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**Table 1 Schedule of Assessments**

Study Procedure	Screening <sup>a</sup>	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET <sup>b</sup>	Week 20 <sup>c</sup>	Week 28 <sup>c</sup>
Visit Number	1	2	3	4	5	6 (Part 1) <sup>d</sup>	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 <sup>s</sup>	X	X <sup>s</sup>	X <sup>s</sup>	X	X	X
<b>Endoscopic Procedure</b>								
Endoscopy (including biopsy) <sup>u</sup>	X <sup>u</sup>					X		
<b>UC Assessments</b>								
Total Mayo score		X <sup>v</sup>					X <sup>v</sup>	
Partial Mayo score				X	X			
Remission stool frequency and pre-UC stool frequency <sup>w</sup>	X							
PRO UC daily e-diary data instruction	X							
PRO UC daily e-diary data <sup>w</sup>	X	X	X	X	X	X	X	
<b>Health Assessment<sup>x</sup></b>								
IBDQ		X			X		X	
		X			X		X	
Hospitalizations, inpatient days, [REDACTED] (HRUA)				X	X		X	X
[REDACTED]				X	X		X	
[REDACTED]			X	X			X	
SF-36 v2, acute form		X			X		X	
[REDACTED]		X					X	
<b>Treatment Procedures</b>								
Randomization		X						
Administration of SHP647 or placebo <sup>y</sup>		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 <sup>z</sup>	X			X	X			

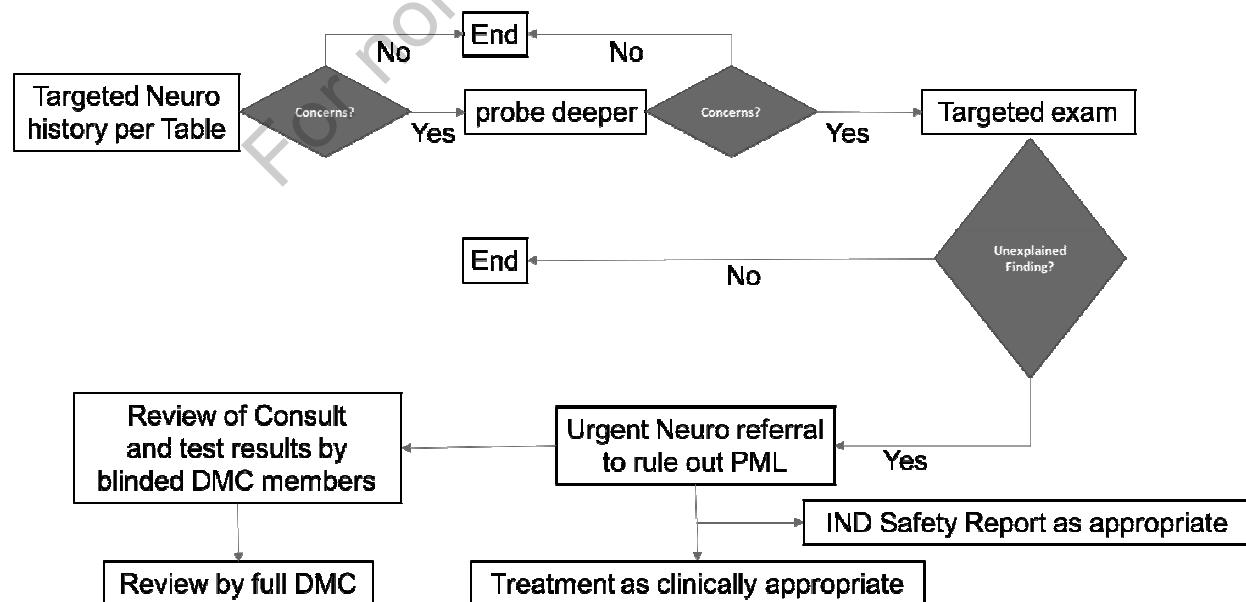
Ab=antibody ADA=antidrug antibodies; β-hCG=beta-human chorionic gonadotropin; [REDACTED]; ECG=electrocardiogram; ED=emergency department;  
 [REDACTED]; ET=early termination; FSH=follicle-stimulating hormone; GDH=glutamate dehydrogenase;  
 HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; 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 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**



## 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  $\delta$  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.

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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.

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.

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 <sub>2κ</sub>	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

**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  $\geq 16$  and  $\leq 80$  years of age at the time of the signing of the informed consent/assent form.

Note: Subjects  $<18$  years of age must weigh  $\geq 40$  kg and must have body mass index  $\geq 16.5$  kg/m<sup>2</sup>.

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

**Table 1 Schedule of Assessments**

Study Procedure	Screening <sup>a</sup>	Baseline	Treatment				Follow-up	
	Weeks -6 to -1	Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12/ET <sup>b</sup>	Week 20 <sup>c</sup>	Week 28 <sup>c</sup>
Visit Number	1	2	3	4	5	6 (Part 1) <sup>d</sup>	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 <sup>u</sup>	X <sup>u</sup>	X <sup>u</sup>	X <sup>u</sup>	X		
Endoscopic Procedure		X <sup>t</sup>	X	X <sup>t</sup>	X <sup>t</sup>	X		X
Endoscopy (including biopsy) <sup>v</sup>	X <sup>v</sup>					X		
UC Assessments								
Total Mayo score		X <sup>w</sup>					X <sup>w</sup>	
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 <sup>x</sup>	X	X	X	X	X	X	X	
Health Assessment <sup>y</sup>								
IBDQ		X			X		X	
Hospitalizations, inpatient days, (HRUA)		X			X		X	X
SF-36, v2, acute form		X			X		X	
Treatment Procedures								
Randomization <sup>z</sup>		X						
Administration of ontamalimab or placebo <sup>z</sup>		X		X	X			
Hypersensitivity monitoring <sup>aa</sup>		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 <sup>ab</sup>	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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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.

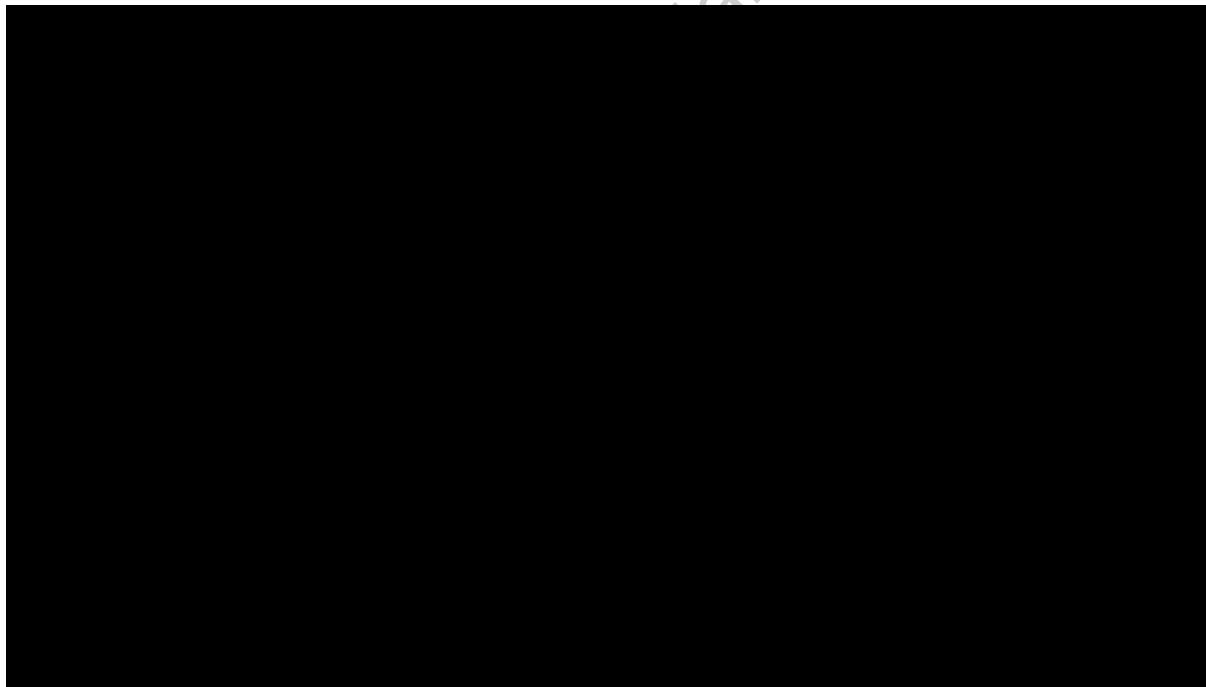
### **2.2.2.2 Other Secondary Objectives**

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 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:



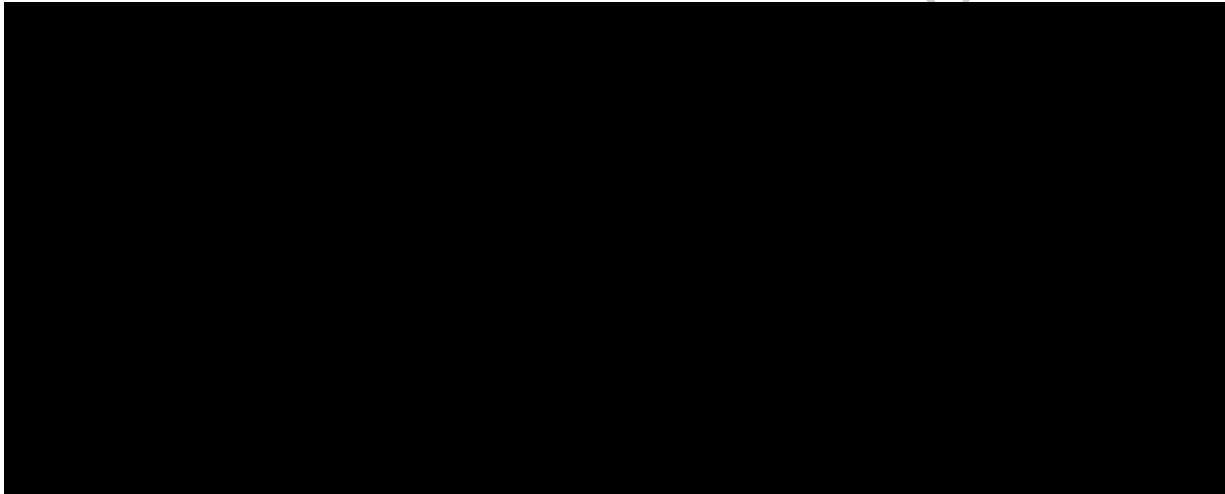
### **2.2.2.2 Other Secondary Objectives**

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.

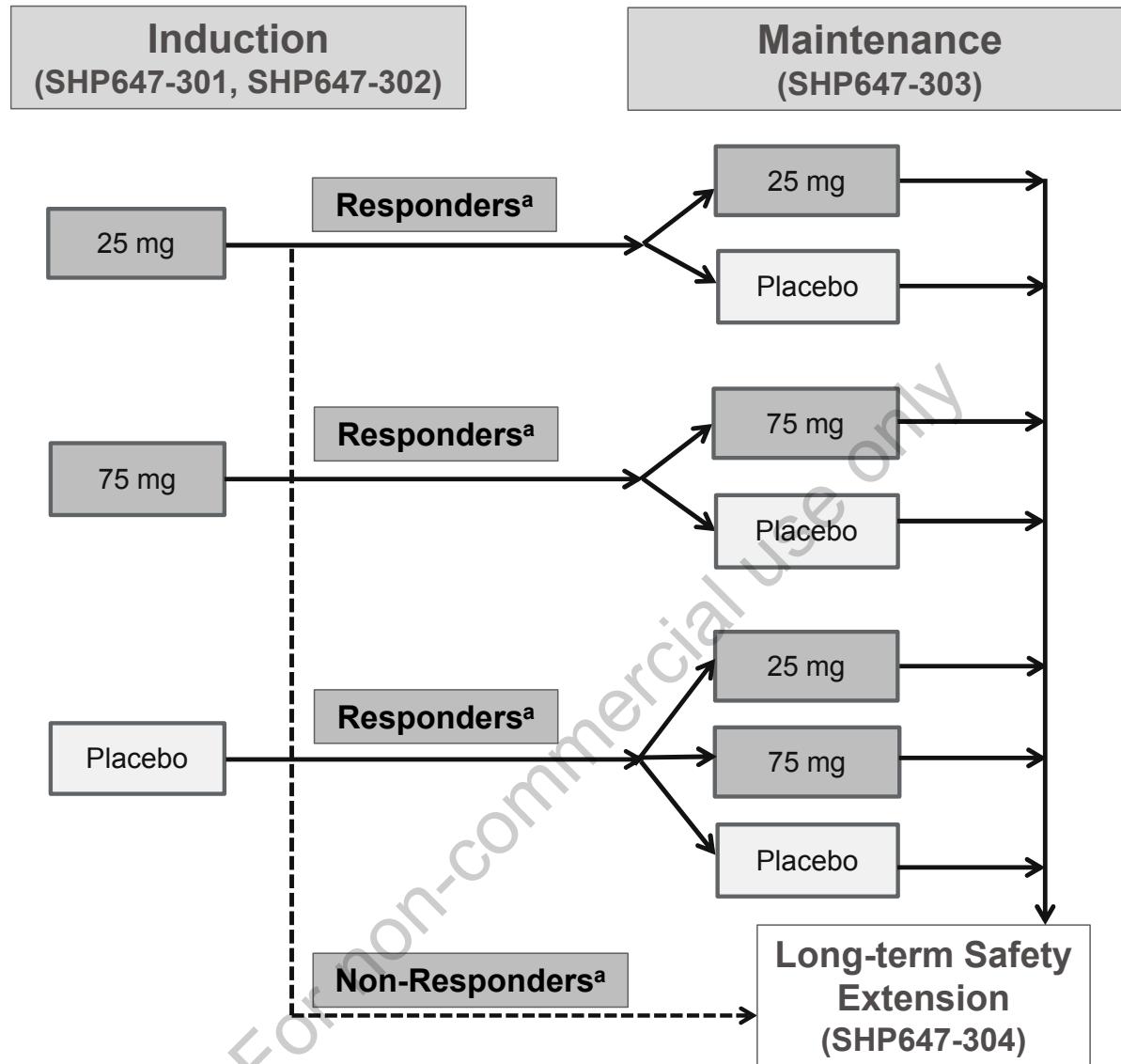
A total of 825 subjects (330 subjects at 25 mg SHP647, 330 subjects at 75 mg SHP647, and 165 placebo subjects) are planned for enrollment into the study ([Figure 1](#)). Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent form.

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](#).

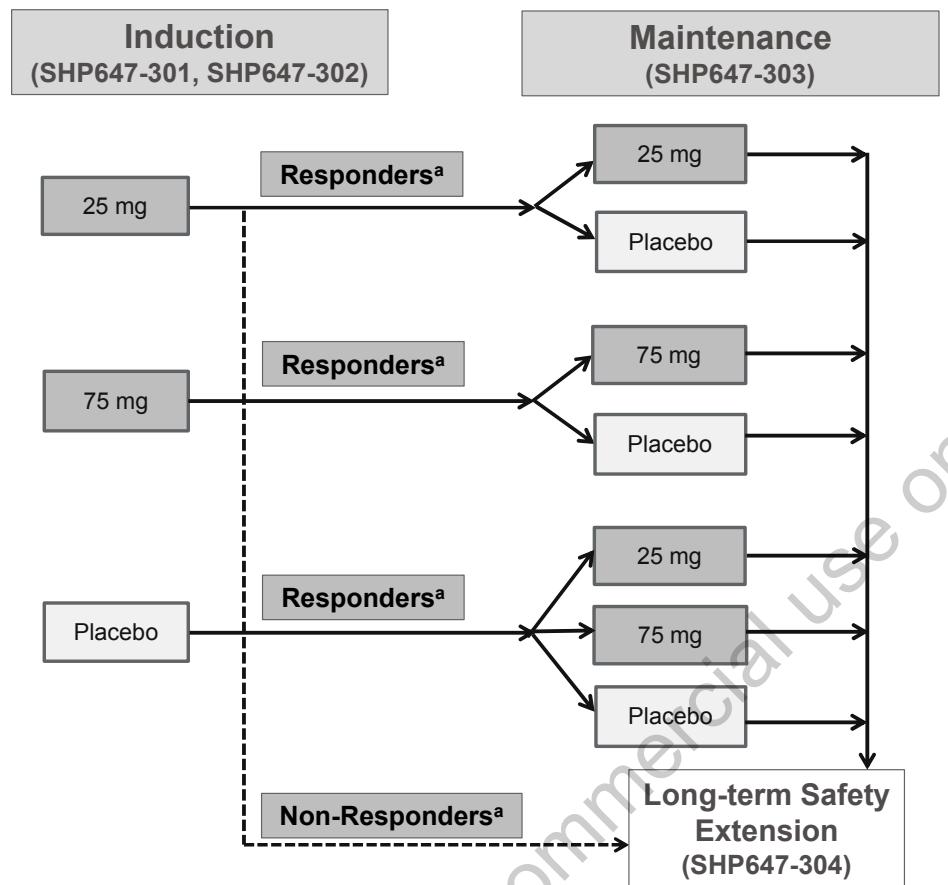
Figure 1 Overview of SHP647 Phase 3 Studies in Ulcerative Colitis



<sup>a</sup> 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  $\geq 1$  point or a subscore for rectal bleeding  $\leq 1$   
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  $\geq 1$  point or an absolute rectal bleeding subscore of  $\leq 1$ .

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



<sup>a</sup> 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  $\geq 1$  point or a subscore for rectal bleeding  $\leq 1$  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  $\geq 1$  point or an absolute rectal bleeding subscore of  $\leq 1$ .

### **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.

## 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.

### **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  $14 \pm 3$  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  $28 \pm 3$  days (Week 4) and Day  $56 \pm 3$  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  $84 \pm 3$  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 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](#).

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

### 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](#).



**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
<b>Total mL</b>			<b>127.5</b>

Ab=antibody; ADA=antidrug antibodies;  $\beta$ -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.

<sup>a</sup>  $\beta$ -hCG testing for female subjects only.

<sup>b</sup> 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.

**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.

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### 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 ( $\beta$ -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.

- 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.

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

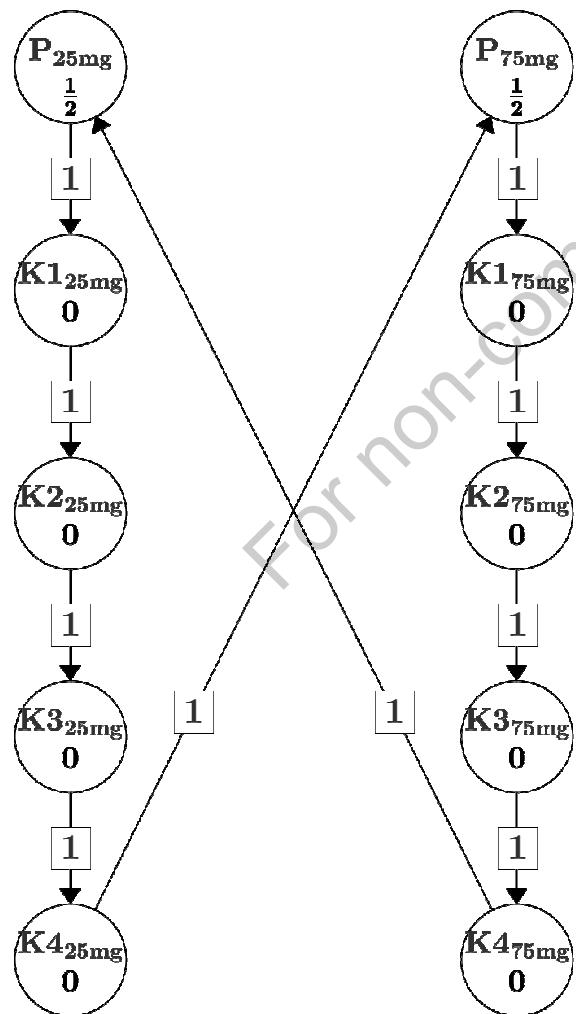
Unless otherwise specified, all efficacy analyses will be based on the FAS and subjects will be analyzed according to their randomized treatment, regardless of the treatment they actually received.

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  $\alpha$  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  $\alpha$  propagation is presented in [Figure 4](#).

**Figure 4: Visualization of Alpha Propagation**



- Partial Mayo score  $\leq 2$  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  $\leq 1$  and a centrally read Geboes score of  $\leq 2$ .
- 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.

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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

**ANSWER** **ANSWER**

10. The following is a list of statements concerning the use of the Internet. Indicate whether each statement is true or false by marking the appropriate letter in the space provided.

Digitized by srujanika@gmail.com

[REDACTED]

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

### **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:

\_\_\_\_\_

**Table 1: Schedule of Assessments**

<b>Study Procedure</b>	<b>Screening<sup>a</sup></b>	<b>Baseline</b>	<b>Treatment</b>				<b>Follow-up</b>	
	<b>Weeks -6 to -1</b>	<b>Week 0/ Day 1</b>	<b>Week 2</b>	<b>Week 4</b>	<b>Week 8</b>	<b>Week 12/ET<sup>b</sup></b>	<b>Week 20<sup>c</sup></b>	<b>Week 28<sup>c</sup></b>
<b>Visit Number</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6 (Part 1)<sup>d</sup></b>	<b>6 (Part 2)</b>	<b>7</b>
<b>Study Day</b>	<b>-42 to 0</b>	<b>1</b>	<b>14 ±3</b>	<b>28 ±3</b>	<b>56 ±3</b>	<b>84 ±3</b>	<b>140 ±7</b>	<b>196 ±7</b>
ADA and NAb sampling		X <sup>u</sup>	X <sup>u</sup>	X <sup>u</sup>	X <sup>u</sup>		X	
<b>Endoscopic Procedure</b>								
Endoscopy (including biopsy) <sup>v</sup>		X <sup>v</sup>				X		
<b>UC Assessments</b>								
Total Mayo score		X <sup>w</sup>					X <sup>w</sup>	
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 <sup>x</sup>	X	X	X	X	X	X	X	
<b>Health Assessment<sup>y</sup></b>								
IBDQ		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	
<b>Treatment Procedures</b>								
Randomization <sup>z</sup>		X						
Administration of SHP647 or placebo <sup>z</sup>		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 <sup>aa</sup>	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;

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.

### 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  $\delta$  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.

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.

## 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  $\geq 16$  and  $\leq 80$  years of age at the time of the signing of the informed consent/assent form.

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

4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for  $\geq 3$  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  $\geq 6$ , including a centrally read endoscopic subscore  $\geq 2$ , rectal bleeding subscore  $\geq 1$ , and stool frequency subscore  $\geq 1$  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).

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).

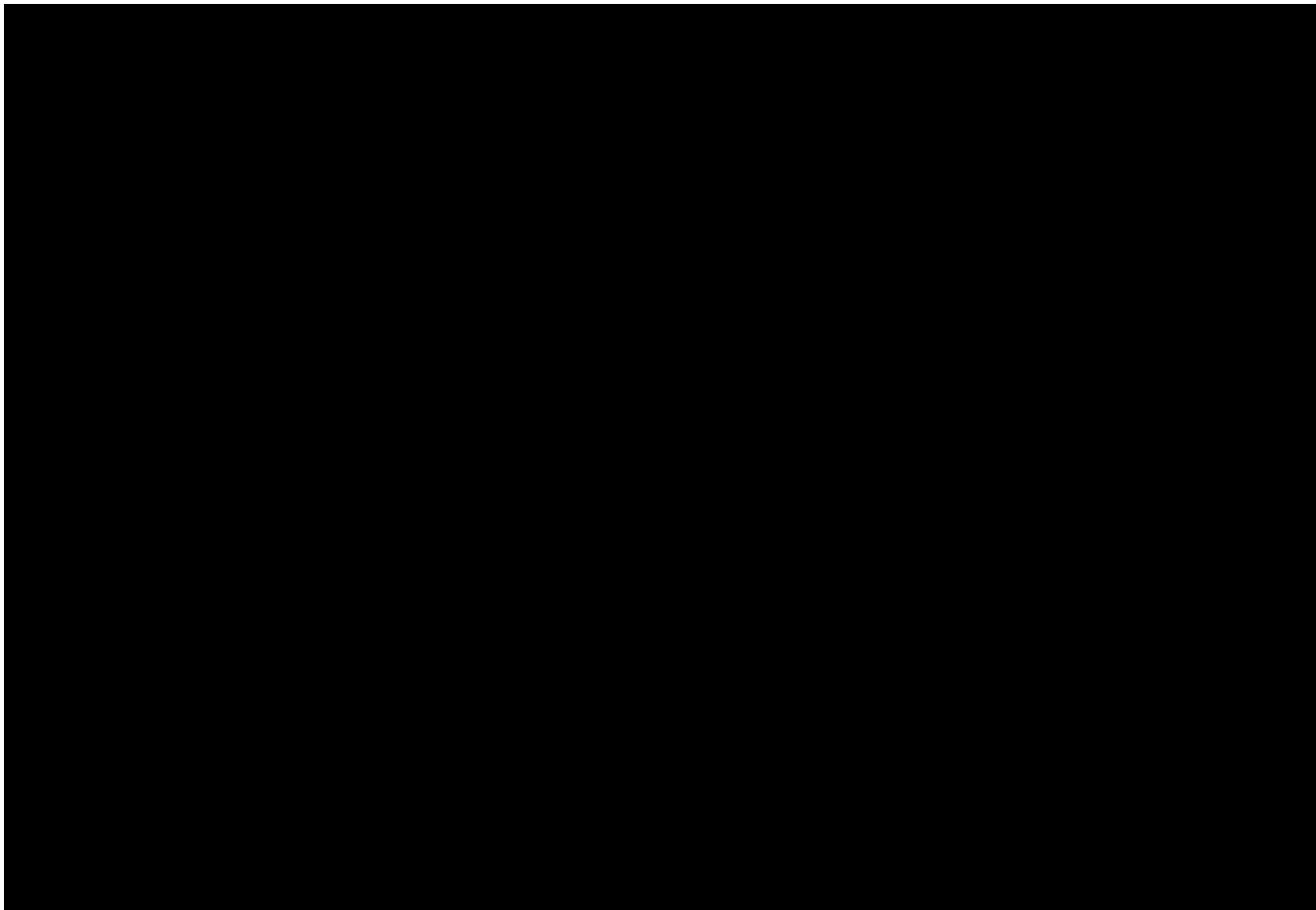
### Inflammatory Bowel Disease Questionnaire (IBDQ)

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

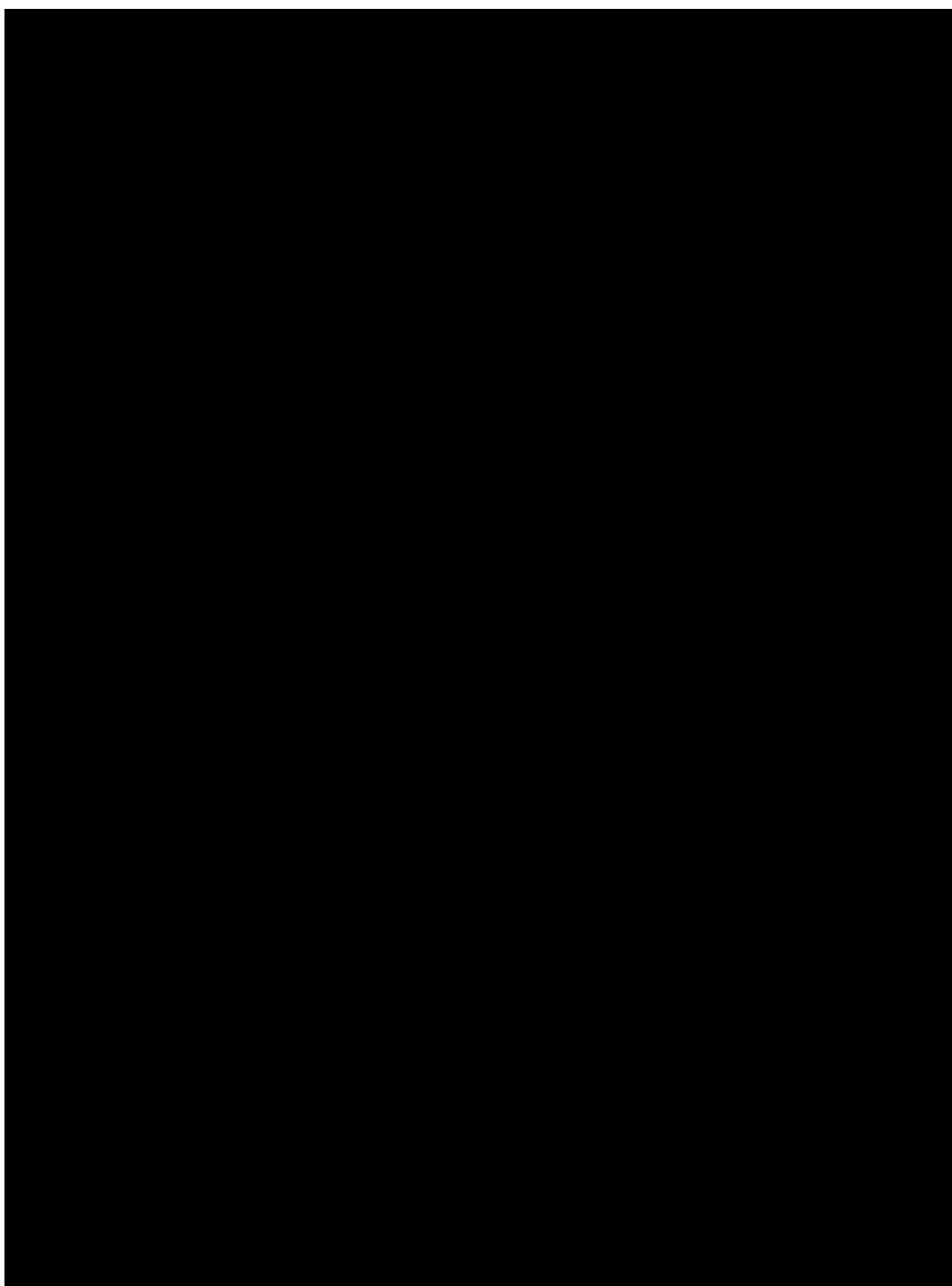
You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

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

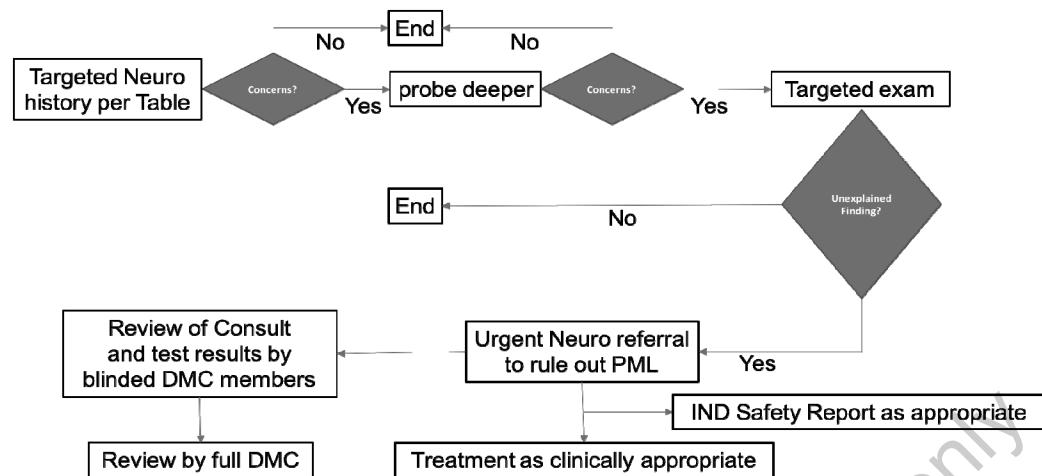
3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from:
1. ALL OF THE TIME
  2. MOST OF THE TIME
  3. A GOOD BIT OF THE TIME
  4. SOME OF THE TIME
  5. A LITTLE OF THE TIME
  6. HARDLY ANY OF THE TIME
  7. NONE OF THE TIME
4. How often during 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



For non-com.  
munications



**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.

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  $\delta$  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.

### **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.

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.

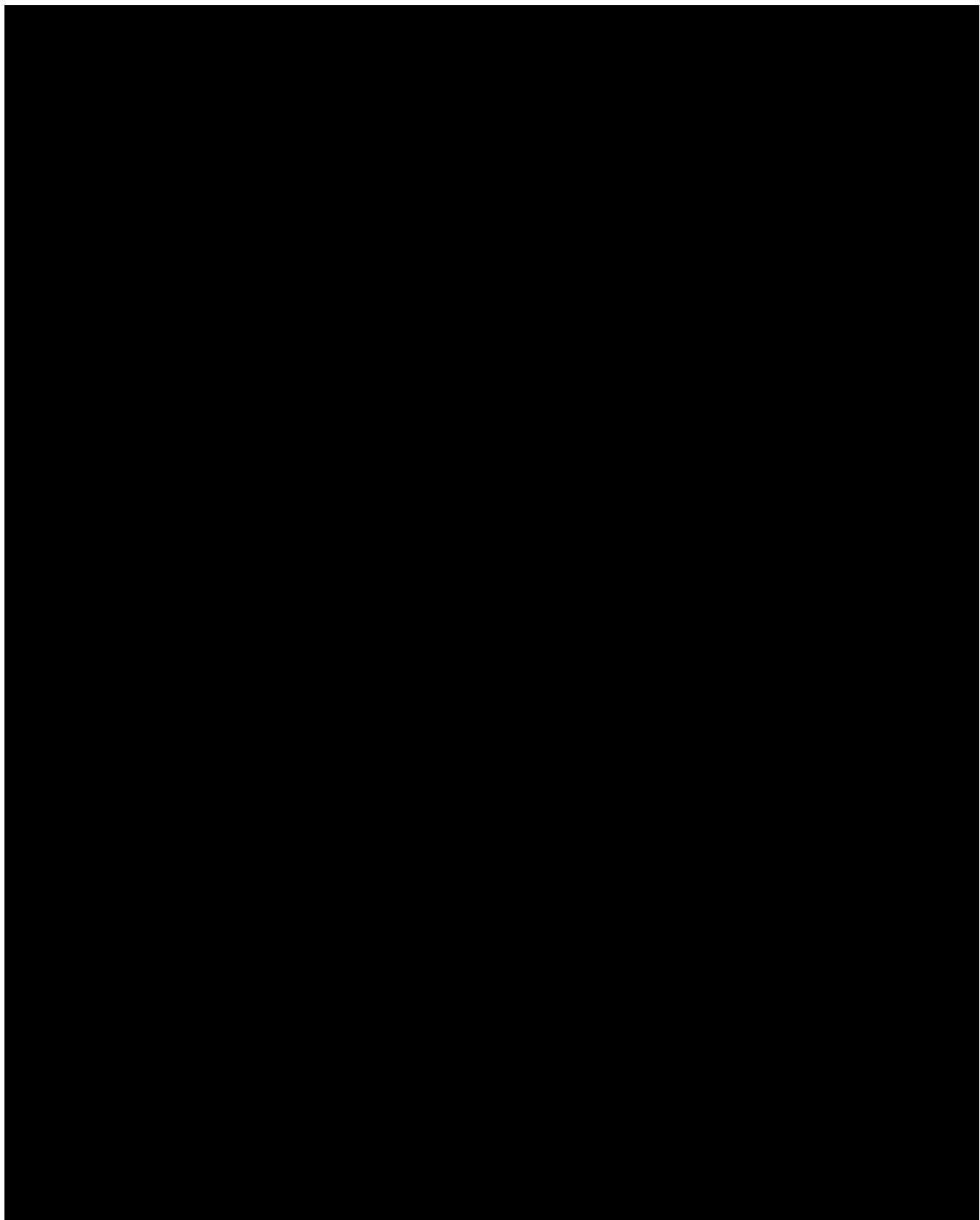
#### 7.2.3.6 Clinical Laboratory Evaluations

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



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.

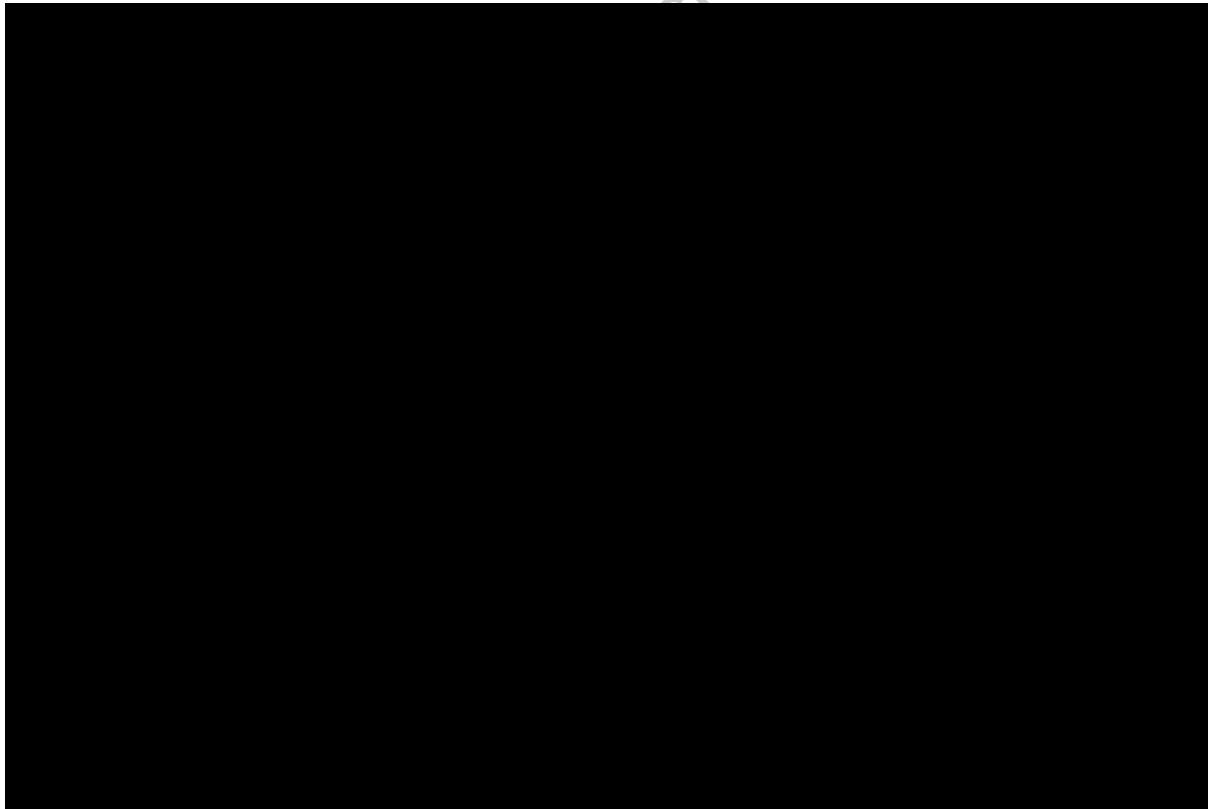
### 2.2.2.2 Other Secondary Objectives

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.

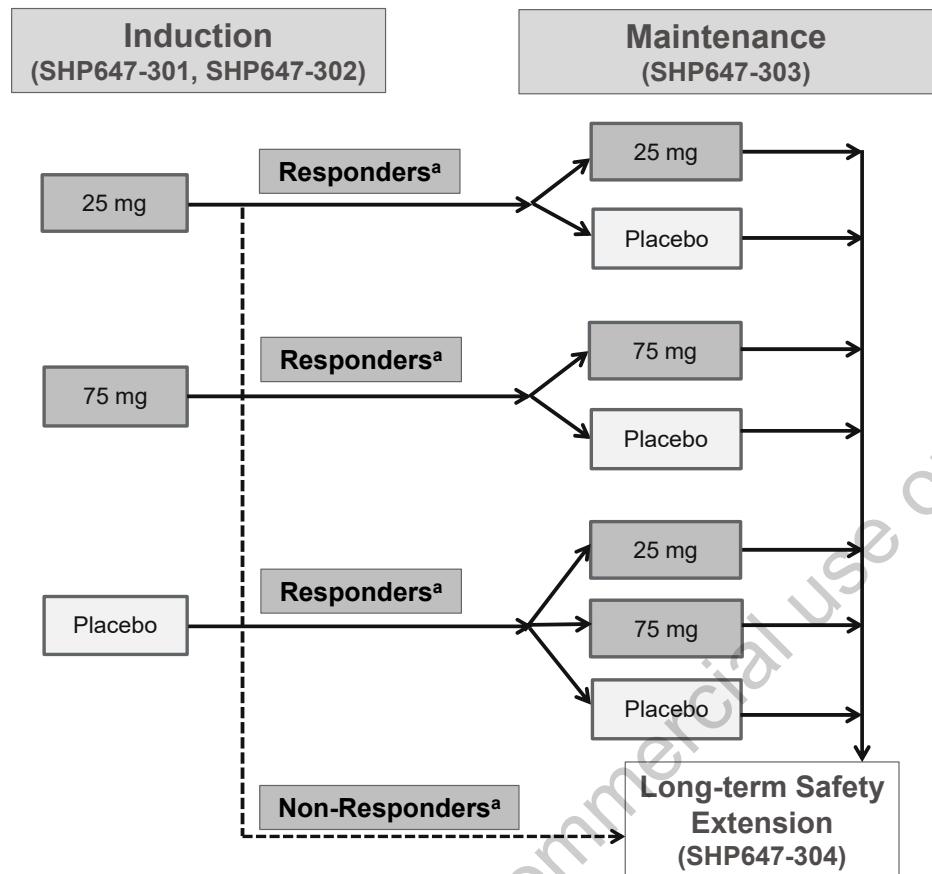
A total of 740 subjects (296 subjects at 25 mg ontamalimab, 296 subjects at 75 mg ontamalimab, and 148 subjects on placebo) are planned for enrollment into the study ([Figure 1](#)). Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent 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**



<sup>a</sup> 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  $\geq 1$  point or a subscore for rectal bleeding  $\leq 1$

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  $\geq 1$  point or an absolute rectal bleeding subscore of  $\leq 1$ .

## 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  $\geq 16$  and  $\leq 80$  years of age at the time of the signing of the informed consent/assent form.

Note: Subjects  $<18$  years of age must weigh  $\geq 40$  kg and must have body mass index  $\geq 16.5$  kg/m<sup>2</sup>.

4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for  $\geq 3$  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  $\geq 6$ , including a centrally read endoscopic subscore  $\geq 2$ , rectal bleeding subscore  $\geq 1$ , and stool frequency subscore  $\geq 1$  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).

## 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.

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  $14 \pm 3$  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  $28 \pm 3$  days (Week 4) and Day  $56 \pm 3$  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  $84 \pm 3$  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  $140 \pm 7$  days or 8 weeks  $\pm 7$  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  $196 \pm 7$  days, or 16 weeks  $\pm 7$  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.

### 7.2.3.3 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.

## 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 <sup>b</sup>
HBcAb	HCV RNA PCR if HCVA <sup>b</sup> 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.

#### 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.

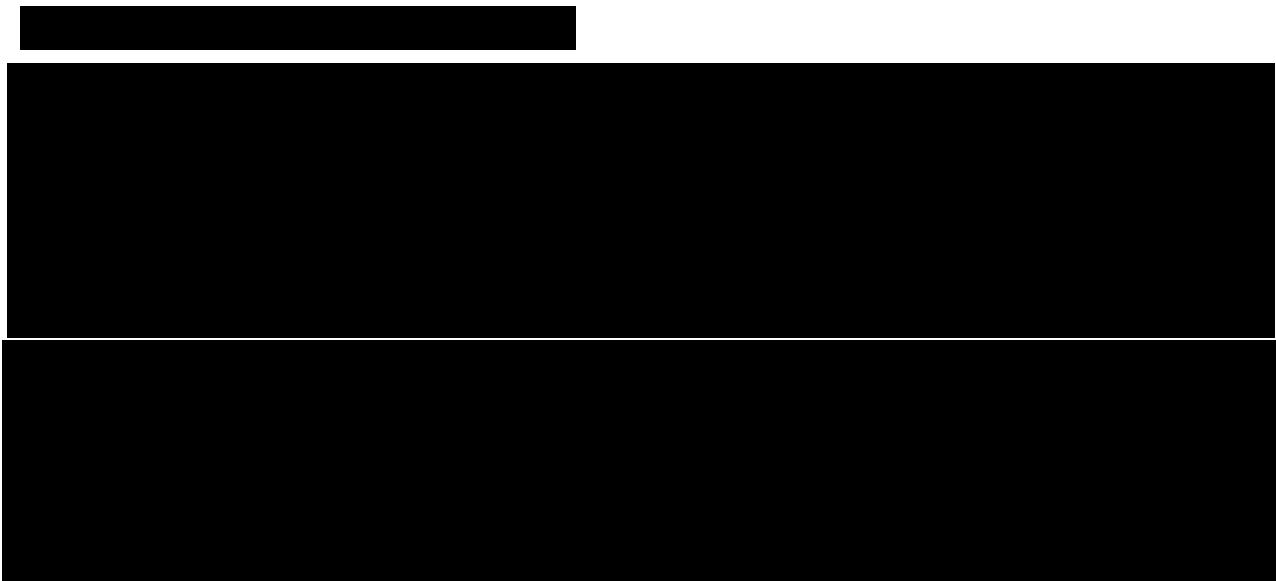
#### Inflammatory Bowel Disease Questionnaire

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 $\beta$ -hCG <sup>a</sup>	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
<b>Total mL</b>			<b>137.5</b>

ADA=antidrug antibody;  $\beta$ -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

<sup>a</sup>  $\beta$ -hCG testing for female subjects only.

<sup>b</sup> 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.

**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

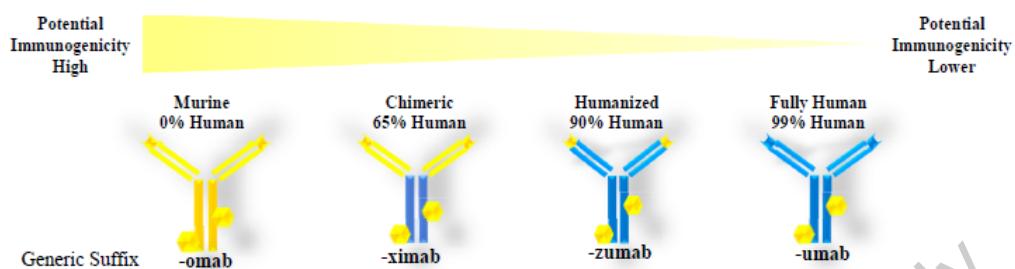
Potential hypersensitivity, serum sickness, vasculitis, and Arthus reactions to ontamalimab will be regarded as AESIs. These events must be reported on Shire “Clinical Study SAE and Nonserious AE as Required by the Protocol Form” and within the time frame mandated for SAEs (see Section 8.2.2).

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](#).

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  $\beta$ -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 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
<b>Normal baseline</b>  ALT $\geq 5 \times$ ULN  <b>Elevated baseline<sup>a</sup>:</b>  ALT $\geq 3 \times$ 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. <sup>c</sup>
<b>Normal baseline</b>  ALT $\geq 8 \times$ ULN  <b>Elevated baseline<sup>a</sup>:</b>  ALT $\geq 5 \times$ 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 investigational product. <sup>b</sup>  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. <sup>c</sup>

(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.

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  $\alpha$  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  $\alpha$  propagation is presented in [Figure 5](#).

- 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  $\leq 1$  and a centrally read Geboes score of  $\leq 2$ .
- 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.

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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

**06 Jul 2017**

**Table 1 Schedule of Assessments**

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

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]

<sup>a</sup> At least 2 visits will be necessary to complete the screening procedures, including endoscopy.

<sup>b</sup> 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.

<sup>c</sup> 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.

<sup>d</sup> 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.

<sup>e</sup> 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.

<sup>f</sup> Medical history will include UC history, cardiac history, and smoking history.

<sup>g</sup> 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.

<sup>h</sup> 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.

<sup>i</sup> 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.

<sup>j</sup> 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.

<sup>k</sup> 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.

<sup>l</sup> 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.

<sup>m</sup> 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

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  $\alpha$  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  $\alpha$  propagation is presented in [Figure 4](#).

#### 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  $\geq 16$  and  $\leq 80$  years of age at the time of the signing of the informed consent/assent form.

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

4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for  $\geq 3$  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  $\geq 6$ , including a centrally read endoscopic subscore  $\geq 2$ , rectal bleeding subscore  $\geq 1$ , and stool frequency subscore  $\geq 1$  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.

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

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]

- 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  $\geq 6$ , including a centrally read endoscopic subscore  $\geq 2$ , rectal bleeding subscore  $\geq 1$ , and stool frequency subscore  $\geq 1$  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  $\geq 8$  years or disease limited to left side of colon (ie, distal to splenic flexure) for  $\geq 10$  years before screening, regardless of age
  - Subjects  $\geq 50$  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).

**Table 1 Schedule of Assessments**

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

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]

- <sup>a</sup> At least 2 visits will be necessary to complete the screening procedures, including endoscopy.
- <sup>b</sup> Subjects who withdraw early during the treatment period should return for the ET visit and then enter into the safety follow-up period.
- <sup>c</sup> 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.
- <sup>d</sup> 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.
- <sup>e</sup> 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.
- <sup>f</sup> Medical history will include UC history, cardiac history, and smoking history.
- <sup>g</sup> 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.
- <sup>h</sup> 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.
- <sup>i</sup> 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.
- <sup>j</sup> 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.
- <sup>k</sup> 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.
- <sup>l</sup> 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.
- <sup>m</sup> 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

### 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.

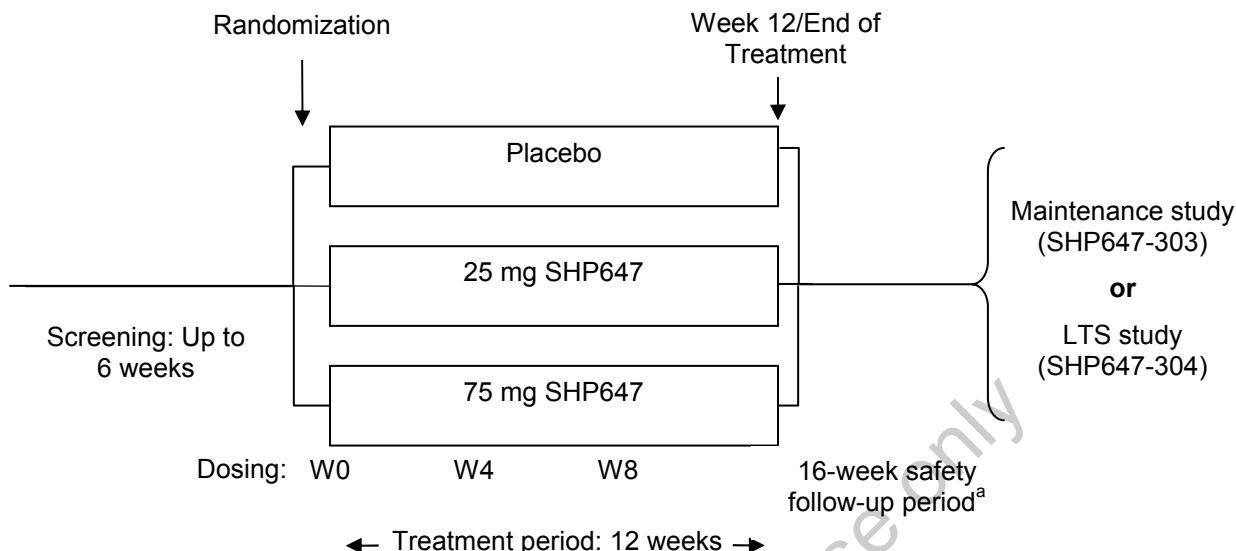
A total of 825 subjects (330 subjects at 25 mg SHP647, 330 subjects at 75 mg SHP647, and 165 placebo subjects) are planned for enrollment into the study ([Figure 1](#)). Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent form.

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 2 Study Design Flow Chart**



LTS=long-term safety extension; W=week

<sup>a</sup> 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**

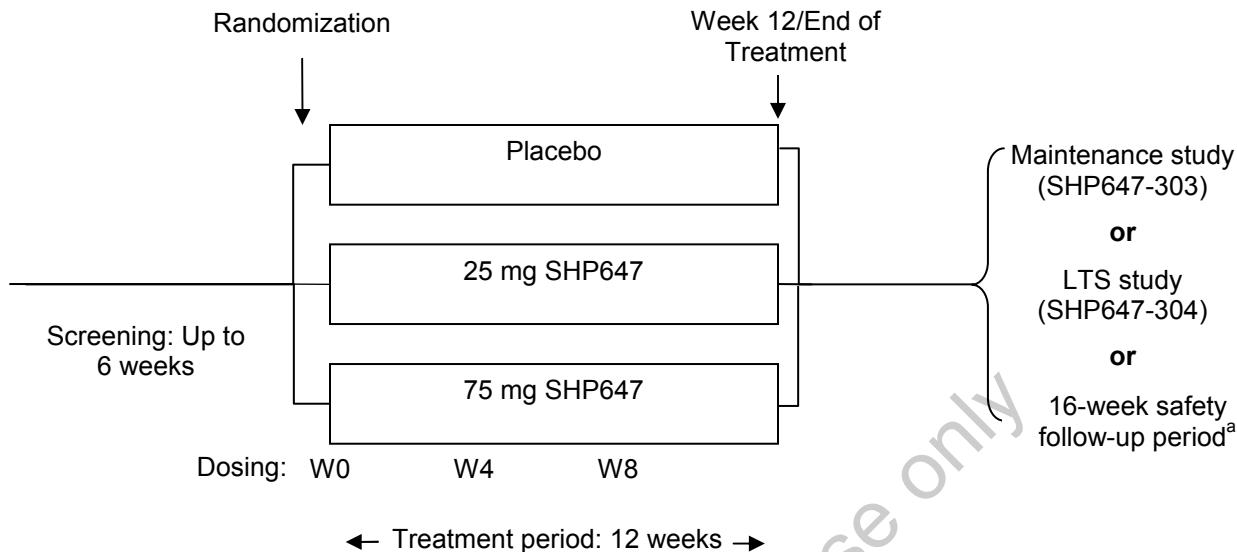
The Mayo score has historically been used as the primary endpoint for pivotal studies of agents intended to treat UC. Over the past decade, health authority thinking regarding efficacy endpoints for UC has evolved such that the traditional Mayo score is no longer recommended. Current regulatory guidance (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”.

**Figure 2: Study Design Flow Chart**



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

<sup>a</sup> 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.

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 <sup>a</sup>			
Rectal 5-ASA		X <sup>a</sup>			
Investigational products			X <sup>b</sup>		
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.

<sup>a</sup> 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).

<sup>b</sup> 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.

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:

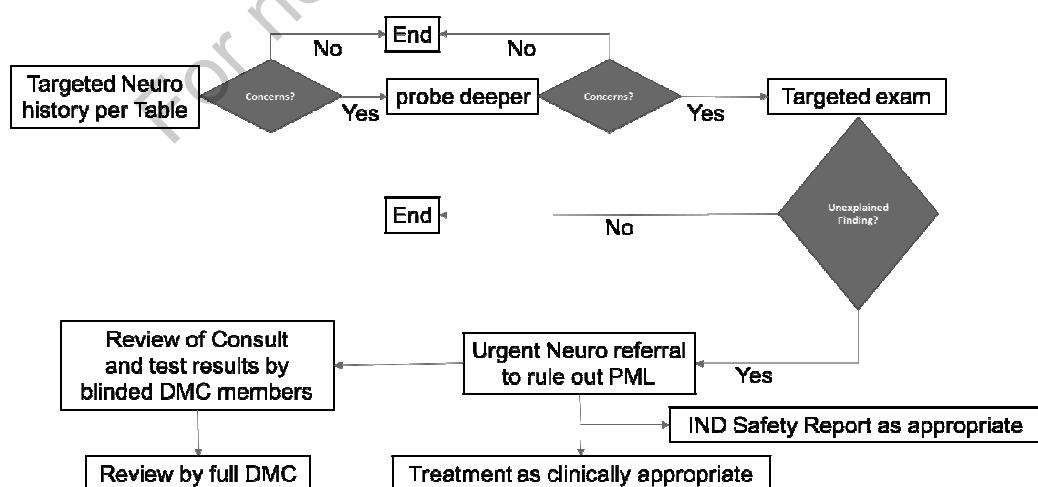
- Stool frequency
- Rectal bleeding severity and frequency
- Diarrhea frequency
- Urgency frequency
- Abdominal pain worst severity.

**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.

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 ( $\beta$ -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.

### 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 <sup>a</sup>	2	1	2
TB test (QuantiFERON TB Gold Plus or PPD)	4	1	4
JCV antibody banked sample	3.5	1	3.5

## 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.

### **8.1.5 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 ( $\beta$ -hCG) test or ultrasound result will determine the pregnancy onset date.

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.

**Table 5: Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin**

Treatment emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
<b>Normal baseline</b>  ALT $\geq$ 5x ULN  <b>Elevated baseline<sup>a</sup>:</b> 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. <sup>c</sup>
<b>Normal baseline</b>  ALT $\geq$ 8x ULN  <b>Elevated baseline<sup>a</sup>:</b> 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. <sup>b</sup>  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. <sup>c</sup>
<b>Normal baseline</b>  ALT $\geq$ 3x ULN  <b>Elevated baseline<sup>a</sup>:</b> 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. <sup>b</sup>  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. <sup>c</sup>

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  $\geq 1$  point or a subscore for rectal bleeding  $\leq 1$ .
- 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  $\leq 2$ .

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

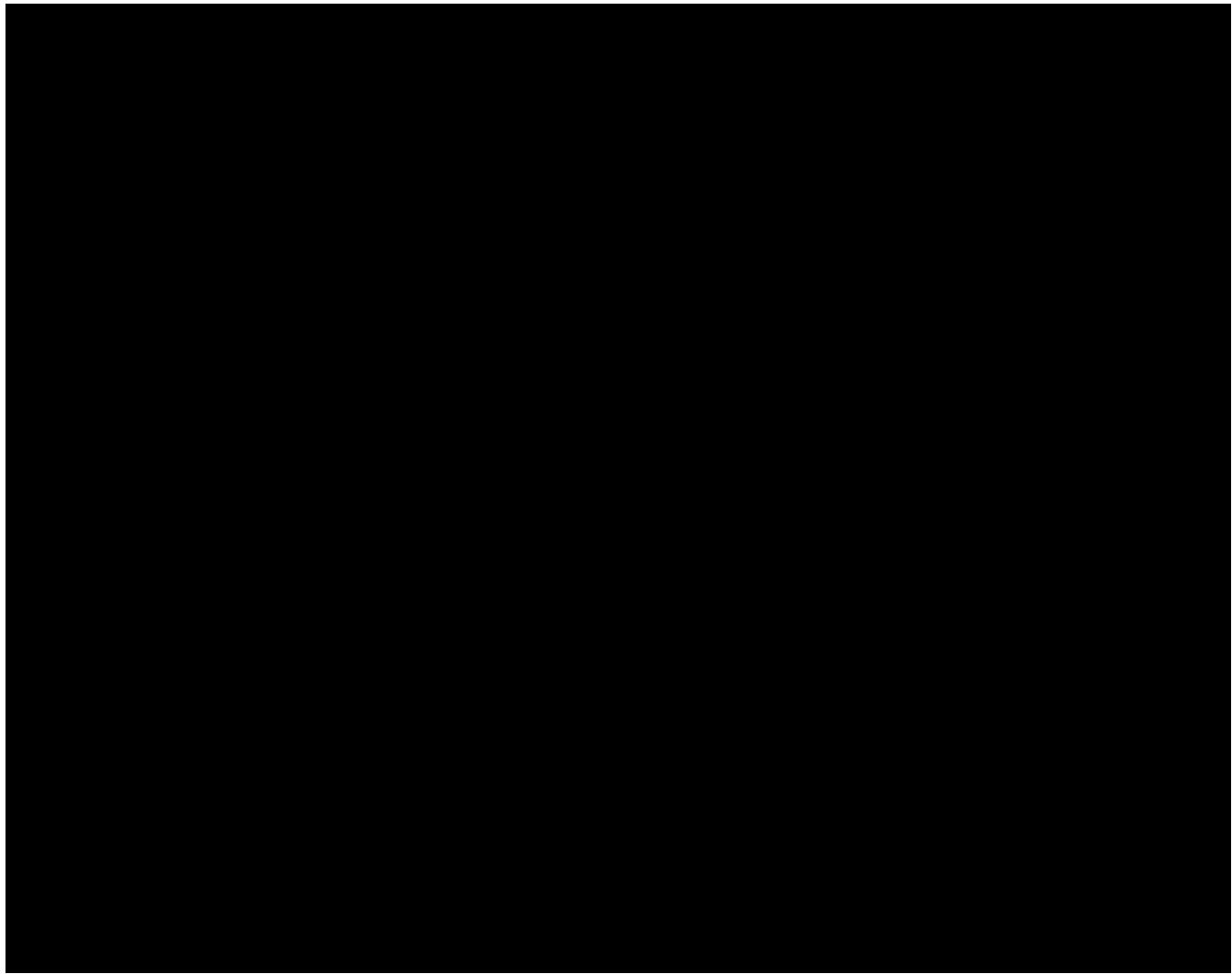
The other secondary endpoints are as follows:

- Remission, defined as a total Mayo score  $\leq 2$  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  $\geq 1$  point or a subscore for rectal bleeding  $\leq 1$ .

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.

## 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.

## Mayo Scoring System for Assessment of Ulcerative Colitis Activity

### Stool frequency<sup>a</sup>

- 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<sup>b</sup>

- 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<sup>c</sup>

- 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<sup>d</sup>

- 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.

- <sup>a</sup> Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency.
  - <sup>b</sup> The daily bleeding score represents the most severe bleeding of the day.
  - <sup>c</sup> 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.
- <sup>d</sup> 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](#).

**Table 1: Schedule of Assessments**

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

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].

<sup>a</sup> At least 2 visits will be necessary to complete the screening procedures, including endoscopy.

<sup>b</sup> 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.

<sup>c</sup> 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.

<sup>d</sup> 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.

<sup>e</sup> 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.

<sup>f</sup> Medical history will include UC history, cardiac history, and smoking history.

<sup>g</sup> 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.

<sup>h</sup> 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.

<sup>i</sup> 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.

<sup>j</sup> 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.

<sup>k</sup> 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.

<sup>l</sup> 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.

<sup>m</sup> 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.

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  $\geq 8$  years or disease limited to left side of colon (ie, distal to splenic flexure) for  $\geq 10$  years before screening, regardless of age.
  - Subjects  $\geq 50$  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).

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

Short Form-36 Health Survey, Acute Form

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## Your Health and Well-Being

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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!*

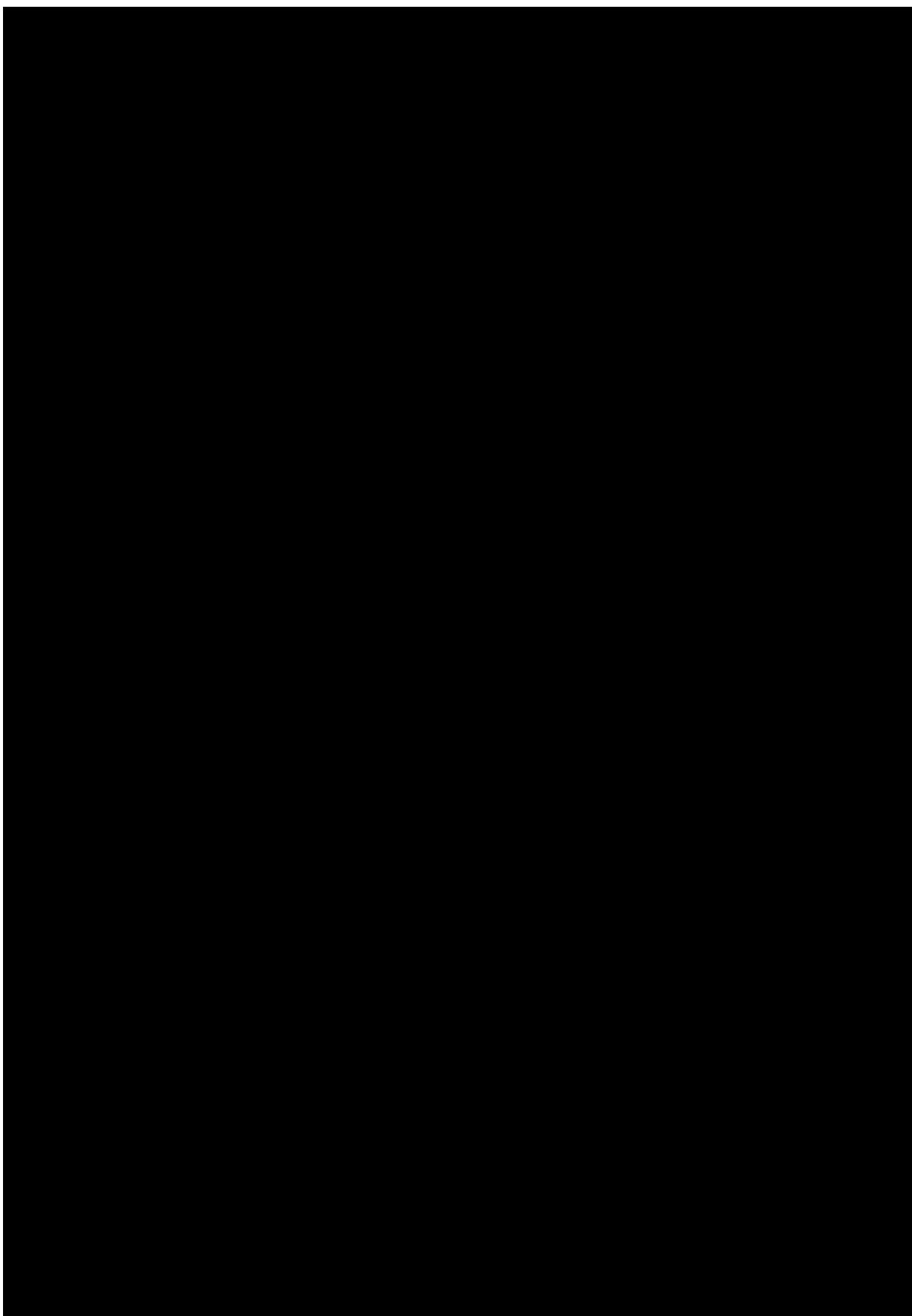
For each of the following questions, please mark an  in the one box that best describes your answer.

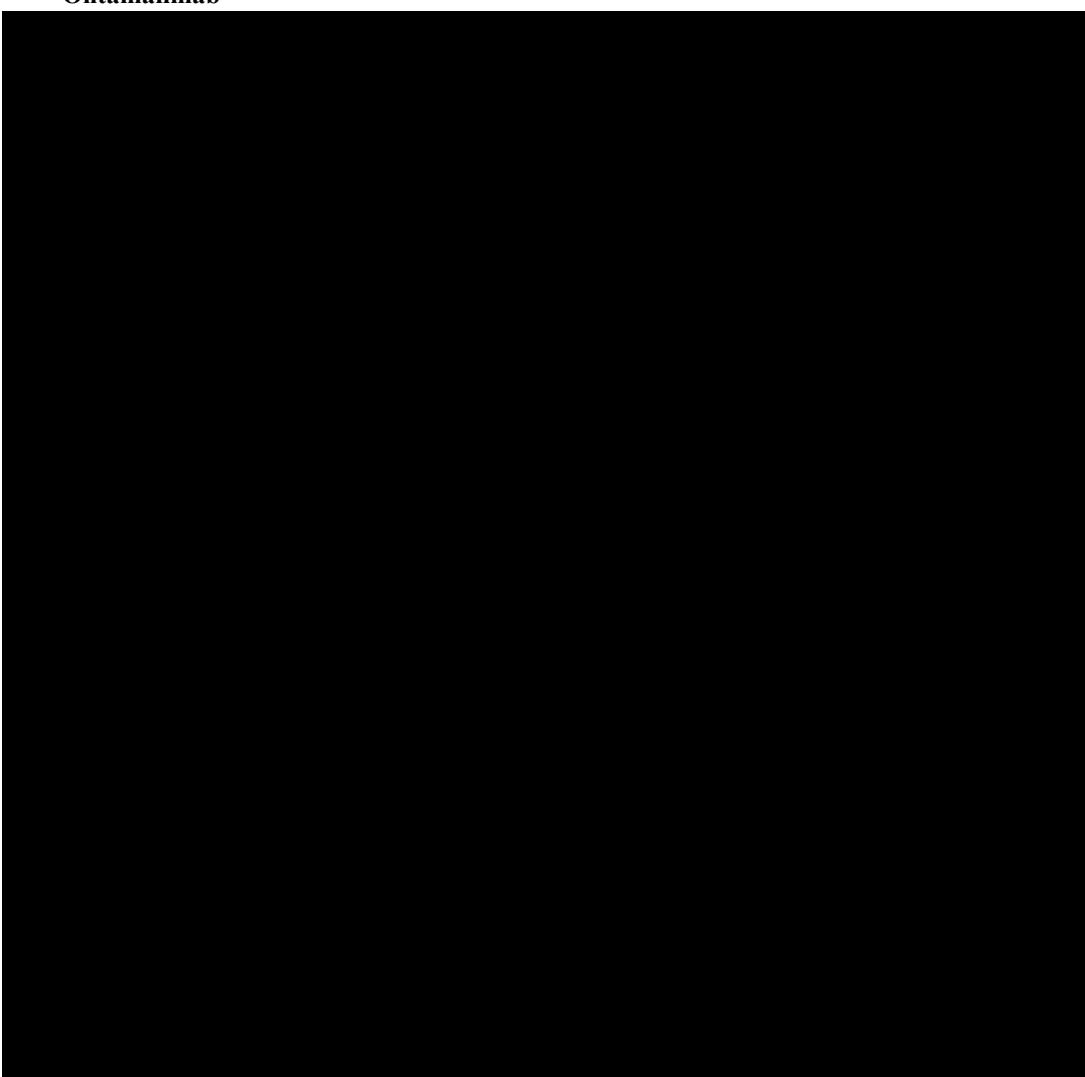
1. In general, would you say your health is:

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?

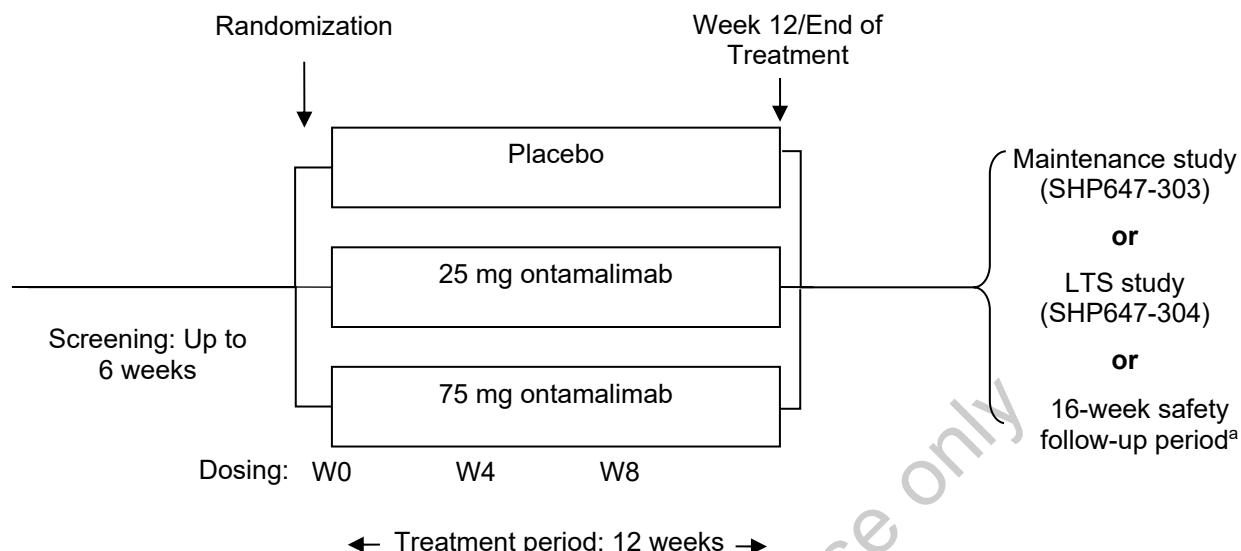
Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/>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





For non-clients

**Figure 2 Study Design Flow Chart**



LTS=long-term safety extension; W=week

<sup>a</sup> 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.

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  $\geq 8$  years or disease limited to left side of colon (ie, distal to splenic flexure) for  $\geq 10$  years before screening, regardless of age
  - Subjects  $\geq 50$  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).

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 <sup>a</sup>			
Rectal 5-ASA		X <sup>a</sup>			
Investigational products			X <sup>b</sup>		
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

<sup>a</sup> 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).

<sup>b</sup> 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.

### 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.

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 ( $\beta$ -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.

## 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.

**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<sup>a</sup> or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

BP=blood pressure; PEF=peak expiratory flow

<sup>a</sup> 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.

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.

**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 $\geq 2$ 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. <sup>b</sup>  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. <sup>c</sup>
<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. <sup>b</sup>  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. <sup>c</sup>

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

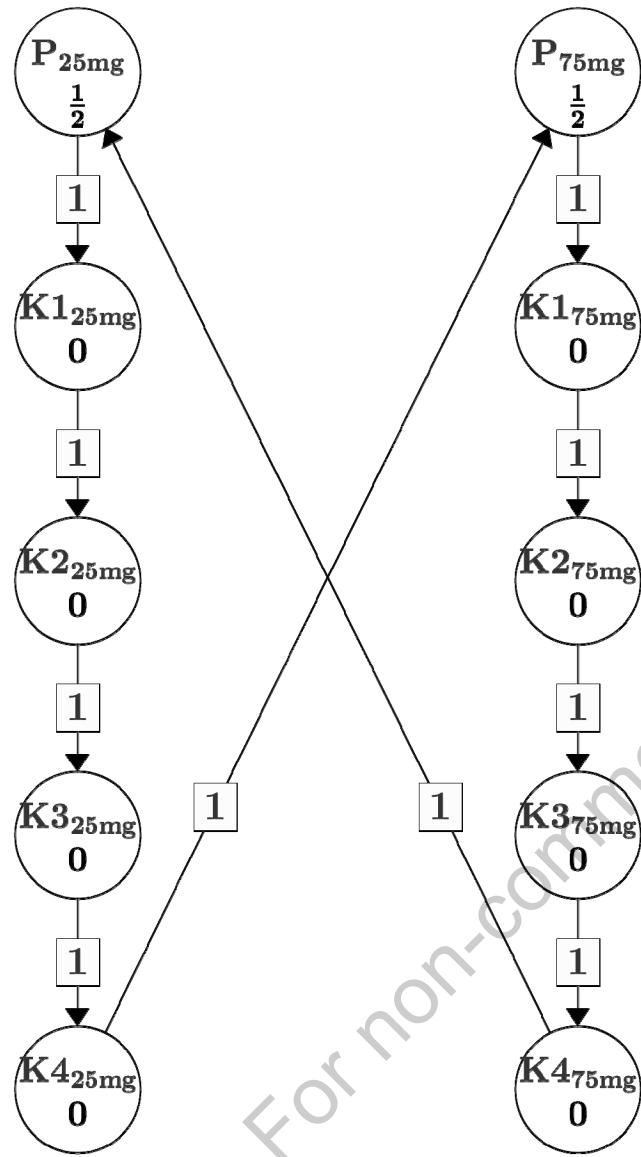
<sup>a</sup> Elevated baseline ALT defined as ALT  $\geq 1.5 \times$  ULN.

<sup>b</sup> Confirmatory repeat liver-related blood tests should be performed within 2 to 3 days before the investigational product is interrupted.

<sup>c</sup> If HBV DNA positive, antivirals would need to be started as soon as possible.

Source: Adapted from [Chalasani and Regev, 2016](#).

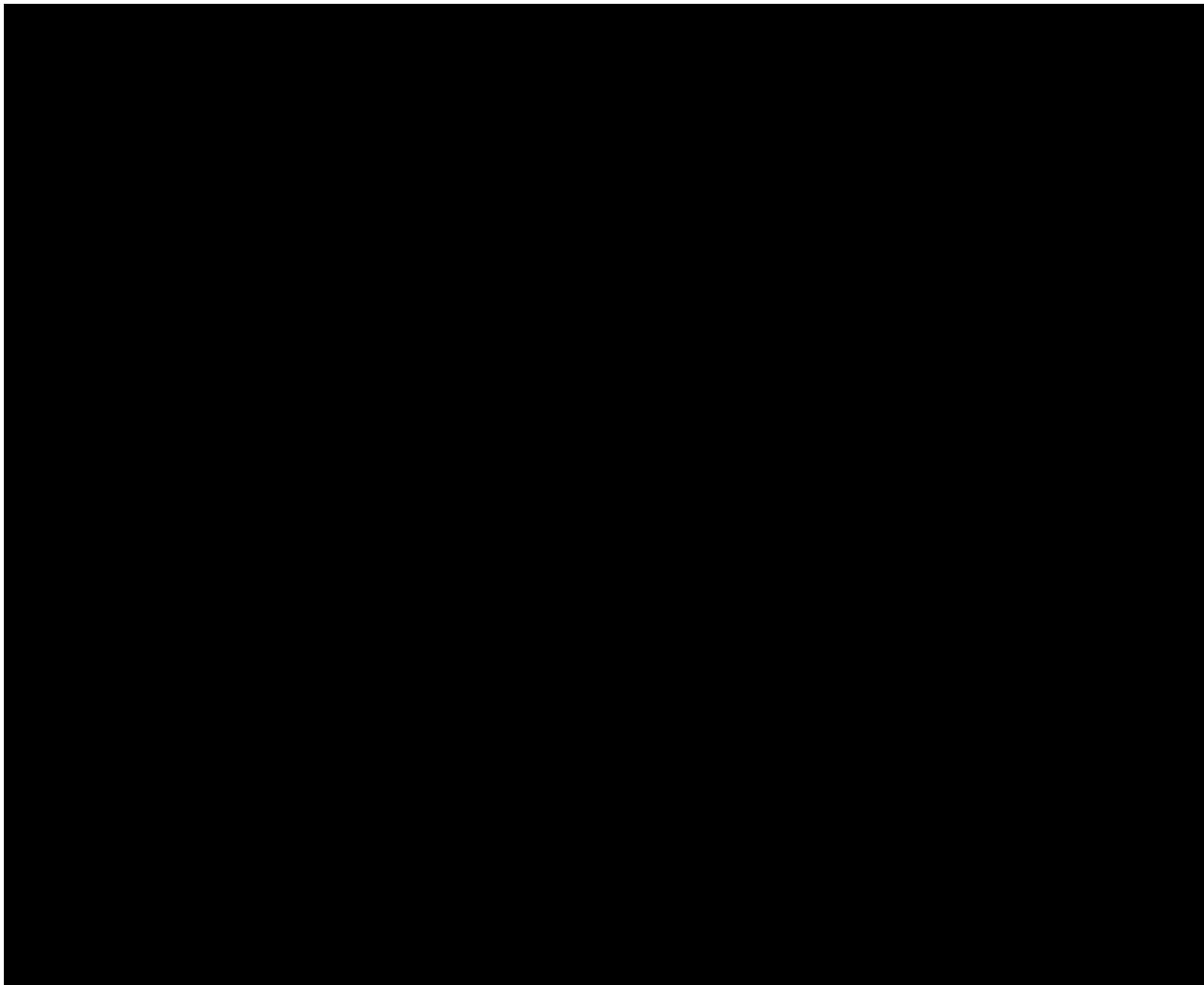
Figure 5 Visualization of Alpha Propagation



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

### 9.8.3 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.

## 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.