Statistical Analysis Plan

NCT Number: NCT03283085

Title: A Phase 3 Long-term Safety Extension Study of SHP647 in Subjects with Moderate to Severe Ulcerative Colitis or Crohn's Disease (AIDA)

Study Number: SHP647-304

Document Version and Date: Version 2.0, 06 September 2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

SHP647
PHASE 3

A Phase 3 Long-term Safety Extension Study of SHP647 in Subjects with Moderate to Severe Ulcerative Colitis or Crohn's Disease (AIDA)

PROTOCOL IDENTIFIER: SHP647-304

Study Sponsor(s): Shire Human Genetic Therapies, Inc. ("Shire"), a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
300 Shire Way, Lexington, MA 02421 US

Author: [redacted], MS
[redacted], Statistics and Quantitative Sciences

Protocol: V1 (13JUL2017)
Amendment 1 (18DEC2017)
Amendment 2 (17SEP2018)
Amendment 3 (07NOV2019)
Amendment 4 (21SEP2020)

SAP Version #: 2.0

SAP Date: 06 Sep 2022

Status: Final

REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	25FEB2021	Final Document
2.0	06Sept2022	Corrected secondary endpoint for response of ulcerative colitis participants from "or a sub-score for RB ≥1" to "or a sub-score for RB ≤1". Added Section 10.2 of conducting sensitivity analyses to assess the impact of the Russian – Ukraine Crisis. Added method to calculate the exact unconditional confidence limits for treatment difference if the number of responders or non-responders in either treatment group is too small (i.e., ≤5) Section 7.1.1.1 updated and removed texts related to Hypersensitivity Adjudication Committee per Protocol Amendment 4. Edited text in Section 5.2 to be consistent with the actual data. Updated Section 12.2 and added analysis visit window for the visits after Week 144. Edited text in Section 5.7, Section 7, and Section 7.5 to be consistent with Protocol Amendment 4. Edited text in Section 12.3 to further clarify the efficacy endpoint derivation before and after Protocol Amendment 4. Added Section 6.3 and Section 7.6.4 to clarify the data before Protocol Amendment 4 will be listed. Added Section 10.3 for possible sensitivity analysis of efficacy endpoints if any significant investigator noncompliance occurs.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

5-ASA	5-aminosalicylic acid
AE	adverse event
BMI	body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRF	case report form
CRP	C-reactive protein
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EOF	end of follow-up
EOT	end of treatment
ET	early termination
FAS	full analysis set
HEOR	Health Economics and Outcomes Research
IBD	inflammatory bowel disease
IP	investigational product
IRT	interactive response technology
LTS	long-term safety
MedDRA	Medical Dictionary for Regulatory Activities
MNT	maintenance study
PCI	potentially clinically important
PD	pharmacodynamic(s)
PGA	physician global assessment
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
RB	rectal bleeding
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SOC	system organ class
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety, Health Economics and Outcomes Research (HEOR), and pharmacodynamic (PD) data as described in the final study protocol amendment 4 dated 21 Sep 2020 (original protocol dated 13 Jul 2017). Specifications for tables, figures, and listings are contained in a separate document. The analysis plans for PD and HEOR patient-reported outcome (PRO) validation, if performed, are prepared separately.

On May 29, 2020, Takeda announced the decision to discontinue the ontamalimab clinical trial program in ulcerative colitis (UC) and Crohn's disease (CD). The planned analyses reflect the early discontinuation of this study.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of long-term treatment with ontamalimab in subjects with moderate to severe UC or CD.

2.1.2 Secondary Objectives – Subjects with Ulcerative Colitis

- To evaluate the maintenance of response to long-term treatment with ontamalimab as measured by clinical composite score and biomarkers, with or without endoscopy.

2.1.3 Secondary Objectives – Subjects with Crohn's Disease

- To evaluate the maintenance of response to long-term treatment with ontamalimab as measured by Crohn's Disease Activity Index (CDAI) score and biomarkers, with or without endoscopy.

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint is the assessment of safety as measured by: incidence and severity of adverse events (AEs); incidence and nature of serious infections; and actual values and change from baseline, as well as incidence of abnormalities, in laboratory tests, electrocardiograms (ECGs), and vital signs. All safety analyses will be performed using the Safety Set. Subjects will be analyzed according to the treatment they actually receive. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be presented by indication separately. Summaries may be presented by the status at entry into this study (eg, induction nonresponder, maintenance ontamalimab completer, maintenance discontinuation rollover, etc.).

2.2.2 Secondary Endpoints – Subjects with Ulcerative Colitis

Treatment response over time, with response defined as clinical composite score that has decreased by ≥2 points and ≥30%, with an accompanying decrease in the subscore for rectal bleeding (RB) ≥1 point or a subscore for RB ≤ 1, and/or composite score that has decreased by ≥30% and ≥3 points compared to the baseline value for the induction studies.

2.2.3 Secondary Endpoints – Subjects with Crohn's Disease

Treatment response over time, with response defined as CDAI score that has decreased by ≥100 points compared to the baseline value for the induction studies and/or Simple Endoscopic Score for Crohn's Disease (SES-CD) that has decreased by ≥25% compared to the baseline value for the induction studies.

3. STUDY DESIGN

3.1 General Description

This is a Phase 3 multicenter extension study designed to evaluate the long-term safety of ontamalimab in subjects with moderate to severe UC or CD. The study has enrolled subjects from 6 separate Phase 3 studies to date: 4 multicenter, randomized, double-blind, placebo-controlled, parallel-group studies evaluating ontamalimab as an induction therapy in subjects with moderate to severe UC (SHP647-301 and SHP647-302) or CD (SHP647-305 and SHP647-306); and 2 multicenter, double-blind, randomized, placebo-controlled, parallel-group studies evaluating ontamalimab as maintenance therapy in subjects with moderate to severe UC (SHP647-303) or CD (SHP647-307). As the induction and maintenance studies will be closed earlier than planned, the study will enroll subjects with moderate to severe UC and CD from the 2 maintenance studies (at the time of their closure) who have responded to active treatment. As the 4 induction studies do not have any subjects eligible for rollover to the SHP647-304 study as of September 2020, no additional subjects will enter from those studies.

This study is planned to become a single-dose study, with the dose to be determined after the analysis of data from the induction studies. This study has been double-blind and will continue as such until the induction study results become available (ie, unblinding will not occur until the final analysis of the induction studies is completed and the lowest effective dose determined), as it is planned that subjects will receive the lowest effective dose based on the results of the induction studies. It is expected that the analysis of these results will demonstrate the efficacy of at least one of the doses and allow for the selection of a single dose, at which time this study will be open-label. If both doses are effective and the difference compared to placebo is similar, then the lowest effective dose will be selected. However, if the results of the induction or maintenance studies show that ontamalimab does not have evidence of efficacy over placebo, this study will be terminated.

All subjects will receive active drug in this study. Eligible subjects entering Study SHP647-304 from the discontinued SHP647-303 and SHP647-307 studies will be assigned to continue their present dose of ontamalimab (if currently receiving active drug) or to return to the dose of active drug associated with previous response (if on placebo). Ongoing subjects in this study will remain on the dose to which they have been previously assigned. Once the final dose has been determined, all subjects will continue on that dose only.

Subjects will come to the investigational site every 4 weeks (unless unable to participate on site due to a pandemic [eg, coronavirus disease (COVID-19)] or other future similar unexpected public health concerns requiring physical distancing that may result in subjects missing their visits), in which case they may qualify for the “Direct to Patient” program for investigational product (IP) administration and appropriate assessments.

The eligibility of a subject for this study will be assessed from study data collected at the following time points:

- For subjects with UC, the Week 12 visit of the induction study (SHP647-301 or SHP647-302) OR the Week 52 or Early Termination (ET) visit of the maintenance study (SHP647-303), which are considered and recorded as the baseline visit for this extension study (with the exception of the treatment response evaluation, for which baseline of the induction study will be used as baseline of this extension study). No additional subjects from the induction studies will be enrolling into Study SHP647-304. Subjects from the maintenance study (SHP647-303) will have the opportunity to enroll into this study at the time of the approval of Amendment 4 if they have benefited from active treatment in the induction or maintenance study.
- For subjects with CD, the Week 16 visit of the induction study (SHP647-305 or SHP647-306) OR the ET or Week 52 visit of the maintenance study (SHP647-307), which will be considered and recorded as the baseline visit for this extension study (with the exception of the treatment response evaluation, for which baseline of the induction study will be used as baseline of this extension study), with an additional window of 1 week for subjects whose treatment failure status is still under evaluation at the time of the Week 52 visit of the maintenance study. No additional subjects from the induction studies will be enrolling into Study SHP647-304. Subjects from the maintenance study (SHP647-307) will have the opportunity to enroll into this study at the time of the approval of Amendment 4 if they have benefited from active treatment in the induction or maintenance study.

Subjects enrolled in this study will receive treatment every 4 weeks, in the form of subcutaneous (SC) injections using prefilled syringes. Subjects will undergo treatment response and safety assessments as outlined in the Schedules of Assessments. Assessments for Year 1 are provided in Table 8 (for subjects with UC) and Table 10 (for subjects with CD). Assessments for Year 2 through the end of the study are provided in Table 9 (for subjects with UC) and Table 11 (for subjects with CD).

At every third visit, subjects with UC will be assessed for ongoing benefit (treatment response) using the clinical composite score or composite score. To facilitate data collection and reliability, subjects will have the option to use a memory aid. Endoscopies are not required, but if performed (eg, for routine surveillance), it is recommended that the Mayo endoscopic subscore be recorded by the endoscopist for assessment. The total Mayo score will be calculated only when endoscopy data are available. The partial Mayo score consists of the Mayo score without the endoscopic sub scores. The composite score is a recommended measure consisting of the Mayo score without the physical global assessment (PGA) subscore. The clinical composite score is a measure consisting of RB plus stool frequency (SF) without the endoscopic and PGA subscore. The data for Mayo scores and composite score will be collected from subjects, who have the option of using a memory aid, for 7 days before each specified visit as in the schedules of assessments. Biomarkers (C-reactive protein [CRP] and fecal calprotectin) will be assessed every 3 months or in case there is a necessity to confirm the loss of clinical treatment response.

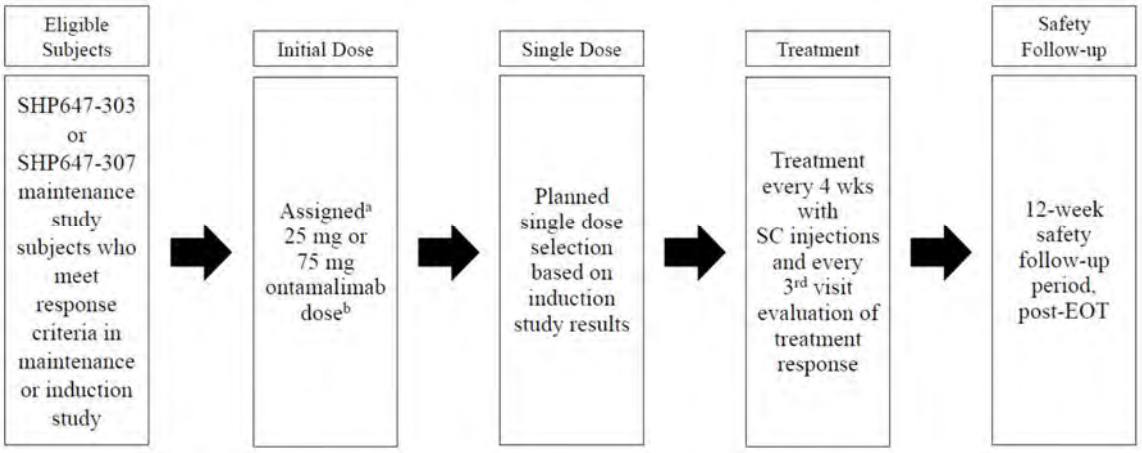
At every third visit, subjects with CD will be assessed for ongoing benefit (treatment response) using the CDAI score (treatment response defined as CDAI-100). Data on CDAI components (abdominal pain severity, very soft stool/liquid stool frequency, general well-being) will be collected from the subjects by the investigators. To facilitate data collection and reliability, subjects will have the option to use a memory aid. Endoscopies are not required, but if performed (eg, for routine surveillance), it is recommended that the SES-CD be recorded by the endoscopist for assessment. The CDAI is a composite measure with 8 components. Five components will be captured at the visits, and 3 components (abdominal pain severity, very soft stool/liquid stool frequency, and general well-being) will be collected from subjects, who have the option of using a memory aid, for 7 days before each specified visit as in the schedules of assessments. Biomarkers (CRP and fecal calprotectin) will be assessed every 3 months or in case there is a necessity to confirm the loss of clinical treatment response.

Treatment response will be assessed at every third visit for all subjects to allow monitoring of clinical benefit derived and evaluation of loss of response throughout the study. At these assessment visits, subjects' response will be evaluated and compared to the value of clinical composite score (for subjects with UC) or CDAI (for subjects with CD) determined at entry into the induction studies. As long as response criteria are satisfied, subjects may remain in the study. If there is a concern regarding loss of response between scheduled assessment visits, assessments may be performed at any scheduled or, if necessary, unscheduled visit to evaluate response. To ensure that placebo-treated subjects from a feeder study (SHP647-301, SHP647-302, SHP647-303, SHP647-305, SHP647-306, or SHP647-307) have sufficient exposure to active drug to permit assessment of treatment response, treatment response will be assessed according to the revised study schedule. Subjects may discontinue participation at any time, for any reason.

If response to IP is lost, based on clinical criteria, or if there is an unexplained clinical exacerbation or unacceptably low level of clinical response, the investigator may assess biomarkers and perform other investigations to exclude other potential causes like Clostridium difficile infection or an appropriate ad-hoc endoscopy to determine whether the loss of response is confirmed or not at an unscheduled visit. The totality of available data will be used to determine ongoing response status and subjects whose loss of response is confirmed.

The overall study design is shown in Figure 1.

Figure 1 Study Design Flow Chart for Subjects who Enter SHP647-304 Under Amendment 4



EOT=end of treatment; SC=subcutaneous; wks=weeks.
[a] Prior to unblinding. Subjects enrolling after unblinding will continue on their selected dose.
[b] Determined by active dose received in maintenance or induction study.
Maintenance studies are SHP647-303 and SHP647-307.
Induction studies are SHP647-301, SHP647-302, SHP647-305, and SHP647-306.

3.2 Randomization

Originally, subjects were to be randomized to treatment in this study. Under Amendment 4 of the protocol, randomization will not be performed, as the aim of the study is to provide subjects with the ontamalimab dose associated with their treatment response.

Following the confirmation of eligibility, subjects will be allocated to receive either 25 mg or 75 mg of ontamalimab SC every 4 weeks depending on which dose they had responded to in a prior study.

Eligible subjects who withdrew from Study SHP647-303 or SHP647-307 due to the early discontinuation of these studies, who received active treatment and showed treatment response at the end of treatment (EOT) visit, will receive the dose of ontamalimab (that resulted in treatment response) in the previous maintenance study every 4 weeks. Eligible subjects currently receiving placebo in maintenance study SHP647-303 or SHP647-307 will receive the same dose of ontamalimab that they received in the previous induction study every 4 weeks.

Subject numbers are assigned to all subjects as they consent to take part in the study. The subject numbers will be different than the numbers assigned in SHP647-301, SHP647-302, SHP647-303, SHP647-305, SHP647-306, and SHP647-307 for subjects who enter from these studies. The randomization number represents a unique number corresponding to IP allocated to the subject, once eligibility has been determined.

If during the study, either the 25 mg or 75 mg dose of ontamalimab is determined to be the efficacious dose, based on emergent data from the induction studies, subjects may have their

treatment assignment switched to that dose, and the study would continue as an open-label study at that dose level, unless neither dose is efficacious, in which case this study will be terminated.

To preserve blinding, all subjects will receive a randomization number, including those subjects who completed a maintenance study (SHP647-303 or SHP647-307) and are to receive the same ontamalimab dose in this study. Individual subject treatment is automatically assigned by the interactive response technology (IRT) system.

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

3.3 Blinding

This is a long-term safety (LTS) extension study. All IP (ontamalimab 25 mg or ontamalimab 75 mg) will appear identical to protect the study blind.

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

This study has been double-blind and will continue as such until the induction study results become available (ie, unblinding will not occur until the final analysis of the induction studies is completed and the lowest effective dose determined), as it is planned that subjects will receive the lowest effective dose based on the results of the induction studies.

The induction studies have now been analyzed and the results show that both the 25 and the 75mg dose have been well tolerated but only the 75mg dose showed significant efficacy in the primary endpoint (and all the key secondary endpoints) of the pooled analysis of the UC induction studies (SHP647-301 and SHP647-302). Therefore, subjects who are starting or continuing to take part in SHP647-304 based on Protocol Amendment 4 will receive the 75mg dose in an open label manner for the rest of the study.

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

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded on the IRT and the source documents. Upon breaking the blind, the subject is withdrawn from the study but should be

followed up for safety purposes. The IRT will notify the relevant personnel in the event of any code break. Code-break information is held by the pharmacist/designated person at the site.

Note: This is applicable only until the time of unblinding.

3.4 Sample Size and Power Considerations

A maximum of 568 subjects are projected to enroll into this study. No formal sample size estimation was performed on this study.

On 29 May 2020, Takeda announced the closure of the ontamalimab Phase 3 clinical development program, which included induction and maintenance studies for subjects with moderate to severe inflammatory bowel disease (IBD) who had failed at least 1 prior treatment. With this closure, the induction and maintenance studies were discontinued before full enrollment, and the planned direct entry of 800 subjects with UC that was added with Amendment 3 was not initiated. The previously projected sample size of 3384 subjects will not be attained.

As of 04 Sep 2020, there were 334 subjects that were enrolled in this SHP647-304 study. With 117 subjects active in the ongoing SHP647 induction and maintenance studies, up to a maximum of 568 subjects may be enrolled into this study.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed an informed consent document for the SHP647-304 study.

4.2 Randomized Set

The Randomized Set will consist of all subjects in the Screened Set for whom a SHP647-304 randomization number has been assigned.

4.3 Safety Set

The Safety Set will consist of all subjects who receive at least 1 dose of IP in the SHP647-304 study.

4.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the randomized set who receive at least 1 dose of IP in the SHP647-304 study.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The number of screened subjects and the number of screen failures will be presented in the overall column. The number of subjects included in each analysis set (i.e., Randomized, Safety, and FAS) will be summarized by treatment group as listed in Appendix 16.12. The percentage, based on the number of subjects in the Safety Set, will be presented for the FAS. The study analysis set classifications of each subject will be listed for the Screened Set. Subjects excluded from the efficacy analysis will be listed for the Randomized Set.

The number and percentage of subjects who completed and prematurely discontinued the study will be presented by treatment group as listed in Appendix 16.12 for the Safety Set. Reasons for premature discontinuation from the study are recorded on the study completion page of the electronic case report form (eCRF). All subjects who prematurely discontinued from the study will be listed for the Safety Set.

In addition, the number of subjects screened, randomized, and completed will be summarized for each site. The duration of enrollment, in days, will be summarized for each site and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site – the first date of informed consent for any subject at that site + 1).

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group as listed in Appendix 16.12 for the Safety Set and FAS. All demographic and baseline characteristics will be listed for the Safety Set.

Subject's age is from the induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306), which is calculated as the difference between the date of birth and the date of informed consent in the induction study. If day of birth is missing, then the day will be imputed as 1; if both the day and month of birth are missing, then the day will be imputed as 1 and the month will be imputed as 1 (January). The following demographic characteristics will be summarized in the following order in the tables: age, age category (<18, 18 to <65, and ≥65; <35 and ≥35), sex (Male, Female), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown), region (North America, Western Europe, Eastern Europe, Asia [Japan/South Korea], ROW [Africa/Australia/Latin America/Middle East]) (refer to Appendix 16.11), race (American Indian or Alaska Native, Asian [Japanese, Korean, Other], Black or African American, White, Native Hawaiian or Other Pacific Islander, and Other), Japanese Ancestry (Currently living in Japan, Born in Japan and currently living outside of Japan for less than 5 years, and Other), and Korean Ancestry (Currently living in Korea, Born in Korea and currently living outside of Korea for less than 5 years, and Other).

There are 3 baselines, defined as the last assessment prior to the first administration of IP in (1) the induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306); (2) maintenance studies (SHP647-303 or SHP647-307); and (3) this LTS extension study (SHP647-304), respectively, unless otherwise specified. The baseline value for a characteristic is

the baseline value of the induction studies. For subjects with UC, the maintenance (MNT) baseline is the value collected at the Week 12 visit of the induction studies (SHP647-301 and SHP647-302). For subjects with CD, the MNT baseline is the value collected at the Week 16 visit of the induction studies (SHP647-305 and SHP647-306). The LTS baseline is the value collected at the Week 12 visit of the UC induction study or Week 16 of the CD induction study or the Week 52 or ET visit of the maintenance study (SHP647-303 or SHP647-307). The following baseline characteristics will be summarized:

For subjects with UC:

- Weight,
- Height,
- Body Mass Index (BMI),
- UC Disease Duration and UC Disease Duration Category (<1 year, ≥1 to <3 years, ≥3 to <7 years, and ≥7 years)
  Disease duration is calculated as the number of years from the date of UC diagnosis to the date of informed consent in the induction study (SHP647-301 or SHP647-302),
- UC Disease Location (Proctitis, Procto-Sigmoidits, Left-sided Colitis, Extensive Colitis/Pancolitis),
- Total Mayo Severity and Total Mayo Severity Category at Baseline (<6, 6 to <9, and ≥9),
- Total Mayo Severity and Total Mayo Severity Category at MNT Baseline (<6, 6 to <9, and ≥9),
- Total Mayo Severity and Total Mayo Severity Category at LTS Baseline (<6, 6 to <9, and ≥9),
- Stool Frequency Score at Baseline (0, 1, 2, and 3),
- Stool Frequency Score at MNT Baseline (0, 1, 2, and 3),
- Stool Frequency Score at LTS Baseline (0, 1, 2, and 3),
- Rectal Bleeding Score at Baseline (0, 1, 2, and 3),
- Rectal Bleeding Score at MNT Baseline (0, 1, 2, and 3),
- Rectal Bleeding Score at LTS Baseline (0, 1, 2, and 3),
- Status at Entry into LTS Study (Induction Nonresponder, Maintenance Ontamalimab Completer, Maintenance Discontinuation Rollover).

The following UC medication history/use will be summarized:

- Immunosuppressant Experienced at LTS Baseline (Yes, No),
- Anti-tumor Necrosis Factor (TNF) Failure (Yes, No),
- Anti-TNF Failure Times (Anti-TNF Naïve, Anti-TNF Experienced without Failure, Failed 1 anti-TNF therapy, Failed 2 anti-TNF therapies, Failed 3 or more anti-TNF therapies),

- Anti-TNF Experienced (Experienced vs. Naïve) (actual status),
- Maximum Prior Treatment Experience (Aminosalicylates Experienced, Glucocorticoid Experienced [further broken down into topical glucocorticoid experienced and systemic glucocorticoid experienced], Immunosuppressant Experienced or Biologic Failure, Immunosuppressant Experienced and Biologic Failure),
- Glucocorticoid Use at Baseline (Yes, No) (actual status),
- Glucocorticoid Use at MNT Baseline (Yes, No) (actual status),
- Glucocorticoid Use at LTS Baseline (Yes, No) (actual status),
- Immunosuppressant Use at LTS Baseline (Yes, No),
- Glucocorticoid Use at LTS baseline AND Immunosuppressant Use at LTS Baseline (Both Glucocorticoid and Immunosuppressant Use, Only Glucocorticoid Use, Only Immunosuppressant Use, Neither Glucocorticoid nor Immunosuppressant Use),
- Glucocorticoid Use at LTS Baseline (Systemic or Topical, Systemic Only, Topical Only, None),
- Systemic Glucocorticoid Dose at LTS Baseline,
- Systemic Glucocorticoid Dose at LTS Baseline Category (≤10, >10),
- 5-aminosalicylic acid (5-ASA) Use at LTS Baseline (Yes, No).

The following outcomes from the induction study will be summarized:

- Actual Treatment Received in the Induction Study (Placebo, Ontamalimab 25 mg, Ontamalimab 75 mg).

The following outcomes from the maintenance study will be summarized:

- Actual Treatment Received in the MNT Study (Placebo, Ontamalimab 25 mg, Ontamalimab 75 mg),
- MNT Treatment Failure Status (Completed without Treatment Failure, Treatment Failure),
- Stool Frequency Subscore with at least a 1-point Change from Induction Study (SHP647-301 or SHP647-302) (Yes, No),
- Rectal Bleeding Subscore (0, 1, 2, 3).

For subjects with CD:

- Weight,
- Height,
- BMI,

- CD Disease Duration (years) and CD Disease Duration Category (<1 year, ≥1 to <3 years, ≥3 to <7 years, and ≥7 years)

  Note: CD disease duration is defined as the number of years from the date of CD diagnosis to the date of informed consent in the induction study (SHP647-305 or SHP647-306),
- CD Disease Location (Small Intestine alone, Colon and/or Rectum alone, Ileo-colitis, Perianal, and Other),
- CDAI Score at Baseline,
- CDAI Score at MNT Baseline,
- CDAI Score at LTS Baseline,
- SES-CD at Baseline (≥17 and <17) (actual status),
- SES-CD at MNT Baseline (≥17 and <17),
- SES-CD at LTS Baseline (≥17 and <17),
- Status at Entry into LTS Study (Induction Nonresponder, Maintenance Ontamalimab Completer, Maintenance Discontinuation Rollover).

The following CD medication history/use will be summarized where "randomization status" refers to SHP647-304 randomization stratification and "actual status" refers to the actual information collected in the case report form (CRF) at LTS baseline:

- Anti-TNF Experienced (Naïve and Experienced) (actual status),
- Anti-TNF Failure (Yes, No),
- Anti-TNF Failure Times (Anti-TNF Naïve, Anti-TNF Experienced without Failure, Failed 1 Anti-TNF Therapy, Failed 2 Anti-TNF Therapies, Failed 3 or more Anti-TNF Therapies),
- Maximum Prior Treatment Experience (Aminosalicylates Experienced, Glucocorticoid Experienced [further broken down into topical glucocorticoid experienced and systemic glucocorticoid experienced], Immunosuppressant Experienced or Biologic Failure, Immunosuppressant Experienced and Biologic Failure),
- Glucocorticoid Use at Baseline (Yes, No) (actual status),
- Glucocorticoid Use at MNT Baseline (Yes, No) (actual status),
- Glucocorticoid Use at LTS Baseline (Yes, No) (actual status),
- Glucocorticoid Use at LTS Baseline (Systemic and Topical, Systemic Only, Topical Only, None),
- Systemic Glucocorticoid Dose at LTS Baseline,
- Systemic Glucocorticoid Dose at LTS Baseline Category (≤10 mg, >10 mg),
- Immunosuppressant Experienced at LTS Baseline (Yes, No),

- Immunosuppressant Use at LTS Baseline (Yes, No),
- Glucocorticoid Use at LTS Baseline AND Immunosuppressant Use at LTS Baseline (Both Glucocorticoid and Immunosuppressant Use, Only Glucocorticoid Use, Only Immunosuppressant Use, Neither Glucocorticoid nor Immunosuppressant Use),
- 5-ASA Use at LTS Baseline (Yes, No).

The following outcomes from the induction study will be summarized:

- Actual Treatment Received in Induction Study (Placebo, Ontamalimab 25 mg, Ontamalimab 75 mg).

The following outcomes from the maintenance study will be summarized:

- Actual Treatment Received in MNT Study (Placebo, Ontamalimab 25 mg, Ontamalimab 75 mg),
- MNT Treatment Failure Status (Completed without Treatment Failure, Treatment Failure),
- Clinical Remission at LTS Baseline (Yes, No),
- Enhanced Endoscopic Response at LTS Baseline as measured by a decrease in SES-CD of at least 50% from induction study (SHP647-305 or SHP647-306) baseline (Yes, No).

5.3 Smoking History

Smoking history will be recorded in the eCRF at the Screening Visit (Visit 1) in the induction studies (SHP647-301 or SHP647-302 and SHP647-305 or SHP647-306) and will be summarized by treatment group as listed in Appendix 16.12. Smoking history will be listed for the Safety Set. Duration of smoking will be calculated as (substance use end date – substance use start date + 1). If substance use end date is missing, then it will be imputed as the randomization date of the induction studies (SHP647-301 or SHP647-302 and SHP647-305 or SHP647-306).

5.4 Medical History

Medical history will be collected at the Screening Visit (Visit 1) in the induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) or maintenance studies (SHP647-303 or SHP647-307) and this extension study (SHP647-304) and will be listed for the Safety Set.

Medical history will be coded using MedDRA Version 19.1 2016 or newer. Induction study and maintenance study medical history will be summarized by the number and percentage of subjects for each treatment group as listed in Appendix 16.12, system organ class (SOC), and preferred term.

Cardiovascular history will be collected at the Screening Visit (Visit 1) in the induction studies (SHP647-301 or SHP647-302 and SHP647-305 or SHP647-306) and will be summarized by treatment group as listed in Appendix 16.12 for the Safety Set. Cardiovascular history will be listed for the Safety Set.

Ulcerative colitis history will be collected at the Screening Visit (Visit 1) in the induction study (SHP647-301 or SHP647-302) and will be listed for the Safety Set.

Crohn's disease history will be collected at the Screening Visit (Visit 1) in the induction study (SHP647-305 or SHP647-306) and will be listed for the Safety Set.

5.5 Prior Medications

Prior medications will be coded using the World Health Organization (WHO) Drug Dictionary dated 01 December 2016 or newer.

Prior medication is defined as any medication with start date prior to the date of the first dose of IP in the SHP647-304 study, and which is ongoing at the date of the baseline visit in the SHP647-304 study. Incomplete medication dates will be imputed as described in Section 12.5.3. Prior treatment includes any treatment (including but not limited to herbal remedies and vitamins) that is ongoing at the time of the baseline visit in the SHP647-304 study. This should include concomitant medications in the induction or maintenance studies that are ongoing at the baseline visit of the SHP647-304 study.

All prior medications, medical/surgical procedures, and therapies will be listed for the Safety Set.

5.6 Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary dated 01 Dec 2016.

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of IP in the SHP647-304 study and continuing after the first dose of IP in the SHP647-304 study, or with a start date between the dates of the first dose of IP in the SHP647-304 study and EOT date, inclusive. Medication that starts after the first dose of SHP647-304 IP will be collected in the SHP647-304 database and will be considered as concomitant medication in SHP647-304. Incomplete medication dates will be imputed as described in Section 12.5.3. Any medication with a start date between the dates of the first dose of IP and EOT date in SHP647-304, inclusive, or with a start date after the EOT date (post-treatment) in SHP647-304 will be considered a post-treatment concomitant medication.

Concomitant medication usage will be summarized by the number and percentage of subjects by treatment group as listed in Appendix 16.12, for subjects receiving each medication within each therapeutic class and preferred term for the Safety Set. Multiple medication usage by a subject in the same category will be counted only once. Summaries are presented separately for "Indication Under Study" and "not for Indication Under Study".

All concomitant medications, medical/surgical procedures, and therapies occurring during the SHP647-304 study will be listed for the Safety Set.

5.7 Exposure to Investigational Product

Investigational product (ontamalimab or placebo) will be administered SC every 4 weeks. Exposure to IP in the SHP647-304 study will be summarized by presenting the number of subjects who had 1 injection, 2 injections, 3 injections, etc. Number of injections received will be summarized by treatment group as listed in Appendix 16.12. The administration records by visit will be listed for the Safety Set.

Exposure to IP in the SHP647-304 study for the Safety Set will be summarized in terms of treatment duration, which is calculated as the number of days from the date of first dose of IP taken in the SHP647-304 study to the date of the last dose of IP taken in the SHP647-304 study + 29 days. Subject years of exposure is calculated as (date of last dose of IP in the SHP647-304 study – date of first dose of IP in the SHP647-304 study + 29)/365.25. Total subject years of exposure is calculated by summing the subject years of exposure for all subjects within each column.

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented to describe the exposure to IP by treatment group as listed in Appendix 16.12.

5.8 Measurements of Treatment Compliance

Compliance for the treatment period is defined as the total number of SC injections administered from the start of treatment in the SHP647-304 study until EOT in the SHP647-304 study divided by the number of injections expected to be taken during that time period, times 100. Percentage compliance will be summarized by treatment group as listed in Appendix 16.12. Compliance will be listed for the Safety Set.

5.9 Protocol Deviations

Protocol deviations will be recorded by Pharmaceutical Product Development (PPD) separately from the clinical database. PPD/Shire will classify significant and nonsignificant protocol deviations per the agreed protocol deviation management plan. The Shire study team will review the protocol deviations and their classifications throughout the study and before treatment unblinding and database lock.

For any criteria for protocol deviations that can be completely implemented by a computer program, the detailed algorithm will be agreed upon. Details of such algorithms will be included in the derived dataset specifications and finalized before treatment unblinding.

Confirmed significant and nonsignificant protocol deviations will be documented in the Protocol Deviation tracker for the study. Significant and nonsignificant protocol deviations will be summarized by category, site, and treatment group as listed in Appendix 16.12 for the Randomized Set. Significant and nonsignificant protocol deviations will be listed for the Randomized Set. The protocol deviations related to COVID-19 will be listed separately for the Randomized Set.

6. TREATMENT RESPONSE ANALYSES

Treatment response analyses will be performed using the FAS.

6.1 Treatment Response Analyses – Subjects with Ulcerative Colitis

6.1.1 Secondary Endpoints

The secondary endpoint is as follows:

- Treatment response over time, with response defined as clinical composite score that has decreased by ≥2 points and ≥30%, with an accompanying decrease in the subscore for RB ≥1 point or a subscore for RB ≤ 1, and/or composite score that has decreased by ≥30% and ≥3 points compared to the baseline value for induction studies.

The clinical composite score is a measure consisting of RB plus stool frequency without endoscopic and PGA subscore.

Secondary endpoints will be summarized by planned treatment group as listed in Appendix 16.12 using descriptive statistics at each assessment visit.

For each treatment group listed in Appendix 16.12 and for each visit, the treatment response rate, including number of subjects, the proportion of all subjects in the treatment group, and corresponding Wilson Score (Yan and Su, 2010) 95% confidence intervals, will be presented.

In the event that the number of responders or non-responders in either treatment group is too small (i.e., ≤5), exact unconditional confidence limits for treatment difference (Chan and Zhang, 1999) will be performed instead. Subjects with missing data to determine endpoint status will be considered as undesired treatment outcome (i.e, non-responders).

An overlay plot of the proportions for these same treatment groups across study visits will also be generated.

6.2 Treatment Response Analyses – Subjects with Crohn's Disease

6.2.1 Secondary Endpoints

The secondary endpoint is as follows:

- Treatment response over time, with response defined as CDAI score that has decreased by ≥100 points compared to the baseline value for induction studies and/or SES-CD that has decreased by ≥25% compared to the baseline value for induction studies.

Secondary endpoints will be summarized by planned treatment group as listed in Appendix 16.12 using descriptive statistics at each assessment visit.

For each treatment group listed in Appendix 16.12 and for each visit, the treatment response rate, including number of subjects, the proportion of all subjects in the treatment group, and corresponding Wilson Score (Yan and Su, 2010) 95% confidence intervals, will be presented.

In the event that the number of responders or non-responders in either treatment group is too small (i.e., ≤5), exact unconditional confidence limits for treatment difference (Chan and Zhang, 1999) will be performed instead. Subjects with missing data to determine endpoint status will be considered as undesired treatment outcome (ie, non-responders).

An overlay plot of the proportions for these same treatment groups across study visits will also be generated.

6.3 Other Efficacy Data

Inpatient hospitalizations and emergency room visits will be listed for the Full Analysis Set.

7. SAFETY ANALYSIS

All safety analyses will be performed using the Safety Set. Safety variables include AEs, clinical laboratory variables, vital signs, and ECG variables. For each safety variable, the last value collected before the first dose of IP will be used as baseline for all analyses of that safety variable. For subjects with UC, the Week 12 visit of the induction study (SHP647-301 or SHP647-302) or the Week 52 or ET visit of the maintenance study (SHP647-303) will be considered and recorded as the baseline visit for this extension study (with the exception of the treatment response evaluation, for which baseline of the induction study will be used as baseline of this extension study). For subjects with CD, the Week 16 visit of the induction study (SHP647-305 or SHP647-306) or the Week 52 or ET visit of the maintenance study (SHP647-307) will be considered and recorded as the baseline visit for this extension study (with the exception of the treatment response evaluation, for which baseline of the induction study will be used as baseline of this extension study), with an additional window of 1 week for subjects whose treatment failure status is still under evaluation at the time of the Week 52 visit of the maintenance study.

Last Observed Value on Treatment will be defined as the last valid assessment obtained after baseline and whilst on IP.

All safety analyses will be conducted according to the treatment the subject actually received. Summaries will be presented by indication separately.

7.1 Adverse Events

Adverse events will be coded using MedDRA Version 19.1 2016.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates or worsening dates at the time of or following the first exposure to investigational product in the SHP647-304 study.

An overall summary of the number of subjects with TEAEs will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to IP, related serious AEs (SAEs), TEAEs leading to study discontinuation, TEAEs leading to study medication discontinuation, and TEAEs leading to death.

The number of events, incidence, and percentage of subjects reporting TEAEs in each treatment group will be summarized by treatment group as listed in Appendix 16.12; by preferred term; by SOC and preferred term; and by SOC, preferred term, and maximum severity. Treatment-emergent AEs considered related to IP will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to IP.

The most common TEAEs (incidence ≥2% in any treatment group) will be summarized by preferred term in descending order of frequency by treatment group as listed in Appendix 16.12.

Serious TEAEs, TEAEs leading to discontinuation of the study or study medication, and injection site AEs will be summarized by SOC, preferred term, and treatment group as listed in Appendix 16.12. Adverse events leading to withdrawal, SAEs, and deaths will be similarly summarized or listed.

7.1.1 Adverse Events of Special Interest and Other Potential Risks

There is 1 identified important potential risk of progressive multifocal leukoencephalopathy (PML). There are 6 other identified potential risks: immunotoxicity, immunogenicity, infection, vascular and thrombotic events, local tolerability, and malignant tumors. Potential risks will be summarized by treatment group as listed in Appendix 16.12. Potential risks will be listed.

7.1.1.1 Hypersensitivity

Potential hypersensitivity reactions such as serum sickness, vasculitis, or Arthus reactions to ontamalimab will be regarded as adverse events of special interest. Reported hypersensitivity events, adjudicated hypersensitivity events, and study drug recommendations will be summarized by treatment group as listed in Appendix 16.12.

The number of hypersensitivity reactions and percentage of subjects with hypersensitivity reactions as adjudicated will be summarized by treatment group as listed in Appendix 16.12; and by SOC, preferred term, and hypersensitivity type. Reported hypersensitivity events and adjudicated hypersensitivity events will be listed for the Safety Set.

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values (in conventional units), the LTS baseline, and changes from the induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline at each assessment time point for quantitative variables will be presented by treatment group as listed in Appendix 16.12 for the following clinical laboratory variables. The number and percentage of subjects for qualitative variables in urinalysis will be presented by treatment group as listed in Appendix 16.12 in the Safety Set.

Serum chemistry

- alkaline phosphatase
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- 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

Urinalysis

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

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 1. The number and percentage of subjects with post-LTS baseline PCI values will be tabulated by treatment group as listed in Appendix 16.12. The percentages will be calculated relative to the number of subjects with at least 1 post-LTS baseline assessment. The numerator is the total number of subjects with at least 1 post-LTS baseline PCI value. A supportive listing of subjects with post-LTS baseline PCI values will be provided including the subject number, induction study baseline, and post-LTS baseline values.

Figures will be presented for hematology and chemistry to show the changes in laboratory parameters over time. Data will be presented as box-and-whisker plots by treatment group as listed in Appendix 16.12 at each visit, with 1 laboratory parameter per page.

Shifts from the induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline category to each visit will be presented for each treatment group and ontamalimab all doses as listed in Appendix 16.12 for hematology, chemistry, and urinalysis. For hematology and chemistry, shifts will be categorized as Low, Normal, or High. For urinalysis, shifts will be categorized as Abnormal or Normal.

All laboratory data will be listed for the Safety Set.

Table 1 Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Age Range	Sex	Outlier Criteria[a]	
			Low	High
Hematology				
Hemoglobin	All		<8 g/dL	NA
Hematocrit	All		<32%	NA
Mean Corpuscular Hemoglobin (MCH)	All		<LLN	>ULN
Mean Corpuscular Hemoglobin Concentration (MCHC)	All		<LLN	>ULN
Mean Corpuscular Volume (MCV)	All		<LLN	>ULN
Erythrocyte (red blood cell)	All		<3.0 × 10^6/µL	NA
Leukocytes (white blood cell)	All		<3.0 × 10^3/µL	>20 × 10^3/µL
Neutrophils (Abs)	All		<1.5 × 10^3/µL	>15 × 10^3/µL
Neutrophils (%)	All		<40%	NA
Lymphocytes (Abs)	All		NA	NA
Lymphocytes (%)	All		<10%	>50%
Monocytes (Abs)	All		NA	NA
Monocytes (%)	All		NA	>25%
Eosinophils (Abs)	All		NA	NA
Eosinophils (%)	All		NA	>10%
Basophils (Abs)	All		NA	NA
Basophils (%)	All		NA	>10%
Platelets	All		<75 × 10^3/µL	>1,000 × 10^3/µL
Chemistry				
Alkaline Phosphatase	All		NA	>2.5 × ULN (or alternatively >400 U/L)
Aspartate Aminotransferase (AST)	All		NA	>2.5 × ULN
Alanine Aminotransferase (ALT)	All		NA	>2.5 × ULN
Total Bilirubin	All		NA	>1.5 × ULN
Total Protein, plasma or serum	All		<5 g/dL	>9 g/dL
Albumin	All		<3 g/dL	NA
Glucose (fasting)	All		<55 mg/dL	>160 mg/dL
Blood Urea Nitrogen (BUN)	All		NA	>2.5 × ULN (or alternatively >29.4 mg/dL)
Creatinine, serum	All		NA	>1.5 × ULN (or alternatively >1.98 mg/dL)
Sodium	All		<130 mEq/L	>150 mEq/L
Potassium, plasma or serum	All		<3 mEq/L	>5.5 mEq/L
Chloride	All		<90 mEq/L	>115 mEq/L
Calcium	All		<8.0 mg/dL	>11.2 mg/dL
Carbon dioxide (NCI uses bicarb)	All		NA	NA
DILI screen (ongoing safety monitoring)	All		NA	AST or ALT >3 × ULN and TBL >2 × ULN
Urinalysis				
Bilirubin	All		NA	NA
Leukocyte esterase	All		NA	NA
Protein	All		NA	>=2+
Glucose	All		NA	NA
Blood	All		NA	NA
Ketones	All		NA	NA
Nitrite	All		NA	NA

Table 1 Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Age Range	Sex	Outlier Criteria[a]	
			Low	High
pH	All		NA	NA
Specific gravity	All		NA	NA
Urobilinogen	All		NA	NA

DILI=drug-induced liver injury; LLN=lower limit of normal provided by the laboratory; NA=not applicable; ULN=upper limit of normal provided by the laboratory.
[a] If criteria in both directions are shown for a single parameter, then abnormalities in each direction are summarized separately.

7.3 Pregnancy Test and Follicle-stimulating Hormone Test

Pregnancy tests are not required for females of nonchildbearing potential. All pregnancy tests data will be listed for the Safety Set.

7.4 Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, body weight, respiratory rate, and temperature) and their changes from induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline at each postbaseline visit and at the end of the study will be presented by treatment group as listed in Appendix 16.12.

For pulse rate, a post-LTS value is considered as a PCI value if it meets both criteria for observed value and change from induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline. For systolic/diastolic blood pressure, a post-LTS baseline value is considered as a PCI value if it meets criteria for observed value or change from induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline. For weight and BMI, a post-LTS baseline value is considered as a PCI value if it meets criteria for change from induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline. The PCI criteria are listed in Table 2. The number and percentage of subjects with PCI post-LTS baseline values will be tabulated by treatment group as listed in Appendix 16.12. The percentages will be calculated relative to the number of subjects with available induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline values and at least 1 post-LTS baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-LTS baseline vital sign value. A supportive listing of subjects with post-LTS baseline PCI values will be provided including the subject number, site, and induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline and post-LTS baseline values.

All vital signs data will be listed for the Safety Set.

Table 2 Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Systolic blood pressure (mmHg)	High	≥180	Increase of ≥20
	Low	≤90	Decrease of ≥20

Table 2 Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤50	Decrease of ≥15
Pulse rate (beats per minute)	High	≥120	Increase of ≥15
	Low	≤50	Decrease of ≥15
Weight (kg)	High	-	Increase of ≥7%
	Low	-	Decrease of ≥7%
BMI (kg/m^2)	High	-	Increase of ≥10%
	Low	<18	Decrease of ≥10%
Temperature (°C)		NA	NA

[a] For pulse rate, a post-baseline value is considered as a PCI value if its meets both criteria for observed value and change from baseline. For systolic/diastolic blood pressure, a post-baseline value is considered as a PCI value if it meets criteria for observed value or change from baseline. For weight and BMI, a post-baseline value is considered as a PCI value if it meets criteria for change from baseline.

7.5 Electrocardiogram (ECG)

A central ECG reader will be used for data collected prior to Protocol Amendment 4. A local ECG reader will be used for data collected after Protocol Amendment 4.

Descriptive statistics for ECG variables (eg, heart rate, PR interval, QRS interval, QT interval, and QTc interval using both Bazett and Fridericia corrections) and their changes from induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline at each assessment time point will be presented by treatment group as listed in Appendix 16.12.

Electrocardiogram interpretation will be summarized by visit. A shift table from induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline to each visit for ECG interpretation results will be presented by treatment group as listed in Appendix 16.12.

Electrocardiogram variable values will be considered PCI if they meet or exceed the upper limit values listed in Table 3. The number and percentage of subjects with available induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) baseline values and post-LTS baseline PCI values will be tabulated by treatment group as listed in Appendix 16.12. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-LTS baseline assessment. The numerator is the total number of subjects with at least 1 post-LTS baseline PCI value.

Listings of ECG data including the central reader's assessment and investigator's interpretation by individual subject will be produced. Separate listings will be produced for subjects with ECG results meeting PCI criteria. Data from unscheduled visits will be listed but not summarized.

Table 3 Criteria for Potentially Clinically Important ECG Values

ECG Parameter	Unit	Higher Limit
QRS interval	msec	≥150
PR interval	msec	≥250
QTc interval	msec	≥500

ECG=electrocardiogram

7.6 Other Safety Data

7.6.1 Targeted Neurological Assessment

The targeted neurological examination and neurological consultation evaluation results with unexplained abnormal neurological findings will be summarized at screening and at each visit and by treatment group as listed in Appendix 16.12. The number and percentage of subjects with a targeted neurological examination in each of the neurological domains (vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior) will be summarized by the result category (abnormal, normal, not done) at each visit and by treatment group as listed in Appendix 16.12. The number and percentage of subjects who were referred for a neurological consultation and the results (no PML, PML, no clinically significant finding, other clinically significant finding, not done, other) will also be summarized by treatment group as listed in Appendix 16.12. The neurological evaluation and consultation results will be listed for the Safety Set.

7.6.2 Contraception Check

Contraception check should be performed for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential. Contraception check results will be listed for the Safety Set.

7.6.3 Physical Examination

Complete and targeted physical examinations will be performed at the time points specified in Table 8, Table 9, Table 10, and Table 11. Physical examination results will be listed for the Safety Set.

7.6.4 Other Safety Data Prior to Protocol Amendment 4

All other safety assessments removed by Protocol Amendment 4 will be listed for the Safety Set.

8. PHARMACOKINETIC ANALYSIS

8.1 Drug Concentration

Serum concentration data collected prior to Amendment 4 (as shown in Table 12, Table 13, Table 14, Table 15, Table 16, and Table 17) will be listed by subject in the Safety Set.

8.2 Handling Below Limit of Quantitation (BLQ) Values

The lower limit of quantification for ontamalimab is 10 ng/mL. Plasma concentrations below the limit of quantification (BLQ) will be presented as BLQ in the listing.

8.3 Pharmacokinetic Parameters

Not applicable.

8.4 Statistical Analysis of Pharmacokinetic Data

Not applicable.

9. PHARMACODYNAMIC ANALYSIS

9.1 Pharmacodynamic Data

Actual values of biomarkers including fecal calprotectin and serum CRP at each sample collection will be listed by subject in the Safety Set.

10. OTHER ANALYSES

10.1 Coronavirus Pandemic

The coronavirus (COVID-19) pandemic of 2019-20 particularly poses risks to the safety of subjects enrolled in clinical trials and the availability and interpretability of data from those trials. COVID-19 impacts on individual subjects collected on COVID-19 CRF pages will be listed for the Randomized Set. Protocol deviations related to COVID-19 will be listed for the Randomized Set. The study disruptions related to COVID-19 will be listed for the Safety Set.

10.2 Russia – Ukraine Crisis

Russia's recent invasion of Ukraine was initiated on 24 February 2022. Due to the ongoing Russia-Ukraine crisis, it is estimated that 17 active sites and potentially 38 subjects in Study SHP647-304 may be affected by the crisis. The crisis may cause both the loss of data, due to discontinuation of patients from the study, missed treatment, missed visits, or missed assessments within a visit, and the inflation of adverse events because of the diminished quality of treatment.

Additional analysis may be performed to evaluate the impact of Russia-Ukraine crisis on the efficacy and safety of all participating subjects focusing on primary and secondary endpoints, including but not limited to the following:

- Data listing of Protocol deviations related to Russia-Ukraine crisis
- Data listing of all subjects potentially affected by Russia-Ukraine crisis, including subject ID, site number, treatment arm, country, enrollment date, discontinuation date/reason

For the primary endpoints, a sensitivity analysis using the Safety Set may be conducted for adverse events by excluding AEs with an onset date on or after 24 February 2022 for the subjects from the potentially affected Russia-Ukraine sites for both UC and CD subjects:

- Overall Treatment-Emergent Adverse Events (TEAEs) by Treatment Group (Safety Set)
- Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group (Safety Set)

For the secondary efficacy endpoints, a sensitivity analysis using Full Analysis Set may be performed by using the same approach as mentioned in Section 6.1.1 and Section 6.2.1 but excluding subjects who were actively enrolled and on treatment during the conflict period beginning 24 February 2022 from the potentially affected Russia-Ukraine sites for both UC and CD subjects:

- Summary of Treatment Response Based on Clinical Composite Score by Treatment Group (SHP647-304 Ulcerative Colitis) (Full Analysis Set)
- Summary of Treatment Response Based on CDAI Score by Treatment Group (SHP647-304 Crohn's Disease) (Full Analysis Set)

10.3 Significant Investigator Noncompliance

If significant noncompliance with regulatory requirements during the course of the study is detected or reported at any clinical site, additional sensitivity analyses may be conducted on the efficacy endpoints by using the same approach but excluding all subjects from the noncompliant site(s).

11. INTERIM ANALYSIS/DATA MONITORING (REVIEW) COMMITTEE

A data monitoring committee (DMC) was set up to review safety during the course of the study. The DMC will not review efficacy data until the time of unblinding. No interim analyses are planned for this study.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, and maximum. For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to 1 level of precision greater than the data collected. Standard deviation will be displayed to 2 levels of precision greater than the data collected.

Categorical and count variables will be summarized by the number of subjects (n) and the percentage of subjects in each category. Percentages will be presented to 1 decimal place. When count data are presented, the percentage will be suppressed when the count is zero. A row denoted "Missing" will be included in count tabulations only if there are missing values. The denominator for all percentages will be the number of subjects in that treatment within the population of interest, unless otherwise specified.

P-values will generally be presented to 4 decimal places; values less than 0.0001 will be presented as <0.0001.

12.2 Definition of Visit Windows

Assessments will be assigned to visits based upon the date on which the assessment took place regardless of the completed CRF page. Assessments will be mapped to visits as outlined in Table 4, Table 5, Table 6, and Table 7. Any other mapping of day of assessment to the planned study day of a visit will use the study day midpoint between planned study days as the dividing line between visits. The 'End of Treatment' (EOT) will be assigned to visit based on the date of assessment. The EOT date is unique for each subject and uses the date recorded on the study completion CRF page.

Should there be more than 1 assessment mapped into a given study visit with non-missing results, the assessment closest to the planned visit will be used for analysis (referred to as analysis visit); in case of ties between observations, the later assessment will be used.

Study day will be calculated as follows:

- If the assessment date is on or after the date of first dose of IP:
  Study day = assessment date – first dosing date + 1
- If the assessment date is before the date of first dose of IP:
  Study day = assessment date – first dosing date

The possibility exists, that subjects who were enrolled before SHP647-304 protocol amendment 4 was implemented could participate in study treatment of SHP647-304 for more than 144 weeks. When on treatment visits beyond 144 weeks occur in the study, data those results will be assigned to visit windows and presented in the same manner as other on treatment visits prior to the Week 144 visit.

Table 4 Analysis Visit Windows (Study Day Based) – Vital Signs and Safety Lab (Chemistry and Urinalysis) (Subjects with UC/CD) and Weight (Subjects with UC)

Visit	Planned Study Day	Start Day of Window	End Day of Window
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	420
Week 72	504	421	588
Week 96	672	589	756
Week 120	840	757	924
Week 144	1008	925	1092
…	…	…	…
Follow-up[a]	EOT date + 84	EOT date + 1	EOF date

CD=Crohn's disease; EOF=end of follow-up; EOT=end of treatment; UC=ulcerative colitis
Note: For subjects whose study participation extends beyond Year 3 (ie, subjects already enrolled in this study prior to the implementation of Amendment 4), assessments will be repeated on the subsequent year rotation beginning with Week 100.
[a] Weight is not calculated at the follow-up visit

Table 5 Analysis Visit Windows (Study Day Based) –Safety Lab (Hematology) (Subjects with UC/CD) and Weight (Subjects with CD)

Visit	Planned Study Day	Start Day of Window	End Day of Window
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week 108	756	715	798
Week 120	840	799	882
Week 132	924	883	966
Week 144	1008	967	1050

Table 5 Analysis Visit Windows (Study Day Based) –Safety Lab (Hematology) (Subjects with UC/CD) and Weight (Subjects with CD)

Visit	Planned Study Day	Start Day of Window	End Day of Window
…	…	…	…
Follow-up	EOT date + 84	EOT date + 1	EOF date

CD=Crohn's disease; EOF=end of follow-up; EOT=end of treatment; UC=ulcerative colitis
Note: For subjects whose study participation extends beyond Year 3 (ie, subjects already enrolled in this study prior to the implementation of Amendment 4), assessments will be repeated on the subsequent year rotation beginning with Week 100.

Table 6 Analysis Visit Windows (Study Day Based) – Neurological Assessments and Treatment Response Assessments (Subjects with UC/CD), Partial Mayo Score (Subjects with UC), CDAI Score (Subjects with CD), Safety Lab (Stool Sample for Fecal Calprotectin, Serum CRP) (Subjects with UC/CD)

Visit	Planned Study Day	Start Day of Window	End Day of Window
Week 12	84	2	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week 108	756	715	798
Week 120	840	799	882
Week 132	924	883	966
Week 144	1008	967	1050
…	…	…	…
Follow-up[a]	EOT date + 84	EOT date + 1	EOF date

CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; EOF=end of follow-up; EOT=end of treatment; UC=ulcerative colitis
Note: For subjects whose study participation extends beyond Year 3 (ie, subjects already enrolled in this study prior to the implementation of Amendment 4), assessments will be repeated on the subsequent year rotation beginning with Week 100.
[a] Treatment Response Assessments, Partial Mayo Score, CDAI scores, Weight, and Safety Lab (Stool Sample for Fecal Calprotectin, Serum CRP) are not calculated at the follow-up visit

Table 7 Analysis Visit Windows (Study Day Based) – ECG Assessments (Subjects with UC/CD)

Visit	Planned Study Day	Start Day of Window	End Day of Window
Week 12	84	2	126
Week 24	168	127	252
Week 48	336	253	504
Week 96	672	505	840
Week 144	1008	841	1176
…	…	…	…

CD=Crohn's disease; ECG=electrocardiogram; EOT=end of treatment; UC=ulcerative colitis
Note: For subjects whose study participation extends beyond Year 3 (ie, subjects already enrolled in this study prior to the implementation of Amendment 4), assessments will be repeated on the subsequent year rotation beginning with Week 100.

12.3 Treatment Response Assessments

12.3.1 Subjects with UC

12.3.1.1 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 8, Table 9, and Section 14.

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:

- Bowel movement frequency (0-3)
- Rectal bleeding (0-3)
- Findings of flexible sigmoidoscopy or endoscopy (0-3)
- Physician global assessment (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. Note: Endoscopy is optional based on Protocol Amendment 4, and the composite score will be computed only if an endoscopy is performed.

The clinical composite score is a measure consisting of RB plus SF without endoscopic and PGA subscore. Subjects will be instructed to maintain a daily memory aid for the 7 days prior to each visit. In the memory aid, subjects will record the total number of bowel movements and the worst RB experienced each day (see Section 12.3.1.2). At the scheduled visit, the investigator will ask the subject to report the daily stool count and RB score and enter the data into the eCRF to calculate the clinical composite (and if appropriate, composite) score for that visit.

The Mayo SF and RB subscores will be calculated based on each subject's data over the most recent 3 days (consecutive or nonconsecutive) prior to the visit, excluding the following days: day of any bowel preparation, day of endoscopy, any days between day of bowel preparation and day of endoscopy, and the 2 days after the day of endoscopy. For the data that was collected prior to Protocol Amendment 4, the most recent 3 days is selected from the last 10 days prior to the scheduled visit start date. The most recent 3 days' subscores will be averaged and rounded to the nearest score according to standard rounding rules.

The mucosal appearance during the sigmoidoscopic portion of the endoscopic examination (if performed) will be assessed for the Mayo endoscopic subscore based on the scoring system provided in the protocol. The endoscopic appearance will be read by the operator or study site investigator using video recorded during the procedure. Locally read endoscopic subscores, if performed, will be used for treatment response 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 subscore must be determined by a physician qualified to perform endoscopy; it is recommended that the same physician performs all such assessments for a particular subject throughout the study, and that the same physician who performed the assessments during the induction study does so during the current study.

The Mayo score data will be listed for the FAS.

12.3.1.2 UC Subject Reporting of Symptoms

Subjects will be asked to report the following signs and symptom data, as experienced over the previous 24 hours and for the 7 days prior to each scheduled visit:

- Stool frequency
- Rectal bleeding severity.

The UC subject reporting of symptoms data will be listed for the FAS.

12.3.2 Subjects with CD

12.3.2.1 SES-CD

The SES-CD will be calculated using the subscores of each of the segments investigated and read by the local endoscopist at each of the visits during which colonoscopy is performed. The baseline score will be based on the colonoscopy that was performed prior to the start time of the first dose of this study. If not taken in this study, the score for the baseline (Week 0/Day 1) visit will be based on the last colonoscopy performed in the study from which the subject is entering.

The SES-CD is a simple scoring system based on 4 endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of affected surface, and presence and severity of stenosis [narrowing]) measured in the same 5 ileocolonic segments as the CD index of severity. Overall, values on the SES-CD range from 0 to 56, with higher values indicating

more severe disease. The 4 endoscopic variables are scored from 0 to 3 in each bowel segment (ileum, right/transverse/left colon, and rectum):

- Presence and size of ulcers (none = score 0; diameter 0.1–0.5 cm = score 1; 0.5–2 cm = score 2; diameter >2 cm = score 3)
- Extent of ulcerated surface (none = 0; <10% =1; 10%–30% = 2; >30% = 3); extent of affected surface (none = 0; <50% = 1; 50%–75% = 2; >75% = 3)
- Presence and type of narrowings (none = 0; single, can be passed = 1; multiple, can be passed = 2; cannot be passed = 3).

The maximum stenosis score in a segment distal to another evaluable segment cannot exceed 2, so the stenosis scores cannot exceed a total of 11 (Reinisch et al., 2017).

The SES-CD data will be listed for the FAS.

12.3.2.2 CDAI

The CDAI is a composite measure with 8 components: 3 components (abdominal pain severity, very soft stool/liquid SF, and general well-being) will be self-reported by the subject, as described in Section 12.3.2.3, and 5 components (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) will be recorded at the time points specified in Table 10, Table 11, and Section 14.

The CDAI scores will be calculated using the following:

- Components 1 to 3 from subject-reported data collected for 7 days before the visit

and

- Components 4 to 8 collected at the visit.

For the data (components 1 to 3) collected prior to Protocol Amendment 4, the most recent 7 days is selected from the last 10 days prior to the scheduled visit start date. If fewer than 7 days are available, the components scores 1 to 3 will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the components scores 1 to 3 will be treated as missing.

Change in CDAI has been used as a primary endpoint in multiple pivotal trials in the CD indication. The algorithm for calculating the CDAI score was first published by William Best and colleagues (Best et al., 1976).

The CDAI data will be listed for the FAS.

12.3.2.3 CD Subject Reporting of Symptoms

Subjects will be asked to recall clinical data for CDAI score for the 7 days prior to each scheduled visit:

- Number of very soft or liquid bowel movements (as shown by Bristol Stool Form Scale type 6/7)

- Level of abdominal pain (using the parameters as described in CDAI)
- Sense of general well-being (using the parameters as described in CDAI)

The CD subject reporting of symptoms data will be listed for the FAS.

The investigator will record this information in the eCRF and use it to calculate the CDAI score for that visit.

12.4 Repeated or Unscheduled Assessments of Safety Parameters

Assessments will be assigned to visits based on the date on which the assessment took place regardless of the completed CRF page. Assessments will be mapped to visits as outlined in Table 4, Table 5, Table 6, and Table 7.

If a subject has more than 1 assessment mapped into a given study visit with nonmissing results, the assessment closest to the planned visit will be used for analysis. However, all post-LTS baseline assessments will be used for PCI value determination.

12.5 Handling of Missing, Unused, and Spurious Data

12.5.1 Missing Date of End of Treatment

When the date of EOT is missing for a subject, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last dose date + 28 days will be used in the calculation of treatment duration.

12.5.2 Missing Date of CD or UC Diagnoses

If day of diagnosis date is missing, then the day will be imputed as 1; if both the day and month of diagnosis date are missing, then the day will be imputed as 1 and the month will be imputed as 1 (January).

12.5.3 Missing Date Information for Prior or Concomitant Medications

The induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) or maintenance studies (SHP647-303 or SHP647-307) imputed dates will be used for prior medications for those collected in the induction studies or maintenance studies.

For concomitant medications collected in the SHP647-304 study, including rescue medications, incomplete (ie, partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, the start date will be imputed first.

12.5.3.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP in the SHP647-304 study will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of IP in the SHP647-304 study, then 31 December will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of IP in the SHP647-304 study, then 01 January will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing, and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IP in the SHP647-304 study, then the day of the date of the first dose of IP in the SHP647-304 study will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of IP in the SHP647-304 study or if both years are the same but the month is before the month of the date of the first dose of IP in the SHP647-304 study, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of IP in the SHP647-304 study or if both years are the same but the month is after the month of the date of the first dose of IP in the SHP647-304 study, then the first day of the month will be assigned to the missing day.

12.5.3.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of IP in the SHP647-304 study is missing, then it will be replaced with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing Day and Month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of IP in the SHP647-304 study, then the day and month of the date of the last dose of IP in the SHP647-304 study will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of IP in the SHP647-304 study, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of IP in the SHP647-304 study, then 01 January will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing, and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP in the SHP647-304 study, then the day of the date of the last dose of IP in the SHP647-304 study will be assigned to the missing day.
- If either the year is before the year of the date of the last dose of IP in the SHP647-304 study or if both years are the same but the month is before the month of the date of the last dose of IP in the SHP647-304 study, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last dose of IP in the SHP647-304 study or if both years are the same but the month is after the month of the date of the last dose of IP in the SHP647-304 study, then the first day of the month will be assigned to the missing day.

12.5.4 Missing Date Information for Adverse Events

For AEs, the default is to impute only incomplete (ie, partially missing) start dates. If start date is missing, no imputation will be performed.

12.5.4.1 Incomplete Start Date

The same rules as in Section 12.5.3.1 will be followed.

12.5.4.2 Incomplete Stop Date

Not applicable.

12.5.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of IP in the SHP647-304 study, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be presented in data listings.

12.5.6 Missing Relationship to Investigational Product for Adverse Events

If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP in the SHP647-304 study, a causality of "Related" will be assigned. The imputed values for relationship to double-blind IP will be used for incidence summaries, while the actual values will be presented in data listings.

12.5.7 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, a character string being reported for a numerical variable, the appropriately

determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

13. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The following changes to the analysis specified in Protocol Amendment 4 dated 21 Sep 2020 (final version 1.0 dated 13 Jul 2017, Amendment 1 dated 18 Dec 2017, Amendment 2 dated 17 Sep 2018, Amendment 3 dated 07 Nov 2019) have been made.

1. Secondary endpoints and safety analysis summaries will not be presented by the status at entry into this study (e.g., induction nonresponder, maintenance ontamalimab completer, maintenance discontinuation rollover, etc.).
2. Summaries will be presented by indication separately but not overall.
3. Efficacy components of partial Mayo score for UC subjects and CDAI score for CD subjects will be summarized every 12 weeks during treatment as part of the treatment response assessment mentioned in the text of Protocol Amendment 4 in addition to every 24 weeks as mentioned in Section 16, Schedule of Assessments.
4. The items mentioned in the "SHP647-304 Protocol Administrative Change / Clarification Memo" dated 01 February 2021 were incorporated into the text of this document and will be implemented as stated in the memo in the summarization of the results of this SHP647-304 study.
5. Secondary endpoint for response of ulcerative colitis participants was changed from "or a subscore for RB ≥1" to "or a subscore for RB ≤1".

15. REFERENCES

Best, W. R., Becktel, J. M., Singleton, J. W. and Kern, F. 1976. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology, 70, 439-44.

Chan I. and Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics.* 1999; 55(4) 1202-1209.

Reinisch, W., Colombel, J.-F., D'Haens, G., Sandborn, W. J., Rutgeerts, P., Geboes, K., Petersson, J., Eichner, S., Zhou, Q., Robinson, A. M., Read, H. A. and Thakkar, R. 2017. Characterisation of Mucosal Healing with Adalimumab Treatment in Patients with Moderately to Severely Active Crohn's Disease: Results from the EXTEND Trial. Journal of Crohn's and Colitis, 11, 425-434.

Yan, X., and Su, X. G. (2010). "Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions." Statistics in Biopharmaceutical Research 2:329–335.

16. APPENDICES

16.1 Schedule of Assessments – Treatment Year 1 (Subjects with UC)

Table 8 Schedule of Assessments – Treatment Year 1 (Subjects with UC)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**None**	**±10 days**											
Informed consent/assent	X												
Eligibility assessment[b]	X												
Medical history[c]	IDT or MNT												
Complete physical examination[d]	IDT or MNT						X						
Targeted physical examination[d]	IDT or MNT												X
Targeted neurological assessment[e,f]	IDT or MNT			X			X			X			X
Vital signs	IDT or MNT	X		X			X			X			X
Weight	IDT or MNT	X		X			X			X			X
12-lead ECG (local)	IDT or MNT			X			X						X
Laboratory (Central)[g]													
Hematology	IDT or MNT	X		X			X			X			X
Serum chemistry[h]	IDT or MNT	X		X			X			X			X
Urinalysis	IDT or MNT	X		X			X			X			X
Urine β-hCG[i]	IDT or MNT	X	X	X	X	X	X	X	X	X	X	X	X
FSH[j]	X												
Contraception check[k]		X	X	X	X	X	X	X	X	X	X	X	X
Stool sample for fecal calprotectin	IDT or MNT						X						X
Serum CRP[l]	IDT or MNT						X						X

Table 8 Schedule of Assessments – Treatment Year 1 (Subjects with UC)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**None**	**±10 days**											
Endoscopic Procedure													
OPTIONAL endoscopy (flexible sigmoidoscopy or colonoscopy)[m]	IDT or MNT	O	O	O	O	O	O	O	O	O	O	O	O
UC Assessments[n]													
OPTIONAL Total Mayo score[o]	IDT or MNT	O	O	O	O	O	O	O	O	O	O	O	O
Partial Mayo score	IDT or MNT						X						X
Treatment response assessment[p,q]	IDT			X			X			X			X
Treatment Procedures													
Administration of ontamalimab[r,s,t]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypersensitivity monitoring[u]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[v]						X						X	

β-hCG=beta-human chorionic gonadotropin; CLIA=Clinical Laboratory Improvement Amendments; CRP=C-reactive protein; DTP=Direct-To-Patient; ECG=electrocardiogram; ET=early termination; FDA=Food and Drug Administration; FSH=follicle-stimulating hormone; GI=gastrointestinal; IDT=induction study (SHP647-301 or SHP647-302); LFT=liver function testing; MNT=maintenance study SHP647-303; O=optional; UC=ulcerative colitis; W=Week.

[a] Baseline = Week 0 (Day 1). For subjects previously enrolled in induction study SHP647-301 or SHP647-302, the baseline visit is the Week 12 study visit (with the exception of treatment response assessment). For subjects entering from maintenance study SHP647-303, the baseline visit is the Week 52 visit (for subjects who completed the study) or the ET visit (for subjects who withdrew early), with the exception of treatment response assessment.

[b] Eligibility will be assessed after the consent form is signed and after procedures are completed at Visit 6, Part 2 in Study SHP647-301 or SHP647-302, or at Visit 14, Part 2 or the ET or Week 52 visit in Study SHP647-303.

[c] Medical history from Studies SHP647-301, SHP647-302, and SHP647-303 will be used as the baseline medical history data for Study SHP647-304.

[d] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

Table 8 Schedule of Assessments – Treatment Year 1 (Subjects with UC)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13
Visit Window	None	±10 days											

[e] 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 progressive multifocal leukoencephalopathy should be excluded. See Section 7.6.1 of Protocol Amendment 4 for further details.

[f] In case of a DTP situation, to be performed by remote visits via virtual communications (eg, TeleHealth application).

[g] Clinical laboratory assays (LFT) can also be performed by the local laboratory in case of issues related to COVID-19 (or other similar pandemic) and if deemed necessary by the investigator to confirm the subject's safety. In such a case, the investigative site must obtain the local laboratory's normal ranges as well as a CLIA certificate and the investigator must add the local laboratory as appropriate.

[h] Subjects performing home administrations consecutively for 3 months will need to perform LFT per FDA requirement. It may be done locally if it is not possible to collect samples at the central laboratory.

[i] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.

[j] For confirmation of postmenopausal status in women who have had 12 consecutive months of spontaneous amenorrhea and are ≥51 years of age. This does not need to be performed if postmenopausal status was confirmed by FSH in induction study SHP647-301 or SHP647-302 or maintenance study SHP647-303.

[k] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential; see Section 4.3 of Protocol Amendment 4.

[l] Samples must be collected before administration of investigational product.

[m] Flexible sigmoidoscopy or colonoscopy (if preferred). Endoscopy is optional for treatment response evaluation after the implementation of Amendment 4; if performed (eg, due to routine cancer surveillance required by GI guidelines or due to local clinical practice), the results should be recorded. If more than 2 endoscopies/colonoscopies are needed in a year, the subject should be discontinued.

[n] Mayo score will be based on subject self-report, with the assistance of a memory aid.

[o] The total Mayo score will be calculated based on the locally read endoscopic subscore (if endoscopy is performed). The total Mayo score will be calculated only when endoscopy data are available.

[p] Measured by clinical composite score and biomarkers, with or without endoscopy. Applicable only after the implementation of Amendment 4.

[q] Subjects will have the option to fill in a memory aid to collect data at least 7 days before each specified visit. See Section 7.3.2.3 of Protocol Amendment 4 for further details.

[r] Interactive response technology will be used for dispensation of study treatment.

[s] Investigational product is to be administered after all other visit assessments have been performed.

[t] In a situation in which a subject is not able to visit the study site due to the COVID-19 public health emergency (or other similar pandemic), DTP investigational product administration options may be available, in accordance with local regulations (refer to DTP guidance document).

[u] At each visit, the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored.

[v] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one at which testing will be done.

Note: See Section 7.3 of Protocol Amendment 4 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.2 Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC)

Table 9 Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC)

Study Procedure	Treatment – Year 2 Through Year 3													Follow-up
	W52/ W100	W56/ W104	W60/ W108	W64/ W112	W68/ W116	W72/ W120	W76/ W124	W80/ W128	W84/ W132	W88/ W136	W92/ W140	W96[a]/ W144	EOT Visit	12 Weeks Post-EOT[b]
Visit Number	14/ 26	15/ 27	16/ 28	17/ 29	18/ 30	19/ 31	20/ 32	21/ 33	22/ 34	23/ 35	24/ 36	25/ 37		
Visit Window	±10 days													
Complete physical examination[c]													X	X
Targeted physical examination[c]												X		
Targeted neurological assessment[d,e]			X			X			X			X	X	X
Vital signs						X						X	X	X
Weight						X						X	X	
12-lead ECG (local)												X	X	
Laboratory (Central)[f]														
Hematology			X			X			X			X	X	X
Serum chemistry[g]						X						X	X	X
Urinalysis						X						X	X	X
Urine β-hCG[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception check[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stool sample for fecal calprotectin						X						X		
Serum CRP[j]						X						X		
Endoscopic Procedure														
OPTIONAL endoscopy (flexible sigmoidoscopy or colonoscopy)[k]	O	O	O	O	O	O	O	O	O	O	O	O	O	O

Table 9 Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC)

Study Procedure	Treatment – Year 2 Through Year 3													Follow-up
	W52/ W100	W56/ W104	W60/ W108	W64/ W112	W68/ W116	W72/ W120	W76/ W124	W80/ W128	W84/ W132	W88/ W136	W92/ W140	W96[a]/ W144	EOT Visit	12 Weeks Post-EOT[b]
Visit Number	14/ 26	15/ 27	16/ 28	17/ 29	18/ 30	19/ 31	20/ 32	21/ 33	22/ 34	23/ 35	24/ 36	25/ 37		
Visit Window	±10 days													
UC Assessments[l]														
OPTIONAL Total Mayo score[m]	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Treatment response assessment[n,o]			X			X			X			X	X	X
Partial Mayo score						X						X	X	
Treatment Procedures														
Administration of ontamalimab[p,q]	X	X	X	X	X	X	X	X	X	X	X	X		
Hypersensitivity monitoring[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[s]					X						X			

β-hCG=beta-human chorionic gonadotropin; CLIA=Clinical Laboratory Improvement Amendments; CRP=C-reactive protein; DTP=Direct-To-Patient; ECG=electrocardiogram; EOT=end of treatment; FDA=Food and Drug Administration; GI=gastrointestinal; LFT=liver function testing; O=optional; UC=ulcerative colitis; W=Week.

[a] After Treatment Year 1, assessments will be repeated on the subsequent year rotation from Week 52.

[b] Subjects will enter a 12-week safety follow-up period, with a visit at the study site at 12 weeks following the EOT visit.

[c] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

[d] Subject will be evaluated to reveal any potential abnormalities in the following neurologic domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, cognition/behavior. See Section 7.6.1 of Protocol Amendment 4 for further details.

[e] In case of a DTP situation, to be performed by remote visits via virtual communications (eg, TeleHealth application).

Table 9 Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC)

Study Procedure	Treatment – Year 2 Through Year 3													Follow-up
	W52/ W100	W56/ W104	W60/ W108	W64/ W112	W68/ W116	W72/ W120	W76/ W124	W80/ W128	W84/ W132	W88/ W136	W92/ W140	W96[a]/ W144	EOT Visit	12 Weeks Post-EOT[b]
Visit Number	14/ 26	15/ 27	16/ 28	17/ 29	18/ 30	19/ 31	20/ 32	21/ 33	22/ 34	23/ 35	24/ 36	25/ 37		
Visit Window	±10 days													

[f] Clinical laboratory assays (LFT) can also be performed by the local laboratory in case of issues related to COVID-19 (or other similar pandemic) and if deemed necessary by the investigator to confirm the subject's safety. In such a case, the investigative site must obtain the local laboratory's normal ranges as well as a CLIA certificate and the investigator must add the local laboratory as appropriate.

[g] Subjects performing home administrations consecutively for 3 months will need to perform LFT per FDA requirement. It may be done locally if it is not possible to collect samples at the central laboratory.

[h] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.

[i] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential; see Section 4.3 of Protocol Amendment 4.

[j] Samples must be collected before administration of investigational product.

[k] Flexible sigmoidoscopy or colonoscopy (if preferred). Endoscopy is optional for treatment response evaluation after the implementation of Amendment 4; if performed (eg, due to routine cancer surveillance required by GI guidelines or due to local clinical practice), the results should be recorded. If more than 2 endoscopies/colonoscopies are needed in a year, the subject should be discontinued.

[l] Mayo score will be based on subject self-report, with the assistance of a memory aid.

[m] The total Mayo score will be calculated based on the locally read endoscopic subscore (if endoscopy is performed). The total Mayo score will be calculated only when endoscopy data are available.

[n] Measured by clinical composite score and biomarkers, with or without endoscopy. Applicable only after the implementation of Amendment 4.

[o] Subjects will have the option to fill in a memory aid to collect data at least 7 days before each specified visit. See Section 7.3.2.3 of Protocol Amendment 4 for further details.

[p] Investigational product is to be administered after all other visit assessments have been performed.

[q] In a situation in which a subject is not able to visit the study site due to the COVID-19 public health emergency (or other similar pandemic), DTP investigational product administration options may be available, in accordance with local regulations (refer to DTP guidance document).

[r] At each visit, the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored.

[s] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one at which testing will be done.

Note: For subjects whose study participation extends beyond Year 3 (ie, subjects already enrolled in this study prior to the implementation of Amendment 4), assessments will be repeated on the subsequent year rotation beginning with Week 100.

See Section 7.3 of Protocol Amendment 4 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.3 Schedule of Assessments – Treatment Year 1 (Subjects with CD)

Table 10 Schedule of Assessments – Treatment Year 1 (Subjects with CD)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**None**	**±10 days**											
Informed consent/assent	X												
Eligibility assessment[b]	X												
Medical history[c]	IDT or MNT												
Complete physical examination[d]	IDT or MNT						X						
Targeted physical examination[d]	IDT or MNT			X						X			X
Targeted neurological assessment[e,f]	IDT or MNT			X			X			X			X
Vital signs	IDT or MNT	X		X			X			X			X
Weight	IDT or MNT	X		X			X			X			X
12-lead ECG (local)	IDT or MNT			X			X						X
Laboratory (Central)[g]													
Hematology	IDT or MNT	X		X			X			X			X
Serum chemistry[h]	IDT or MNT	X		X			X			X			X
Urinalysis	IDT or MNT	X		X			X			X			X
Urine β-hCG[i]	IDT or MNT	X	X	X	X	X	X	X	X	X	X	X	X
FSH[j]	X												
Contraception check[k]		X	X	X	X	X	X	X	X	X	X	X	X
Stool sample for fecal calprotectin	IDT or MNT						X						X
Serum CRP[l]	IDT or MNT						X						X

Table 10 Schedule of Assessments – Treatment Year 1 (Subjects with CD)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**None**	**±10 days**											
Endoscopic Procedure													
OPTIONAL colonoscopy[m]	IDT or MNT	O	O	O	O	O	O	O	O	O	O	O	O
CD Assessments[n]													
OPTIONAL SES-CD[o]	IDT or MNT	O	O	O	O	O	O	O	O	O	O	O	O
CDAI	IDT or MNT						X						X
Treatment response assessment[p,q]	IDT			X			X			X			X
Treatment Procedures													
Administration of ontamalimab[r,s,t]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypersensitivity monitoring[u]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[v]						X						X	

β-hCG=beta-human chorionic gonadotropin; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CLIA=Clinical Laboratory Improvement Amendments; CRP=C-reactive protein; DTP=Direct-To-Patient; ECG=electrocardiogram; ET=early termination; FSH=follicle-stimulating hormone; GI=gastrointestinal; IDT=induction study (SHP647-305 or SHP647-306); LFT=liver function testing; MNT=maintenance study SHP647-307; O=optional; SES-CD=Simple Endoscopic Score for Crohn's Disease; W=Week.

[a] Baseline = Week 0 (Day 1). For subjects previously enrolled in induction study SHP647-305 or SHP647-306, the baseline visit is the Week 16 study visit (with the exception of treatment response assessment). For subjects entering from maintenance study SHP647-307, the baseline visit is the Week 52 visit (for subjects who completed the study) or the ET visit (for subjects who withdrew early), with the exception of treatment response assessment.
If results for confirmation of treatment failure are pending at the time of the end of study visit in Study SHP647-307, sites will have 1 additional week to confirm final status of the subject (treatment failure or not) before enrolling the subject in Study SHP647-304.

[b] Eligibility will be assessed after the consent form is signed and after procedures are completed at Visit 7, Part 2 in Study SHP647-305 or SHP647-306, or at Visit 14, Part 2 or the ET or Week 52 visit in Study SHP647-307.

[c] Medical history from Studies SHP647-305, SHP647-306, and SHP647-307 will be used as the baseline medical history data for Study SHP647-304.

[d] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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 and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

Table 10 Schedule of Assessments – Treatment Year 1 (Subjects with CD)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13
Visit Window	None	±10 days											

[e] 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 progressive multifocal leukoencephalopathy should be excluded. See Section 7.6.1 of Protocol Amendment 4 for further details.

[f] In case of a DTP situation, to be performed by remote visits via virtual communications (eg, TeleHealth application).

[g] Clinical laboratory assays (LFT) can also be performed by the local laboratory in case of issues related to COVID-19 (or other similar pandemic) and if deemed necessary by the investigator to confirm the subject's safety. In such a case, the investigative site must obtain the local laboratory's normal ranges as well as a CLIA certificate and the investigator must add the local laboratory as appropriate.

[h] Subjects performing home administrations consecutively for 3 months will need to perform LFT per FDA requirement. It may be done locally if it is not possible to collect samples at the central laboratory.

[i] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.

[j] For confirmation of postmenopausal status in women who have had 12 consecutive months of spontaneous amenorrhea and are ≥51 years of age. This does not need to be performed if postmenopausal status was confirmed by FSH in induction study SHP647-305 or SHP647-306 or maintenance study SHP647-307.

[k] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential; see Section 4.3 of Protocol Amendment 4.

[l] Samples must be collected before administration of investigational product.

[m] Colonoscopy is optional for treatment response evaluation after the implementation of Amendment 4; if performed (eg, due to routine cancer surveillance required by GI guidelines or due to local clinical practice), the results should be recorded. If more than 2 colonoscopies are needed in a year, the subject should be discontinued.

[n] CDAI score will be calculated based on data reported by the subject, with the assistance of a memory aid, as well as data obtained at the site visit.

[o] Endoscopies are not required, but if performed, it is recommended that the SES-CD be recorded by the endoscopist for assessment. SES-CD total score will be calculated based on the locally read endoscopic subscores for each of the segments investigated.

[p] Measured by CDAI score and biomarkers, with or without endoscopy. Applicable only after the implementation of Amendment 4.

[q] Subjects will have the option to fill in a memory aid to collect data at least 7 days before each specified visit. See Section 7.3.3.4 of Protocol Amendment 4 for further details.

[r] Interactive response technology will be used for dispensation of study treatment.

[s] Investigational product is to be administered after all other visit assessments have been performed.

[t] In a situation in which a subject is not able to visit the study site due to the COVID-19 public health emergency (or other similar pandemic), DTP investigational product administration options may be available, in accordance with local regulations (refer to DTP guidance document).

[u] At each visit, the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored.

[v] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one at which testing will be done.

Note: See Section 7.3 of Protocol Amendment 4 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.4 Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD)

Table 11 Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD)

Study Procedure	Treatment – Year 2 Through Year 3													Follow-up
	W52/ W100	W56/ W104	W60/ W108	W64/ W112	W68/ W116	W72/ W120	W76/ W124	W80/ W128	W84/ W132	W88/ W136	W92/ W140	W96[a]/ W144	EOT Visit	12 Weeks Post-EOT[b]
Visit Number	**14/ 26**	**15/ 27**	**16/ 28**	**17/ 29**	**18/ 30**	**19/ 31**	**20/ 32**	**21/ 33**	**22/ 34**	**23/ 35**	**24/ 36**	**25/ 37**		
Visit Window	**±10 days**													
Complete physical examination[c]													X	X
Targeted physical examination[c]			X			X			X			X		
Targeted neurological assessment[d,e]			X			X			X			X	X	X
Vital signs						X						X	X	X
Weight						X						X	X	
12-lead ECG (local)												X	X	
Laboratory (Central)[f]														
Hematology			X			X			X			X	X	X
Serum chemistry[g]						X						X	X	X
Urinalysis						X						X	X	X
Urine β-hCG[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception check[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stool sample for fecal calprotectin						X						X		
Serum CRP[j]						X						X		
Endoscopic Procedure														
OPTIONAL colonoscopy[k]	O	O	O	O	O	O	O	O	O	O	O	O	O	O

Table 11 Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD)

Study Procedure	Treatment – Year 2 Through Year 3													Follow-up
	W52/ W100	W56/ W104	W60/ W108	W64/ W112	W68/ W116	W72/ W120	W76/ W124	W80/ W128	W84/ W132	W88/ W136	W92/ W140	W96[a]/ W144	EOT Visit	12 Weeks Post-EOT[b]
Visit Number	14/ 26	15/ 27	16/ 28	17/ 29	18/ 30	19/ 31	20/ 32	21/ 33	22/ 34	23/ 35	24/ 36	25/ 37		
Visit Window	±10 days													
CD Assessments[l]														
OPTIONAL SES-CD[m]	O	O	O	O	O	O	O	O	O	O	O	O	O	O
CDAI						X						X	X	
Treatment response assessment[n,o]			X			X			X			X	X	
Treatment Procedures														
Administration of ontamalimab[p,q]	X	X	X	X	X	X	X	X	X	X	X	X		
Hypersensitivity monitoring[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[s]					X						X			

β-hCG=beta-human chorionic gonadotropin; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CLIA=Clinical Laboratory Improvement Amendments; CRP=C-reactive protein; DTP=Direct-To-Patient; ECG=electrocardiogram; EOT=end of treatment; FDA=Food and Drug Administration; GI=gastrointestinal; LFT=liver function testing; O=optional; SES-CD=Simple Endoscopic Score for Crohn's Disease; W=Week.

[a] After Treatment Year 1, assessments will be repeated on the subsequent year rotation from Week 52.

[b] Subjects will enter a 12-week safety follow-up period, with a visit at the study site at 12 weeks following the EOT visit.

[c] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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 and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

[d] Subject will be evaluated to reveal any potential abnormalities in the following neurologic domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, cognition/behavior. See Section 7.6.1 of Protocol Amendment 4 for further details.

[e] In case of a DTP situation, to be performed by remote visits via virtual communications (eg, TeleHealth application).

[f] Clinical laboratory assays (LFT) can also be performed by the local laboratory in case of issues related to COVID-19 (or other similar pandemic) and if deemed necessary by the investigator to confirm the subject's safety. In such a case, the investigative site must obtain the local laboratory's normal ranges as well as a CLIA certificate and the investigator must add the local laboratory as appropriate.

Table 11 Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD)

Study Procedure	Treatment – Year 2 Through Year 3													Follow-up
	W52/ W100	W56/ W104	W60/ W108	W64/ W112	W68/ W116	W72/ W120	W76/ W124	W80/ W128	W84/ W132	W88/ W136	W92/ W140	W96[a]/ W144	EOT Visit	12 Weeks Post-EOT[b]
Visit Number	14/ 26	15/ 27	16/ 28	17/ 29	18/ 30	19/ 31	20/ 32	21/ 33	22/ 34	23/ 35	24/ 36	25/ 37		
Visit Window	±10 days													

[g] Subjects performing home administrations consecutively for 3 months will need to perform LFT per FDA requirement. It may be done locally if it is not possible to collect samples at the central laboratory.
[h] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.
[i] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential; see Section 4.3 of Protocol Amendment 4.
[j] Samples must be collected before administration of investigational product.
[k] Colonoscopy is optional for treatment response evaluation after the implementation of Amendment 4; if performed (eg, due to routine cancer surveillance required by GI guidelines or due to local clinical practice), the results should be recorded. If more than 2 colonoscopies are needed in a year, the subject should be discontinued.
[l] CDAI score will be calculated based on data reported by the subject, with the assistance of a memory aid, as well as data obtained at the site visit.
[m] Endoscopies are not required, but if performed, it is recommended that the SES-CD be recorded by the endoscopist for assessment. SES-CD total score will be calculated based on the locally read endoscopic subscores for each of the segments investigated.
[n] Measured by CDAI and biomarkers, with or without endoscopy. Applicable only after the implementation of Amendment 4.
[o] Subjects will have the option to fill in a memory aid to collect data at least 7 days before each specified visit. See Section 7.3.3.4 of Protocol Amendment 4 for further details.
[p] Investigational product is to be administered after all other visit assessments have been performed.
[q] In a situation in which a subject is not able to visit the study site due to the COVID-19 public health emergency (or other similar pandemic), DTP investigational product administration options may be available, in accordance with local regulations (refer to DTP guidance document).
[r] At each visit, the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored.
[s] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one at which testing will be done.

Note: For subjects whose study participation extends beyond Year 3 (ie, subjects already enrolled in this study prior to the implementation of Amendment 4), assessments will be repeated on the subsequent year rotation beginning with Week 100.
See Section 7.3 of Protocol Amendment 4 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.5 Schedule of Assessments Under Amendment 3 – Treatment Year 1 (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Table 12 Schedule of Assessments – Treatment Year 1 (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**None**	**±10 days**											
Informed consent/assent	X												
Eligibility assessment[b]	X												
Medical history[c]	IDT or MNT												
Complete physical examination[d]	IDT or MNT						X						
Targeted physical examination[d]	IDT or MNT												X
Targeted neurological assessment[e,f]	IDT or MNT			X			X			X			X
Vital signs	IDT or MNT	X		X			X			X			X
Weight	IDT or MNT	X		X			X			X			X
12-lead ECG (local)	IDT or MNT			X			X						X
Laboratory (Central)[g]													
Hematology	IDT or MNT	X		X			X			X			X
Serum chemistry[h]	IDT or MNT	X		X			X			X			X
Urinalysis	IDT or MNT	X		X			X			X			X
Urine β-Hcg[i]	IDT or MNT	X	X	X	X	X	X	X	X	X	X	X	X
FSH[j]	X												
Contraception check[k]		X	X	X	X	X	X	X	X	X	X	X	X
Stool sample for fecal calprotectin	IDT or MNT						X						X
Serum CRP[l]	IDT or MNT						X						X
Serum soluble MAdCAM[i]	IDT or MNT						X						X

Table 12 Schedule of Assessments – Treatment Year 1 (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**None**	**±10 days**											
Blood β_7^+ T cells[i]	IDT or MNT						X						X
Pharmacokinetic sampling[i]	IDT or MNT	X		X			X						X
ADA and NAb sampling[i]	IDT or MNT	X		X			X						X
Endoscopic Procedure													
Endoscopy (flexible sigmoidoscopy or colonoscopy)[j]	IDT or MNT												X
UC Assessments[k]													
Total Mayo score	IDT or MNT												X[l]
Partial Mayo score	IDT or MNT			X			X			X			
PRO-UC daily e-diary data instruction	X												
PRO-UC daily e-diary data[m]	IDT or MNT			X			X			X			X
Health Assessments[n]													
IBDQ	IDT or MNT						X						X
EQ-5D-5L	IDT or MNT						X						X
Hospitalizations, inpatient days, ED visits (HRUA)	IDT or MNT	X	X	X	X	X	X	X	X	X	X	X	X
WPAI-UC	IDT or MNT						X						X
SF-36-v.2, acute	IDT or MNT						X						X
TSQM	IDT or MNT						X						X
Treatment Procedures													
Randomization[o]	X												
Administration of ontamalimab[o,p]	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 12 Schedule of Assessments – Treatment Year 1 (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**None**	**±10 days**											
Hypersensitivity monitoring [q]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[v]						X						X	

β-Hcg=beta-human chorionic gonadotropin; CLIA=Clinical Laboratory Improvement Amendments; CRP=C-reactive protein; DTP=Direct-To-Patient; ECG=electrocardiogram; ET=early termination; FDA=Food and Drug Administration; FSH=follicle-stimulating hormone; GI=gastrointestinal; IDT=induction study (SHP647-301 or SHP647-302); LFT=liver function testing; MNT=maintenance study SHP647-303; O=optional; UC=ulcerative colitis; W=Week.

[a] Baseline = Week 0 (Day 1). For subjects previously enrolled in induction study SHP647-301 or SHP647-302, the baseline visit is the Week 12 study visit (with the exception of treatment response assessment). For subjects entering from maintenance study SHP647-303, the baseline visit is the Week 52 visit (for subjects who completed the study) or the ET visit (for subjects who withdrew early), with the exception of treatment response assessment.

[b] Eligibility will be assessed after the consent form is signed and after procedures are completed at Visit 6, Part 2 in Study SHP647-301 or SHP647-302, or at Visit 14, Part 2 or the ET or Week 52 visit in Study SHP647-303.

[c] Medical history from Studies SHP647-301, SHP647-302, and SHP647-303 will be used as the baseline medical history data for Study SHP647-304.

[d] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

[e] 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 progressive multifocal leukoencephalopathy should be excluded.

[f] In case of a DTP situation, to be performed by remote visits via virtual communications (eg, TeleHealth application).

[g] Clinical laboratory assays (LFT) can also be performed by the local laboratory in case of issues related to COVID-19 (or other similar pandemic) and if deemed necessary by the investigator to confirm the subject's safety. In such a case, the investigative site must obtain the local laboratory's normal ranges as well as a CLIA certificate and the investigator must add the local laboratory as appropriate.

[h] Subjects performing home administrations consecutively for 3 months will need to perform LFT per FDA requirement. It may be done locally if it is not possible to collect samples at the central laboratory.

[i] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.

[j] For confirmation of postmenopausal status in women who have had 12 consecutive months of spontaneous amenorrhea and are ≥51 years of age. This does not need to be performed if postmenopausal status was confirmed by FSH in induction study SHP647-301 or SHP647-302 or maintenance study SHP647-303.

[k] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential; see Section 4.3 of Protocol Amendment 4.

[l] Samples must be collected before administration of investigational product.

Table 12 Schedule of Assessments – Treatment Year 1 (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W0/ Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13
Visit Window	None	±10 days											

[m] Flexible sigmoidoscopy or colonoscopy (if preferred). Endoscopy is optional for treatment response evaluation after the implementation of Amendment 4; if performed (eg, due to routine cancer surveillance required by GI guidelines or due to local clinical practice), the results should be recorded. If more than 2 endoscopies/colonoscopies are needed in a year, the subject should be discontinued.

[n] Mayo score will be based on subject self-report, with the assistance of a memory aid.

[o] The total Mayo score will be calculated based on the locally read endoscopic subscore (if endoscopy is performed). The total Mayo score will be calculated only when endoscopy data are available.

[p] Measured by clinical composite score and biomarkers, with or without endoscopy. Applicable only after the implementation of Amendment 4.

[q] Subjects will have the option to fill in a memory aid to collect data at least 7 days before each specified visit.

[r] Interactive response technology will be used for dispensation of study treatment.

[s] Investigational product is to be administered after all other visit assessments have been performed.

[t] In a situation in which a subject is not able to visit the study site due to the COVID-19 public health emergency (or other similar pandemic), DTP investigational product administration options may be available, in accordance with local regulations (refer to DTP guidance document).

[u] At each visit, the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary, until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored.

[v] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one at which testing will be done.

Note: See Section 7.3 of Protocol Amendment 3 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.6 Schedule of Assessments Under Amendment 3 – Treatment Year 2 Through End of Study (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Table 13 Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[p]	EOT	8 W post-EOT[q]	16 W post-EOT[q]
Visit Number	14	15	16	17	18	19	20	21	22	23	24	25			
Visit Window	±7 days														
Complete physical examination[a]													X		X
Targeted physical examination[a]												X			
Targeted neurological assessment[b]			X			X			X			X	X		X
Vital signs						X						X	X		X
Weight						X						X	X		
12-Lead ECG												X	X		
Laboratory															
Hematology			X			X			X			X	X		X
Serum chemistry						X						X	X		X
Urinalysis						X						X	X		X
Urine β–hCG[c]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Contraception check[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Stool sample for fecal calprotectin						X						X	X		
Serum CRP[e]						X						X	X		
Serum soluble MAdCAM[e]						X						X	X		

Table 13 Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[p]	EOT	8 W post-EOT[q]	16 W post-EOT[q]
Visit Number	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**			
Visit Window	**±7 days**														
Blood β_7^+ T cells[e]						X						X	X		
Pharmacokinetic sampling[e]						X[f]						X[f]			
ADA and NAb sampling[e]						X[f]						X[f]	X		
Endoscopic Procedure															
Endoscopy (flexible sigmoidoscopy or colonoscopy)[g]												X	X[h]		
UC Assessments[i]															
Total Mayo score												X[j]	X[j]		
Partial Mayo score			X			X			X						
PRO-UC daily e-diary data[k]			X			X			X			X	X		
Health Assessments[l]															
IBDQ						X						X	X		
EQ-5D-5L						X						X	X		
Hospitalizations, inpatient days, ED visits (HRUA)	X	X	X	X	X	X	X	X	X	X	X	X	X		X
WPAI-UC						X						X	X		
SF-36-v.2, acute						X						X	X		
TSQM						X						X	X		

Table 13 Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[p]	EOT	8 W post-EOT[q]	16 W post-EOT[q]
Visit Number	14	15	16	17	18	19	20	21	22	23	24	25			
Visit Window	±7 days														
Treatment Procedures															
Administration of ontamalimab[m]	X	X	X	X	X	X	X	X	X	X	X	X			
Hypersensitivity monitoring [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[o]					X						X				

ADA=antidrug antibody; β-hCG=beta-human chorionic gonadotropin; CRP=C-reactive protein; ECG=electrocardiogram; ED=emergency department; e-diary=electronic diary; EOT=end of treatment; EQ-5D-5L=European Quality of Life 5 Dimensions, 5 Levels questionnaire; HRUA=Healthcare Resource Utilization Assessment; IBDQ=Inflammatory Bowel Disease Questionnaire; MAdCAM=mucosal addressin cell adhesion molecule; NAb=neutralizing antibody; PRO=patient-reported outcome; SF-36=Short Form-36 Health Survey; TSQM=Treatment Satisfaction Questionnaire for Medication; UC=ulcerative colitis; W=week; WPAI-UC=Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

[a] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

[b] Subject will be evaluated to reveal any potential abnormalities in the following neurologic domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, cognition/behavior.

[c] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.

[d] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential.

[e] Samples must be collected before administration of investigational product.

[f] Samples are to be collected in Year 2 only (ie, at Weeks 72 and 96) and not in subsequent years.

[g] Flexible sigmoidoscopy or colonoscopy (if preferred). At Week 96 and annually, subjects at risk for colorectal cancer must undergo a colonoscopy (for cancer surveillance, including removal of adenomatous polyps with histopathology assessment).

[h] Endoscopy is to be done at the EOT visit unless performed for any reason within 12 weeks before the EOT visit.

[i] Mayo and PRO-UC assessments will be based on subject daily e-diary entries.

Table 13 Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[p]	EOT	8 W post-EOT[q]	16 W post-EOT[q]
Visit Number	14	15	16	17	18	19	20	21	22	23	24	25			
Visit Window	±7 days														

[j] The total Mayo score will be calculated based on the locally read endoscopic subscore.
[k] PRO-UC daily e-diary will be available daily throughout the study. Subjects will be required to enter e-diary data at least 10 days before each specified visit. Compliance is assessed by site staff at each specified visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <8 out of 10 diary entries) when compared with the previous visit.
[l] All health outcome/patient-reported questionnaires should be completed before completing any other visit assessments.
[m] Investigational product is to be administered after all other visit assessments have been performed.
[n] At each visit the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored until the adjudication committee determines whether testing is appropriate.
[o] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one where testing will be done.
[p] After Treatment Year 1, assessments will be repeated on the subsequent year rotation from Week 52.
[q] Subjects will enter a 16-week safety follow-up period, with visits at 8 weeks and 16 weeks following the EOT visit. The 8-week visit post-EOT will routinely be conducted by telephone; however, as an exception the visit can be performed as a study site visit if preferred. The 16-week visit post-EOT will take place at the study site.

Note: See Section 7.3 of Protocol Amendment 3 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.7 Schedule of Assessments Under Amendment 3 – Treatment Year 1 (UC Subjects, Direct Entry)

Table 14 Schedule of Assessments – Treatment Year 1 (UC Subjects, Direct Entry)

Study Procedure	Screening[a]	Baseline	Treatment – Year 1											
	W -6 to -1	W 0/ Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**-42 to 0**		**±7 days**											
Informed consent/assent	X													
Eligibility assessment	X	X												
Demographics and medical history[b]	X													
Complete physical examination[c]	X							X						
Targeted physical examination[c]		X												X
Targeted neurological assessment[d]	X				X			X			X			X
Vital signs[e]	X	X	X		X			X			X			X
Height	X													
Weight	X	X	X		X			X			X			X
12-Lead ECG[e]	X	X			X			X						X
Chest x-ray[f]	X													
Laboratory														
Hematology	X[g]	X	X		X			X			X			X
Serum chemistry	X[g]	X	X		X			X			X			X
Urinalysis	X[g]	X	X		X			X			X			X
Stool microbiology[h]	X[g]													
HBsAg, HBcAb, HCVAb[i]	X[g]													
HIV testing per local regulation[j]	X													
FSH[k]	X[g]													
Serum β–hCG[l]	X[g]													
Urine β–hCG[l]		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 14 Schedule of Assessments – Treatment Year 1 (UC Subjects, Direct Entry)

Study Procedure	**Screening[a]**	**Baseline**	**Treatment – Year 1**											
	W -6 to -1	**W 0/ Day 1**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**-42 to 0**		**±7 days**											
Contraception check[m]	X		X	X	X	X	X	X	X	X	X	X	X	X
TB test (PPD or QuantiFERON-TB Gold Plus)[n]	X[h]													
JCV antibody banked sample[o]		X												
Stool sample for fecal calprotectin		X						X						X
Serum CRP[p]		X						X						X
Serum soluble MAdCAM[p]		X						X						X
Blood β_7^+ T cells[p]		X						X						X
Pharmacokinetic sampling[p]		X	X		X			X						X
ADA and NAb sampling[p]		X	X		X			X						X
Anti-vedolizumab antibody sampling [p]*(only for subjects previously treated with vedolizumab)*		X												
Endoscopic Procedure														
Endoscopy (flexible sigmoidoscopy or colonoscopy)[q] — Centrally read	X[q]													
Endoscopy (flexible sigmoidoscopy or colonoscopy)[q] — Locally read	X[q]				X									X
UC Assessments														
Total Mayo score		X[r]												X[r]
Partial Mayo score			X	X	X			X			X			
Remission stool frequency and pre-UC stool frequency	X													
PRO-UC daily e-diary data instruction	X	X												

Table 14 Schedule of Assessments – Treatment Year 1 (UC Subjects, Direct Entry)

Study Procedure	Screening[a]	Baseline	Treatment – Year 1											
	W -6 to -1	W 0/ Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**-42 to 0**		**±7 days**											
PRO-UC daily e-diary data[s]	X	X	X	X	X			X			X			X
Health Assessments[t]														
IBDQ		X						X						X
EQ-5D-5L		X						X						X
Hospitalizations, inpatient days, ED visits (HRUA)		X	X	X	X	X	X	X	X	X	X	X	X	X
WPAI-UC		X						X						X
SF-36-v.2, acute		X						X						X
TSQM		X						X						X
Treatment Procedures														
Randomization[u]		X												
Administration of ontamalimab [u,v]		X	X	X	X	X	X	X	X	X	X	X	X	X
Hypersensitivity monitoring [w]		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[x]	X						X						X	

Table 14 Schedule of Assessments – Treatment Year 1 (UC Subjects, Direct Entry)

Study Procedure	Screening[a]	Baseline	Treatment – Year 1											
	W -6 to -1	W 0/ Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Visit Number	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Visit Window	-42 to 0		±7 days											

ADA=antidrug antibody; β-hCG=beta-human chorionic gonadotropin; CRP=C-reactive protein; ECG=electrocardiogram; ED=emergency department; e-diary=electronic diary; EQ-5D-5L=European Quality of Life 5 Dimensions, 5 Levels questionnaire; 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; HRUA=Healthcare Resource Utilization Assessment; IBDQ=Inflammatory Bowel Disease Questionnaire; JCV=John Cunningham virus; MAdCAM=mucosal addressin cell adhesion molecule; NAb=neutralizing antibody; PGA=physician global assessment; PPD=purified protein derivative; PRO=patient-reported outcome; SF-36=Short Form-36 Health Survey; TB=tuberculosis; TSQM=Treatment Satisfaction Questionnaire for Medication; UC=ulcerative colitis; W=week; WPAI-UC=Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

[a] At least 2 visits will be necessary to complete the screening procedures, including endoscopy.
[b] Medical history will include UC history, cardiac history, and smoking history.
[c] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.
[d] 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 progressive multifocal leukoencephalopathy should be excluded.
[e] 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.
[f] A chest x-ray performed up to 12 weeks before screening may be used if available; the official reading must be located in the subject's source documentation.
[g] 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.
[h] Diagnosis of *Clostridium difficile* infection should be made using the central laboratory. If for any reason the central laboratory is not available, see Appendix 4 of Protocol Amendment 3 for guidance regarding alternate diagnostic algorithms. When a subject experiences an increase in gastrointestinal symptoms, which could be an exacerbation of disease, an infectious etiology must be evaluated including testing for *C. difficile* as described in Appendix 4 of Protocol Amendment 3.
[i] Subjects who test negative for HBsAg but positive for HBcAb without HBV DNA may be considered eligible. For subjects who test positive for HBcAb and negative for HBsAg, a blood sample should be taken for HBV DNA. Blood for HBV DNA reflex testing is collected for required subjects only. If HBV DNA is positive, these subjects will not be eligible.
[j] Documentation of a negative HIV test result within 6 months prior to screening will be accepted.
[k] For confirmation of postmenopausal status in women who have had 12 consecutive months of spontaneous amenorrhea and are ≥51 years of age.
[l] For females of childbearing potential who are not surgically sterile, do not have confirmed ovarian failure, or do not meet the definition of postmenopausal as described in Section 4.4.1 and Section 7.2.5.8 of Protocol Amendment 3. The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.
[m] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential; see Section 4.4 of Protocol Amendment 3.
[n] A documented negative PPD test within 12 weeks before screening visit is acceptable. Interferon gamma release assay official reading and method or test must be located in the source documentation (see Section 7.2.5.7 of Protocol Amendment 3).
[o] A serum sample will be collected and banked. It may be analyzed if a subject shows neurologic symptoms suggestive of progressive multifocal leukoencephalopathy.

Table 14 Schedule of Assessments – Treatment Year 1 (UC Subjects, Direct Entry)

Study Procedure	Screening[a]	Baseline	Treatment – Year 1											
	W -6 to -1	W 0/ Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Visit Number	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Visit Window	-42 to 0		±7 days											

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

[q] Flexible sigmoidoscopy or colonoscopy (if preferred) at screening must be performed on all subjects after the majority of other eligibility criteria (eg, laboratory values) are met. Endoscopy must be performed during the screening period within 10 days before baseline (Visit 1), preferably within 5 to 7 days before the baseline visit, to obtain the centrally read endoscopic subscore. The screening endoscopy will be both centrally and locally read. All subsequent endoscopy results will be read only by local reader. Subjects at risk of colorectal cancer, as defined in exclusion criterion 5, must have a colonoscopy performed at screening, unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidence of dysplasia and colon cancer must be available in the source documents. At Week 48, subjects at risk for colorectal cancer must undergo a colonoscopy (for cancer surveillance, including removal of adenomatous polyps with histopathology assessment).

[r] Mayo score will be based on subject daily e-diary entries. The Mayo score at baseline will be calculated based on the stool frequency subscore and rectal bleeding subscore, reported by subjects in the PRO-UC daily e-diary and PGA obtained at baseline and using the centrally and locally read endoscopic subscores for the endoscopy performed during the screening period. The centrally read endoscopic subscore will be used for eligibility determination and locally read endoscopic subscore will be used for baseline efficacy assessment. At all other visits requiring endoscopy, the Mayo score will be calculated based on the stool frequency subscore and rectal bleeding subscore reported by subjects in the PRO-UC daily e diary and PGA and the locally read endoscopic subscore.

[s] PRO-UC daily e-diary will be available daily throughout the study. Subjects will be required to enter e-diary data daily through Week 12; thereafter, subjects will be required to enter e-diary data for at least 10 days before each specified visit. 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, <8 out of 10 diary entries) when compared with the previous visit. Compliance will be calculated based upon required e-diary data entry as indicated above.

[t] All health outcome/patient-reported questionnaires should be completed before completing any other visit assessments.

[u] Interactive response technology will be used for randomization and dispensation of study treatment.

[v] Investigational product is to be administered after all other visit assessments have been performed.

[w] Beginning at Visit 1, at each visit the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary, until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored until the adjudication committee determines whether testing is appropriate.

[x] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one where testing will be done.

Note: See Section 7.2 of Protocol Amendment 3 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.8 Schedule of Assessments Under Amendment 3 – Treatment Year 2 Through End of Study (UC Subjects, Direct Entry)

Table 15 Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Direct Entry)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[p]	EOT	8 W post-EOT[q]	16 W post-EOT[q]
Visit Number	15	16	17	18	19	20	21	22	23	24	25	26			
Visit Window	±7 days														
Complete physical examination[a]													X		X
Targeted physical examination[a]												X			
Targeted neurological assessment[b]			X			X			X			X	X		X
Vital signs						X						X	X		X
Weight						X						X	X		
12-Lead ECG												X	X		
Laboratory															
Hematology			X			X			X			X	X		X
Serum chemistry						X						X	X		X
Urinalysis						X						X	X		X
Urine β–hCG[c]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Contraception check[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Stool sample for fecal calprotectin						X						X	X		
Serum CRP[e]						X						X	X		
Serum soluble MAdCAM[e]						X						X	X		
Blood β_7^+ T cells[e]						X						X	X		

Table 15 Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Direct Entry)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[p]	EOT	8 W post-EOT[q]	16 W post-EOT[q]
Visit Number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**			
Visit Window	**±7 days**														
Pharmacokinetic sampling[e]						X[f]						X[f]			
ADA and NAb sampling[e]						X[f]						X[f]	X		
Endoscopic Procedure															
Locally read endoscopy (flexible sigmoidoscopy or colonoscopy)[g]												X	X[h]		
UC Assessments[i]															
Total Mayo score												X[j]	X[j]		
Partial Mayo score			X			X			X						
PRO-UC daily e-diary data[k]			X			X			X			X	X		
Health Assessments[l]															
IBDQ						X						X	X		
EQ-5D-5L						X						X	X		
Hospitalizations, inpatient days, ED visits (HRUA)	X	X	X	X	X	X	X	X	X	X	X	X	X		X
WPAI-UC						X						X	X		
SF-36-v.2, acute						X						X	X		
TSQM						X						X	X		

Table 15 Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Direct Entry)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[p]	EOT	8 W post-EOT[q]	16 W post-EOT[q]
Visit Number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**			
Visit Window	**±7 days**														
Treatment Procedures															
Administration of SHP647[m]	X	X	X	X	X	X	X	X	X	X	X	X			
Hypersensitivity monitoring[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[o]					X						X				

ADA=antidrug antibody; β-hCG=beta-human chorionic gonadotropin; CRP=C-reactive protein; ECG=electrocardiogram; ED=emergency department; e-diary=electronic diary; EOT=end of treatment; EQ-5D-5L=European Quality of Life 5 Dimensions, 5 Levels questionnaire; HRUA=Healthcare Resource Utilization Assessment; IBDQ=Inflammatory Bowel Disease Questionnaire; MAdCAM=mucosal addressin cell adhesion molecule; NAb=neutralizing antibody; PRO=patient-reported outcome; SF-36=Short Form-36 Health Survey; TSQM=Treatment Satisfaction Questionnaire for Medication; UC=ulcerative colitis; W=week; WPAI-UC=Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

[a] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

[b] Subject will be evaluated to reveal any potential abnormalities in the following neurologic domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, cognition/behavior.

[c] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.

[d] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential.

[e] Samples must be collected before administration of investigational product.

[f] Samples are to be collected in Year 2 only (ie, at Weeks 72 and 96) and not in subsequent years.

[g] Flexible sigmoidoscopy or colonoscopy (if preferred). At Week 96 and annually, subjects at risk for colorectal cancer must undergo a colonoscopy (for cancer surveillance, including removal of adenomatous polyps with histopathology assessment).

[h] Endoscopy is to be done at the EOT visit unless performed for any reason within 12 weeks before the EOT visit.

[i] Mayo and PRO-UC assessments will be based on subject daily e-diary entries.

[j] The total Mayo score will be calculated based on the locally read endoscopic subscore.

Table 15 Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Direct Entry)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[p]	EOT	8 W post-EOT[q]	16 W post-EOT[q]
Visit Number	15	16	17	18	19	20	21	22	23	24	25	26			
Visit Window	±7 days														

[k] PRO-UC daily e-diary will be available daily throughout the study. Subjects will be required to enter e-diary data at least 10 days before each specified visit. Compliance is assessed by site staff at each specified visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <8 out of 10 diary entries) when compared with the previous visit.

[l] All health outcome/patient-reported questionnaires should be completed before completing any other visit assessments.

[m] Investigational product is to be administered after all other visit assessments have been performed.

[n] At each visit the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored until the adjudication committee determines whether testing is appropriate.

[o] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one where testing will be done.

[p] After Treatment Year 1, assessments will be repeated on the subsequent year rotation from Week 52.

[q] Subjects will enter a 16-week safety follow-up period, with visits at 8 weeks and 16 weeks following the EOT visit. The 8-week visit post-EOT will routinely be conducted by telephone; however, as an exception the visit can be performed as a study site visit if preferred. The 16-week visit post-EOT will take place at the study site.

Note: See Section 7.2 of Protocol Amendment 3 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.9 Schedule of Assessments Under Amendment 3 – Treatment Year 1 (CD Subjects, Entering from Study SHP647-305, Study SHP647-306, or Study SHP647-307)

Table 16 Schedule of Assessments – Treatment Year 1 (CD Subjects, Entering from Study SHP647-305, Study SHP647-306, or Study SHP647-307)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W 0/ Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13
Visit Window	None	±7 days											
Informed consent/assent	X												
Eligibility assessment[b]	X												
Medical history[c]	IDT or MNT												
Complete physical examination[d]	IDT or MNT						X						
Targeted physical examination[d]	IDT or MNT			X						X			X
Targeted neurological assessment[e]	IDT or MNT			X			X			X			X
Vital signs	IDT or MNT	X		X			X			X			X
Weight	IDT or MNT	X		X			X			X			X
12-Lead ECG	IDT or MNT			X			X						X
Laboratory													
Hematology	IDT or MNT	X		X			X			X			X
Serum chemistry	IDT or MNT	X		X			X			X			X
Urinalysis	IDT or MNT	X		X			X			X			X
Urine β–hCG[f]	IDT or MNT	X	X	X	X	X	X	X	X	X	X	X	X
FSH[g]	X												
Contraception check[h]		X	X	X	X	X	X	X	X	X	X	X	X
Stool sample for fecal calprotectin	IDT or MNT						X						X

Table 16 Schedule of Assessments – Treatment Year 1 (CD Subjects, Entering from Study SHP647-305, Study SHP647-306, or Study SHP647-307)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W 0/ Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**None**	**±7 days**											
Serum CRP[i]	IDT or MNT						X						X
Serum soluble MAdCAM[i]	IDT or MNT						X						X
Blood β_7^+ T cells[i]	IDT or MNT						X						X
Pharmacokinetic sampling[i]	IDT or MNT	X		X			X						X
ADA and NAb sampling[i]	IDT or MNT	X		X			X						X
CD Assessments[j] Including Endoscopic Procedure													
Colonoscopy	IDT or MNT												X
SES-CD	IDT or MNT												X
CDAI	IDT or MNT			X			X			X			X[k]
PRO-CD daily e-diary data instruction	X												
PRO-CD daily e-diary data[l]	IDT or MNT			X			X			X			X
Health Assessments[m]													
IBDQ	IDT or MNT						X						X
EQ-5D-5L	IDT or MNT						X						X
Hospitalizations, inpatient days, ED visits (HRUA)	IDT or MNT	X	X	X	X	X	X	X	X	X	X	X	X
WPAI-CD	IDT or MNT						X						X
SF-36-v.2, acute	IDT or MNT						X						X
TSQM	IDT or MNT						X						X

Table 16 Schedule of Assessments – Treatment Year 1 (CD Subjects, Entering from Study SHP647-305, Study SHP647-306, or Study SHP647-307)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W 0/ Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit Window	**None**	**±7 days**											
Treatment Procedures													
Randomization[n]	X												
Administration of ontamalimab[n,o]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypersensitivity monitoring[p]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[q]						X						X	

ADA=antidrug antibody; β-hCG=beta-human chorionic gonadotropin; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; ECG=electrocardiogram; ED=emergency department; e-diary=electronic diary; EQ-5D-5L=European Quality of Life 5 Dimensions, 5 Levels questionnaire; ET=early termination; FSH=follicle-stimulating hormone; HRUA=Healthcare Resource Utilization Assessment; IBDQ=Inflammatory Bowel Disease Questionnaire; IDT=induction study (SHP647-305 or SHP647-306); MAdCAM=mucosal addressin cell adhesion molecule; MNT=Maintenance Study SHP647-307; NAb=neutralizing antibody; PRO=patient-reported outcome; SES-CD=Simple Endoscopic Score for Crohn's Disease; SF-36=Short Form-36 Health Survey; TSQM=Treatment Satisfaction Questionnaire for Medication; W=week; WPAI-CD=Work Productivity and Activity Impairment Questionnaire – Crohn's Disease.

[a] Baseline = Week 0 (Day 1). For subjects previously enrolled in induction study SHP647-305 or SHP647-306, the baseline visit is the Week 16 study visit. For subjects entering from maintenance study SHP647-307, the baseline visit is the Week 52 visit (for subjects who completed the study) or the ET visit (for subjects who withdrew early).
If results for confirmation of treatment failure are pending at the time of the end of study visit in study SHP647-307, sites will have 1 additional week to confirm final status of the subject (treatment failure or not) before enrolling the subject to study SHP647-304.

[b] Eligibility will be assessed after the consent form is signed and after procedures are completed at Visit 7, Part 2 in study SHP647-305 or SHP647-306, or at Visit 14, Part 2 or the ET visit in study SHP647-307.

[c] Medical history from studies SHP647-305, SHP647-306 and SHP647-307 will be used as the baseline medical history data for study SHP647-304.

[d] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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 and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

[e] 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 progressive multifocal leukoencephalopathy should be excluded.

Table 16 Schedule of Assessments – Treatment Year 1 (CD Subjects, Entering from Study SHP647-305, Study SHP647-306, or Study SHP647-307)

Study Procedure	Baseline[a]	Treatment – Year 1											
	W 0/ Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13
Visit Window	None	±7 days											

[f] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.

[g] For confirmation of postmenopausal status in women who have had 12 consecutive months of spontaneous amenorrhea and are ≥51 years of age. This does not need to be performed if postmenopausal status was confirmed by FSH in induction study SHP647-305 or SHP647-306 or maintenance study SHP647-307.

[h] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential.

[i] Samples must be collected before administration of investigational product.

[j] PRO assessments will be based on subject daily e-diary entries. CDAI score will be calculated based on data collected in the subject diary as well as data obtained at the site visit.

[k] SES-CD total score will be calculated based on the locally read endoscopic subscores for each of the segments investigated.

[l] PRO-CD daily e-diary will be available daily throughout the study, Subjects will be required to enter e-diary data at least 14 days before each specified visit. Compliance is assessed by site staff at each specified visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <12 out of 14 diary entries) when compared with the previous visit.

[m] All health outcome/patient-reported questionnaires should be completed before completing any other visit assessments.

[n] Interactive response technology will be used for randomization and dispensation of study treatment.

[o] Investigational product is to be administered after all other visit assessments have been performed.

[p] At each visit the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored until the adjudication committee determines whether testing is appropriate.

[q] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one where testing will be done.

Note: See Section 7.2 of Protocol Amendment 3 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.10 Schedule of Assessments Under Amendment 3 – Treatment Year 2 Through End of Study (CD Subjects, Entering from Study SHP647 305, SHP647-306, or SHP647-307)

Table 17 Schedule of Assessments – Treatment Year 2 Through End of Study (CD Subjects, Entering from Study SHP647-305, SHP647-306, or SHP647-307)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[o]	EOT	8 W post-EOT[p]	16 W post-EOT[p]
Visit Number	14	15	16	17	18	19	20	21	22	23	24	25			
Visit Window	±7 days														
Complete physical examination[a]													X		X
Targeted physical examination[a]			X			X			X			X			
Targeted neurological assessment[b]			X			X			X			X	X		X
Vital signs						X						X	X		X
Weight						X						X	X		
12-Lead ECG												X	X		
Laboratory															
Hematology			X			X			X			X	X		X
Serum chemistry						X						X	X		X
Urinalysis						X						X	X		X
Urine β–hCG[c]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Contraception check[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Stool sample for fecal calprotectin						X						X	X		
Serum CRP[e]						X						X	X		
Serum soluble MAdCAM[e]						X						X	X		

Table 17 Schedule of Assessments – Treatment Year 2 Through End of Study (CD Subjects, Entering from Study SHP647-305, SHP647-306, or SHP647-307)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[o]	EOT	8 W post-EOT[p]	16 W post-EOT[p]
Visit Number	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**			
Visit Window	**±7 days**														
Blood β_7^+ T cells[e]						X						X	X		
Pharmacokinetic sampling[e]						X[f]						X[f]			
ADA and NAb sampling[e]						X[f]						X[f]	X		
CD Assessments[g] Including Endoscopic Procedure															
Colonoscopy												X	X[h]		
SES-CD												X[i]	X[i]		
CDAI			X			X			X			X	X		
PRO-CD daily e-diary data[j]			X			X			X			X	X		
Health Assessments[k]															
IBDQ						X						X	X		
EQ-5D-5L						X						X	X		
Hospitalizations, inpatient days, ED visits (HRUA)	X	X	X	X	X	X	X	X	X	X	X	X	X		X
WPAI-CD						X						X	X		
SF-36-v.2, acute						X						X	X		
TSQM						X						X	X		
Treatment Procedures															

Table 17 Schedule of Assessments – Treatment Year 2 Through End of Study (CD Subjects, Entering from Study SHP647-305, SHP647-306, or SHP647-307)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[o]	EOT	8 W post-EOT[p]	16 W post-EOT[p]
Visit Number	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**			
Visit Window	**±7 days**														
Administration of ontamalimab[l]	X	X	X	X	X	X	X	X	X	X	X	X			
Hypersensitivity monitoring [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[n]					X						X				

ADA=antidrug antibody; β-hCG=beta-human chorionic gonadotropin; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; ECG=electrocardiogram; ED=emergency department; e-diary=electronic diary; EOT=end of treatment; EQ-5D-5L=European Quality of Life 5 Dimensions, 5 Levels questionnaire; HRUA=Healthcare Resource Utilization Assessment; IBDQ=Inflammatory Bowel Disease Questionnaire; MAdCAM=mucosal addressin cell adhesion molecule; NAb=neutralizing antibody; PRO=patient-reported outcome; SES-CD=Simple Endoscopic Score for Crohn's Disease; SF-36=Short Form-36 Health Survey; TSQM=Treatment Satisfaction Questionnaire for Medication; W=week; WPAI-CD=Work Productivity and Activity Impairment Questionnaire – Crohn's Disease.

[a] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; 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 and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

[b] Subject will be evaluated to reveal any potential abnormalities in the following neurologic domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, cognition/behavior.

[c] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.

[d] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential.

[e] Samples must be collected before administration of investigational product.

[f] Samples are to be collected in Year 2 only (ie, at Weeks 72 and 96) and not in subsequent years.

[g] PRO assessments will be based on subject daily e-diary entries. CDAI score will be calculated based on data collected on patient diary as well as data obtained at the site visit.

[h] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; eyes;

Table 17 Schedule of Assessments – Treatment Year 2 Through End of Study (CD Subjects, Entering from Study SHP647-305, SHP647-306, or SHP647-307)

Study Procedure	Treatment – Subsequent Years													Follow-up	
	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96[o]	EOT	8 W post-EOT[p]	16 W post-EOT[p]
Visit Number	14	15	16	17	18	19	20	21	22	23	24	25			
Visit Window	±7 days														

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 and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

[i] Subject will be evaluated to reveal any potential abnormalities in the following neurologic domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, cognition/behavior.

[j] The urine pregnancy test will be performed at the site using test kits supplied by the central laboratory.

[k] Contraception check should be made for female subjects of childbearing potential and male subjects who are with a partner of childbearing potential.

[l] Samples must be collected before administration of investigational product.

[m] Samples are to be collected in Year 2 only (ie, at Weeks 72 and 96) and not in subsequent years.

[n] PRO assessments will be based on subject daily e-diary entries. CDAI score will be calculated based on data collected on patient diary as well as data obtained at the site visit.

[o] Colonoscopy is to be done at the EOT visit unless performed for any reason within 12 weeks before the EOT visit.

[p] SES-CD total score will be calculated based on the locally read endoscopic subscores for each of the segments investigated.

[q] PRO-CD daily e-diary will be available daily throughout the study. Subjects will be required to enter e-diary data at least 14 days before each specified visit. Compliance is assessed by site staff at each specified visit. The site staff will instruct the subject on the appropriate use of the e-diary, particularly when compliance is below 80% (eg, <12 out of 14 diary entries) when compared with the previous visit.

[r] All health outcome/patient-reported questionnaires should be completed before completing any other visit assessments.

[s] Investigational product is to be administered after all other visit assessments have been performed.

[t] At each visit the subject will be assessed for the presence of Type I and Type III hypersensitivity reactions since the prior visit. If a suspected hypersensitivity reaction has occurred, the next dose of investigational product should be withheld if necessary until the precise etiology (investigational product related or not) has been determined. If a Type III reaction is suspected, appropriate samples for testing will be collected and stored until the adjudication committee determines whether testing is appropriate.

[u] Stool sample collection kit will be dispensed to the subject to take home at the visit prior to the one where testing will be done.

[v] After Treatment Year 1, assessments will be repeated on the subsequent year rotation from Week 52.

[w] Subjects will enter a 16-week safety follow-up period, with visits at 8 weeks and 16 weeks following the EOT visit. The 8-week visit post-EOT will routinely be conducted by telephone; however, as an exception the visit can be performed as a study site visit if preferred. The 16-week visit post-EOT will take place at the study site.

Note: See Section 7.2 of Protocol Amendment 3 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

16.11 Geographic Regions

Table 18 Geographic Regions

Country	Region
Japan	Asia
Korea, Republic of	Asia
Bosnia and Herzegovina	Eastern Europe
Bulgaria	Eastern Europe
Croatia	Eastern Europe
Czech Republic	Eastern Europe
Estonia	Eastern Europe
Hungary	Eastern Europe
Lithuania	Eastern Europe
Poland	Eastern Europe
Romania	Eastern Europe
Russia	Eastern Europe
Serbia	Eastern Europe
Slovakia	Eastern Europe
Ukraine	Eastern Europe
Austria	Western Europe
Belgium	Western Europe
Germany	Western Europe
France	Western Europe
Greece	Western Europe
Ireland	Western Europe
Italy	Western Europe
Netherlands	Western Europe
Portugal	Western Europe
Spain	Western Europe
Switzerland	Western Europe
United Kingdom	Western Europe
Argentina	ROW
Australia	ROW
Brazil	ROW
Colombia	ROW
Lebanon	ROW
Israel	ROW
Mexico	ROW
New Zealand	ROW
South Africa	ROW
Turkey	ROW

Table 18 Geographic Regions

Country	Region
Canada	North America
United States	North America

ROW (Africa/Australia/Latin America/Middle East); Asia (Japan/South Korea)

16.12 Treatment Groups

Data will be presented by SHP647-304 treatment group as follows:

- Ontamalimab 25 mg (subjects who enrolled and terminated prior to SHP647-304 Amendment 4)
- Ontamalimab 25 mg then 75 mg (subjects who were enrolled prior to SHP647-304 Amendment 4 and received 25 mg)
- Ontamalimab 75 mg (subjects who received 75 mg prior to Amendment 4 or enrolled under SHP647-304 Amendment 4)
- All doses*

* Treatment groups with * will not be shown in the secondary endpoint's summary tables.