (SHP647-303; for subjects who achieve clinical response) or an LTS study (SHP647-304; for subjects who do not achieve a clinical response). Subjects who withdraw early from the 12-week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

Inclusion and exclusion criteria:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must be between ≥ 16 and ≤ 80 years of age at the time of the signing of the informed consent/assent form.

Note: Subjects <18 years of age must weigh ≥ 40 kg and must have body mass index ≥ 16.5 kg/m².

4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for ≥ 3 months before screening. The following must be available in each subject's source documentation:
 - A biopsy report to confirm the histological diagnosis

- A report documenting disease duration based upon prior colonoscopy.
Note: If this documentation is not available at the time of screening, a colonoscopy with biopsy to confirm the diagnosis is required during the screening period.
5. Subjects must be willing to undergo a flexible sigmoidoscopy or colonoscopy (if preferred), including biopsy sample collection, during screening after all other inclusion criteria have been met.
 6. Subjects must have moderate to severe active UC, defined as a total Mayo score of ≥ 6 , including a centrally read endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 at baseline (Visit 2).
 7. Subjects must have evidence of UC extending proximal to the rectum (ie, not limited to proctitis).
 8. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as mesalamine (5-aminosalicylic acid [5-ASA]), glucocorticoids, immunosuppressants (azathioprine, 6-mercaptopurine, or methotrexate), or anti-TNF (see Appendix 4 of the protocol for guidance).
 9. Subjects receiving any treatment(s) for UC described in Section 5.2.1 of the protocol are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
 10. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception (ie, highly effective methods for female and medically appropriate methods for male study subjects) (as described in Section 4.4 of the protocol) for the duration of the study.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subjects with indeterminate colitis, microscopic colitis, nonsteroidal anti-inflammatory drug-induced colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of Crohn's disease.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for UC during the treatment period.
5. Subjects at risk for colorectal cancer must have a colonoscopy (Eaden and Mayberry, 2002) performed during the screening period with results available within 10 days before the baseline visit (Visit 2), unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidence of dysplasia and colon cancer must be available in the source documents.

Subjects at risk for colorectal cancer include, but are not limited to:

- Subjects with extensive colitis for ≥ 8 years or disease limited to left side of colon (ie, distal to splenic flexure) for ≥ 10 years before screening, regardless of age
 - Subjects ≥ 50 years of age at the time of signing of the informed consent form.
6. Subjects have had prior treatment with ontamalimab (formerly PF-00547659; SHP647).
 7. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
 8. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
 9. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).

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10. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than their current background UC treatment) within 30 days before baseline (Visit 2).
11. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
12. Subjects have received parenteral or rectal glucocorticoids, or rectal 5-ASA, within 14 days before screening endoscopic procedure.
13. Subjects have received leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange within 30 days before baseline (Visit 2).
14. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before baseline (Visit 2).
15. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).
16. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis (subjects with *C. difficile* infection at screening may be allowed re-test after treatment), evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
17. Subjects with abnormal chest x-ray findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation.)
18. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) or subjects with this history who have not completed a generally accepted full course of treatment before randomization are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed.

Subjects who have no history of previously diagnosed active or latent TB are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥ 5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before screening. If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

- An IGRA is strongly recommended for subjects with a prior Bacillus Calmette-Guérin vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON TB Gold Plus In-Tube Test.
- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent TB, a positive test on repeat will exclude the subject. Subjects with a history of active or latent TB infection must follow instructions for "Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met" in this criterion.
- Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray, taken within the 12 weeks before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
 - A chest x-ray performed within 12 weeks before or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.
19. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
20. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy based on the targeted neurological assessment during the screening period (see Section 7.2.3.3 of the protocol).
21. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
22. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
- Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal (except disease under study), endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study
 - Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence)
 - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening
 - History of significant cerebrovascular disease within 24 weeks before screening.
23. Subjects who have had significant trauma or major surgery within 4 weeks before the screening visit (Visit 1), or with any major elective surgery scheduled to occur during the study.
24. Subjects with evidence of cirrhosis with or without decompensation.
25. Subjects with primary sclerosing cholangitis.
26. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Note: if a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if no presence of hepatitis B virus (HBV) DNA is confirmed by HBV DNA polymerase chain reaction reflex testing performed in the central laboratory.
27. Subjects with chronic hepatitis C virus (HCV) (positive HCV antibody [HCVAb] and HCV RNA). Note: Subjects who are HCVAb positive without evidence of HCV RNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCV RNA at least 12 weeks prior to baseline]).
28. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening. Note: Screening laboratory tests, if the results are considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results must be reviewed for eligibility prior to the screening endoscopy procedure.

- Alanine aminotransferase and aspartate aminotransferase levels $\geq 3.0 \times$ the upper limit of normal (ULN)
- Total bilirubin level $\geq 1.5 \times$ ULN or $> 2.0 \times$ ULN if the subject has a known documented history of Gilbert's syndrome)
- Hemoglobin level ≤ 80 g/L (8.0 g/dL)
- Platelet count $\leq 100 \times 10^9/\text{L}$ (100,000 cells/mm³) or $\geq 1000 \times 10^9/\text{L}$ (1,000,000 cells/mm³)*
- White blood cell count $\leq 3.5 \times 10^9/\text{L}$ (3500 cells/mm³)
- Absolute neutrophil count $< 2 \times 10^9/\text{L}$ (2000 cells/mm³)
- Serum creatinine level $> 1.5 \times$ ULN or estimated glomerular filtration rate $< 30 \text{ mL/min}/1.73 \text{ m}^2$ based on the abbreviated Modification of Diet in Renal Disease Study Equation.
*Note: If platelet count is $< 150,000$ cells/mm³, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.

29. Subjects with known human immunodeficiency virus (HIV) infection based on documented history, with positive serological test, or positive HIV serologic test at screening, tested at the site's local laboratory in accordance with country requirements, or tested at the central laboratory. Note: A documented negative HIV test within 6 months of screening is acceptable and does not need to be repeated.
30. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse or dependency of any kind, including abuse of medicinal marijuana (cannabis).
31. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
32. Female subjects who are planning to become pregnant during the study period.
33. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm, and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
34. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: Up to 6 weeks
- Planned duration of treatment period: 12 weeks
- Planned duration of follow-up period: 16 weeks

Endpoints and statistical analysis:

Analysis Sets:

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

The full analysis set (FAS) will consist of all subjects in the randomized set who have received at least 1 dose of investigational product.

The per-protocol set will consist of all subjects in the FAS who do not have predefined protocol deviations that may affect the primary efficacy endpoint.

The completer set will consist of all subjects in the FAS who have completed the final scheduled primary assessment for this study.

[REDACTED]

[REDACTED]

Primary Efficacy Endpoint:

Unless otherwise specified, all efficacy analyses will be based on the FAS and subjects will be analyzed according to their randomized treatment, regardless of the treatment they actually received.

The primary efficacy endpoint is remission at the Week 12 visit. Remission is defined as a composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy as follows:

- stool frequency subscore of 0 or 1 with at least a 1-point change from baseline
 - AND
- rectal bleeding subscore of 0
 - AND
- endoscopic subscore of 0 or 1 (modified, excludes friability).

The primary efficacy endpoint will be compared for each active treatment group (25 mg or 75 mg ontamalimab) to the placebo group using a Cochran-Mantel Haenszel chi-square test stratified by status of prior anti-TNF treatment and glucocorticoid use at baseline (Visit 2). Subjects with missing remission data at the Week 12 visit will be considered failures and counted as nonresponders. The endoscopy score will be based on centrally read results.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata, $j=1$ to m . The common treatment difference is a weighted average of the stratum-specific treatment differences.

The global family-wise Type I error rate (FWER) for the statistical tests of the primary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al. (2009) will be utilized to propagate α from primary to key secondary endpoints and between the 2 ontamalimab treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the primary endpoint (P) and alpha is propagated in a hierarchical manner to each of the 4 key secondary endpoints (K1-K4) within a pairwise treatment comparison.

Key Secondary Efficacy Endpoints:

- Endoscopic remission, as defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability), at the Week 12 visit.
- Clinical remission, as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at the Week 12 visit.
- Clinical response based on composite score at the Week 12 visit. Clinical response (composite) is defined as a decrease from baseline in the composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 .
- Mucosal healing based on endoscopic and histological assessment at the Week 12 visit. Mucosal healing is defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability) and centrally read Geboes score of ≤ 2 .

The key secondary endpoints will be analyzed using the same approach as described for the primary efficacy endpoint. Subjects with missing key secondary endpoint data at the Week 12 visit will be considered failures and counted as nonresponders.

Other Secondary Efficacy Endpoints:

- Remission, defined as a total Mayo score ≤ 2 with no individual subscore (stool frequency, rectal bleeding, endoscopy [modified, excludes friability], and physician's global assessment) exceeding 1, at the Week 12 visit.
- Clinical response based on total Mayo score at the Week 12 visit. Clinical response (Mayo) is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or an absolute subscore for rectal bleeding ≤ 1 .
- Partial Mayo score ≤ 2 with no individual subscore > 1 at the Week 4, 8, and 12 visits. The partial Mayo score does not include the endoscopy subscore.
- Clinical remission as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at Weeks 4 and 8.
- Endoscopic remission at the Week 12 visit with endoscopic subscore of 0.
- Clinical remission at the Week 4, 8, and 12 visits with both rectal bleeding and stool frequency subscores of 0.
- Deep remission at the Week 12 visit. Deep remission is defined as both endoscopic and rectal bleeding subscores of 0, and stool frequency subscore ≤ 1 and a centrally read Geboes score of ≤ 2 .
- Change from baseline at the Week 12 visit in abdominal pain, diarrhea, and urgency item scores, absolute stool frequency, absolute rectal bleeding and total sign/symptom score based on subject daily e-diary entries (average of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency).
- Change from baseline in IBDQ domain and total (absolute) scores (time frame: Week 0, Week 8, up to Week 12, or early termination [ET]).
- Change from baseline in SF-36, version 2, acute (physical and mental component summary scores and individual domain scores) to the Week 12/ET visit.
- Incidence of all-cause hospitalizations and total inpatient days.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods.

Binary endpoints will be analyzed using the same approach as described for the primary endpoint. Subjects with missing binary endpoint data at a visit will be considered failures and counted as nonresponders.

Continuous endpoints that are only measured at baseline and the Week 12 visit will be analyzed using an analysis of covariance model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% confidence intervals (CIs) for least squares mean treatment differences will be provided.

Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation. The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

Safety Analyses:

All safety analyses will be performed using the safety set. Subjects will be analyzed according to the treatment they actually received.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, serious AEs, and deaths will be similarly summarized or listed. Adverse events of special interest will be summarized by treatment group.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

Antidrug antibody data will be summarized by treatment group and visit.

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STUDY SCHEDULE

Table 1 Schedule of Assessments

Study Procedure	Screening^a	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET^b	Week 20^c	Week 28^c
Visit Number	1	2	3	4	5	6 (Part 1)^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3	84 ±3	140 ±7	196 ±7
Informed consent/assent	X							
Eligibility assessment	X	X				X ^e		
Demographics and medical history ^f	X							
Complete physical examination ^g	X					X		X
Targeted physical examination ^g		X						
Targeted neurological assessment ^h	X					X		X
Vital signs ⁱ	X	X		X	X	X		X
Height	X							
Weight	X	X		X	X	X		X
12-lead ECG ^j	X	X				X		
Chest x-ray ^j	X							
Contraception check ^k	X	X	X	X	X	X		X
Laboratory Assessments								
Hematology	X ^l	X ^l		X	X	X		X
Serum chemistry	X ^l	X		X	X	X		X
Urinalysis	X ^l	X		X	X	X		X
Stool microbiology ^m	X ^l							
HBsAg, HBcAb, HCVAb ⁿ	X ^l							
HIV testing per local regulation ^o	X							
FSH ^p	X ^l							
Serum β-hCG ^q	X ^l							
Urine β-hCG ^q		X		X	X	X		X
TB test (PPD or QuantiFERON TB Gold Plus) ^r		X ^l						
JCV antibody banked sample ^s		X						
[REDACTED]		X		X		X		
[REDACTED]		X ^t		X ^t		X ^t		
[REDACTED]		X ^t		X ^t		X ^t		
[REDACTED]		X ^t		X ^t		X ^t		

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Visit Number	1	2	3	4	5	6 (Part 1) ^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3	84 ±3	140 ±7	196 ±7
ADA and NAb sampling		X ^u	X ^u	X ^u	X ^u	X		
Endoscopic Procedure		X ^t	X	X ^t	X ^t	X		X
Endoscopy (including biopsy) ^v	X ^v					X		
UC Assessments								
Total Mayo score		X ^w					X ^w	
Partial Mayo score				X	X			
Remission stool frequency and pre-UC stool frequency	X							
PRO-UC daily e-diary data instruction	X							
PRO-UC daily e-diary data ^x	X	X	X	X	X	X	X	
Health Assessment ^y								
IBDQ		X			X		X	
Hospitalizations, inpatient days, (HRUA)		X			X		X	X
SF-36, v2, acute form		X			X		X	
Treatment Procedures								
Randomization ^z		X						
Administration of ontamalimab or placebo ^z		X		X	X			
Hypersensitivity monitoring ^{aa}		X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample ^{ab}	X			X	X			

ADA=antidrug antibody; β-hCG=beta-human chorionic gonadotropin; [REDACTED]; ECG=electrocardiogram; ED=emergency department; e-diary=electronic diary; [REDACTED]; ET=early termination; FSH=follicle-stimulating hormone; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCVAb=hepatitis C virus antibody; HEENT=head, eyes, ears, nose, and throat;

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Visit Number	1	2	3	4	5	6 (Part 1) ^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3	84 ±3	140 ±7	196 ±7

HIV=human immunodeficiency virus; HRUA=Healthcare Resource Utilization Assessment; IBDO=Inflammatory Bowel Disease Questionnaire; IGRA=interferon-gamma release assay; JCV=John Cunningham virus; LTS=long-term safety extension; [REDACTED]; NAb=neutralizing antibody; PGA=physician global assessment; [REDACTED]; [REDACTED]; PML=progressive multifocal leukoencephalopathy; PPD=purified protein derivative; PRO=patient-reported outcome; SF-36 v2=Short Form-36 Health Survey, version 2; TB=tuberculosis; [REDACTED]; UC=ulcerative colitis; [REDACTED]

^a At least 2 visits will be necessary to complete the screening procedures, including endoscopy.

^b Subjects who withdraw early during the treatment period should return for the ET visit and then enter into the safety follow-up period.

^c Participation in the safety follow-up period is not required if subject is entering the maintenance study (SHP647-303) or LTS (SHP647-304) at the completion of the Week 12 visit. For subjects participating in the 16-week safety follow-up period (not entering the maintenance study or LTS study), the Week 20 (Visit 7) visit will routinely be conducted by telephone; however, as an exception the visit can be performed as a study site visit if preferred. The Week 28 (Visit 8) visit will be at the study site.

^d Part 1 of Visit 6 must be completed within 10 days (preferably, within 5 to 7 days) before Part 2; this will allow sufficient time for data from the centrally read endoscopy to be available at Part 2 of the visit.

^e The outcome of Visit 6, Part 2 is used to assess eligibility to enroll in the maintenance (SHP647-303) or LTS (SHP647-304) studies. Eligibility for SHP647-303 and SHP647-304 will be assessed under those respective protocols.

^f Medical history will include UC history, cardiac history, and smoking history.

^g Complete physical examination includes the review of the following body systems: general appearance, skin, HEENT, heart, lungs, confrontational visual fields (eyes), breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes. Targeted physical examination includes the review of the following body systems: skin, heart, lungs, confrontational visual fields (eyes), abdomen, and examination of body systems where there are symptom complaints by the subject.

^h Subjects will be evaluated to reveal any potential abnormalities in the following neurologic domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior. Subjects with any unexplained positive item at screening that is suggestive of PML should be excluded. See Section 7.2.3.3 for further details.

ⁱ Vital signs (including blood pressure, pulse, respiratory rate, and temperature) and 12-lead ECG should be performed before collection of blood samples for laboratory assessments and before endoscopic procedure.

^j A chest x-ray performed up to 12 weeks before screening (Visit 1) may be used if available; the official reading must be located in the subject's source documentation.

^k Contraception check should be performed for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential. See Section 4.4 for further details.

^l Screening laboratory test results, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results of repeated tests must be reviewed for eligibility prior to the screening endoscopy procedure.

^m Diagnosis of *Clostridium difficile* infection should be made using the central laboratory. If for any reason the central laboratory is not available, see Appendix 5 for guidance

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Visit Number	1	2	3	4	5	6 (Part 1)^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3	84 ±3	140 ±7	196 ±7

regarding alternate diagnostic algorithms. When a subject experiences an increase in gastrointestinal symptoms, which could be an exacerbation of disease, an infectious etiology must be evaluated including testing for *C. difficile* as described in [Appendix 5](#).

- ⁿ Subjects who test negative for HBsAg but positive for HBcAb without HBV DNA may be considered eligible. For subjects who test positive for HBcAb and negative for HBsAg, a blood sample should be taken for HBV DNA. Blood for HBV DNA reflex testing is collected for required subjects only. If HBV DNA is positive, these subjects will not be eligible.
- ^o Documentation of a negative HIV test result within 6 months prior to screening will be accepted.
- ^p For confirmation of postmenopausal status in females who have had 12 consecutive months of spontaneous amenorrhea and are ≥51 years of age.
- ^q For females of childbearing potential who are not surgically sterile, do not have confirmed ovarian failure, or do not meet the definition of postmenopausal as described in Section 4.4.1 and Section 7.2.3.7.
- ^r A documented negative IGRA or PPD test within 12 weeks before screening (Visit 1) is acceptable provided that an IGRA result or PPD official reading and method is located in the source documentation.
- ^s A serum sample will be collected and banked. It may be analyzed if a subject shows neurologic symptoms suggestive of PML.
- ^t The sample must be collected before administration of investigational product.
- ^u The █ sample must be collected before administration of investigational product.
- ^v Flexible sigmoidoscopy or colonoscopy (if preferred) at screening must be performed on all subjects after the majority of other eligibility criteria (eg, laboratory values) are met. Endoscopy must be performed during the screening period within 10 days before baseline (Visit 2), preferably within 5 to 7 days before the baseline visit, to obtain the centrally read endoscopic subscore. Biopsy samples will be collected for histological evaluation using the Geboes Score classification for the key secondary efficacy endpoint and █. Subjects at risk of colorectal cancer, as defined in exclusion criterion 5 (see Section 4.2), must have a colonoscopy performed at screening, unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidence of dysplasia and colon cancer must be available in the source documents.
- ^w Mayo score will be based on subject daily e-diary entries. The Mayo score at baseline will be calculated based on the stool frequency subscore and rectal bleeding subscore, reported by subjects in the PRO-UC daily e-diary and PGA obtained at baseline and the centrally read endoscopic subscore for the endoscopy performed during the screening period. The Mayo score at the Week 12 visit will be calculated based on the stool frequency subscore and rectal bleeding subscore reported by subjects in the PRO-UC daily e-diary and PGA and the centrally read endoscopic subscore for the endoscopy performed at Week 12, Visit 6 (Part 1). See Section 7.2.2.2 for further details.
- ^x PRO-UC daily e-diary will be collected using a daily e-diary during the treatment period. Collection of the daily e-diary data must begin at least 10 days before the baseline visit (Visit 2). The subject should be provided with the handheld device to take home on their first visit. See Section 7.2.2.3 for further details. Compliance is assessed by site staff at each visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <23 out of 28 e-diary entries) when compared with the previous visit.
- ^y All health outcome or patient-reported questionnaires should be completed before completing any other visit assessments.

Table 1 Schedule of Assessments

Study Procedure	Screening ^a	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET ^b	Week 20 ^c	Week 28 ^c
Visit Number	1	2	3	4	5	6 (Part 1) ^d	6 (Part 2)	7
Study Day	-42 to 0	1	14 ±3	28 ±3	56 ±3	84 ±3	140 ±7	196 ±7

^a Interactive response technology will be used for randomization and dispensation of study treatment.

^{aa} Beginning at Visit 2, at each visit the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored until the adjudication committee determines whether testing is appropriate.

^{ab} Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the visit at which testing will be done.

Note: See Section 7.2 for the order in which assessments should be performed. Timing of visits is relative to baseline (Visit 2).

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Ulcerative colitis (UC) is a chronic, relapsing disease marked by ulceration and inflammation of the colonic mucosa and submucosa. Initially it usually involves the rectum but may extend proximally to involve a portion of, or the entirety of, the colon. In the early stages, hemorrhagic and erythematous tissue is observed, progressing to mucosal ulceration with purulent exudates in severe cases. The ulceration pattern is continuous and may extend the entire length of the colon. Perforation of the bowel wall causing ileus and peritonitis can occur with transmural extension of the ulceration. Bloody diarrhea with or without mucus and lower abdominal pain with periods of remission and exacerbation are the most common symptoms.

The incidence of UC is estimated to be up to 24.3 cases per 100,000 persons per year in Europe and up to 19.2 cases per 100,000 persons per year in North America. No clear difference in incidence has been observed between men and women. Although UC can occur at any age, peak incidence has been observed in the second to fourth decades of life ([Molodecky et al., 2012](#)). Ulcerative colitis is a lifelong condition with a serious effect on the quality of life. Current treatment primarily consists of symptomatic management with dietary modifications and opiate antidiarrheal drugs (loperamide), as well as disease modifying agents such as 5-aminosalicylic acid (5-ASA), systemic glucocorticoids, immunosuppressive agents (azathioprine [AZA]/6-mercaptopurine [6-MP], cyclosporine), and biologic therapy with anti-tumor necrosis factor (TNF) or anti-integrin agents. Despite recent advances, there is still an unmet need for an effective pharmacological treatment that will induce and maintain remission.

1.2 Product Background and Clinical Information

The selectivity of lymphocyte homing to specialized lymphoid tissue and mucosal sites of the gastrointestinal (GI) tract is influenced by the endothelial expression of mucosal addressin cell adhesion molecule (MAdCAM). MAdCAM is a member of the immunoglobulin super family of cell adhesion molecules and is mostly expressed on the cell surface of high endothelial venules of organized intestinal lymphoid tissue such as Peyer's patches and mesenteric lymph nodes ([Briskin et al., 1997](#); [Shyjan et al., 1996](#); [Liaskou et al., 2011](#)). MAdCAM plays a role in gut immune surveillance, and also appears to facilitate excessive lymphocyte infiltration under conditions of chronic GI inflammation. The $\alpha_4\beta_7$ integrin is the recognized ligand for MAdCAM, and expression of this ligand on populations of CD4 $^{+}$ and CD8 $^{+}$ T cells, as well as on subsets of B cells, distinguishes them as unique gut homing lymphocytes.

Ontamalimab (previously known as PF-00547659 and SHP647) is a fully human immunoglobulin G2 kappa (IgG2 κ) monoclonal antibody that binds to human MAdCAM to reduce lymphocyte homing to the gut and GI inflammation. Ontamalimab binds MAdCAM-1 with high affinity and selectivity that prevents the binding of $\alpha_4\beta_7^{+}$ lymphocytes to MAdCAM expressing sites in the high endothelial venules of the GI tract.

1.3 Benefit/Risk Assessment

Ontamalimab has been evaluated in Phase 1 and Phase 2 clinical studies in subjects with UC and Crohn's disease (CD). In UC Study A7281009, induction with ontamalimab at doses of 7.5 mg, 22.5 mg, or 75 mg once every 4 weeks (Q4W) resulted in statistically significantly higher proportions of subjects in remission at Week 12 based on total Mayo score (both local and central read) when compared with placebo treatment. In CD Study A7281006, induction with ontamalimab did not meet the primary endpoint; no statistically significant differences were observed between the active treatment arms and the placebo arm in CD Activity Index-70 response rate at Week 8 or Week 12. Post hoc analyses suggested evidence of drug effect in subjects with more inflammation at baseline, as indicated by higher serum concentrations of C-reactive protein (CRP) or Simple Endoscopic Score for CD.

In UC induction Study A7281009, decreases in fecal calprotectin were observed in all groups, including placebo; however, there were no statistically significant differences in the decrease in fecal calprotectin between any dose level of ontamalimab and placebo. Decreases in high-sensitivity (hs)CRP were also observed in all 4 treatment groups; however, other than the 75 mg dose group at Week 12, no statistically significant differences were observed in active treatment versus placebo. In the induction Study A7281006 in subjects with CD, compared to placebo, nominally statistically significant decreases in fecal calprotectin were observed in the 75 mg group at Week 8 and in the 22.5 mg and 75 mg groups at Week 12. Generally, decreases from baseline in hsCRP were observed in all 4 treatment groups over the 12-week induction period. Compared to placebo, nominally statistically significant decreases in hsCRP were observed in all 3 active treatment groups (22.5 mg, 75 mg, and 225 mg) at Week 12. There was no evidence of a dose response for either of these parameters. A nominally statistically significant increase was observed in circulating β 7⁺ central memory T lymphocytes at Weeks 8 and 12, consistent with the predicted mechanism of action.

The most common serious adverse events (SAEs) across all studies were CD and UC. In Study A7281006, the randomized, placebo-controlled induction study in CD, treatment-emergent adverse events (TEAEs) were most commonly reported within the GI disorders system organ class (SOC) followed by the infections and infestations SOC. The most common all-causality TEAEs were CD (worsening and progression of underlying disease), followed by pyrexia, headache, and arthralgia, all of which had similar incidences in the placebo treatment group compared with the active treatment groups. In Study A7281009, the randomized, placebo-controlled induction study in UC, TEAEs were most commonly reported within the GI disorders SOC followed by the infections and infestations SOC. The most common all-causality TEAE was headache, followed by abdominal pain, nasopharyngitis, UC (worsening and progression of underlying disease), and nausea, all with similar incidence between placebo- and drug-treated subjects.

The long-term, open-label safety studies (Studies A7281007 and A7281010) were not placebo-controlled, but permitted exposure to the investigational product at doses of 75 mg or 225 mg Q4W for 18 and 36 months, respectively. In Study A7281007, the most common all-causality TEAE was CD (worsening or progression), arthralgia, nasopharyngitis, and abdominal

pain. In Study A7281010, the most common all-causality TEAEs were UC (worsening or progression), arthralgia, and nasopharyngitis.

Ontamalimab appears to be generally well tolerated, with the majority of TEAEs distributed at similar frequencies among treatment arms with only peripheral edema, gastroenteritis, and arthralgia more frequently reported in ontamalimab- than placebo-treated subjects in the pooled induction studies. In the placebo-controlled induction studies, nasopharyngitis was not reported more frequently in ontamalimab- than placebo-treated subjects, but occurred at relatively high frequency during long-term safety studies. Ontamalimab does not appear to be associated with impaired central nervous system (CNS) immune surveillance. No case of progressive multifocal leukoencephalopathy (PML) or myocarditis has been reported. Ontamalimab, in doses of 7.5 mg, 22.5 mg, and 75 mg, appears to increase the rate of remission in subjects with UC, and may have an effect in patients with CD who have greater evidence of inflammation based on biomarker or endoscopic data.

Always refer to the latest version of the ontamalimab investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding the pharmacokinetics (PK), efficacy, and safety of ontamalimab.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Ontamalimab, a fully human IgG_{2κ} antihuman MAdCAM monoclonal antibody, is under development for the treatment of UC. Ontamalimab prevents the binding of α₄β₇⁺ lymphocytes to MAdCAM-expressing sites with high affinity and selectivity. Principal sites of MAdCAM expression on normal tissue include intestine, pancreas, stomach, esophagus, spleen, and to a lesser extent lung, liver, and bladder but not the CNS ([Steffen et al., 1996](#)).

Although selective targeting of the MAdCAM receptors is a novel approach, the basic interference of lymphocyte homing by preventing the binding of these α₄β₇⁺ lymphocytes to the MAdCAM receptor and the resultant efficacy in UC is well established ([Feagan et al., 2013](#)). Ontamalimab is differentiated from other molecules used for the treatment of UC in that it blocks the interaction of α₄β₇⁺ lymphocytes to the MAdCAM receptor by selectively binding to MAdCAM in the gut (and related tissues) whereas other molecules only target the integrins on the infiltrating lymphocytes. Additionally, ontamalimab does not bind to the vascular cell adhesion molecule; therefore, ontamalimab is not expected to be an effective treatment for multiple sclerosis, or affect lymphocyte homing or surveillance in the CNS.

This study is designed to evaluate the efficacy of ontamalimab in inducing remission in subjects with moderate to severe UC.

Ontamalimab has been investigated in subjects with moderate to severe UC in 3 completed studies: 2 dose-finding studies (A7281001 and A7281009) and an open-label, long-term safety extension (LTS) study (A7281010), which was ongoing at the time of the original protocol and has since completed. Phase 1 Study A7281001 evaluated both single (0.03–10.0 mg/kg intravenous [IV]; 3.0 mg/kg subcutaneous [SC]) and multiple doses (0.1–3.0 mg/kg IV; 0.3 and 1.0 mg/kg SC) of ontamalimab in subjects with UC. Safety evaluation revealed a safety profile for ontamalimab similar to that of placebo, with no pattern of adverse events (AEs) suggestive of increased risk of opportunistic infections or CNS effects, and no evidence of adverse effects on laboratory parameters, electrocardiograms (ECGs), vital signs, or neurological function. Events leading to withdrawal were due to exacerbations of the underlying UC.

Study A7281009 was a Phase 2b proof-of-concept (randomized, double-blind, placebo-controlled, parallel, dose-ranging) study designed to evaluate the efficacy, safety, and PK of ontamalimab in subjects with moderate to severe UC. Treatment was assigned in a 1:1:1:1:1 ratio to dose levels of 7.5, 22.5, 75, or 225 mg ontamalimab or placebo administered SC Q4W at Weeks 0, 4, and 8. The primary endpoint of the study was the proportion of subjects in clinical remission at Week 12, with remission defined as a total Mayo score of ≤2 with no individual subscore >1 (see [Appendix 2](#) for details of the Mayo score). More subjects were in clinical remission at Week 12 in the ontamalimab-treated groups than in the placebo group, with statistical significance achieved for the 7.5, 22.5, and 75 mg doses ([Vermeire et al., 2017](#)). Based upon the total Mayo score with a centrally read endoscopic severity component, the increase in clinical remission rates over placebo at Week 12 for the 7.5, 22.5, and 75 mg doses were 8.0% (p=.043), 12.8% (p=.010), and 11.8% (p=.012), respectively. When the clinical remission rate at Week 12 was analyzed by stratum of previous anti-TNF exposure (experienced or naïve), a

similar trend was observed across dose levels in both the anti-TNF experienced and anti-TNF naïve subjects. There was no evidence of an adverse safety signal, and there was no increase in the frequency of infections in MAdCAM-bearing tissues as evidenced by similar rates of nasopharyngitis among treatment arms.

Based on the efficacy and safety data in Study A7281009 and the systemic population PK and pharmacodynamic (PD) modeling and simulation, clinical remission, clinical response and mucosal healing rates were higher in subjects with UC receiving doses of 22.5 and 75 mg Q4W than in those receiving doses of 7.5 mg and 225 mg Q4W. The induction responses were not demonstrated either at Week 4 or Week 8, but were observed at Week 12 regardless of dose level. No difference in the clinical responses between a 22.5 mg dose and a 25 mg dose is expected based on the current understanding of the mode of action of ontamalimab and clinical observations to date. To better understand the exposure (dose)-response relationship in this population and understand individual patient exposure needs, the 25 and 75 mg doses (Q4W) will be tested in the Phase 3 program. Therefore, SC doses of 25 mg or 75 mg of ontamalimab or placebo on Day 1 (Week 0), Week 4, and Week 8 are recommended for the 2 planned Phase 3 studies SHP647-301 and SHP647-302. The Phase 1 study, A7281001, which investigated the safety, tolerance, PK, and PD properties of ontamalimab, supports further clinical development of ontamalimab using SC administration.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of ontamalimab in inducing remission, based on composite score of patient-reported symptoms and centrally read endoscopy, in subjects with moderate to severe UC.

2.2.2 Secondary Objectives

2.2.2.1 Key Secondary Objectives

The key secondary objectives are as follows:

- To evaluate the efficacy of ontamalimab in achieving endoscopic remission, based on centrally read endoscopy
- To evaluate the efficacy of ontamalimab in achieving clinical remission, based on composite score of patient-reported symptoms
- To evaluate the efficacy of ontamalimab in inducing clinical response, based on composite score of patient-reported symptoms and centrally read endoscopy
- To evaluate the efficacy of ontamalimab in achieving mucosal healing, based on a centrally read endoscopic and histological assessment using the Geboes Score grading system.

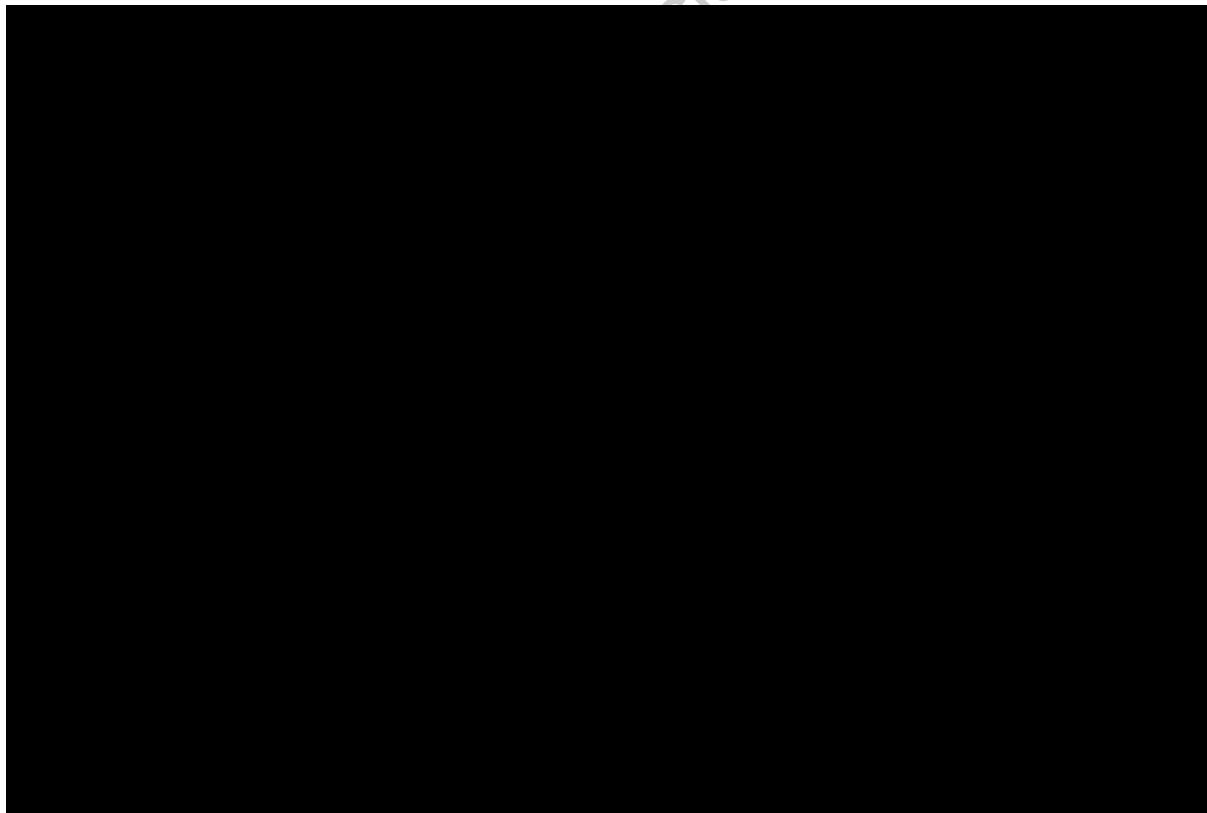
2.2.2.2 Other Secondary Objectives

The other secondary objectives are as follows:

- To evaluate the safety and tolerability of ontamalimab
- To evaluate the effect of ontamalimab induction treatment on other clinical and endoscopic outcomes (including Mayo-based remission and clinical response, partial Mayo score over time, clinical remission over time, endoscopic remission, and deep remission)
- To evaluate the effect of ontamalimab on abdominal pain, urgency, diarrhea, and absolute stool frequency and bleeding scores
- To evaluate the effect of ontamalimab on health-related quality of life (HRQL) (as measured by the Inflammatory Bowel Disease Questionnaire [IBDQ] and the Short Form-36 Health Survey [SF-36])
- To evaluate the effect of ontamalimab on incidence of hospitalizations and total inpatient days.

2.2.3 Exploratory Objectives

The exploratory objectives of the study are as follows:



3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of ontamalimab in inducing remission in subjects with moderate to severe UC.

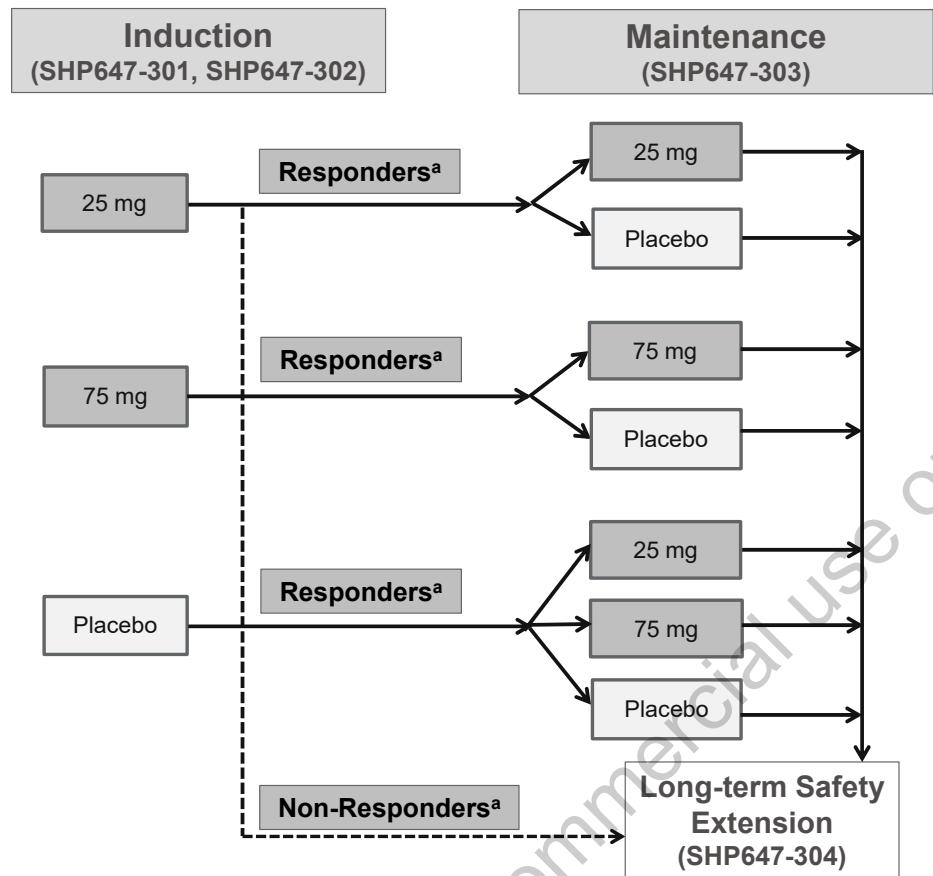
A total of 740 subjects (296 subjects at 25 mg ontamalimab, 296 subjects at 75 mg ontamalimab, and 148 subjects on placebo) are planned for enrollment into the study ([Figure 1](#)). Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent form.

The study consists of a screening period up to 6 weeks and a 12-week treatment period. After the screening period, eligible subjects will be randomly assigned to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo) in a 2:2:1 ratio. Randomization will be stratified based upon the subject's status of prior anti- TNF treatment (naïve or experienced) and glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline). Subjects will receive SC injections of ontamalimab or placebo, using a prefilled syringe (PFS), on Week 0/Day 1 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 5). Subjects will undergo efficacy, [REDACTED] safety, and health outcome assessments at these visits as detailed in [Table 1](#).

At the end of the 12-week treatment period, eligible subjects will be offered the opportunity to participate in a double-blind maintenance study (SHP647-303; for subjects who achieve clinical response) or an LTS study (SHP647-304; for subjects who do not achieve a clinical response) as shown in [Figure 1](#). Subjects who withdraw early from the 12-week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

The overall study design is shown in [Figure 2](#).

Figure 1 Overview of Ontamalimab Phase 3 Studies in Ulcerative Colitis



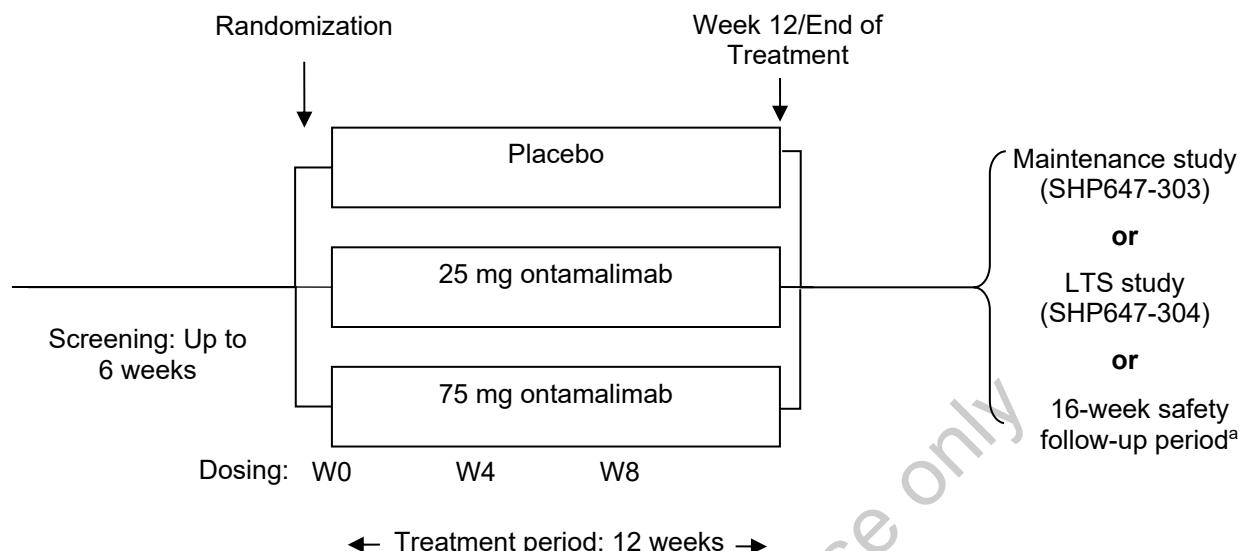
^a Clinical response is defined as:

1. A decrease from the induction study (SHP647-301 or SHP647-302) baseline in the composite score of patient-reported symptoms using daily electronic-diary and centrally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1

OR

2. A decrease from the induction study (SHP647-301 or SHP647-302) baseline total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 .

Figure 2 Study Design Flow Chart



LTS=long-term safety extension; W=week

^a Subjects who withdraw early from the 12-week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period.

3.1.1 Rationale for Primary Endpoint

The Mayo score has historically been used as the primary endpoint for pivotal studies of agents intended to treat UC. Over the past decade, health authority thinking regarding efficacy endpoints for UC has evolved such that the traditional Mayo score is no longer recommended. Current regulatory guidance (Food and Drug Administration [FDA] Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry [Draft], 2016; European Medicines Agency [EMA] Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis [Draft], 2016) includes a dual measurement of patient-reported signs and symptoms outcomes (stool frequency and rectal bleeding), and clinician-reported endoscopic outcomes (scoring any endoscopy with evidence of friability as a 2), including histology. Per agreement with health authorities, these 3 outcomes will be reported as a composite score.

Data will be collected to calculate the total Mayo score using both the traditional and modified endoscopy subscore as a sensitivity analysis and to estimate the impact of the modification on the primary endpoint. The clinical relevance of the traditional Mayo score is supported by its correlation with significant improvement in disease-specific HRQL as measured by the IBDQ and in generic HRQL as measured by the SF-36 questionnaire.

3.1.2 Rationale for Key Secondary Endpoints:

The first 2 key secondary endpoints are included to comply with EMA advice. The EMA would agree to the composite primary endpoint only if supported by a key secondary analysis, where the patient-reported symptoms and clinician-reported endoscopy are analyzed as “co-primary”.

The clinical response endpoint is based on the new composite score, and also represents 1 of the entry criteria for the maintenance study. This endpoint has not been previously tested.

Mucosal healing as a key secondary endpoint comprises both endoscopic and histologic components as recommended in the draft FDA and EMA guidance on UC (FDA Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry [Draft], 2016; EMA Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis [Draft], 2016).

The Geboes Score (see [Appendix 2](#)) will be used to evaluate histologic remission and to complement the endoscopic subscore in the assessment of mucosal healing for the key secondary endpoint.

3.2 Duration and Study Completion Definition

Each subject's final visit in this study may be at the end of the treatment period (Week 12) if continuing to Study SHP647-303 or SHP647-304, or at the end of the safety follow-up period (Week 28) if not continuing to either of these studies. In either case, the final visit will be in person at the site. A subject's maximum duration of participation is expected to be approximately 34 weeks: a screening period of up to 6 weeks, a treatment period of 12 weeks, and a safety follow-up period of 16 weeks (if applicable). It is expected that the study will be completed in approximately 3 years.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

It is anticipated that the study will be conducted in at least 18 countries. Regions will include North America, Europe, the Middle East, and Africa, Latin America, and Asia-Pacific. Approximately 210 sites will be utilized.

4 STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed. Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must be between ≥ 16 and ≤ 80 years of age at the time of the signing of the informed consent/assent form.

Note: Subjects <18 years of age must weigh ≥ 40 kg and must have body mass index ≥ 16.5 kg/m².

4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for ≥ 3 months before screening. The following must be available in each subject's source documentation:
 - A biopsy report to confirm the histological diagnosis
 - A report documenting disease duration based upon prior colonoscopy.

Note: If this documentation is not available at the time of screening, a colonoscopy with biopsy to confirm the diagnosis is required during the screening period.

5. Subjects must be willing to undergo a flexible sigmoidoscopy or colonoscopy (if preferred), including biopsy sample collection, during screening after all other inclusion criteria have been met.
6. Subjects must have moderate to severe active UC, defined as a total Mayo score of ≥ 6 , including a centrally read endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 at baseline (Visit 2).
7. Subjects must have evidence of UC extending proximal to the rectum (ie, not limited to proctitis).
8. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as mesalamine (5-ASA), glucocorticoids, immunosuppressants (AZA, 6-MP, or methotrexate [MTX]), or anti-TNF (see [Appendix 4](#) for guidance).

9. Subjects receiving any treatment(s) for UC described in Section 5.2.1 are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
10. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception (ie, highly effective methods for female and medically appropriate methods for male study subjects) (as described in Section 4.4) for the duration of the study.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Subjects with indeterminate colitis, microscopic colitis, nonsteroidal anti-inflammatory drug-induced colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of CD.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for UC during the treatment period.
5. Subjects at risk for colorectal cancer must have a colonoscopy ([Eaden and Mayberry, 2002](#)) performed during the screening period with results available within 10 days before the baseline visit (Visit 2), unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidence of dysplasia and colon cancer must be available in the source documents.

Subjects at risk for colorectal cancer include, but are not limited to:

- Subjects with extensive colitis for ≥ 8 years or disease limited to left side of colon (ie, distal to splenic flexure) for ≥ 10 years before screening, regardless of age
 - Subjects ≥ 50 years of age at the time of signing of the informed consent form.
6. Subjects have had prior treatment with ontamalimab (formerly PF-00547659; SHP647).
 7. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
 8. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
 9. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).

10. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than their current background UC treatment) within 30 days before baseline (Visit 2).
11. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
12. Subjects have received parenteral or rectal glucocorticoids, or rectal 5-ASA, within 14 days before screening endoscopic procedure.
13. Subjects have received leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange within 30 days before baseline (Visit 2).
14. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before baseline (Visit 2).
15. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).
16. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis (subjects with *C. difficile* infection at screening may be allowed re-test after treatment), evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
17. Subjects with abnormal chest x-ray findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation.)
18. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) or subjects with this history who have not completed a generally accepted full course of treatment before randomization are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed.

Subjects who have no history of previously diagnosed active or latent TB are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥ 5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before screening. If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

- An IGRA is strongly recommended for subjects with a prior Bacillus Calmette-Guérin vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON TB Gold Plus In-Tube Test.

- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent TB, a positive test on repeat will exclude the subject. Subjects with a history of active or latent TB infection must follow instructions for “Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met” in this criterion.
- Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray, taken within the 12 weeks before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
 - A chest x-ray performed within 12 weeks before or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.
19. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
20. Subjects with any unexplained symptoms suggestive of PML based on the targeted neurological assessment during the screening period (see Section 7.2.3.3).
21. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
22. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
- Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious

illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study

- Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence)
 - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening (Visit 1)
 - History of significant cerebrovascular disease within 24 weeks before screening (Visit 1).
23. Subjects who have had significant trauma or major surgery within 4 weeks before the screening visit (Visit 1), or with any major elective surgery scheduled to occur during the study.
24. Subjects with evidence of cirrhosis with or without decompensation.
25. Subjects with primary sclerosing cholangitis.
26. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Note: if a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if no presence of hepatitis B virus (HBV) DNA is confirmed by HBV DNA polymerase chain reaction (PCR) reflex testing performed in the central laboratory.
27. Subjects with chronic hepatitis C virus (HCV) (positive HCV antibody [HCVAb] and HCV RNA). Note: Subjects who are HCVAb positive without evidence of HCV RNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCV RNA at least 12 weeks prior to baseline]).
28. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening. Note: Screening laboratory tests, if the results are considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results must be reviewed for eligibility prior to the screening endoscopy procedure.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels $\geq 3.0 \times$ the upper limit of normal (ULN)
 - Total bilirubin level $\geq 1.5 \times$ ULN or $> 2.0 \times$ ULN if the subject has a known documented history of Gilbert's syndrome
 - Hemoglobin level ≤ 80 g/L (8.0 g/dL)
 - Platelet count $\leq 100 \times 10^9/\text{L}$ ($100,000 \text{ cells/mm}^3$) or $\geq 1000 \times 10^9/\text{L}$ ($1,000,000 \text{ cells/mm}^3$)*
 - White blood cell count $\leq 3.5 \times 10^9/\text{L}$ (3500 cells/mm^3)
 - Absolute neutrophil count $< 2 \times 10^9/\text{L}$ (2000 cells/mm^3)

- Serum creatinine level $>1.5 \times \text{ULN}$ or estimated glomerular filtration rate $<30 \text{ mL/min}/1.73\text{m}^2$ based on the abbreviated Modification of Diet in Renal Disease Study Equation.
*Note: If platelet count is $<150,000 \text{ cells/mm}^3$, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.
- 29. Subjects with known human immunodeficiency virus (HIV) infection based on documented history, with positive serological test, or positive HIV serologic test at screening, tested at the site's local laboratory in accordance with country requirements or tested at the central laboratory. Note: A documented negative HIV test within 6 months of screening is acceptable and does not need to be repeated.
- 30. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse or dependency of any kind, including abuse of medical marijuana (cannabis).
- 31. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or ECG abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
- 32. Female subjects who are planning to become pregnant during the study period.
- 33. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm, and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
- 34. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

4.3 Restrictions

Smoking can have an influence on the severity of UC disease symptoms. Subjects should inform the investigator of any changes to their smoking habits during the study; however, these data will not be captured in the electronic case report form (eCRF). Use of nicotine patches should be recorded as concomitant medication (see Section 5.2).

For the purposes of this protocol, dietary supplements (such as vitamins, minerals, purified food substances, and herbs with pharmaceutical properties) are considered to be concomitant medications (see Section 5.2).

4.4 Reproductive Potential

The potential effects of ontamalimab on embryofetal or postnatal development have not been assessed in humans. Preliminary results from an enhanced pre- and postnatal development toxicity study of ontamalimab in nonhuman primates indicated that, at the dose levels tested

(30 and 60 mg/kg), infant losses were increased in ontamalimab-exposed animals when compared both to control animals in the study and to the historical control animal data from the testing facility. The relevance of this finding to humans is unknown but cannot be excluded. Based on the exposure in the Phase 2 clinical study A7281009 (area under the concentration-time curve [AUC] from 0 to 672 hours [AUC_{0-672h}] at 6140 µg·h/mL following repeated SC administration of 75 mg SHP647 Q4W), maternal exposure (AUC) in cynomolgus monkeys within a similar duration at 30 and 60 mg/kg once every 10 days is approximately 77 times and 172 times the clinical exposure, respectively.

To minimize the risk of unintentional exposure of the embryo or fetus in the clinical study, all sexually active male and female subjects who, in the opinion of the investigator, are biologically capable of having children and with their partners are at risk of pregnancy, must agree to use an appropriate form of contraception (ie, highly effective methods for female and medically appropriate methods for male study subjects), in accordance with the package instructions/leaflet, for the duration of the active treatment period and for at least 16 weeks after the last dose of investigational product.

True abstinence is considered to be a highly effective contraception (ie, a method that results in a failure rate of <1% per year) when it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to investigational product, and withdrawal are not appropriate methods of contraception.

During the screening visit, the investigator or designee in consultation with the subject will confirm the subject's childbearing potential status. For subjects of childbearing potential, it must be confirmed and documented that the subject has selected the most appropriate method of contraception (ie, highly effective methods for female and medically appropriate methods for male study subjects) from the permitted list of contraception methods. Subjects must affirm the consistent and correct use of at least 1 of these selected methods. Regular contraception check discussions will take place at the time points specified in [Table 1](#) (ie, at each site visit) and will be documented. In addition, the subject must be instructed to call the site immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

4.4.1 Contraceptive Methods for Female Study Subjects

Sexually active females of childbearing potential must already be using an established highly effective form of contraception, and must be advised to use appropriate contraceptives throughout the study period and for 16 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the clinical study. The following highly effective contraceptive methods are considered to be methods with low user dependency:

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

- Male sterilization/vasectomized partner
- Implantable progesterone-only hormonal contraception associated with inhibition of ovulation.

Female subjects should be in one of the following categories:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥51 years of age); postmenopausal status should be confirmed by follicle-stimulating hormone (FSH) testing.
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks poststerilization or has medically confirmed ovarian failure.
- Females of childbearing potential with a negative serum pregnancy test result at screening and a negative urine pregnancy test result at baseline (Visit 2). Females of childbearing potential must agree to practice true abstinence (refrain from sexual activity that could result in pregnancy) or agree to use appropriate methods of highly effective contraception.

Highly effective contraception (ie, methods that result in a failure rate of <1% per year when used consistently and correctly) are:

- Combined (estrogen- and progestogen-containing) hormonal contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal) stabilized for at least 30 days before the screening visit (Visit 1)
- Progestogen-only hormonal contraception associated with inhibition of ovulation plus a barrier method
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization/vasectomized partner with documented absence of sperm in the postvasectomy ejaculate
- True abstinence (see Section 4.4).

4.4.2 Contraceptive Methods for Male Study Subjects

Contraception is required for all sexually active male subjects, who with their female sexual partners, must agree to use one of the following appropriate methods of contraception throughout the study period and for 16 weeks following the last dose of investigational product.

Appropriate methods of contraception for male subjects are:

- Male condom with spermicide; however, if spermicide is not available in the country, additional contraception (ie, one of those listed below) must be used in addition to a male condom
- Male sterilization with documented absence of sperm in the postvasectomy ejaculate.

Appropriate methods for female sexual partners of male subjects are (unless the female sexual partner is sterile [surgically or documented nonsurgical sterility]):

- Use of a highly effective method of contraception listed in Section 4.4.1 OR an acceptable method of contraception (failure rate of >1% per year)
 - Female condom with spermicide (use by female sexual partner); however, if spermicide is not available in the country, additional contraception (ie, one of those listed below) must be used in addition to a female condom
 - Intrauterine device with spermicide
 - Contraceptive sponge with spermicide
 - Intravaginal system (eg, vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide).

4.5 Withdrawal of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 12/early termination (ET; Visit 6) are to be performed. All subjects who discontinue treatment with investigational product should also undergo the protocol-specified 16-week safety follow-up period. In the event that subjects are unable to attend in person for the follow-up visits, all efforts should be made to collect information on AEs and concomitant medications.

Comments (spontaneous or elicited) or complaints made by the subject must be recorded. The reason for termination and date of stopping investigational product must be recorded.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

Additional reasons a subject may be withdrawn from study treatment include but are not limited to:

- Adverse events
- Serious AEs
- Pregnancy
- Protocol deviations

- Failure to return for visits.

A subject should be withdrawn from study treatment:

- If a new therapy is initiated for UC, or
- If a subject undergoes surgery for UC.

Subjects who withdraw from study treatment due to an increase in disease symptoms may see nonstudy-related physicians for treatment, and may receive treatments prohibited during the treatment periods of this study.

If a subject withdraws their consent, no further evaluation should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

4.5.2 Reasons for Withdrawal

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Other (if "other" is selected, the investigator must specify the reason)
- Death
- Physician decision
- Pregnancy
- Screen failure
- Site terminated by sponsor.

4.5.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point before the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and that they return their electronic diary (e-diary).

5 PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal remedies and vitamins) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the first dose of investigational product. Use of biologics for indications other than UC during the 90 days before screening must also be recorded.

Prior and concomitant UC-specific treatments from the previous 10 years will be recorded. The subject's entire history of biologic UC-specific treatments will be recorded.

Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or 5-ASA, glucocorticoids, immunosuppressants (AZA, 6-MP, or MTX), or anti-TNF agents. Please see [Appendix 4](#) for guidance on defining prior treatment failure and intolerance to prior treatment for UC.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the safety follow-up period, inclusive.

5.2.1 Permitted Treatment

Subjects must remain on stable doses of permitted UC treatments until completion of the Week 12 visit, unless decreases are required because of AEs. Stable doses of the following treatments for UC are permitted as concomitant medication:

- Oral 5-ASA or sulfasalazine, providing that the dose is stable for at least 2 weeks before baseline (Visit 2)
- Immunosuppressants (AZA, 6-MP, or MTX), providing that the dose is stable for at least 8 weeks before baseline (Visit 2)
- Oral glucocorticoids (prednisone or equivalent [see [Appendix 3](#)] up to a maximum of 20 mg/day or oral budesonide up to a maximum of 9 mg/day or oral beclomethasone up to a maximum of 5 mg/day), providing that the dose is stable for at least 2 weeks before screening endoscopic procedure.

Note: Rectal 5-ASA and parenteral or rectal glucocorticoids are prohibited from within 14 days before screening endoscopic procedure.

Subjects using medicinal marijuana (cannabis) under a physician's prescription, and who obtain the product from a licensed pharmacy or provider, should continue to use it under the same regimen for the duration of the study, unless otherwise instructed by the investigator or treating physician. Such subjects must be using the product, in a stable regimen, for at least 3 months before screening.

Routine nonlive vaccinations are allowed during the study.

Dietary and herbal supplements and probiotics are allowed in the study, provided they are being taken at stable doses at the time of the baseline visit (Visit 2) and for the duration of the study. They should be recorded as concomitant medications.

Use of nicotine patches should be recorded as concomitant medication.

5.2.2 Prohibited Treatment

Table 2 details the minimum required number of days before baseline (Visit 2) for common prior treatments that are excluded medications for this study.

Table 2 Common Excluded Treatments

Treatment	Permanently Excluded	Minimum Required Number of Days Before Baseline (Visit 2)			
		14	30	60	90
Ontamalimab (PF-00547659; SHP647) in a previous study	X				
Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab)	X				
Parenteral and rectal glucocorticoids		X ^a			
Rectal 5-ASA		X ^a			
Investigational products			X ^b		
Live (attenuated) vaccine			X		
Nonbiologics with immunomodulatory properties (other than their current background UC treatment)			X		
Anti-TNF treatment				X	
Leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange			X		
Biologics with immunomodulatory properties (other than anti-TNFs) including biosimilars					X

5-ASA=5-aminosalicylate; TNF=tumor necrosis factor; UC=ulcerative colitis

^a The minimum required number of days before baseline (Visit 2) for rectal 5-ASA and parenteral or rectal glucocorticoids is defined as 14 days before screening endoscopic procedure (see Section 4.2, exclusion criterion 12).

^b Or 5 half-lives if longer.

Treatments not listed in **Table 2** may be considered allowable; see Section 5.2.1 for further details.

No new nonpharmacological therapies that might affect bowel habit or GI function should be started during the study.

5.2.3 Rescue Therapy

Subjects must maintain their stable dose of background UC treatment, unless dose reduction or discontinuation is required due to associated AEs. If a subject requires initiation of a new therapy or increase in glucocorticoids for UC above the SHP647-301 or SHP647-302 baseline, the subject should be withdrawn from study treatment and enter the safety follow-up period, and appropriate treatment should be given at the discretion of the investigator.

Subjects who enter the safety follow-up period will no longer need to abstain from the medications that were prohibited during the baseline and treatment periods. High-dose glucocorticoids and other UC treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated during the safety follow-up period without prior discussion with the sponsor study physician or designee due to the long half-life of ontamalimab.

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6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is ontamalimab, which will be provided as a sterile aqueous buffered solution for SC administration in a glass PFS with a fixed needle. Each PFS contains 1 mL of ontamalimab solution for injection at an appropriate concentration to provide the intended dose of drug (25 or 75 mg). Additional information is provided in the current ontamalimab IB.

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain ontamalimab.

6.1.1 Blinding the Treatment Assignment

The placebo syringes and solution will match the ontamalimab syringes in appearance. The fill volume for all syringes will be the same.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive response technology (IRT) system will be used for screening and enrolling subjects, recording subject visits, randomization, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and emergency unblinding. Please refer to the Study Manual for additional details regarding the IRT system.

6.2.2 Allocation of Subjects to Treatment

This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule.

The total Mayo score will be calculated at baseline (Visit 2) before randomization. Endoscopic subscore based on the central reader's assessment will be used to determine eligibility. Subjects with a total Mayo score of ≥ 6 , including a centrally read endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 , and who fulfill all other eligibility criteria, will be randomized in a ratio of 2:2:1 via a computer-generated randomization schedule to receive SC injections of 25 mg ontamalimab, 75 mg ontamalimab, or placebo, respectively. The randomization will be performed centrally and stratified by status of prior anti-TNF therapy (2 strata: naïve versus experienced) and glucocorticoid use at baseline (2 strata: on glucocorticoids at baseline versus not on glucocorticoids at baseline).

To ensure that the allocation of subjects with prior anti-TNF therapy exposure is similar to that observed in Study A7281009, the percentage of subjects with prior anti-TNF therapy exposure will be capped at 60% of the sample population. Additionally, in Japan only, enrollment of Japanese subjects with prior anti-TNF therapy exposure will be capped at 60%, to ensure comparability to the rest of the global study population. There will be no cap on the number of anti-TNF naïve subjects randomized.

Subject numbers are assigned to all eligible subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number will be assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. Individual subject treatment will be automatically assigned by the IRT system.

Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

6.2.3 Dosing

Investigational product (ontamalimab or placebo) will be administered subcutaneously by qualified site personnel Q4W (Weeks 0, 4, and 8). See Section 7.2 for the timing of dosing relative to other procedures.

Investigational product should be administered in the anterolateral right or left thigh. If there are clinical reasons why the investigational product cannot be administered in the thigh, the investigational product may be administered in the deltoid area or abdomen with appropriate documentation. The location of the investigational product administration will be recorded.

After the first administration of investigational product, the subject must be observed by a member of the study staff for at least 30 minutes (the total duration should be determined at the discretion of the investigator). For subsequent administrations, observation of the subject is at the discretion of the investigator. Injection site and allergic reaction monitoring should be completed by a member of the study staff.

Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is dispensed by qualified staff members.

6.2.4 Unblinding the Treatment Assignment

Whenever possible, the investigator or subinvestigator should contact the Shire physician and/or assigned medical monitor before breaking the blind. It is understood that in an emergency situation it may not be possible to communicate with the study team before breaking the blind. The safety of the subject should be of primary concern. When the blinding code is broken the reasons must be fully documented.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded on the IRT and the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. The IRT will notify the relevant personnel in the event of any code break. Code-break information is held by the pharmacist/designated person at the site.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

The sponsor will provide the investigator with packaged investigational product labeled in accordance with specific country regulatory requirements. All investigational product is labeled with a minimum of the following: protocol number, medication identification number, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements “For clinical trial use only” and/or “CAUTION: New Drug – Limited by Federal (or US) Law to Investigational Use”, and the sponsor’s name and address.

Additional labels may be applied in order to meet local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name.

Additional labels may not be added without the sponsor’s prior written agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled containers: PFS with nominal fill volume of 1 mL. The PFS will be packaged in a labeled carton.

Changes to sponsor-supplied packaging before dosing may not occur without prior written agreement by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or delegated member of the study team. The pharmacist or delegated team member will enter the unique subject identifier on the investigational product labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible

for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified minimum/maximum thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

The investigational product should be protected from light and should not be frozen. Do not shake.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented in the subject's source document and/or other investigational product record.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

With the written agreement of the sponsor, at the end of the study all unused stock may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational products must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, cartons) or at the individual count level for opened containers/packaging. The pharmacist or delegated team member will record details on the drug accountability form.

7 STUDY PROCEDURES

7.1 Study Schedule

The investigator may schedule visits (unscheduled visits) in addition to those listed on the schedule of activities ([Table 1](#)) in order to conduct evaluations or assessments required to protect the well-being of the subject.

7.1.1 Screening Period

7.1.1.1 Screening Visit (Visit 1)

Subjects will be screened within 6 weeks before the baseline visit (Visit 2) to determine eligibility to participate in the study and to perform the other assessments and procedures specified in [Table 1](#). Each subject or subject's parent or legally authorized representative must participate in the informed consent process and provide written informed consent/assent before any assessments or procedures specified in the protocol are performed. Screening assessments may take place over more than 1 day (at least 2 visits will be necessary to complete the screening procedures, including endoscopy).

A screen failure is a subject who has given informed consent or assent, as applicable (and whose parents or legally authorized representatives have given informed consent, as applicable), failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria, and has not been randomized or administered investigational product.

A subject may be rescreened if their condition has changed and they may potentially be eligible. Subjects may be rescreened 1 time. Note: Screening laboratory tests, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results of repeated tests must be reviewed for eligibility prior to the screening endoscopy procedure.

Flexible sigmoidoscopy or colonoscopy (if preferred) must be performed on all subjects after the majority of other eligibility criteria (eg, laboratory values) are met. Endoscopy must be performed during the screening period within 10 days before baseline (Visit 2), preferably within 5 to 7 days before the baseline visit, to obtain the centrally read endoscopic subscore (see [Section 7.2.2.1](#)). Biopsy samples will be collected for histological evaluation using the Geboes Score classification and [REDACTED]. Subjects at risk of colorectal cancer, as defined in exclusion criterion 5 (see [Section 4.2](#)), must have a colonoscopy performed at screening, unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no presence of dysplasia and colon cancer must be available in the source documents.

If a subject has had the following procedures performed as a part of standard medical care within 12 weeks before screening visit (Visit 1), these procedures do not need to be repeated as a part of screening:

- Chest x-ray
- Documented negative PPD test or IGRA for TB.

7.1.1.2 Baseline Visit (Visit 2; Week 0)

The baseline visit will take place on Day 1 (Week 0). The assessments and procedures specified in [Table 1](#) will be performed.

After eligibility has been reconfirmed and all baseline procedures and assessments have been completed, each subject will be randomized to 1 of the 3 treatment groups as described in Section [6.2.2](#) and the first dose of investigational product will be administered.

Results of the baseline laboratory tests are not required for investigational product administration but must be reviewed as soon as possible thereafter.

7.1.2 Treatment Period

7.1.2.1 Visit 3 (Week 2)

Visit 3 is scheduled to take place on Day 14 ± 3 days (Week 2). The assessments and procedures specified in [Table 1](#) will be performed.

7.1.2.2 Visits 4 and 5 (Weeks 4 and 8)

Visits 4 and 5 are scheduled to take place on Day 28 ± 3 days (Week 4) and Day 56 ± 3 days (Week 8), respectively. The assessments and procedures specified in [Table 1](#) will be performed.

7.1.2.3 Final On-treatment Visits: Visit 6, Parts 1 and 2 (Week 12/Early Termination)

The Week 12/ET visit (Visit 6) consists of 2 parts.

Part 1 of Visit 6 must be completed within 10 days (preferably, within 5 to 7 days) before Part 2; this will allow sufficient time for data from the centrally read endoscopy to be available at Part 2 of the visit. The Week 12/ET assessments and procedures that will take place during Part 1 are specified in [Table 1](#).

Part 2 of Visit 6 will take place on Day 84 ± 3 days. The Week 12/ET assessments and procedures that will take place during Part 2 are specified in [Table 1](#).

At Part 2 of Visit 6, after review of the Mayo score, health outcome assessments, and safety assessments, it will be determined whether the subject should enter the safety follow-up period of this study or enroll in the maintenance (SHP647-303) or LTS (SHP647-304) studies. Entry into the maintenance or LTS studies is dependent upon the subject's response and whether the subject agrees to participate.

The Week 12 assessments and procedures will also form the ET assessments for any subjects who are withdrawn early or discontinued from the study.

7.1.3 Follow-up Period: Visits 7 and 8 (Weeks 20 and 28)

Subjects who are withdrawn early from the study, or who do not enter either the maintenance or LTS studies, should enter the 16-week safety follow-up phase for safety monitoring.

During the safety follow-up period, the Week 20 visit (Visit 7) will take place on Day 140 ± 7 days or 8 weeks ± 7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study. This visit will routinely be conducted by telephone; however, as an exception the visit can be performed as a study site visit if preferred.

At the end of the safety follow-up period, there will be a visit at the site on Day 196 ± 7 days, or 16 weeks ± 7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study, which will form the Week 28 visit (Visit 8). The assessments and procedures specified in [Table 1](#) will be performed, including querying for SAEs, AEs, and concomitant medications and procedures. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see [Section 8.1](#)).

Subjects who are proceeding to the maintenance or LTS studies will not enter the safety follow-up period.

7.1.4 Additional Care of Subjects After the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator, which may make it unfeasible to perform the tests and procedures. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject.

When timing of procedures and assessments coincide, the following order should be followed:

- Health outcome and patient-reported questionnaires
- Vital signs and ECG
- Laboratory sample collection
- Endoscopy (generally performed at a separate visit; see [Section 7.2.2.1](#)).
- Investigational product administration.

Note: Blood and tissue samples may be stored for up to the duration allowed by local regulations, but for no longer than 25 years.

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics will be recorded at the screening visit (Visit 1).

Each subject's stool frequency before symptoms of UC started or during remission will be recorded at the screening visit. The reference/normal stool frequency questions in [Appendix 2](#) will be asked and the responses documented.

7.2.2 Efficacy

The primary efficacy endpoint is remission at the Week 12 visit. Remission is defined as a composite score of patient-reported symptoms using a daily e-diary and centrally read endoscopy as described in Section [9.8.1](#).

7.2.2.1 Endoscopy and Histology

Endoscopy will be performed at the time points specified in [Table 1](#) and will consist of either flexible sigmoidoscopy or colonoscopy (if preferred).

If it is necessary, bowel preparation should be conducted as per local routine. The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during endoscopy at baseline. The endoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's medical record.

During endoscopy, 2 biopsy samples will be collected from the most inflamed area of the sigmoid colon at screening and Week 12/ET. Endoscopy and biopsy procedures will be defined in an endoscopy instructions manual and/or reference card(s), on which all sites will be trained. Endoscopy results will be reviewed by a central reader.

Biopsy samples will be centrally reviewed using the Geboes Score classification system and [REDACTED] (see [Appendix 2](#)) for the evaluation of histological disease severity in UC with higher numbers corresponding to more inflammation. The Geboes score will be used for the key secondary efficacy evaluation and [REDACTED].

Subjects at risk for colorectal cancer (see exclusion criterion number 5) must have a colonoscopy performed during the screening period with results available within 10 days before the baseline visit (Visit 2), unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidence of dysplasia and colon cancer must be available in the source documents.

7.2.2.2 Mayo Score

The Mayo score is a measure of UC disease activity. Mayo scores (total or partial) will be recorded at the time points specified in [Table 1](#).

The total 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 2](#)):

- Stool frequency (0-3)
- Rectal bleeding (0-3)
- Findings of endoscopy (0-3)
- Physician global assessment (PGA; 0-3).

The partial Mayo score consists of the Mayo score without the endoscopic subscores and ranges from 0 to 9 points.

The composite score is a recommended measure consisting of the Mayo score without the PGA subscore and ranges from 0 to 9 points. The composite score will be used for the primary efficacy endpoint.

Calculation of the total and partial Mayo scores and composite score requires a self-assessment by the subject for stool frequency and the amount of blood in the stool. These data on stool frequency and rectal bleeding will be captured in the patient-reported outcome (PRO)-UC daily e-diary (see Section [7.2.2.3](#)).

The Mayo stool frequency and rectal bleeding subscores will be calculated based on each subject's daily e-diary data recorded over the most recent 3 days (consecutive or nonconsecutive) of the last 10 days prior to the visit excluding the following days: day of any bowel preparation, day of endoscopy, any days between day of bowel preparation and day of endoscopy, and the 2 days after the day of endoscopy.

The mucosal appearance during the sigmoidoscopic portion of the endoscopic examination will be assessed for the Mayo endoscopic subscore based on the scoring system provided in the protocol (see [Appendix 2](#)). The endoscopic appearance will be read by a central reader through video recorded during the procedure. Centrally read endoscopic subscores will be used for both eligibility and efficacy analyses.

The PGA acknowledges the 3 other criteria: the subject's recollection of abdominal discomfort and general sense of well-being and other observations (such as physical findings and the subject's performance status). The endoscopic subscore and the PGA must be performed by a physician qualified to perform endoscopy, and it is recommended that the same physician performs all such assessments for a particular subject throughout the study.

7.2.2.3 Patient-reported Outcome – Ulcerative Colitis Daily E-diary

Patient-reported UC signs and symptom data will be collected using a daily e-diary starting during the screening period. Collection of the daily e-diary data must begin at least 10 days before the baseline visit (Visit 2). Subjects will enter data on UC signs and symptoms items using an electronic handheld device that will be provided to subjects at the start of the study. Compliance is assessed by site staff at each visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <23 out of 28 e-diary entries) when compared with the previous visit.

Subjects will be asked to record the following signs and symptom data, as experienced over the previous 24 hours, in the e-diary:

- Stool frequency
- Rectal bleeding severity and frequency
- Diarrhea frequency
- Urgency frequency
- Abdominal pain worst severity.

The full PRO-UC e-diary consists of 6 items. The first 2 items (stool frequency and rectal bleeding severity) will be used to determine the Mayo stool frequency and rectal bleeding subscores, which will be used to calculate the total and partial Mayo scores and the composite score. The PRO-UC e-diary is presented in [Appendix 2](#).

7.2.3 Safety

7.2.3.1 Medical and Medication History

Medical history will be documented at screening (Visit 1), including UC history, cardiac history, and smoking history. Prior and concomitant medications and procedures will also be documented.

7.2.3.2 Physical Examination (Including Height and Weight)

Complete and targeted physical examinations will be performed at the time points specified in [Table 1](#). Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; confrontational visual fields (eyes); breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; back; and lymph nodes. Targeted physical examination includes the review of the following body systems: skin, heart, lungs, confrontational visual fields (eyes), abdomen, and examination of body systems where there are symptom complaints by the subject.

Weight will be measured at the time points specified in [Table 1](#). Height will be measured at screening (Visit 1) only.

Changes after the screening visit that are deemed clinically significant in the opinion of the investigator will be recorded as an AE.

7.2.3.3 Targeted Neurological Assessment

Targeted neurological assessments to monitor the development of signs and/or symptoms of PML will be performed at the time points specified in [Table 1](#). Subjects will be evaluated to reveal any potential abnormalities in the following neurological domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior.

If any abnormalities are indicated, subjects will be further evaluated to help clarify any potential abnormal responses. Focus will be placed on possible alternative etiology (eg, fracture or stroke). If additional evaluation reveals an unexplained new abnormality, neurologic examination(s), targeted to the abnormal domain, will be performed by an investigator or qualified personnel.

Subjects with any unexplained positive neurological assessment item at screening should be excluded from enrollment in the study (exclusion criterion 20, Section [4.2](#)).

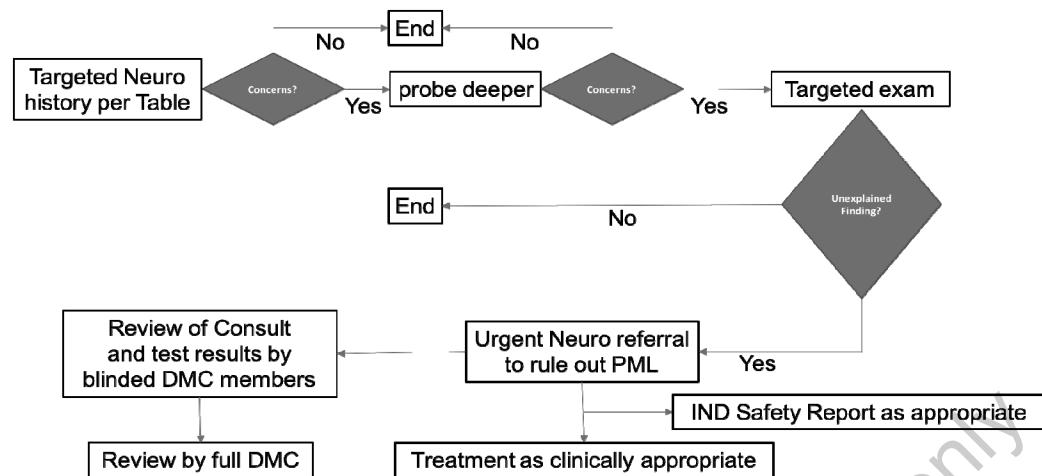
A step-wise approach for the proposed neurological assessment plan is provided in [Table 3](#).

Table 3 Quarterly Neurological Assessments

Domain	Step 1: Interim Neurologic History and Targeted Neurological Examination	Step 2: If Abnormal Response
Vision	Diplopia or visual/visual field loss	Perform visual field assessment
Motor	Major motor weakness (eg, legs, arms)	Test leg strength (hopping, foot tapping), finger tapping, pronator drift and bilateral muscle strength
Tactile sensation	Paresthesia, anesthesia in any domain (peripheral, central)	Pinprick test
Coordination/Cerebellar	Clumsiness, difficulty with walking, writing, or fine motor skills, etc.	Finger-nose, heel-shin, heel-toe walk, writing sample, draw a clock
Speech	Dysarthria, expressive aphasia	Naming objects, repeat multipart phrase, observe for dysarthria or aphasia
Verbal comprehension	Agnosia, receptive aphasia	Test to follow routine commands, eg, close eyes, touch finger to ear.
Cognition/Behavior	New onset of difficulties with memory or thinking, important changes in behavior	Recall 3 objects over 1 minute, serial 7 s, proverbs. Changes in activities of daily living over prior 6 months

Additionally, should there be any unexplained abnormal neurological findings, the subject is to be urgently referred to a neurologist. The sites will immediately inform the sponsor of any such occurrences. If the neurologist confirms the presence of PML, appropriate actions, including discontinuation of investigational product, will be taken. Suspected PML cases will be reviewed promptly by data monitoring committee (DMC) members with PML expertise and presented at the next scheduled DMC meeting(s). If PML is diagnosed, the treatment code will be unblinded and there will be an urgent meeting of the DMC. A flow diagram of the quarterly assessments and actions is presented in [Figure 3](#). Any concerns from the DMC will be promptly communicated to the sponsor, investigator, and treating neurologist.

Figure 3 Flow Diagram for Quarterly Neurological Assessments



DMC=data monitoring committee; IND=investigational new drug; neuro=neurological; PML=progressive multifocal leukoencephalopathy

It is important to note that assessments based on neurological evaluations are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and data from neurological assessment collected from subjects. Investigators may determine if any finding on neurological testing constitutes an AE. Adverse event incidence rates will not be calculated from these neurological evaluation data but rather from the AE information recorded by the investigator.

7.2.3.4 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, “Have you had any health problems since your last visit?”). Adverse events are collected from the time informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3. (See Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.3.5 Vital Signs

Vital signs will be measured at the time points specified in Table 1. Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data. Vital signs include blood pressure, pulse, respiratory rate, and temperature. Vital signs should be recorded before laboratory blood collection and endoscopic procedures are performed.

Single measurements of sitting blood pressure will be recorded at each time point. Blood pressure should be determined by cuff with the subject’s arm supported at the level of the heart and recorded to the nearest mmHg using the same method, the same arm (preferably the dominant arm), and the same position throughout the study.

Respiratory rate will be measured with the subject in a comfortable position. The observer should hold the extremity of the subject as a distraction for the subject (ie, pretending he/she is taking the subject's radial pulse) and count the respiration for 1 minute.

Body temperature should be taken using a thermometer and reported in degrees Celsius or Fahrenheit.

Any deviations from baseline (Visit 2) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE, unless documented in the subject's medical history as a pre-existing medical condition.

7.2.3.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values that are unexpected or not explained by the subject's clinical condition may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Screening laboratory tests, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. The following clinical laboratory assessments will be performed at the time points specified in [Table 1](#):

Serum chemistry

alkaline phosphatase	blood urea nitrogen
AST	creatinine
ALT	sodium
total bilirubin	potassium
total protein	chloride
albumin	calcium
glucose	carbon dioxide

Hematology

hemoglobin	neutrophils
hematocrit	lymphocytes
mean corpuscular hemoglobin	monocytes
mean corpuscular hemoglobin concentration	eosinophils
mean corpuscular volume	basophils
erythrocyte (red blood cell) count	platelet count
leukocyte (white blood cell) count	

Virology

HBsAg	HCVA ^b
HBcAb	HCV RNA PCR if HCVA ^b is positive
hepatitis B DNA if HBsAg is negative and HBcAb is positive	HIV

Urinalysis

glucose	bilirubin
protein	ketones
specific gravity	hemoglobin
pH	urobilinogen
nitrite	leukocyte esterase

Virology test results must be confirmed as negative before enrollment in the study; if a virology test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor, but will not be collected in the eCRF.

Stool microbiology will be performed at the screening visit (Visit 1) or at any time a subject experiences an increase in GI symptoms (see Section 7.2.3.12). Diagnosis of *C. difficile* infection should be made using the central laboratory. If, for any reason, the central laboratory is not available, see [Appendix 5](#) for guidance regarding diagnostic algorithms.

A TB test (PPD or QuantiFERON TB Gold Plus) will be performed at the screening visit (Visit 1). A documented negative PPD test within 12 weeks before screening (Visit 1) is acceptable. The IGRA official reading and method or test must be located in the source documentation.

A serum sample will be collected and banked for John Cunningham virus antibody testing. It may be analyzed if a subject shows neurologic symptoms suggestive of PML.

All laboratory assessments should be performed at central laboratories, with the exception of the following assessments: stool microbiology (local or central laboratory) and TB test (PPD or QuantiFERON TB Gold Plus) (refer to laboratory manual for details).

7.2.3.7 Pregnancy Test and Follicle-stimulating Hormone Test

A beta-human chorionic gonadotropin (β -hCG) pregnancy test will be performed on all females of childbearing potential at the time points specified in [Table 1](#) if pregnancy is suspected or on withdrawal of the subject from the study. A serum pregnancy test will be performed at the screening visit (Visit 1); all other pregnancy tests will be urine tests.

Pregnancy tests are not required for females of nonchildbearing potential who have undergone hysterectomy or bilateral oophorectomy, have medically confirmed ovarian failure, or are medically confirmed postmenopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; postmenopausal status should be confirmed by FSH testing in females who have had 12 consecutive months of spontaneous amenorrhea and are 51 years of age or older).

7.2.3.8 Electrocardiogram

A 12-lead ECG will be recorded at the time points specified in [Table 1](#). When timing of measurements coincide, ECGs should be performed before laboratory blood collection and endoscopic procedure.

A central ECG reader will be used in this study. The eligibility of the subject is based on the assessment of the ECG by the investigator. If abnormal results are observed following assessment by the central reader, the investigator, in consultation with the appointed sponsor or contract research organization (CRO) medical monitor, reconfirms subject eligibility to continue.

7.2.3.9 Chest X-ray

A chest x-ray will be performed during screening (Visit 1). If a subject has had a chest x-ray performed as a part of standard medical care within 12 weeks before screening (Visit 1), it does not need to be repeated as a part of screening. The official reading must be located in the subject's source documentation.

7.2.3.10 Antidrug Antibodies

Blood samples for measurement of antidrug antibodies (ADAs) and neutralizing antibodies (NABs) will be collected at the time points specified in [Table 1](#). Blood samples must be collected before the administration of investigational product at that visit.

7.2.3.11 Monitoring for Type I and Type III Immune Reactions

Subjects will be educated on the signs and symptoms of hypersensitivity reactions and how to respond to them. In addition, subjects will be instructed to report hypersensitivity AEs to the investigator at the time of occurrence, and to seek immediate medical care if hypersensitivity develops. At each visit, the subject will be queried for adverse events of special interest (AESIs) related to hypersensitivity.

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Subjects will be also instructed to report AEs such as serum-sickness, vasculitis, Arthus reaction, and severe injection-related reactions to the investigator, and to seek immediate medical care if these events are severe in intensity.

Subjects who experience a hypersensitivity reaction or severe or serious injection-related reaction (eg, shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs) should discontinue investigational product until the adjudication committee assesses the case and finalizes recommendation of permanent discontinuation or rechallenge with investigational product.

Subjects who experience an AE suggestive of the presence of circulating immune complexes formation (eg, fever, rash [including hives], arthralgia, myalgia, vasculitis, Arthus reaction, general ill feeling, itching, and swollen lymph nodes) will have the related AEs reviewed by the adjudication committee and if the AEs are assessed as related to formation of circulating of immune complexes and not related to underlying disease, blood samples will be collected and stored at the central laboratory. Tests will be performed as confirmatory of presence of circulating immune complexes at the request of the adjudication committee.

Further details of hypersensitivity reactions as AESIs are provided in Section 8.1.3.1.

7.2.3.12 Evaluation of Increased Gastrointestinal Symptoms

When a subject experiences an increase in GI symptoms, which could be an exacerbation of disease, an infectious etiology must be evaluated including testing for *C. difficile* as described in [Appendix 5](#).

In each case, the appropriate AE (eg, infection, exacerbation) should be recorded in the subject's source document.

7.2.4 Others

Category	Sample Count
0	~100
1	~100
2	~100
3	~100
4	0
5	~100
6	~100
7	~100
8	~100
9	~100

7.2.4.3 Health-related Quality-of-Life Assessments

Each subject will complete the HRQL assessments at the site during the visits specified in [Table 1](#), using an electronic device. All health outcome and patient-reported questionnaires should be completed before any other assessments. The study site staff should check for completion of all PRO questionnaires.

It is important to note that PRO assessments are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and PRO data collected from subjects. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded by the investigator.

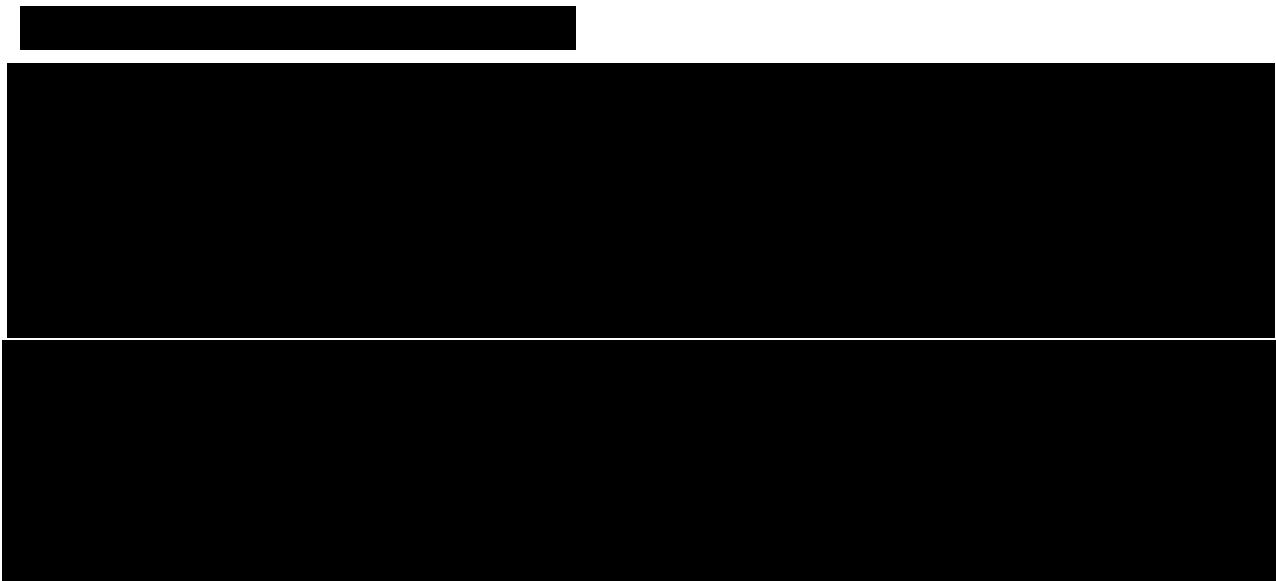
Inflammatory Bowel Disease Questionnaire

The IBDQ is a psychometrically validated PRO instrument for measuring the disease-specific HRQL in subjects with inflammatory bowel disease (IBD), including UC. The IBDQ consists of 32 items, which are grouped into 4 domains: bowel function, emotional status, systemic symptoms, and social function ([Irvine et al., 1994](#)). 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 HRQL. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement.

The IBDQ is presented in [Appendix 2](#).



Short Form-36 Health Survey, Acute Form

The SF-36 is a generic quality-of-life instrument that has been widely used to assess HRQL of subjects. Generic instruments are used in general populations to assess a wide range of domains applicable to a variety of health states, conditions, and diseases. The SF-36 consists of 36 items that are aggregated into 8 multi-item scales (physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional, and mental health), with scores ranging from 0 to 100 ([Ware and Sherbourne, 1992](#)). Higher scores indicate better HRQL.



7.2.4.4 Healthcare Resource Utilization Assessments

Hospitalizations, inpatient days, and ED visits will be recorded at the time points specified in [Table 1](#). Ulcerative colitis-related and other surgeries will be collected from subjects during the treatment period.

7.2.5 Volume of Blood to Be Drawn from Each Subject

Table 4 Volume of Blood to Be Drawn from Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Hematology	2	6	12
Serum chemistry	4	6	24
HBsAg	2	1	2
HBcAb	2	1	2
HCVAb	2	1	2
HBV DNA	6	1	6
HIV	2	1	2
FSH	2	1	2
Serum β -hCG ^a	2	1	2
TB test (QuantiFERON TB Gold Plus or PPD)	4	1	4
JCV antibody banked sample	3.5	1	3.5
[REDACTED]			
[REDACTED]	2	3	6
[REDACTED]	5	3	15
[REDACTED]	4	3	12
[REDACTED]	5	5	25
ADA and NAb sampling	3	6	18
Total mL			137.5

ADA=antidrug antibody; β -hCG=beta-human chorionic gonadotropin; [REDACTED]; FSH=follicle-stimulating hormone; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCVAb=hepatitis C virus antibody; HIV=human immunodeficiency virus; JCV=John Cunningham virus; [REDACTED]
[REDACTED]; NAb=neutralizing antibody; PPD=purified protein derivative; TB=tuberculosis

^a β -hCG testing for female subjects only.

^b If a catheter is used, the first mL is to be discarded; then take 4 mL into appropriate tube for [REDACTED]. A total of 5 mL of blood drawn has been used in determination of sample volume.

The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 137.5 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Council for Harmonisation [ICH] Guidance E2A 1995).

All AEs are collected from the time the informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured in the subject's source document. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the subject's source document.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia before dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded in the subject's source document).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as “not related.” Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.” The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject’s medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject’s underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Adverse Events of Special Interest

Adverse events of special interest will be captured and monitored during this study. Investigators will report all AESIs to the sponsor, regardless of causality, using the same timelines as described for SAE reporting (see Section 8.2.2). The following describe the AESIs and the criteria for reporting AESIs.

8.1.3.1 Hypersensitivity

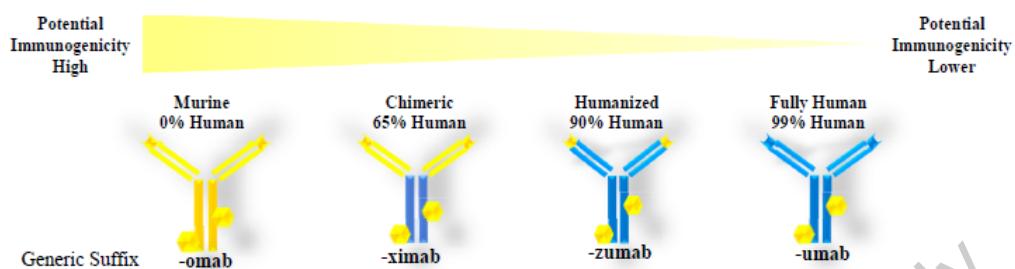
Potential hypersensitivity, serum sickness, vasculitis, and Arthus reactions to ontamalimab will be regarded as AESIs. These events must be reported on Shire “Clinical Study SAE and Nonserious AE as Required by the Protocol Form” and within the time frame mandated for SAEs (see Section 8.2.2).

It is well known that the administration of foreign proteins can cause immune responses including hypersensitivity reactions such as anaphylaxis and serum sickness. Other immune responses to foreign proteins include the development of ADAs and NAbs.

Monoclonal antibodies have been used in human therapeutics since the 1980s. The first monoclonal antibody approved for human use (ORTHOCLONE OKT3®), was a murine protein which caused rapid production of NAbs. Since then, much effort has been expended to reduce the immunogenicity of these useful therapeutic proteins by reducing the extent of “foreignness” from chimeric antibodies such as infliximab, to humanized antibodies such as vedolizumab, and

finally to fully human antibodies such as adalimumab and ontamalimab (Isabwe et al., 2018) (see [Figure 4](#)).

Figure 4 Potential Immunogenicity of Therapeutic Monoclonal Antibodies



Ontamalimab is a fully human antibody of the immunoglobulin G2 subclass. In Phase 1 and Phase 2 clinical trials of ontamalimab, in which over 700 subjects were treated for up to 3 years, there has been no case of anaphylaxis. There have been 2 reported cases of drug hypersensitivity: serum sickness attributed to concomitant administration of penicillin; and a reaction characterized by dyspnea, facial erythema, and chest pain with onset 2 days after administration of the fifth dose of ontamalimab. The latter event mimicked a reaction that the subject had previously experienced after 4 doses of infliximab. In addition, low titer activity has been observed in ADA assays, including pretreatment samples and placebo-treated subjects, and no subject has had a 2-fold or greater increase in ADA titer. Analysis of PK and clinical parameters has shown no difference between subjects whose ADA assays results are positive as compared with those who are negative.

Nonetheless, the possibility of a hypersensitivity reaction occurring after drug exposure cannot be fully ruled out. The reactions of concern are Type I (anaphylaxis) and Type III (immune complex) reactions. The clinical presentation of anaphylactic reactions is described in [Table 5](#).

Table 5 Clinical Criteria for Diagnosing Anaphylaxis (Type 1 Hypersensitivity)

Anaphylaxis is highly likely when below criterion and at least any one of the following criteria a and b are fulfilled:

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST 1 OF THE FOLLOWING:

- a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- b) Reduced BP^a or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

BP=blood pressure; PEF=peak expiratory flow

^a Low systolic BP for children is defined as less than 90 mmHg from 11 to 17 years.

Source: Adapted from [Sampson et al., 2006](#).

Type III hypersensitivity responses, including those mediated by immune complexes and T-cells (delayed hypersensitivity responses in the older literature), are relatively rare with respect to therapeutic protein products and a high degree of clinical suspicion is necessary for the diagnosis (Center for Drug Evaluation and Research - Guidance for industry: Immunogenicity assessment for therapeutic protein products, 2014). Type III hypersensitivity reactions involve the formation of biologic/ADA immune complexes in the circulation which, when present in the correct stoichiometric ratio, become deposited in tissues. Once immune complexes are deposited, they can elicit complement activation and inflammation, leading to tissue damage. When immune complexes are deposited in tissues, they tend to localize in small postcapillary venules where there is loss of laminar blood flow, in sites of ultrafiltration where there is high pressure and fenestrated endothelium (eg, choroid plexus, ciliary body, synovium, and glomeruli), in sites of turbulent blood flow (eg, coronary artery branches off aorta, aortic bifurcations, and cardiac valve leaflets), and in renal glomerular endothelium.

Signs and symptoms of immune complex deposition typically have onset 1 to 3 weeks after exposure ([Warrington et al., 2018](#)) usually improving in 7 to 10 days, with full recovery in 2 to 4 weeks and may include fever, rash (including hives), arthralgia, myalgia, vasculitis, Arthus reaction, general ill feeling, itching, and swollen lymph nodes. Some of these findings, such as fever, rash, arthralgia, and myalgia are consistent with findings associated with IBD and may therefore be very difficult to assign to a particular etiology. When such a reaction is suspected, samples for laboratory assessment will be obtained and stored. Tests will be performed if the diagnosis is confirmed and requested by the adjudication committee.

8.1.4 Outcome Categorization

The outcome of AEs must be recorded during the course of the study in the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown.

8.1.5 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.6 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.7 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire

Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum. If the pregnancy outcome is a live birth, the vital status and clinical condition of the infant should be obtained and documented at 1 year postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire “Clinical Study Serious Adverse Event and Nonserious AE as Required by the Protocol Form”. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire “Clinical Study Serious Adverse Event and Nonserious AE as Required by the Protocol Form” as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β -hCG test or ultrasound result will determine the pregnancy onset date.

8.1.8 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a nonmedical purpose (eg, to alter one’s state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional administration of investigational product at a dose interval that is less than 2 weeks between doses
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

There is no specific antidote for overdose with ontamalimab. Treatment should be symptomatic and supportive.

8.1.9 Unexpected Adverse Event

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the reference safety information (RSI).

“Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

8.1.10 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is Section 6.8 of the ontamalimab IB, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.8) unless they result in an SAE.

The investigator must complete, sign, and date the Shire “Clinical Study Serious Adverse Event and Nonserious AE as Required by the Protocol Form” and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or email the form to the Shire Global Drug Safety Department. A copy of the Shire “Clinical Study Serious Adverse Event and Nonserious AE as Required by the Protocol Form” (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death.
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an ED or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section [7.1.3](#) and must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor or the CRO is responsible for notifying the relevant regulatory authorities, US central institutional review boards (IRBs), and European Union (EU) central ethics committees (ECs) of related, unexpected SAEs (ie, SUSARs).

In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs (ie, SUSARs) occurring during all interventional studies across the ontamalimab program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.2.8 Safety Monitoring for Potential Cases of Drug-induced Liver Injury

The following safety monitoring and stopping criteria are provided for elevated hepatic blood tests based on normal and elevated baseline ALT and total bilirubin levels.

Abnormal values in ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities per [Table 6](#) should be evaluated further to definitively determine the etiology of the abnormal laboratory values. The measurement(s) should be reconfirmed with another blood draw preferably within 48 to 72 hours of the initial finding of potential concern. Please refer to laboratory manual for further instructions.

Guidance for Dosing Interruption: Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

Table 6 Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment-emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
Normal baseline ALT $\geq 5 \times$ ULN Elevated baseline^a: ALT $\geq 3 \times$ baseline <i>or</i> ≥ 300 U/L (whichever occurs first)	Normal <u>Patients with Gilbert's syndrome or hemolysis:</u> No change in baseline TBL	None	Repeat ALT, AST, ALP, TBL, in 2-5 days. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation. ^c
Normal baseline ALT $\geq 8 \times$ ULN Elevated baseline^a: ALT $\geq 5 \times$ baseline or ≥ 500 U/L (whichever occurs first)	Normal <u>Patients with Gilbert's syndrome or hemolysis:</u> No change in baseline TBL	None	Interrupt investigational product. ^b Initiate close monitoring and workup for competing etiologies. Investigational product can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation. ^c

Table 6 Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment-emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
<u>Normal baseline</u> ALT $\geq 3 \times$ ULN	TBL ≥ 2 mg/dL increased over baseline <i>or</i> <u>Patients with Gilbert's syndrome or hemolysis:</u> Doubling of baseline direct bilirubin	None	Interrupt investigational product. ^b Initiate close monitoring and workup for competing etiologies. Investigational product can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation. ^c
<u>Normal baseline</u> ALT $\geq 5 \times$ ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain <i>or</i> Immunologic symptoms Rash Eosinophilia > 5%	Interrupt investigational product. ^b Initiate close monitoring and workup for competing etiologies. Investigational product can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation. ^c

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBV=hepatitis B virus; TBL=total bilirubin; ULN=upper limit of normal

^a Elevated baseline ALT defined as ALT $\geq 1.5 \times$ ULN.

^b Confirmatory repeat liver-related blood tests should be performed within 2 to 3 days before the investigational product is interrupted.

^c If HBV DNA positive, antivirals would need to be started as soon as possible.

Source: Adapted from [Chalasani and Regev, 2016](#).

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol in the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered in the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. It is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, antibodies to investigational product, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, before unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed. The SAP will be finalized before unblinding to preserve the integrity of the statistical analysis and study conclusions.

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC, USA).

Unless otherwise specified, summary tabulations will be presented by treatment group. All data listings will be sorted by treatment group, site, and subject number, and will include the subject's age, sex, and race.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation, minimum, and maximum values will be presented.

9.5 Planned Interim Analysis, Adaptive Design, Data Monitoring Committee, and Hypersensitivity Adjudication Committee

There is no planned interim analysis or adaptive design in this study.

An external DMC will be established to review the overall safety of the study subjects on an ongoing basis.

The DMC will be responsible for the ongoing monitoring of safety of subjects enrolled in the study according to the DMC charter. Recommendations made by the DMC to alter the conduct of the study or to amend the protocol will be forwarded to Shire for review and for a final decision. Shire or its designee will notify investigative sites and regulatory authorities as appropriate, of DMC recommendations (which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints).

Further details regarding the DMC can be found in the DMC charter, which will be available before the administration of investigational product to any subject. Analyses of the data for DMC review will be conducted according to the DMC charter and the DMC SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not applicable.

An external hypersensitivity adjudication committee will be established to review data from subjects who experience a suspected Type I or Type III hypersensitivity reaction in order to confirm the nature and etiology of the reaction, to determine whether testing should be performed on stored blood samples, and to finalize recommendations of permanent discontinuation or rechallenge with investigational product. Further details regarding the adjudication committee can be found in the adjudication charter.

9.6 Sample Size Calculation and Power Considerations

Graphical methods are used to control the global family-wise Type I error rate (FWER) at the .05 level (2-sided) for the comparisons of the 2 ontamalimab treatment groups with the placebo group. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the primary endpoint. Therefore, the power analysis and sample size estimation were calculated based on the chi-square test of proportions using nQuery Advisor Version 7.0

(Statistical Solutions Ltd, Cork, Ireland) for an individual ontamalimab dose compared with placebo.

Power calculations are made based on assuming a .025 (2-sided) significance level for each pairwise treatment comparison. Approximately 1346 subjects will be screened to randomize 740 subjects (2:2:1 allocation ratio: 296 subjects in the 25 mg ontamalimab treatment group, 296 subjects in the 75 mg ontamalimab treatment group, and 148 subjects in the placebo group) which would yield an approximately 90% power to detect individual pairwise treatment difference in the primary efficacy endpoint, remission at Week 12, of 11% (5% placebo versus 16% ontamalimab). Expected remission rates at Week 12 are based on observed rates from the A7281009 study and placebo remission rates from literature ([Feagan et al., 2013](#); [Sandborn et al., 2017](#)). No adjustment for missing data is required in these sample size calculations as subjects with missing data for remission at Week 12 are imputed as failures and the above rates account for these subjects.

With the sample size of 740 subjects, [Table 7](#) provides the power for detecting a treatment difference between a ontamalimab treatment group and the placebo group for the key secondary endpoints.

Table 7 Power to Detect the Corresponding Treatment Effect for Key Secondary Endpoints

Key Secondary Endpoint at Week 12	SHP647 Premise	Placebo Premise	Power
Endoscopic remission	24%	8%	0.98
Clinical remission	30%	16%	0.85
Clinical response by composite score	50%	35%	0.78
Mucosal healing	15%	5%	0.84

9.7 Study Population

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

The full analysis set (FAS) will consist of all subjects in the randomized set who have received at least 1 dose of investigational product.

The per-protocol (PP) set will consist of all subjects in the FAS who do not have predefined protocol deviations that may affect the primary efficacy endpoint.

The completer set will consist of all subjects in the FAS who have completed the final scheduled primary assessment for this study.



9.8 Efficacy Analyses

Unless otherwise specified, all efficacy analyses will be based on the FAS and subjects will be analyzed according to their randomized treatment, regardless of the treatment they actually received.

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is remission at the Week 12 visit. Remission is defined as a composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy as follows:

- stool frequency subscore of 0 or 1 with at least a 1-point change from baseline

AND

- rectal bleeding subscore of 0

AND

- endoscopic subscore of 0 or 1 (modified, excludes friability).

The primary efficacy endpoint will be compared for each active treatment group (25 mg or 75 mg ontamalimab) to the placebo group using a Cochran-Mantel Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment and glucocorticoid use at baseline (Visit 2). Subjects with missing remission data at the Week 12 visit will be considered failures and counted as nonresponders. The endoscopy score will be based on centrally read results.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata, $j=1$ to m . The common treatment difference is a weighted average of the stratum-specific treatment differences.

The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% confidence interval (CI) using the method of Yan and Su (2010) and CMH p-value will be presented for each active treatment group to placebo comparison.

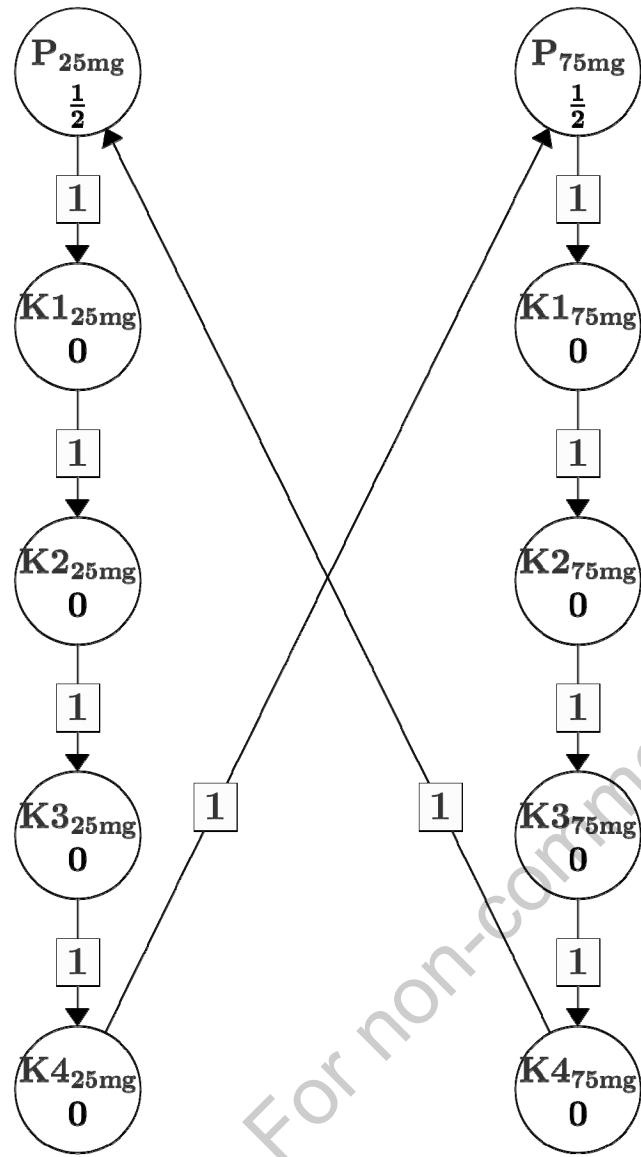
Sensitivity/supplementary analyses which explore the impact of missing data on the primary efficacy endpoint will be conducted. These analyses may compare imputations of the missing values which favor placebo (eg, worst case) and/or imputations which favor active treatment (eg, best case). In addition, imputation methods based on informative missingness and other missing data mechanisms may be performed. Additional sensitivity/supplementary analyses will also be conducted using the PP analysis set and the completer set. Additional analyses may be developed in the SAP. All sensitivity/supplementary analyses will be described in the SAP.

Prespecified subgroup analyses are planned for the primary endpoint including, but not limited to gender, prior anti-TNF treatment, glucocorticoid use at baseline, region, age group, randomization stratum, and other important subgroups. A full list of important subgroups will be described within the SAP. Within subgroups, efficacy endpoints will be compared for each active treatment group (25 mg ontamalimab and 75 mg ontamalimab) with the placebo group using a Chi-square test. Subjects with missing remission data at the Week 12 visit will be considered failures and counted as nonresponders. The endoscopy subscore will be based on centrally read results. The estimate of the treatment difference, along with the corresponding Newcombe (hybrid-score) 95% CI and Chi-square test p-value, will be presented.

Adjustments for Multiplicity

The global FWER for the statistical tests of the primary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al. (2009) will be utilized to propagate α from primary to key secondary endpoints and between the 2 ontamalimab treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the primary endpoint (P) and alpha is propagated in a hierarchical manner to each of the 4 key secondary endpoints (K1-K4) within a pairwise treatment comparison. A graphical visualization of the α propagation is presented in [Figure 5](#).

Figure 5 Visualization of Alpha Propagation



Only p-values that are significant according to this graphical approach are inferential and statistically significant. All other p-values are descriptive.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoints are as follows:

- Endoscopic remission, as defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability), at the Week 12 visit.
- Clinical remission, as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at the Week 12 visit.
- Clinical response based on composite score at the Week 12 visit. Clinical response (composite) is defined as a decrease from baseline in the composite score of patient-reported symptoms using daily e-diary and centrally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 .
- Mucosal healing based on endoscopic and histological assessment at the Week 12 visit. Mucosal healing is defined by centrally read endoscopic subscore 0 or 1 (modified, excludes friability) and centrally read Geboes score of ≤ 2 .

Similar to the primary endpoint, the 4 key secondary endpoints will all be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

The key secondary endpoints will be analyzed using the same approach as described for the primary efficacy endpoint. Subjects with missing key secondary endpoint data at the Week 12 visit will be considered failures and counted as nonresponders.

In addition, the sensitivity/supplementary analyses and prespecified subgroup analyses described for the primary endpoint will be repeated for the key secondary endpoints.

9.8.2.2 Other Secondary Efficacy Endpoints

The other secondary endpoints are as follows:

- Remission, defined as a total Mayo score ≤ 2 with no individual subscore (stool frequency, rectal bleeding, endoscopy [modified, excludes friability], and physician's global assessment) exceeding 1, at the Week 12 visit.
- Clinical response based on total Mayo score at the Week 12 visit. Clinical response (Mayo) is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥ 1 point or a subscore for rectal bleeding ≤ 1 .
- Partial Mayo score ≤ 2 with no individual subscore > 1 at the Week 4, 8, and 12 visits. The partial Mayo score does not include the endoscopy subscore.

- Clinical remission as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from baseline in stool frequency subscore, and rectal bleeding subscore of 0, at Weeks 4 and 8.
- Endoscopic remission at the Week 12 visit with endoscopic subscore of 0.
- Clinical remission at the Week 4, 8, and 12 visits with both rectal bleeding and stool frequency subscores of 0.
- Deep remission at the Week 12 visit. Deep remission is defined as both endoscopic and rectal bleeding subscores of 0, and stool frequency subscore ≤ 1 and a centrally read Geboes score of ≤ 2 .
- Change from baseline at the Week 12 visit in abdominal pain, diarrhea, and urgency item scores, absolute stool frequency, absolute rectal bleeding and total sign/symptom score based on subject daily e-diary entries (average of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency).
- Change from baseline in IBDQ domain and total (absolute) scores (time frame: Week 0, Week 8, up to Week 12, or ET).
- Change from baseline in SF-36, version 2, acute (physical and mental component summary scores and individual domain scores) to the Week 12/ET visit.
- Incidence of all-cause hospitalizations and total inpatient days.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods.

Binary endpoints will be analyzed using the same approach as described for the primary endpoint. Subjects with missing binary endpoint data at a visit will be considered failures and counted as nonresponders.

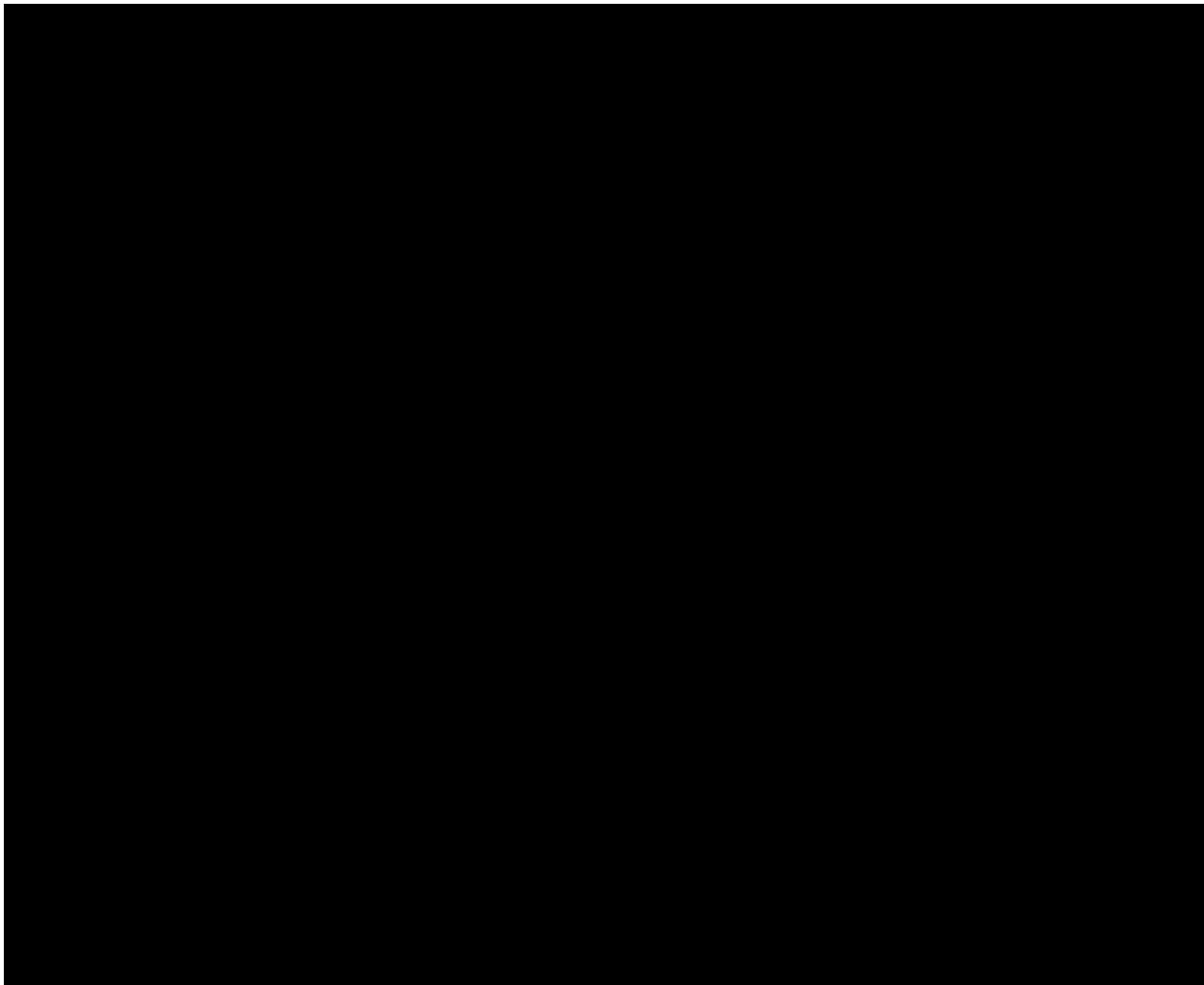
Continuous endpoints that are only measured at baseline and the Week 12 visit will be analyzed using an analysis of covariance model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences will be provided.

Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation. The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), and glucocorticoid use at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

Full details of the analysis of other secondary efficacy endpoints will be included in the SAP.

9.8.3 Exploratory Efficacy Endpoints

The exploratory endpoints are as follows:



Exploratory efficacy endpoints will be summarized with descriptive statistics and presented by treatment group. Exploratory efficacy endpoints will be analyzed using the same approach described as for the other secondary endpoints. See Section [9.8.2.2](#) for an overview of the planned analyses. Full details for the analysis of exploratory efficacy endpoints will be included in the SAP.

9.9 Safety Analyses

All safety analyses will be performed using the safety set. Subjects will be analyzed according to the treatment they actually received.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities.

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Treatment-emergent AEs are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by SOC, by preferred term, and by treatment group.

Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, SAEs, and deaths will be similarly summarized or listed. Adverse events of special interest will be summarized by treatment group.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

Antidrug antibody data will be summarized by treatment group and visit.

Further details of safety analyses will be described in the SAP.

9.10 Other Analyses

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before and during the study (including annual safety reporting, ie, Development Safety Update Reports). The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place before the start of the study. An insurance certificate is supplied to the CRO and investigator as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will upload the clinical study report to the EudraCT database and will also provide a summary of the clinical study report to the CRO for submission to the competent authority of the countries concerned as required by local regulatory requirement(s). This requirement will be fulfilled within 1 year for nonpediatric studies as per guidance. The ECs will be provided with a copy of the same summary as locally required.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor and/or its representatives will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site before commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's or subject's legally authorized representative's consent and/or assent, as applicable, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any coinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor or designee. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded in eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. The eCRFs must be completed by the investigator or designee as stated in the site delegation log.

All data in the eCRF will have a separate source (eg, paper or electronic PRO); no data will be recorded directly in the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject e-diary, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The clinical research associate/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, x-rays, etc.). Nonstudy site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and/or assent from all study subjects before any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of

what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor before the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) before study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved before site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Before implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor or designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market ontamalimab; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish before release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint

or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term “publication” refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor’s confidential information shall be submitted for publication without the sponsor’s prior written agreement to publish and shall be given to the sponsor for review at least 60 days before submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor’s presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

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APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Protocol Amendment 2	11 Nov 2019	Global
Protocol Amendment 1	05 Sep 2018	Global
Original Protocol	06 Jul 2017	Global

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Emergency Contact Information Section 8.2.2, Reporting Procedures	Replaced “Shire Global Pharmacovigilance” with “the Shire Global Drug Safety Department.”	To provide updated emergency contact information.
Section 8.2.4, Serious Adverse Event Collection Time Frame	Updated the global fax number and email address for serious adverse event reporting.	The email address was updated in accordance with SHP647-302 Protocol Administrative Change Memo #4, dated 03 May 2018.
Product Quality Complaints	Updated the email address for reporting of product complaints that originate in the European Union and Rest of World. The email address now is the same for all regions.	To provide updated information for reporting of product complaints.
Study Synopsis, Site(s) and Region(s) Section 3.3, Sites and Regions	Revised the anticipated number of study sites from 175 to 210.	To provide a revised projection for the number of study sites expected to participate.
Study Synopsis, Objectives, Other Secondary Section 2.2.2.2, Other Secondary Objectives Section 2.2.3, Exploratory Objectives	Added text to clarify the endpoints associated with the other secondary objectives based on “other clinical outcomes” and [REDACTED]	To clarify the measures that support those objectives.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #1 to indicate that subjects with non-steroidal anti-inflammatory drug-induced colitis will be excluded.	To further define the exclusion of subjects with colitis.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Added exclusion criterion #10: “Subjects have received any nonbiologic treatment with immunomodulatory properties (other than their current background UC treatment) within 30 days before baseline (Visit 2).”	To indicate exclusion of subjects with prior nonbiologic treatment with immunomodulatory properties within the specified timeframe.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria Section 5.2.2, Prohibited Treatments	Added exclusion criterion #13: “Subjects have received leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange within 30 days before baseline (Visit 2).”	To indicated exclusion of subjects with prior apheresis or plasma exchange within the specified timeframe.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #16 (now #18) to clarify that subjects with a history of <i>Mycobacterium tuberculosis</i> (TB) infection will be excluded.	To further define the exclusion of subjects with any history of positive TB.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria Section 7.2.3.6, Clinical Laboratory Evaluations	Revised the name of interferon gamma release assay (IGRA) from “QuantiFERON TB Gold In-Tube Test” to “QuantifERON TB Gold Plus In-Tube Test.”	To reflect a change in assay for detection of TB.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #22 (now #24) to indicate that subjects with cirrhosis with or without decompensation will be excluded.	To further define the exclusion of subjects with compromised liver function.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Moved exclusion of subjects with primary sclerosing cholangitis from exclusion criterion #22 to new criterion #25.	To further define the exclusion of subjects with compromised liver function.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #24 (now #26) to indicate that subjects with negative HBsAg but positive HBcAb may be eligible if no presence of HBV DNA is confirmed.	To clarify that subjects with positive HBcAb, without HBV DNA, may be eligible for the study.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #25 (now #27) to indicate that subjects with chronic hepatitis C (HCV) without evidence of HCVRNA within 12 weeks of baseline may be considered eligible.	To clarify that subjects with chronic HCV, without HCVRNA, may be eligible for the study.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	05 Sep 2018	Global
Section(s) Affected by Change	Description of Change	Rationale
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	<p>Updated exclusion criterion #26 (now #28) to indicate that subjects meeting the following lab criteria would be excluded:</p> <ul style="list-style-type: none"> • ALT or AST $\geq 3 \times$ULN • Total bilirubin level ≥ 1.5 times the ULN (>2 times the ULN if subject has a known documented history of Gilbert's syndrome) <p>Added a note to exclusion criterion #26 (now #28) to specify that, if platelet count is $<150,000$ cells/mm³, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.</p>	To align criteria with FDA guidelines.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #28 (now #30) to include exclusion of subjects with abuse of medicinal marijuana. Deleted former exclusion criterion #28 related to medicinal marijuana dependency.	To indicate that subjects with medicinal marijuana abuse would be excluded.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #31 (now #33) to indicate the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including male subjects are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and for 16 weeks after last dose of investigational product.	To specify the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including sperm banking or donation for male subjects and egg donation or harvest for female subjects.
Study Synopsis, Endpoints and statistical analysis, Analysis Sets Section 9.7, Study Population	[REDACTED]	For clarity and consistency of how these are defined across the Phase 3 protocols.

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Study Synopsis, Endpoints and statistical analysis, Analysis Sets Section 9.8.1, Primary Efficacy Endpoint Section 9.8.2, Secondary Efficacy Endpoints Section 9.8.3, Exploratory Efficacy Endpoints	Removed “subjects with” and “proportion of subjects with” from the efficacy endpoints where applicable.	To describe the endpoints correctly.
Study Synopsis, Safety Analyses Section 9.9, Safety Analyses	Added further details on planned summary presentations for the safety analyses. Clarified definition of TEAE.	For clarity.
Section 1.3, Benefit and Risk Assessment	Added new section describing risk and benefits of SHP647 treatment.	To provide updated risk and benefit information for SHP647.
Schedule of Assessments, footnote “m” Section 7.2.3.6, Clinical Laboratory Evaluations	Updated SOA footnote “m” and added text in Section 7.2.3.6 to clarify that diagnosis of <i>C. difficile</i> infection should be made using the central laboratory. Added diagnostic algorithms and relevant related to <i>C. difficile</i> testing and diagnosis.	To provide appropriate guidance regarding laboratory testing for <i>C. difficile</i> infection.
Schedule of Assessments, footnote “o”	Added new row to SOA and footnote ‘o’ to indicate HIV tests may be performed at local laboratories (per local requirements) if documentation of a negative HIV test within 6 months of screening is unavailable.	To clarify the timing of acceptable documentation of HIV status.
Schedule of Assessments, footnote “v” Section 2.2.3, Exploratory Objectives Section 7.1.1.1, Screening Visit (Visit 1) Section 7.2.2.1, Endoscopy and Histology Section 9.8.3, Exploratory Efficacy Endpoints Appendix 2, Scales and Assessments	[REDACTED]	[REDACTED]

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Section 3.1, Study Design and Flow Chart	Updated Figure 2 to show more clearly the possible paths for subjects following completion of the 12-week treatment period, ie either entering the maintenance study SHP647-303, entering the LTS study SHP647-304, or entering the 16-week safety follow-up period in this induction study.	To provide clarity regarding the flow of subjects following completion of the 12-week treatment period in this study.
Section 4.4, Reproductive Potential	Made edits to clarify the appropriate methods of contraception for female and male subjects of reproductive potential.	To clarify language regarding appropriate contraceptive methods for subjects of reproductive potential.
Section 4.5.1, Subject Withdrawal Criteria	Added pregnancy to the list of reasons a subject may be withdrawn from study treatment.	For clarity and consistency with language in Section 8.1.6.
Section 5.2.2, Prohibited Treatments	Updated Table 2 to add nonbiologics with immunomodulatory properties as prohibited medications.	To include nonbiologics with immunomodulatory properties as prohibited medications.
Section 6.2.2, Allocation of Subjects to Treatment	Added language to place a cap on the Japan-specific sample population with prior anti-TNF exposure at 60%.	To ensure comparability to the rest of the global population, which has the same cap on prior anti-TNF therapy exposure.
Section 7.1.3, Follow-up Period: Visits 7 and 8 (Weeks 20 and 28)	Revised text to clarify that the 16-week safety follow-up period is timed relative to the End of Treatment visit, not to the subject's last dose of investigational product.	To accurately reflect the timing for the start of the safety follow-up period and align with the Schedule of Assessments. This change was made with SHP647-302 Protocol Administrative Change Memo #1 (dated 08 Aug 2017).
Section 7.2, Study Evaluations and Procedures	Added statement that blood and tissue samples may be stored for up to the duration allowed by local regulations, but for no longer than 25 years. Revised from "blood sample collection" to "laboratory sample collection" to clarify that this includes other sample collection, eg urine. Moved investigational product administration to the last bullet point in the ordering of procedures.	To provide clarity regarding the length of time that blood and tissue samples may be stored. This change was made with SHP647-302 Protocol Administrative Change Memo #2 (dated 07 Sep 2017). To improve clarity. To improve clarity.

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Section 7.2.2.2, Mayo score	Removed language stating that endoscopic appearance would be read locally; it is to be centrally read only.	To clarify that endoscopic appearance will be read centrally, not locally.
Section 7.2.3.5, Vital Signs	Removed language that specified measuring body temperature orally with a digital thermometer or by using tympanic temperature.	To clarify how body temperature should be obtained.
Section 7.2.3.6, Clinical Laboratory Evaluations	Added information on laboratory testing for <i>C. difficile</i> infection, including diagnostic algorithms.	To provide appropriate guidance regarding laboratory testing for <i>C. difficile</i> infection.
Section 7.2.5, Volume of Blood to be Drawn for Each Subject	Made corrections to the blood sample volumes for hematology, serum chemistry, and serum CRP, and the approximate total blood volume in Table 4 (Volume of Blood to be Drawn for Each Subject) and in the paragraph thereafter. Added sample collections/blood volumes for HIV and HBV DNA. Updated the blood sample volumes and approximate total blood volume to reflect these changes.	To reflect accurately the blood sample volumes for hematology, serum chemistry, and serum CRP, and reflect addition of HIV and HBV DNA testing.
Section 8.1.8, Unexpected Adverse Event Section 8.1.9, Suspected Unexpected Serious Adverse Reaction	Added definitions of unexpected adverse event and suspected unexpected serious adverse reaction.	To define unexpected adverse event and suspected unexpected serious adverse reaction.
Section 8.2.7, Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting	Added text to clarify that “related, unexpected SAEs” refers to “SUSARs.”	To clarify that “related, unexpected SAEs” refers to “SUSARs.”
Section 8.2.8, Safety Monitoring Rules	Added new section describing safety monitoring and stopping algorithms for elevated hepatic blood tests.	To provide appropriate guidance on patients who have been enrolled with elevated liver function test values or who experience and increase in liver function test(s) during the study.
Section 10, Sponsor’s and Investigator’s Responsibilities	Added a statement that compliance with the noted regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.	To clarify that the study is conducted in accordance with the ethical principles in the Declaration of Helsinki.

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Section 10.1.1, Good Clinical Practice Compliance	Added language to clarify that the sponsor will ensure that local regulatory requirements are met during the study, including annual safety reporting, ie, Development Safety Update Reports.	To clarify language regarding regulatory reporting requirements.
Appendix 2, Mayo Scoring System for Assessment of Ulcerative Colitis Activity	Added a footnote ("c") to the Mayo Scoring System for Assessment of Ulcerative Colitis Activity to clarify that the "findings on endoscopy" scoring represents the modified endoscopy subscore and that data will be collected to calculate the total Mayo score using both the modified endoscopy subscore and traditional endoscopy subscore, which will be used as a sensitivity analysis and to estimate the impact of the modification on the primary endpoint.	To provide clarity regarding Mayo Scoring System and use of the modified and traditional endoscopy scores. This change was described in SHP647-302 Protocol Administrative Change Memo #2 (dated 07 Sep 2017).
Appendix 2, Scales and Assessments	[REDACTED]	[REDACTED]
Appendix 4, Determination of Failure or Intolerance to Prior Treatment for Ulcerative Colitis	Added new appendix section, "Determination of Failure or intolerance to Prior Treatment for Ulcerative Colitis" to provide guidance as related to inclusion criterion #8 in which subjects meeting these criteria on prior conventional treatments (eg, sulfasalazine, mesalamine, glucocorticoids, immunosuppressants, or anti-TNF) may be eligible for this study.	To provide additional granularity regarding the eligibility of subjects who demonstrated inadequate response, loss of response, or intolerance on conventional treatment.
Appendix 5, Guidance for Treatment of Increased Gastrointestinal Symptoms	Added new Appendix 5, "Guidance for Treatment of Increased Gastrointestinal Symptoms related to diagnosis and treatment of <i>C. difficile</i> infection."	To provide updated treatment guidance for subjects diagnosed with <i>C. difficile</i> infection.
Throughout protocol	Minor changes to wording.	To improve clarity, consistency, and remove redundancy of text.

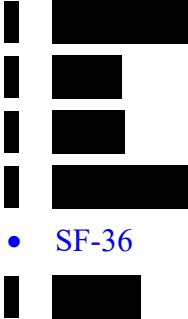
APPENDIX 2 SCALES AND ASSESSMENTS

The following scales/assessments will be used in the study and are provided in this appendix:

- Stool frequency screening questions
- Mayo scoring system
- Geboes score grading system



- PRO-UC diary
- IBDQ



- SF-36



For questionnaires, language-specific validated versions will be used only.

Stool Frequency Screening Questions

1. Think back to before you ever had symptoms of UC. How many bowel movements did you typically have in a 24-hour period before ever having symptoms of UC?

Number of bowel movements in a 24-hour period before ever having symptoms of UC:

2. Remission of ulcerative colitis (UC) is defined as a time when your symptoms have gone away, you're feeling well, and/or your UC is no longer impacting your regular daily activities. Have you ever experienced a remission of UC?

- Yes
- No

If YES,

When you are in remission how many bowel movements do you typically have in a 24-hour period? Remember that remission is a time when your symptoms have gone away, you're feeling well, and/or your UC is no longer impacting your regular daily activities.

Number of bowel movements in a 24-hour period when in remission:

Mayo Scoring System for Assessment of Ulcerative Colitis Activity

Stool frequency^a

- 0 = Normal number of stools for this subject
 - 1 = 1 to 2 stools more than normal
 - 2 = 3 to 4 stools more than normal
 - 3 = 5 or more stools more than normal
- Subscore, 0 to 3

Rectal bleeding^b

- 0 = No blood seen
 - 1 = Streaks of blood with stool less than half the time
 - 2 = Obvious blood (more than just streaks) or streaks of blood with stool most of the time
 - 3 = Blood alone passes
- Subscore, 0 to 3

Findings on endoscopy^c

- 0 = Normal or inactive disease
 - 1 = Mild disease (erythema, decreased vascular pattern)
 - 2 = Moderate disease (marked erythema, lack of vascular pattern, any friability, erosions)
 - 3 = Severe disease (spontaneous bleeding, ulceration)
- Subscore, 0 to 3

Physician's global assessment^d

- 0 = Normal
 - 1 = Mild disease
 - 2 = Moderate disease
 - 3 = Severe disease
- Subscore, 0 to 3

The total Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.

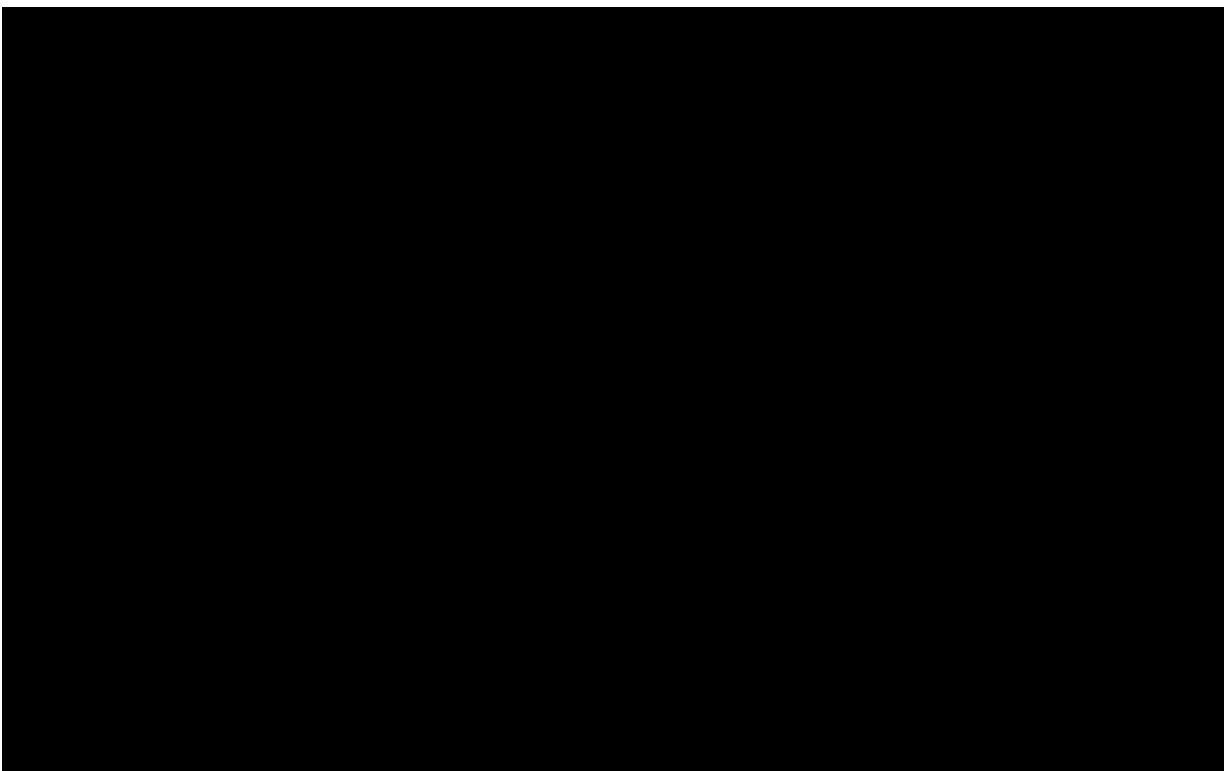
- ^a Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency.
- ^b The daily bleeding score represents the most severe bleeding of the day.
- ^c Findings on endoscopy scoring represents the modified endoscopy subscore (value of 1 does not include friability).
- Note: Data will be collected to calculate the total Mayo score using both the modified endoscopy subscore and traditional endoscopy subscore (value of 1 including mild friability) as a sensitivity analysis and to estimate the impact of the modification on the primary endpoint.
- ^d The physician's global assessment acknowledges the three other criteria, the subject's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the subject's performance status.

Source: [Schroeder et al., 1987](#).

Geboes Score Grading System

Grade 0 – Structural (architectural change)	
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1 – Chronic inflammatory infiltrate	
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2A – Lamina propria eosinophils	
Subgrades	
2A.0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
Grade 2B – Lamina propria neutrophils	
Subgrades	
2B.0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3 – Neutrophils in epithelium	
Subgrades	
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4 – Crypt destruction	
Subgrades	
4.0	None
4.1	Probable – local excess of neutrophils in part of crypt
4.2	Probable – marked attenuation
4.3	Unequivocal crypt destruction
Grade 5 – Erosion or ulceration	
Subgrades	
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

Source: [Geboes et al., 2000](#).



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Patient-reported Outcomes – Ulcerative Colitis (PRO-UC) Diary Version 1

Item #	Item
1.	<p>Please indicate how often you had a bowel movement over the past 24 hours. A bowel movement is defined as a trip to the toilet and passing stool (liquid, soft, or solid), passing blood only, passing blood and mucus, or passing mucus only.</p> <p>Enter number of bowel movements passed:</p>
2.	<p>Please rate your worst experience of rectal bleeding over the past 24 hours.</p> <ul style="list-style-type: none">• No blood seen• Streaks of blood with stool less than half of the time• Obvious blood (more than just streaks) or streaks of blood with stool most of the time• Blood alone passes
3.	<p>You indicated you had X bowel movements in the past 24 hours. Of these, how many had blood, either in the stool, in the toilet bowl, or on the toilet paper?</p> <p>Enter the number of bowel movements with blood:</p>
4.	<p>You indicated you had X bowel movements in the past 24 hours. Of these, how many were loose or watery?</p> <p>Enter number of loose or watery bowel movements:</p>
5.	<p>You indicated you had X bowel movements in the past 24 hours. How many of those involved urgency (having to suddenly rush to the toilet to make it on time)?</p> <p>Enter number of bowel movements with urgency:</p>
6.	<p>Please rate your worst abdominal pain over the past 24 hours.</p> <ul style="list-style-type: none">• 0-10 numeric rating scale, with 0 anchor at “No pain” and 10 at “Worst Imaginable Pain”

Inflammatory Bowel Disease Questionnaire (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks.

You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from:
 1. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
 2. EXTREMELY FREQUENT
 3. VERY FREQUENT
 4. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 5. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 6. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
 7. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from:
 1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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

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

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

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

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

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

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

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

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

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

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

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

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:
1. A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
 2. A LOT OF DIFFICULTY
 3. A FAIR BIT OF DIFFICULTY
 4. SOME DIFFICULTY
 5. A LITTLE DIFFICULTY
 6. HARDLY ANY DIFFICULTY
 7. NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES
13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME
14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from:
1. ALL OF THE TIME
 2. MOST OF THE TIME
 3. A GOOD BIT OF THE TIME
 4. SOME OF THE TIME
 5. A LITTLE OF THE TIME
 6. HARDLY ANY OF THE TIME
 7. NONE OF THE TIME

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from:

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

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

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

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

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

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

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

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

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

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

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

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

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

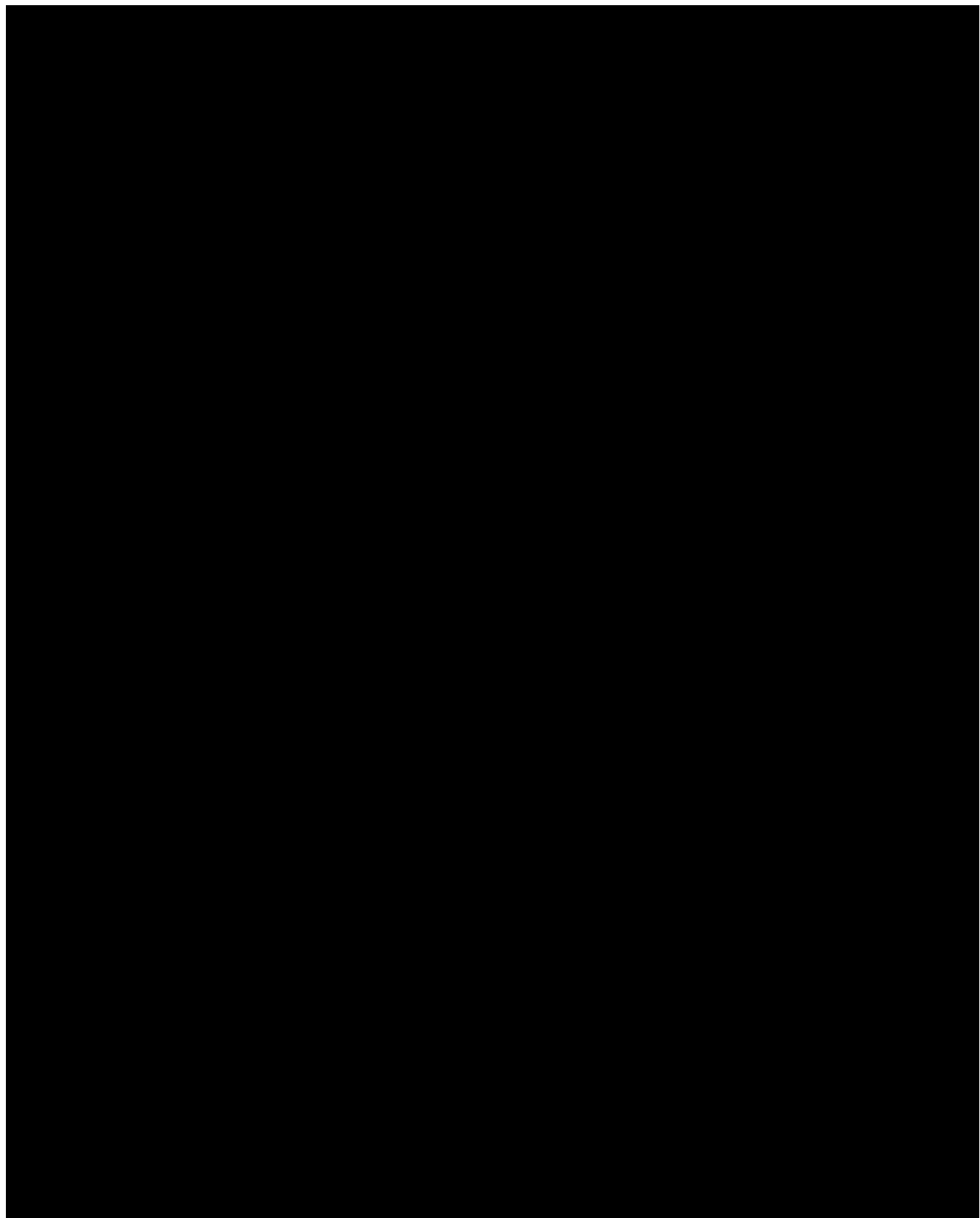
31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from:

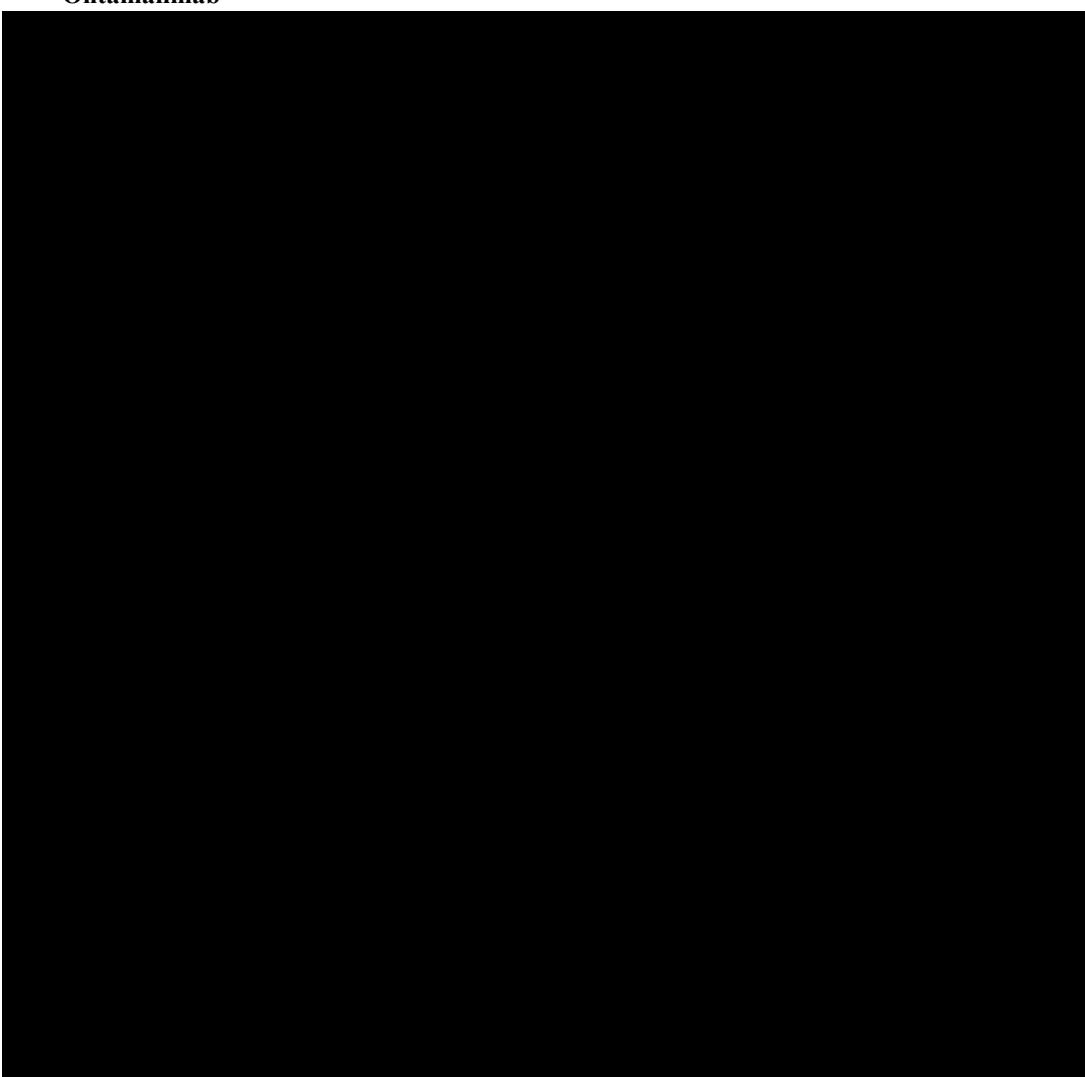
1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

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

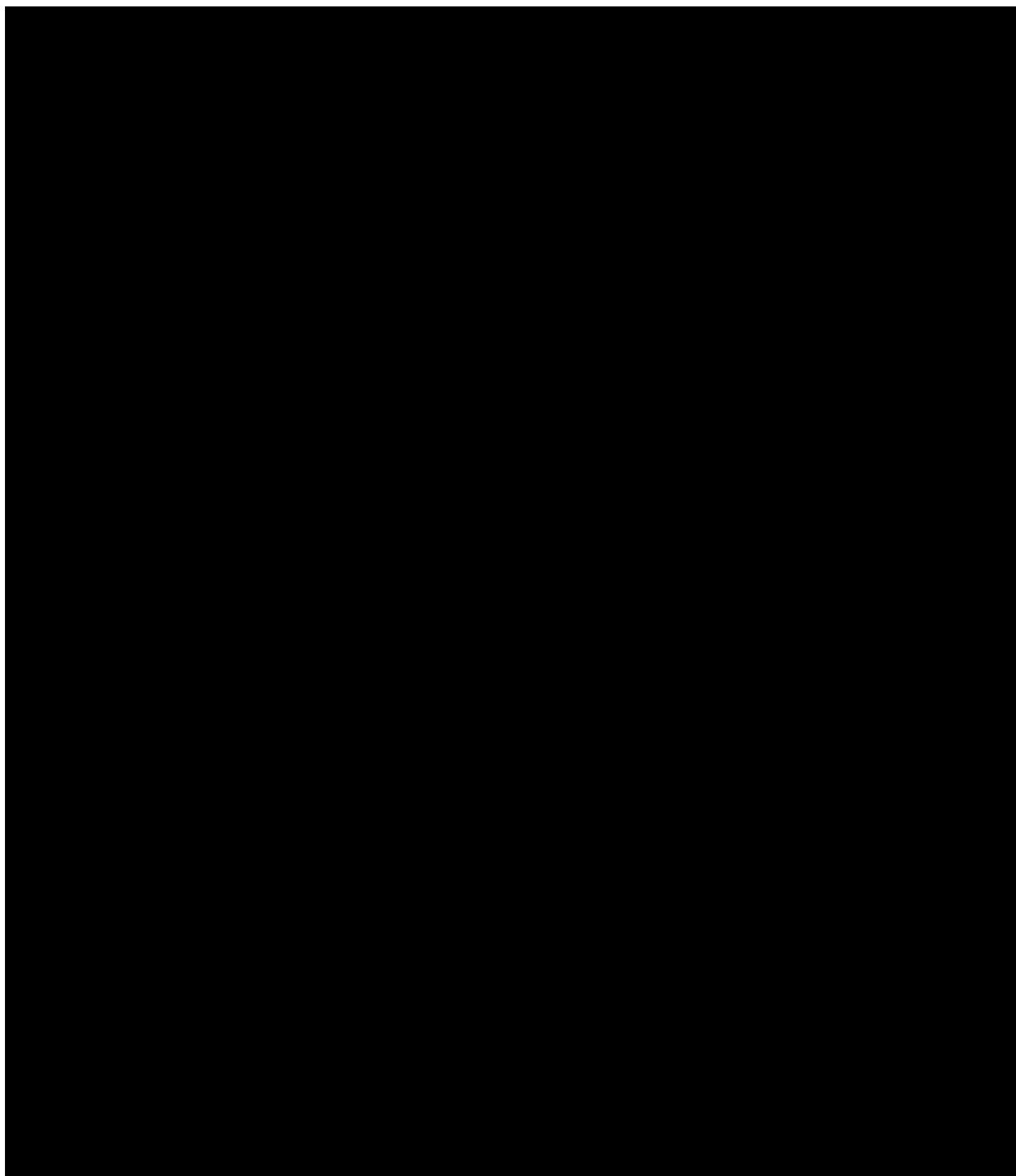
1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2. GENERALLY DISSATISFIED, UNHAPPY
3. SOMEWHAT DISSATISFIED, UNHAPPY
4. GENERALLY SATISFIED, PLEASED
5. SATISFIED MOST OF THE TIME, HAPPY
6. VERY SATISFIED MOST OF THE TIME, HAPPY
7. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

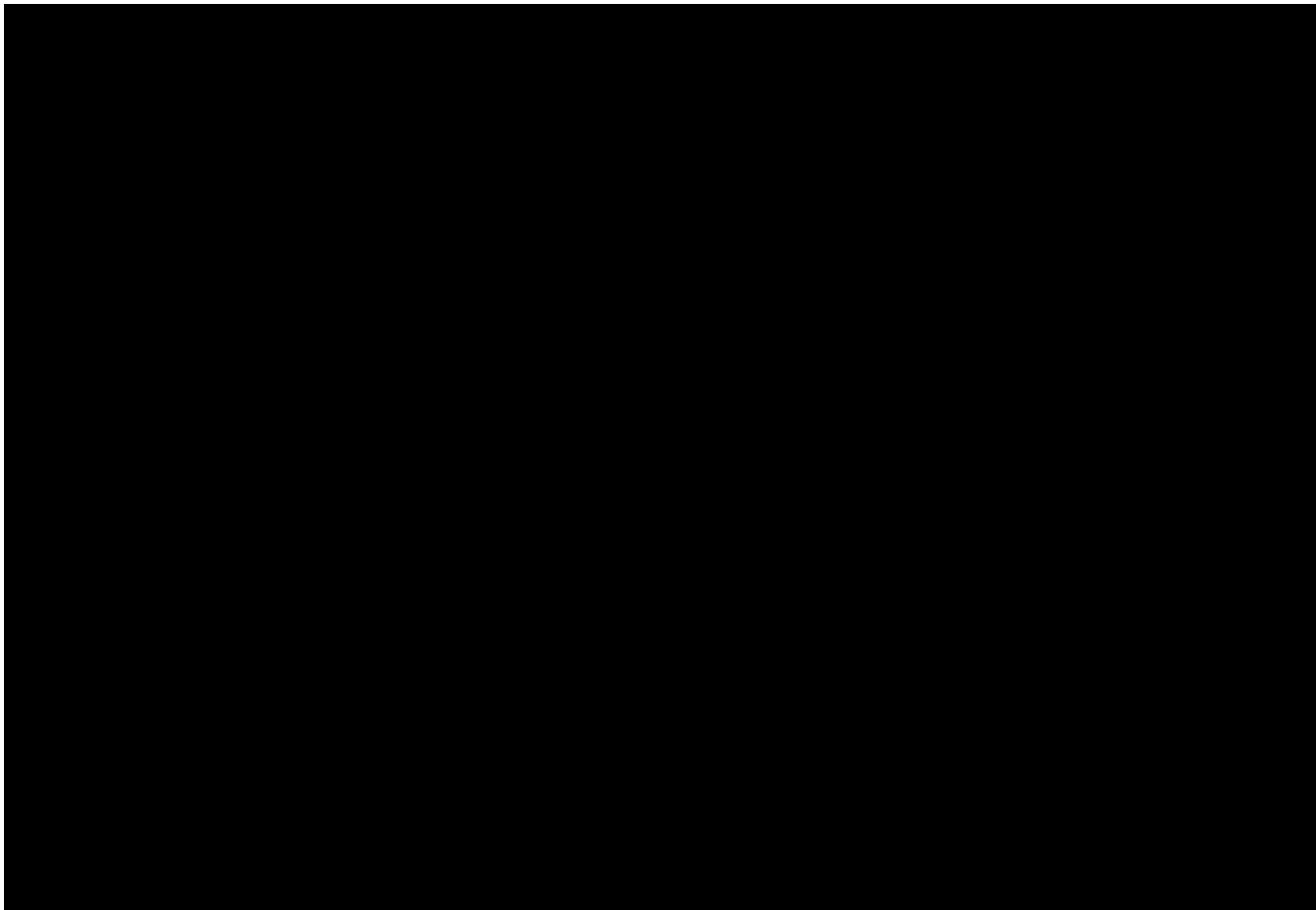






For non-clients





For non-com.
munications

Short Form-36 Health Survey, Acute Form

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an in the one box that best describes your answer.

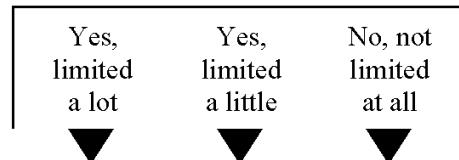
1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?



- a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports 1 2 3
- b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf 1 2 3
- c Lifting or carrying groceries 1 2 3
- d Climbing several flights of stairs 1 2 3
- e Climbing one flight of stairs 1 2 3
- f Bending, kneeling, or stooping 1 2 3
- g Walking more than a mile 1 2 3
- h Walking several hundred yards 1 2 3
- i Walking one hundred yards 1 2 3
- j Bathing or dressing yourself 1 2 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

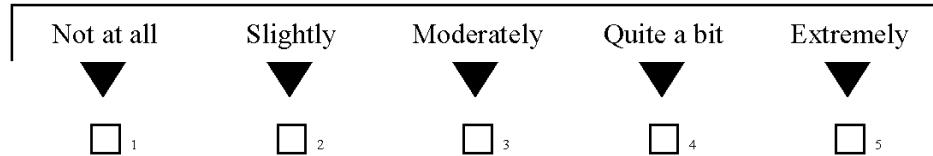
- a. Cut down on the amount of time you spent on work or other activities 1..... 2..... 3..... 4..... 5
- b. Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c. Were limited in the kind of work or other activities 1..... 2..... 3..... 4..... 5
- d. Had difficulty performing the work or other activities (for example, it took extra effort) 1..... 2..... 3..... 4..... 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

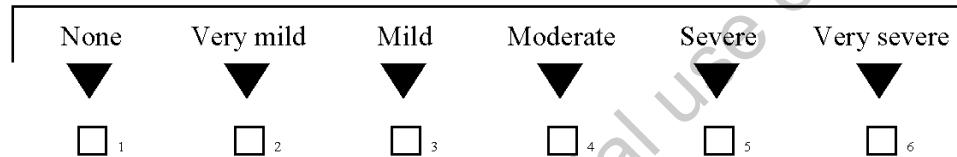
All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Cut down on the amount of time you spent on work or other activities 1..... 2..... 3..... 4..... 5
- b. Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c. Did work or other activities less carefully than usual 1..... 2..... 3..... 4..... 5

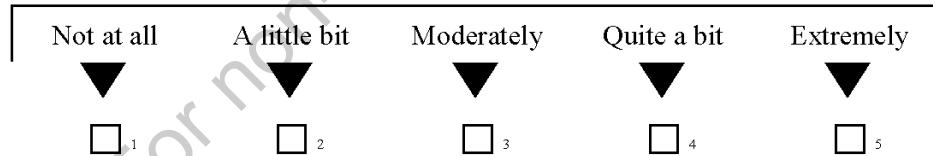
6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much bodily pain have you had during the past week?



8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Did you feel full of life? 1..... 2..... 3..... 4..... 5
- b Have you been very nervous?..... 1..... 2..... 3..... 4..... 5
- c Have you felt so down in the dumps that nothing could cheer you up?..... 1..... 2..... 3..... 4..... 5
- d Have you felt calm and peaceful?..... 1..... 2..... 3..... 4..... 5
- e Did you have a lot of energy?..... 1..... 2..... 3..... 4..... 5
- f Have you felt downhearted and depressed?..... 1..... 2..... 3..... 4..... 5
- g Did you feel worn out?
- h Have you been happy?..... 1..... 2..... 3..... 4..... 5
- i Did you feel tired?

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

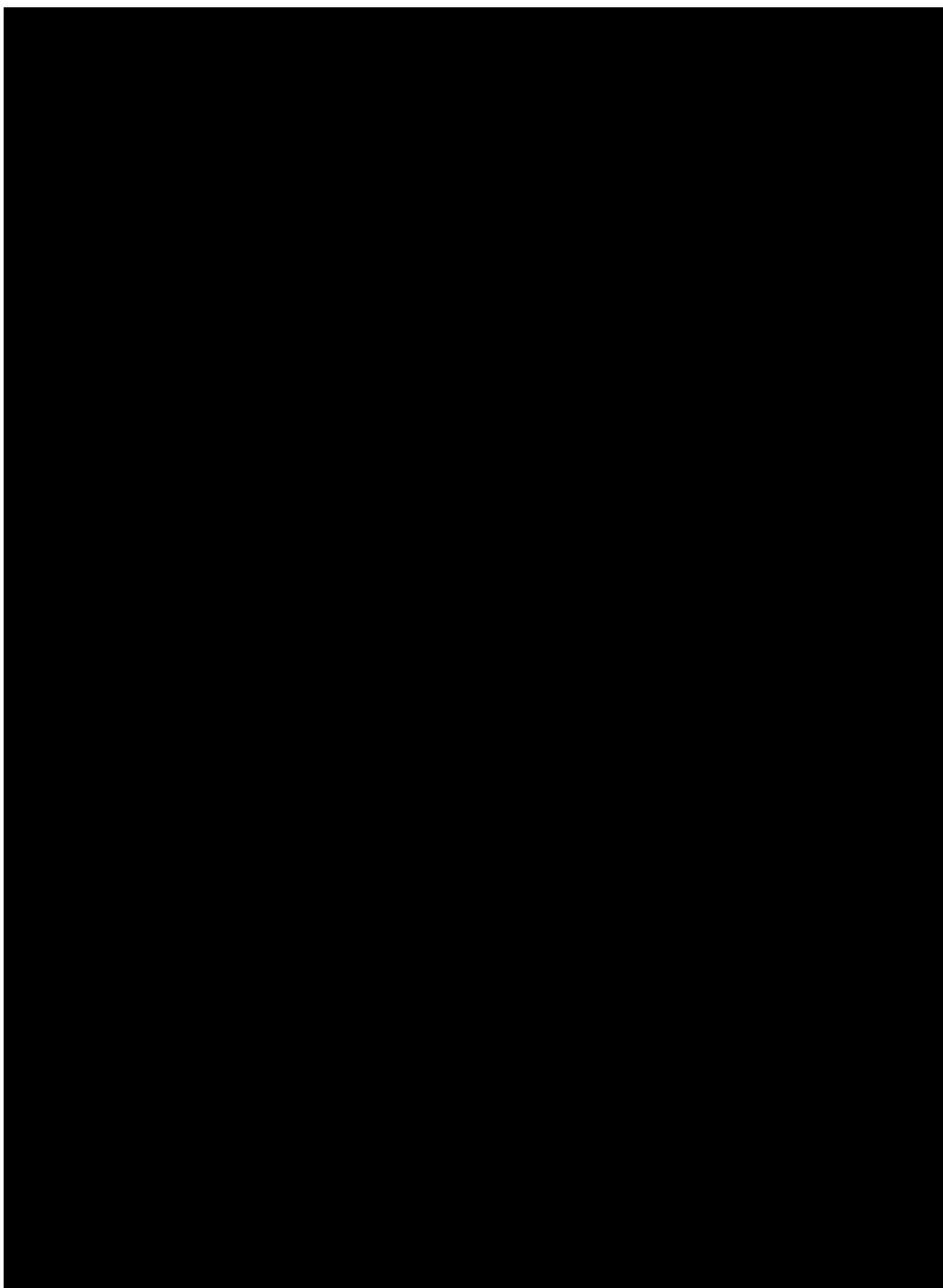
All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

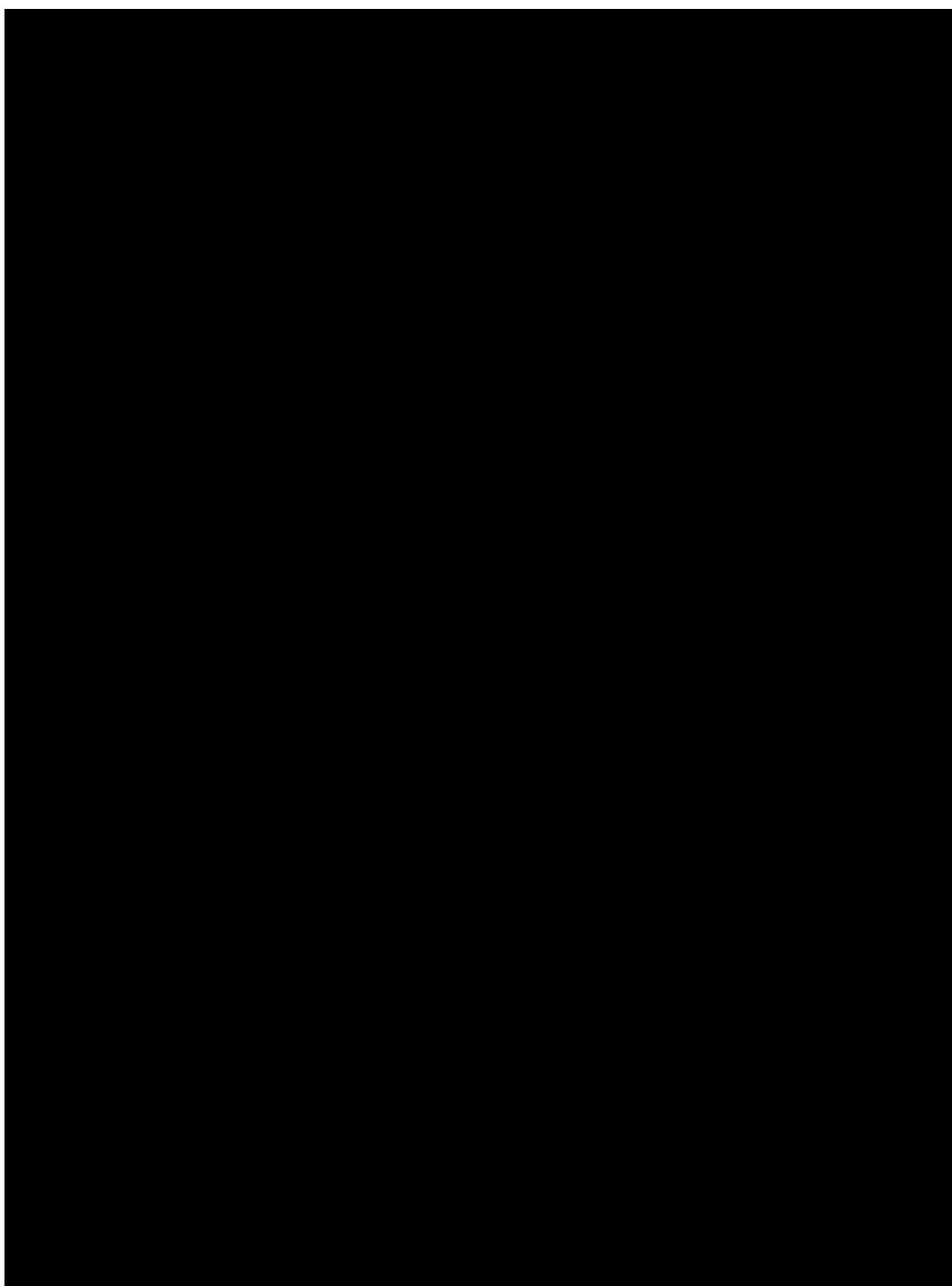
11. How TRUE or FALSE is each of the following statements for you?

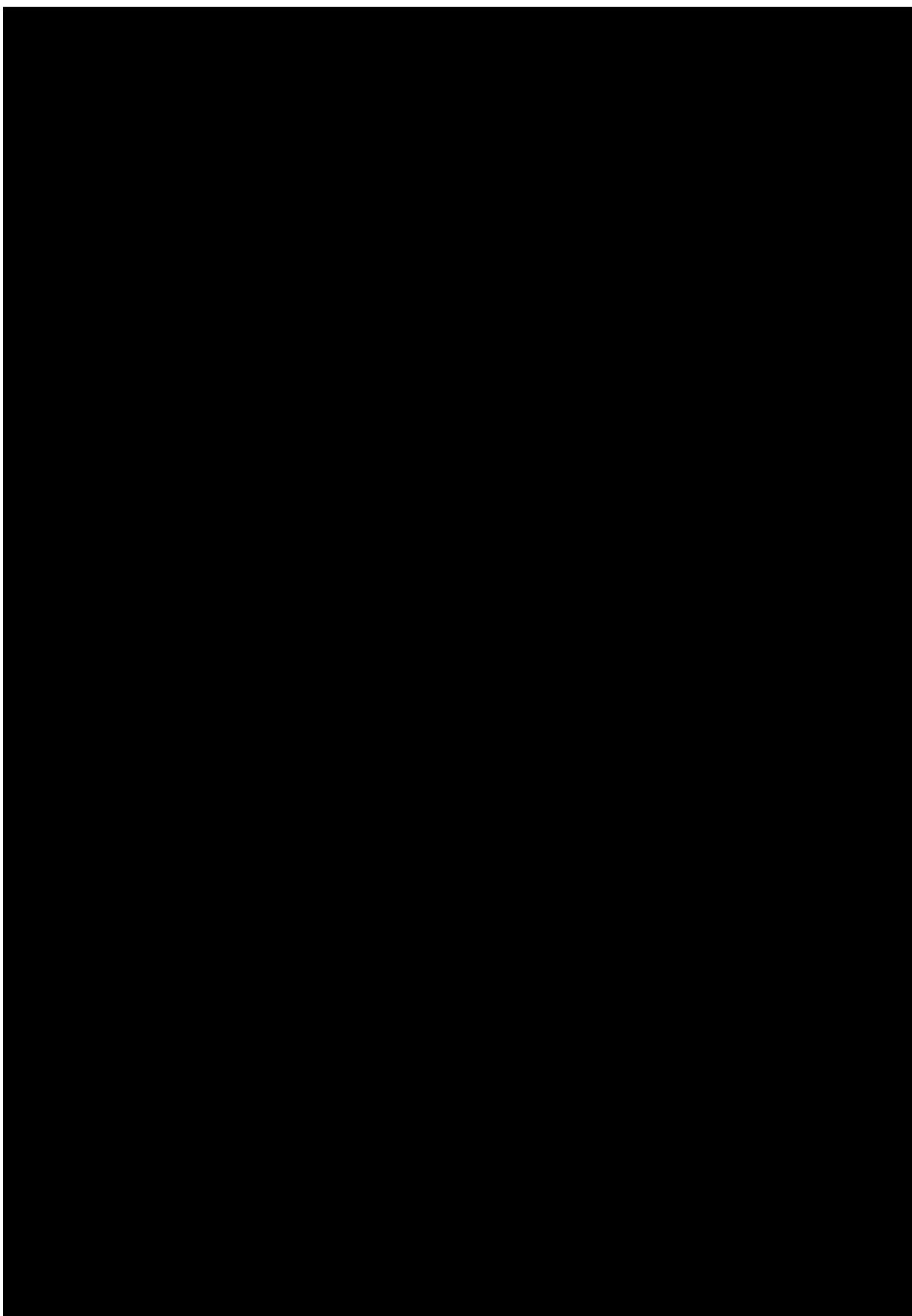
Definitely true	Mostly true	Don't know	Mostly false	Definitely false

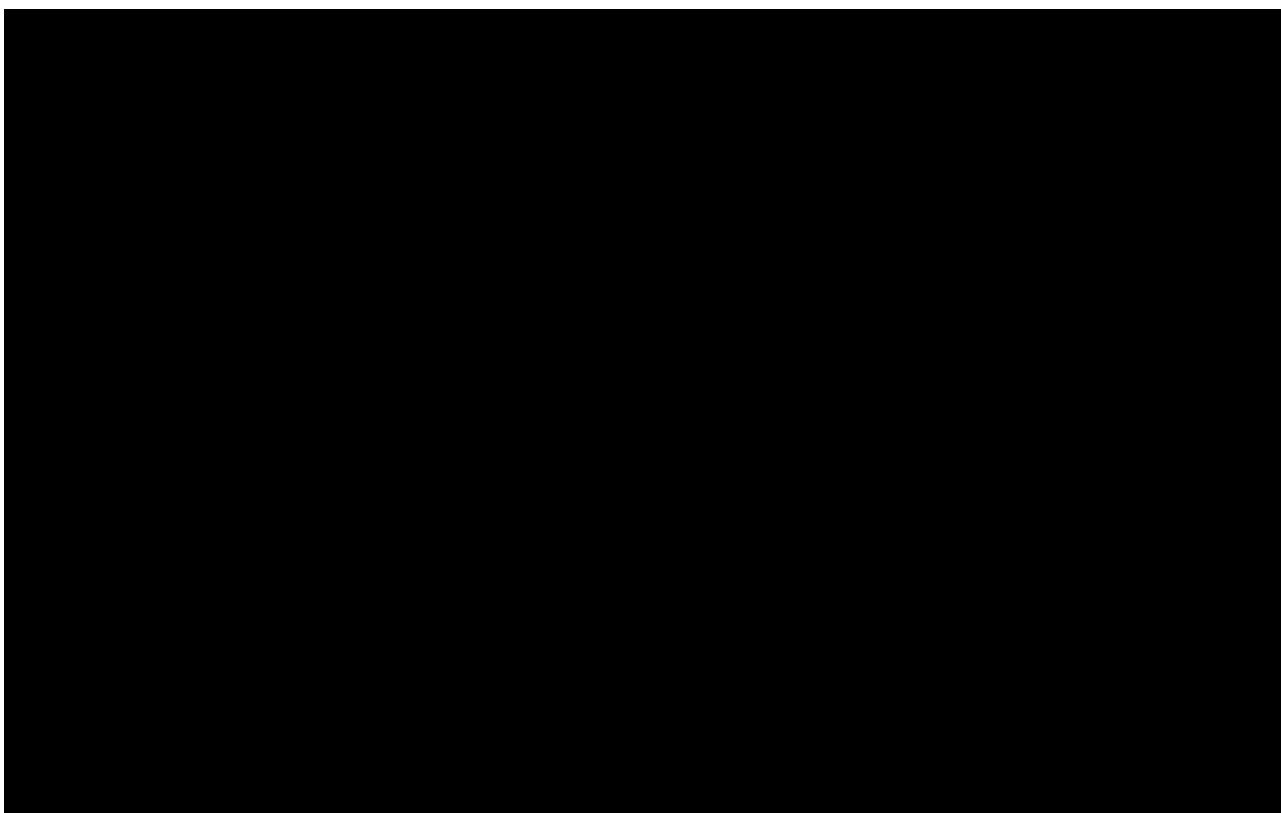
- a I seem to get sick a little easier than other people 1 2 3 4 5
- b I am as healthy as anybody I know 1 2 3 4 5
- c I expect my health to get worse 1 2 3 4 5
- d My health is excellent 1 2 3 4 5

Thank you for completing these questions!









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APPENDIX 3 GLUCOCORTICOID EQUIVALENT DOSES

Glucocorticoid	Equivalent Dose (mg)
<i>Short Acting:</i>	
Cortisone	25
Hydrocortisone	20
<i>Intermediate Acting:</i>	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
<i>Long Acting:</i>	
Betamethasone	0.6
Dexamethasone	0.75

Reference: [Lacy et al., 2001-2002.](#)

APPENDIX 4 DETERMINATION OF FAILURE OR INTOLERANCE TO PRIOR TREATMENT FOR ULCERATIVE COLITIS

The information below should serve as guidance. Local therapeutic standards and investigator judgment should be considered.

AMINOSALICYLATES

Mesalamine (5-ASA)

Inadequate response to or loss of response: defined as persistent signs and symptoms of active disease despite treatment with mesalamine for at least 8 weeks at daily doses of 4.8 g/day.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to mesalamine treatment.

As guidance, the US package insert of mesalamine lists the following AEs. Please check the respective latest label of your country as well ([Lialda®](#), 2018):

Renal impairment including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure

Acute intolerance syndrome includes cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash

Hypersensitivity reactions including cardiac hypersensitivity reactions (myocarditis and pericarditis)

Hepatic impairment: hepatic failure in patients with pre-existing liver disease

Photosensitivity in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema

Other treatment-related AEs: headache, flatulence, abnormal liver function test, alopecia, pruritus, tachycardia, hypertension, hypotension, acne, prurigo, rash, urticaria, abdominal distention, colitis, diarrhea, pancreatitis, rectal polyp, vomiting, decreased platelet count, arthralgia, back pain, somnolence, tremor, pharyngolaryngeal pain, asthenia, face edema, fatigue, pyrexia, ear pain. Based on postmarketing experience when it is not always possible to reliably establish a causal relationship to drug exposure: lupus-like syndrome, drug fever, pericarditis, pericardial effusion, myocarditis, pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer, jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, Kawasaki-like syndrome including changes in liver enzymes, agranulocytosis, aplastic anemia, anaphylactic reaction, angioedema, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), myalgia, lupus-like syndrome, peripheral neuropathy, Guillain-Barre syndrome, transverse myelitis, intracranial hypertension, interstitial nephritis, nephrogenic diabetes insipidus, interstitial lung disease, hypersensitivity pneumonitis (including interstitial pneumonitis,

allergic alveolitis, eosinophilic pneumonitis), psoriasis, pyoderma gangrenosum, erythema nodosum, photosensitivity, oligospermia

Sulfasalazine (SSZ)

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite treatment with at least one 8-week induction regimen at daily dose at 4g/day.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to sulfasalazine treatment.

As guidance, the US package insert of sulfasalazine lists the following AEs. Please check the respective latest label of your country as well ([Azulfidine®](#), 2016):

Hypersensitivity reactions: erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, drug rash with eosinophilia and systemic symptoms (DRESS), anaphylaxis, serum sickness syndrome, interstitial lung disease, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, lupus erythematosus-like syndrome, hepatitis and hepatic necrosis with or without immune complexes, fulminant hepatitis, sometimes leading to liver transplantation, parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection, and alopecia

Blood dyscrasias: agranulocytosis, leukopenia, myelodysplastic syndrome, aplastic anemia, megaloblastic (macrocytic) anemia, hemolytic anemia, cyanosis, methemoglobinemia, Heinz body anemia, hypoprothrombinemia, and thrombocytopenia

Gastrointestinal reactions: hepatitis, hepatic failure, pancreatitis, bloody diarrhea, impaired folic acid absorption, impaired digoxin absorption, stomatitis, diarrhea, abdominal pains, and neutropenic enterocolitis

Central nervous system reactions: transverse myelitis, convulsions, meningitis, transient lesions of the posterior spinal column, cauda equina syndrome, Guillain-Barre syndrome, peripheral neuropathy, mental depression, vertigo, hearing loss, insomnia, ataxia, hallucinations, tinnitus, and drowsiness

Renal reactions: toxic nephrosis with oliguria and anuria, nephritis, nephrotic syndrome, urinary tract infections, hematuria, crystalluria, proteinuria, and hemolytic-uremic syndrome

Other reactions: urine discoloration and skin discoloration, Goiter production, diuresis and hypoglycemia, oligospermia. Based on postmarketing experience when it is not always possible to reliably establish a causal relationship to drug exposure: elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure, folate deficiency, nephrolithiasis, oropharyngeal pain, angioedema

In addition, anorexia, headache, nausea, vomiting, gastric distress, pruritus, urticaria, rash, fever, sore throat, fever, pallor, purpura

GLUCOCORTICOIDS

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or intravenously for 1 week OR 2 failed attempts to taper corticosteroids to below a dose equivalent to 10 mg prednisone (oral) daily.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to glucocorticoid treatment.

As guidance, the US package insert of Medrol® lists the following AEs. Please check the respective latest label of your country as well ([Medrol®, 2018](#)):

Fluid and electrolyte disturbances: sodium retention, congestive heart failure, hypertension, fluid retention, potassium loss, and hypokalemic alkalosis

Musculoskeletal: muscle weakness, loss of muscle mass, steroid myopathy, osteoporosis, tendon rupture, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, and pathologic fracture of long bones

Gastrointestinal: peptic ulcer with or without perforation and hemorrhage, pancreatitis, abdominal distention, and ulcerative esophagitis

Dermatologic: impaired wound healing, petechiae and ecchymoses, thin fragile skin, facial erythema, and increased sweating

Neurological: increased intracranial pressure with papilledema (pseudo-tumor cerebri), convulsions, vertigo, and headache

Psychic derangements: euphoria, insomnia, mood swings, personality changes, severe depression, psychotic manifestations, aggravated existing emotional instability or psychotic tendencies

Endocrine: Cushingoid state, secondary adrenocortical and pituitary unresponsiveness, menstrual irregularities, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements of insulin or oral hypoglycemic agents in diabetics

Ophthalmic: posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, and secondary ocular infections

Metabolic: negative nitrogen balance due to protein catabolism

Other: urticaria and other allergic, anaphylactic or hypersensitivity reactions

IMMUNOSUPPRESSANTS

Azathioprine (AZA)

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite a history of AZA use for at least 12 weeks at daily doses ≥ 1.5 mg/kg, including its use as adjunctive therapy or steroid-sparing therapy.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related AZA treatment.

As guidance, the US package insert of an AZA product lists the following AEs. Please check the respective latest label of your country as well ([Imuran®](#), 2014):

Gastrointestinal hypersensitivity reaction characterized by severe nausea, vomiting and potentially with diarrhea, rash, fever, malaise, myalgia, elevations in liver enzymes, and occasionally, hypotension

Hypersensitivity pancreatitis

Hepatotoxicity that may be associated with anorexia, diarrhea, jaundice and ascites

Cytopenias: leukopenia, thrombocytopenia, anemias including macrocytic anemia, and/or pancytopenia, bone marrow suppression, and myelotoxicity

Serious infections (bacterial, viral, fungal, protozoal, and opportunistic infections, including reactivation of latent infections) secondary to treatment

Other: skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea, negative nitrogen balance, reversible interstitial pneumonitis, hepatosplenic T-cell lymphoma and Sweet's syndrome (acute febrile neutrophilic dermatosis)

Mercaptopurine (6-MP)

Inadequate response or loss of response defined as persistent signs and symptoms of active disease despite a history of 6-MP use for at least 12 weeks at daily doses ≥ 0.75 mg/kg, including its use as adjunctive therapy or steroid-sparing therapy.

Intolerance defined as documented treatment discontinuation for AEs suspected to be related to 6-MP treatment.

As guidance, the US package insert of a 6-MP product lists the following AEs. Please check the respective latest label of your country as well ([Purinethol®](#), 2011):

Myelosuppression: anemia, leukopenia, and thrombocytopenia

Embryo-fetal toxicity

Treatment-related malignancies

Renal: hyperuricemia and/or hyperuricosuria

Gastrointestinal: including hepatotoxicity: elevated transaminases, elevated bilirubin, ascites potentially intestinal ulceration, oral lesions, nausea, vomiting, anorexia, diarrhea and sprue-like symptoms, pancreatitis

Miscellaneous: skin rashes, hyperpigmentation, alopecia, drug fever, oligospermia

Methotrexate (MTX)

Inadequate response or loss of response: defined as failure to respond to at least one 8-week regimen of or maintain remission at doses of at least 15 mg/week, given by the intramuscular or subcutaneous route.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to MTX treatment.

As guidance, the US package insert of an MTX product lists the following AEs. Please check the respective latest label of your country as well ([Methotrexate®](#), 2018):

Alimentary system: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis

Blood and lymphatic system disorders: anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia, lymphadenopathy and lymphoproliferative disorders, hypogammaglobulinemia

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus)

Central Nervous System: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions, cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy

Hepatobiliary: acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity decrease in serum albumin, and liver enzyme elevations

Infection: opportunistic infections eg, *Pneumocystis carinii* pneumonia, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, *H. simplex* hepatitis, and disseminated *H. simplex*

Musculoskeletal system: stress fracture

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology

Pulmonary system: respiratory fibrosis, respiratory failure, interstitial pneumonitis, chronic interstitial obstructive pulmonary disease

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis

Urogenital system: severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects

Other: nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis, anaphylactoid reactions

ANTI-TNF AGENTS

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite at least one 4-week induction regimen with the following minimum doses of:

- infliximab (5 mg/kg IV, 2 doses at least 2 weeks apart) or
- adalimumab (one 80 mg SC dose followed by one 40 mg dose at least 2 weeks apart) or
- golimumab (one 200 mg SC dose followed by 100 mg dose at least 2 weeks apart)

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to anti-TNF agents.

As guidance, the US package insert of Humira lists the following AEs. Please check the respective latest labels for the other anti-TNF agents and the labels of your country as well ([Humira®](#), 2017):

Anaphylaxis or serious allergic reactions: generalized rash and flushing, hypersensitivity reactions including angioneurotic edema

Development of neutralizing autoantibodies

Body as a whole: pain in extremity, pelvic pain, surgery, thorax pain

Cardiovascular system: arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, heart failure

Gastrointestinal: cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, vomiting, nausea, abdominal pain, hepatic reactions including acute liver failure, hepatic necrosis

Lupus-like syndrome

Endocrine system: parathyroid disorder

Hemic and lymphatic system: cytopenias, pancytopenia, agranulocytosis, polycythemia

Infections: tuberculosis (new and reactivation of latent tuberculosis) and opportunistic infections pneumonia, septic arthritis, prosthetic and postsurgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis

Metabolic and nutritional disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculoskeletal system: arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: adenoma

Nervous system: confusion, paresthesia, subdural hematoma, tremor

Respiratory system: upper respiratory infection, sinusitis, flu syndrome, asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion

Special senses: cataract

Thrombosis: thrombosis leg

Urogenital system: cystitis, kidney calculus, menstrual disorder

Other: headache, rash, injection site reaction, infusion-related reactions such as fever or chills, cardiopulmonary reactions such as chest pain, hypotension, hypertension, or dyspnea and/or pruritus or urticaria, back pain, urinary tract infection, hypertension

TOFACITINIB

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite at least an 8-week induction regimen with the following minimum doses of:

- 5 or 10 mg given orally twice daily for induction for 8 weeks

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to tofacitinib.

As guidance, the US package insert of Xeljanz lists the following AEs. Please check the respective latest labels for your country as well ([XELJANZ®](#), 2019):

Serious infections: upper respiratory tract infections, nasopharyngitis, urinary tract infections, pneumonia, cellulitis, Herpes zoster, and urinary tract infection, tuberculosis, opportunistic infections (excluding tuberculosis), diverticulitis, gastroenteritis

Malignancies: solid cancers (lung, breast, gastric, colorectal, renal cell, and prostate), lymphoma, malignant melanoma, nonmelanoma skin cancer

Laboratory abnormalities: lymphopenia, neutropenia, liver enzyme elevations (ALT, AST, bilirubin), elevated cholesterol levels (including includes hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased), serum creatinine elevations, increased blood creatine phosphokinase

Blood and lymphatic system disorders: anemia

Metabolism and nutrition disorders: dehydration

Psychiatric disorders: insomnia

Nervous system disorders: paresthesia, headache

Respiratory, thoracic and mediastinal disorders: dyspnea, cough, sinus congestion, interstitial lung disease

Gastrointestinal disorders: abdominal pain, dyspepsia, vomiting, gastritis, nausea, diarrhea

Hepatobiliary disorders: hepatic steatosis

Skin and subcutaneous tissue disorders: rash, erythema, pruritus, acne

Musculoskeletal, connective tissue, and bone disorders: musculoskeletal pain, arthralgia, tendonitis, joint swelling

Neoplasms benign, malignant, and unspecified (including cysts and polyps): nonmelanoma skin cancers

General disorders and administration site conditions: pyrexia, fatigue, peripheral edema

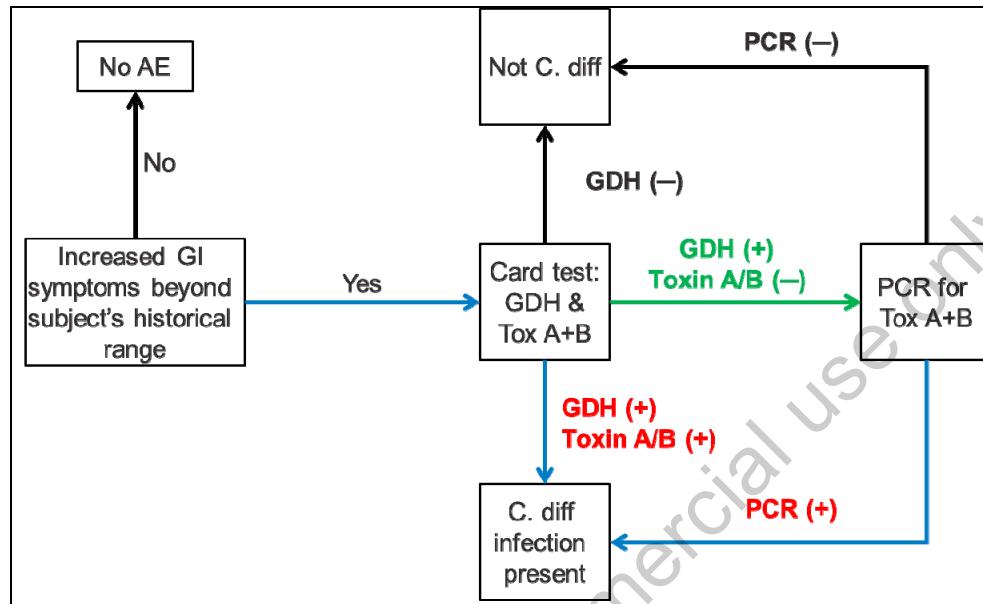
Drug hypersensitivity: angioedema, urticaria

Cardiovascular: pulmonary embolism

APPENDIX 5 GUIDANCE FOR DIAGNOSIS AND TREATMENT OF INCREASED GASTROINTESTINAL SYMPTOMS

If, for any reason, the central laboratory is not available, the preferred diagnostic algorithm is to use the Alere Quik Chek card test ([Figure A1](#)).

Figure A1 Algorithm for *C. difficile* Diagnosis Using the Quick Check Card Test



If the Alere Quik Chek card test is not available, then a diagnosis may be established by following either of the algorithms shown in [Figure A2](#) (using PCR for toxin), [Figure A3](#) using toxigenic culture or [Figure A4](#) (using toxigenic culture, followed by PCR). The rationale for the method in [Figure A3](#) is that the majority of PCR tests are expected to be negative for toxin, thus obviating the need for the test at the central laboratory. The expected turnaround time at the central laboratory for a GDH card test is expected to be shorter than that for stool culture for *C. difficile* at the local laboratory. The details of the sensitivity and specificity of these tests were reported by Khanna ([Khanna et al., 2017](#)).

When medically reasonable, treatment decisions should be deferred until an etiology has been determined. When this is not feasible, management of symptoms should be dictated by the clinical situation.

Figure A2 Alternative 1 for *C. difficile* Testing Using Local Laboratory When No Alere Quick Chek Card Test is Available

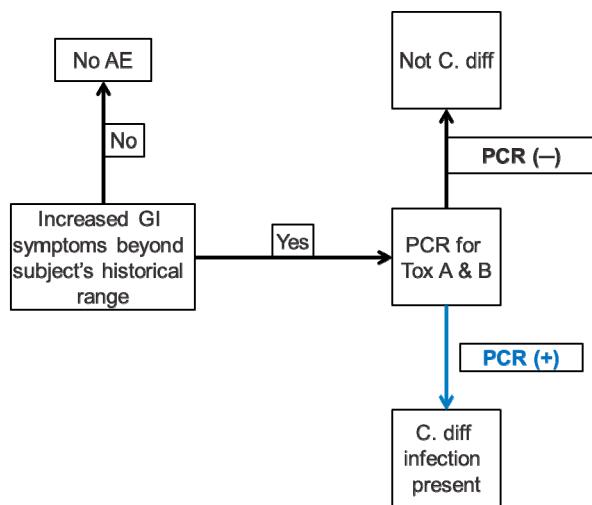


Figure A3 Alternative 2 for *C. difficile* Testing Using Local Laboratory When No Card Test is Available

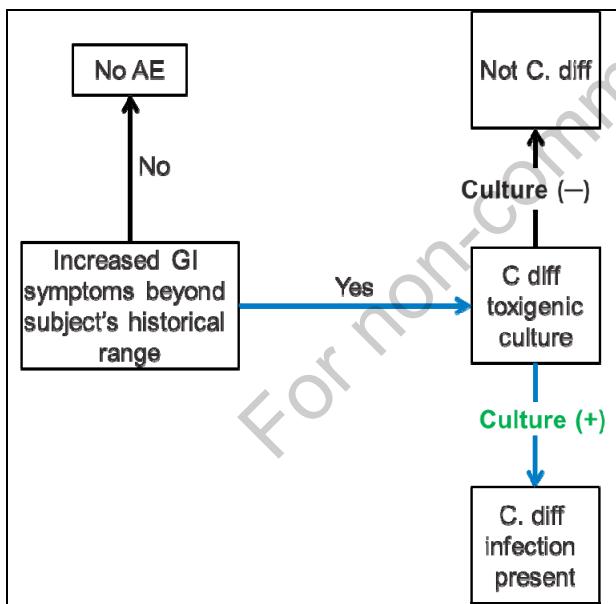
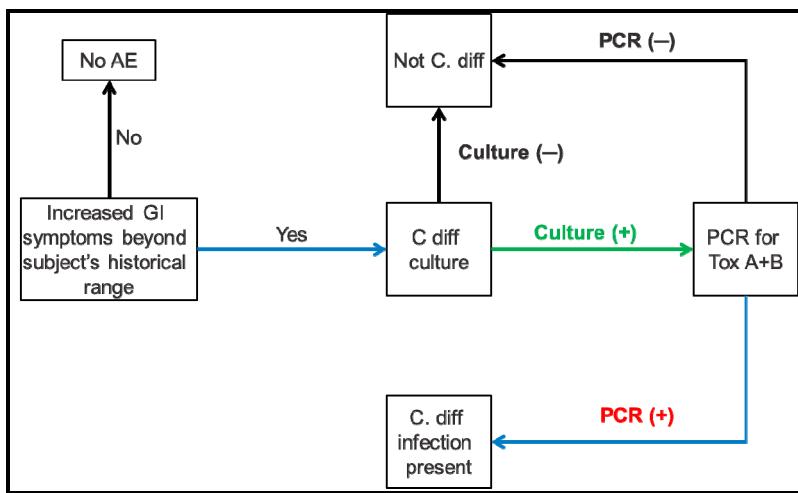


Figure A4 Alternative 3 for *C. difficile* Testing Using Local Laboratory When No Alere Quick Chek Card Test is Available



Treatment

When medically reasonable, treatment decisions should be deferred until an etiology has been determined. When this is not feasible, management of symptoms should be dictated by the clinical situation. **If management requires a prohibited treatment (eg, IV glucocorticoids for induction or maintenance studies) the subject should be withdrawn from treatment.**

If treatment has been deferred, once an etiology is determined (eg, *C. difficile*, disease exacerbation, Campylobacter), appropriate treatment should be promptly implemented without waiting for a scheduled visit. If the etiology is determined to be *C. difficile*, treatment guidelines conforming to the current Infectious Diseases Society of America recommendations for *C. difficile* infection ([McDonald et al., 2018](#)) or the recent expert review on *C. difficile* infection in IBD ([Khanna et al., 2017](#)) should be consulted.

If *C. difficile* infection was identified, clinical improvement should be noted within about 5 days after the start of treatment. If improvement does not occur, the etiology is most likely an IBD flare secondary to *C. difficile* and treatment failure assessment should proceed per the protocol. Another possible explanation is primary failure of *C. difficile* therapy which is unlikely.

If an infectious etiology other than *C. difficile* is identified, it should be managed as appropriate, with reference to current clinical guidelines ([Shane et al., 2017](#)).

If any infectious etiology is determined, the site should contact the medical monitor to make him or her aware of the diagnosis and to discuss treatment and ongoing study participation.