Clinical Study Protocol

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: Amendment 4, 21 September 2020

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.

PROTOCOL: SHP647-304

TITLE:	A Phase 3 Long-term Safety Extension Study of SHP647 in Subjects with Moderate to Severe Ulcerative Colitis or Crohn's Disease (AIDA)
DRUG:	Ontamalimab (SHP647)
IND:	100,222
EUDRACT NO.:	2017-000574-11
SPONSOR:	Shire Human Genetic Therapies, Inc. ("Shire"), a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 300 Shire Way, Lexington, MA 02421 US
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted], MD, PhD
PROTOCOL HISTORY:	Protocol Amendment 4: 21 Sep 2020 Protocol Amendment 3: 07 Nov 2019 Protocol Amendment 2: 17 Sep 2018 Protocol Amendment 1: 18 Dec 2017 Original Protocol: 13 Jul 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: DocuSigned by: [redacted]	**Date:** 22-Sep-2020 | 19:05:54 JST
[redacted], MD	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP647-304.

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

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

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

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

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

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

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

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	**Amendment Date**	**Global/Region/Country/Site Specific**
4	**21 Sep 2020**	**Global**

Protocol Amendment Summary and Rationale:

The main purpose of SHP647-304 Amendment 4 is to allow subjects with moderate to severe ulcerative colitis (UC) or Crohn's disease (CD) to enter this study following discontinuation of the Phase 3 maintenance studies (SHP647-303 or SHP647-307) or those already enrolled in this study (SHP647-304) and who are responding to active treatment to receive ontamalimab treatment under a reduced schedule of assessments to minimize subject burden, as it is expected that this study will be completed in no more than 3 years (ie, by December 2023) if not terminated early. Certain types of pharmacodynamic assessments have been reduced, and efficacy and pharmacokinetic assessments have been removed. Response to ontamalimab treatment will be assessed throughout the study, and safety will continue to be monitored closely. The safety follow-up period has been reduced from 16 weeks to 12 weeks, based on emergent data on the half-life of ontamalimab (16 days).

If an efficacious dose is determined based on data from the induction studies, the study is planned to become a single-dose study, with the dose to be chosen after the analysis of data from those 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. In the occurrence that the analysis of these results demonstrates the efficacy of at least one of the doses investigated, this dose will be selected to be administered open label in this study. If both doses are effective and the difference compared to placebo is similar, then the lowest effective dose will be selected. However, if no efficacious dose is found, then the study will be terminated.

Amendment 4 removes the planned direct-entry of new subjects with UC that was added with Amendment 3 (dated 07 Nov 2019). No subject new to the program had been enrolled directly prior to, nor since, the company decision to close the ontamalimab clinical development program.

This amendment also provides clarification around home administration of investigational product, a provision that has been implemented in response to the World Health Organization (WHO) officially declaring the novel Coronavirus a pandemic on 11 March 2020. This amendment incorporates changes to provide flexibility in timing of site visits, to identify home healthcare solutions as permitted by local regulations, and to maintain subject safety and confidentiality and study integrity in the context of healthcare delivery challenges presented by the COVID-19 pandemic.

The significant changes in SHP647-304 Protocol Amendment 4 relative to the previous edition, SHP647-304 Protocol Amendment 3, are captured below.

Protocol Amendment		
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Amendment Number **4**	**Amendment Date** **21 Sep 2020**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Protocol Signature Page	Updated sponsor signatory.	Administrative change.
Product Quality Complaints	Updated the email address for product quality complaints.	Administrative change.
Global	Replaced electronic diary with memory aid throughout the document.	Memory aid can be applicable for this type of long-term study for practical reasons.
Global	Removed direct-entry of subjects with UC.	Due to the discontinuation of the ontamalimab clinical trial program and because no subjects had been enrolled directly prior to this decision.
Global	Changed the safety follow-up period from 16 weeks to 12 weeks.	Due to the emergent data on the half-life of ontamalimab (16 days).
Global	Updated the term 'MAdCAM' to 'MAdCAM-1' throughout the document.	As per the latest version of the ontamalimab Investigator's Brochure, Edition 9.0.
Study Synopsis, Number of Subjects (total and for each treatment arm)	Revised total sample size projection.	Due to the early discontinuation of the induction (SHP647-301, SHP647-302, SHP647-305, and SHP647-306) and maintenance (SHP647-303 and SHP647-307) studies and the removal of the criteria for direct-entry of subjects with UC in Study SHP647-304.
Study Synopsis, Site(s) and Region(s) Section 3.3, Sites and Regions	Updated the number of sites and the countries in which the study will be conducted.	To reflect the changes due to discontinuation of the induction and maintenance studies.
Study Synopsis, Objectives Section 2.2, Study Objectives	Added a secondary objective to evaluate the maintenance of response to long-term treatment with ontamalimab as measured by the clinical composite score (for subjects with UC) or CDAI score (for subjects with CD) and biomarkers, with or without endoscopy.	The study drug will be available for those who have been benefiting from it.

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Study Synopsis, Rationale Section 2.1, Rationale for the Study	Added text to report the discontinuation of the ontamalimab Phase 3 clinical development program and the intention to continue this long-term safety extension study, which is expected to be completed in no more than 3 years (ie, by December 2023) if not terminated early, to provide active treatment to subjects already enrolled who are responding to treatment and to subjects entering who have responded to active treatment.	In 2019, Takeda formally acquired Shire, the sponsor of 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. Per the announcement, the induction and maintenance studies will be closed earlier than originally planned. In recognition that this could potentially cause hardships for subjects who were benefiting from this investigational treatment, this long-term safety extension study, which is expected to be completed in no more than 3 years (ie, by December 2023), may continue to provide active treatment to subjects already enrolled who are responding to treatment and to subjects entering from a maintenance study who have responded to treatment (ie, in the induction or maintenance studies and who meet the entry criteria). 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.
Study Synopsis, Rationale Study Synopsis, Methodology Section 2.1, Rationale for the Study Section 3.1, Study Design Section 6.1.1, Blinding the Treatment Assignment Section 6.2.4, Unblinding the Treatment Assignment	Added text to describe the unblinding of the study following the completion of the final analysis of the induction studies.	To reflect the discontinuation of ontamalimab Phase 3 clinical development program.

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Study Synopsis, Methodology Section 3.1, Study Design and Flowchart	Addition of details about Direct to Patient [DTP] program/provision for home administration of investigational product. Added text that no additional subjects from the induction studies will be enrolled in Study SHP647-304. Revised the criteria for enrollment from maintenance studies SHP647-303 and SHP647-307 into Study SHP647-304. Removed pharmacokinetic and health outcome assessments. Updated randomization details.	To comply with study procedures as per the protocol 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. To reflect that the induction studies will no longer have active subjects due to the discontinuation of the program. To enable the subjects to continue active treatment who had ever responded to active treatment in the Phase 3 clinical development program. To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program. To reflect the discontinuation of ontamalimab Phase 3 clinical development program.

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Study Synopsis, Methodology Section 3.1, Study Design and Flowchart	Updated the duration for the entry of subject data from 10 days (for subjects with UC) and 14 days (for subjects with CD) before each specified visit (using diaries) to 7 days (for all subjects) before each specified visit (using memory aids). Updated language to specify that endoscopy is optional and that, if performed, it is recommended that the Mayo endoscopic subscore be recorded (for subjects with UC) and that the SES-CD is recorded (for subjects with CD). Added text that at every third visit, the subject will be assessed for ongoing benefit (treatment response) using the clinical composite score or composite score (for subjects with UC) and CDAI score (for subjects with CD). Biomarkers (C-reactive protein and fecal calprotectin) will be assessed every 3 months or in case there is a necessity to confirm the loss of clinical treatment response. Revised patient-reported CD sign and symptoms data (rectal bleeding frequency, rectal urgency frequency, vomiting frequency, nausea severity, incontinence frequency, total stool frequency) to 'general well-being'. The term 'potential treatment failure' has been replaced by the term 'loss of response'. Added criteria for the loss of response and included clinical composite score (for subjects with UC) and CDAI score (for subjects with CD) for the evaluation of loss of response.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program. To determine if the subject is receiving benefit from active treatment.

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Study Synopsis, Rationale Study Synopsis, Methodology Study Synopsis, Maximum duration of subject involvement in the study Section 3.1, Study Design and Flowchart Section 3.2, Duration and Study Completion Definition	Updated the subject's maximum duration of study participation from approximately 7 years to no more than 3 years (ie, a subject's participation is not planned to extend beyond 2023).	To more accurately reflect the expected maximum duration of study participation.
Study Synopsis, Maximum duration of subject involvement in the study Section 3.2, Duration and Study Completion Definition	Updated the time of study completion from approximately 7 years to no more than 3 years (ie, a subject's participation is not expected to extend beyond 2023).	To more accurately reflect the expected duration of the study based on changes to study plans.
Study Synopsis, Inclusion and exclusion criteria Section 4, Study Population	Revised inclusion criterion 3 describing the milestones that subjects who rollover from maintenance studies to Study SHP647-304 must meet. Reduced inclusion/exclusion criteria for subjects with CD.	To align with the change in study design and as per the early discontinuation of induction and maintenance studies and the removal of criteria for direct-entry of subjects with UC.
Study Synopsis, Endpoints and statistical analysis Section 9.7, Study Population	Reduced analysis sets.	Due to the early discontinuation of the study and limited sample size, previously planned analyses will no longer be conducted.
Study Synopsis, Safety Endpoints Study Synopsis, Secondary Endpoints Section 9.8.1.1, Secondary Endpoints (Subjects with UC) Section 9.8.2.1, Secondary Endpoints (Subjects with CD) Section 9.9, Safety Analyses	Updated endpoints to reflect the inclusion of maintenance discontinuation rollover subjects. Removed secondary and exploratory endpoints and assessments that are no longer applicable under Amendment 4.	To align with the change in study entry criteria. To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.

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Table 1, Schedule of Assessments – Treatment Year 1 (Subjects with UC) Table 2, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC) Table 3, Schedule of Assessments – Treatment Year 1 (Subjects with CD) Table 4, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD)	Updated the visit window for all study procedures (including safety follow-up) from ±7 days to ±10 days. Specified that laboratory assessments will be performed by the central laboratory and 12-lead electrocardiogram will be read by the local reader. Added treatment response assessment.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program. To comply with study procedures as per the protocol 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. To determine if subjects are receiving benefit from active treatment.
Table 1, Schedule of Assessments – Treatment Year 1 (Subjects with UC), footnote "f" Table 2, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC), footnote "e" Table 3, Schedule of Assessments – Treatment Year 1 (Subjects with CD), footnote "f" Table 4, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD), footnote "e"	Added footnote that in case of a DTP situation, some procedures will be performed by remote visits via virtual communications.	To comply with study procedures as per the protocol 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.
Table 1, Schedule of Assessments – Treatment Year 1 (Subjects with UC), footnote "g" Table 2, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC), footnote "f" Table 3, Schedule of Assessments – Treatment Year 1 (Subjects with CD), footnote "g" Table 4, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD), footnote "f"	Added footnote to allow clinical laboratory assays (liver function testing) to be done by local laboratory in case of issues related to COVID-19 (or other similar pandemic).	To comply with study procedures as per the protocol 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.

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Table 1, Schedule of Assessments – Treatment Year 1 (Subjects with UC), footnote "h" Table 2, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC), footnote "g" Table 3, Schedule of Assessments – Treatment Year 1 (Subjects with CD), footnote "h" Table 4, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD), footnote "g"	Added footnote to specify that subjects performing home administrations consecutively for 3 months will need to perform liver function testing per FDA requirement, which may be done locally if it is not possible to collect samples at the central laboratory.	To comply with the FDA requirements.
Table 1, Schedule of Assessments – Treatment Year 1 (Subjects with UC), footnote "m" Table 2, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC), footnote "k" Table 3, Schedule of Assessments – Treatment Year 1 (Subjects with CD), footnote "m" Table 4, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD), footnote "k" Section 7.3.2.1, Endoscopy Section 7.3.3.1, Colonoscopy	Updated language to specify that endoscopy (flexible sigmoidoscopy or colonoscopy for subjects with UC)/colonoscopy (for subjects with CD) is optional; that, if performed, the results are to be recorded; and that if more than 2 endoscopies/colonoscopies are needed in a year, the subject should be discontinued.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.

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Table 1, Schedule of Assessments – Treatment Year 1 (Subjects with UC), footnote "p" Table 2, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC), footnote "n" Table 3, Schedule of Assessments – Treatment Year 1 (Subjects with CD), footnote "p" Table 4, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD), footnote "n"	Added footnote to report the assessment of treatment response and also to clarify that it is applicable only after the implementation of Amendment 4.	To align with the change in study design as per the early discontinuation of induction and maintenance studies.
Table 1, Schedule of Assessments – Treatment Year 1 (Subjects with UC), footnote "q" Table 2, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC), footnote "o" Table 3, Schedule of Assessments – Treatment Year 1 (Subjects with CD), footnote "q" Table 4, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD), footnote "o" Section 7.3.2.2, Mayo Score Section 7.3.2.3, Ulcerative Colitis Memory Aid Section 7.3.3.3, Crohn's Disease Activity Index Section 7.3.3.4, Crohn's Disease Memory Aid	Updated the duration for the entry of subject data from 10 days (for subjects with UC) before each specified visit and 14 days (for subjects with CD) before each specified visit (using diaries) to 7 days (for all subjects) before each specified visit (using memory aids).	To adopt for memory aid data collection.

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Table 1, Schedule of Assessments – Treatment Year 1 (Subjects with UC), footnote "t" Table 2, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC), footnote "q" Table 3, Schedule of Assessments – Treatment Year 1 (Subjects with CD), footnote "t" Table 4, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD), footnote "q"	Addition of details around DTP program/provision for home administration of investigational product.	To comply with study procedures as per the protocol 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.
Table 2, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with UC) Table 4, Schedule of Assessments – Treatment Year 2 Through Year 3 and End of Study (Subjects with CD)	Revised tables to reflect duration of treatment. Added note on study participation extending beyond Year 3.	To reflect the discontinuation of ontamalimab Phase 3 clinical development program.
Section 2.2, Study Objectives	Removed the secondary and exploratory objectives that are no longer applicable under Amendment 4.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.
Section 3.1, Study Design and Flow Chart	Added study design flow chart for subjects enrolling under Amendment 4 (Figure 1).	To show the change in study design and treatment allocation of subjects entering from the discontinued maintenance studies.
Section 3.2, Duration and Study Completion Definition Section 7.2, Study Schedule	Updated subject's expected maximum study duration and overall study duration to no more than 3 years. Added text on allowing EOT and 12-week safety follow-up visits to be conducted at subject's home 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.	To reflect the discontinuation of ontamalimab Phase 3 clinical development program. To comply with study procedures as per the protocol 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.

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Study Synopsis, Methodology Section 4.4.1, Loss of Response	Added the steps to be performed if the response criteria are not satisfied.	To facilitate correct clinical judgment.
Section 4.4.2, Subject Withdrawal Criteria	Removed information around treatment failure assessment and stopping criteria. Added text regarding subject withdrawal from the study due to personal concerns related to COVID-19 (or other similar pandemic).	An even stricter criterion (treatment response/loss of treatment response) will guide study drug and study discontinuation. To address the situation if the subject withdraws from the study 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.
Section 4.4.3, Reason for Withdrawal	Replaced the term 'treatment failure' with 'loss of response'. Added text regarding subject withdrawal from the study due to personal concerns related to COVID-19 (or other similar pandemic).	To reflect the discontinuation of ontamalimab Phase 3 clinical development program. To address the situation if the subject withdraws from the study 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..
Section 5, Prior and Concomitant Treatment	Added text around change in permitted treatment when the subject is known to have been infected with the COVID-19 virus (Section 5.3). Updated details on permitted glucocorticoid use and prior treatments.	To comply with study procedures as per the protocol 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.
Section 6.2.2, Allocation of Subjects to Treatment	Added text to specify dose allocation in subjects who withdrew from Studies SHP647-303 or SHP647-307.	To provide the dose allocation for the maintenance discontinuation rollover subjects with the change in study entry criteria.

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Section 6.2.3, Dosing	Addition of details around DTP program/provision for home administration of investigational product, which has been implemented due to the COVID-19 pandemic situation. Added the criteria of delayed dosing and missed dosing 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.	To comply with study procedures as per the protocol 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.
Section 6.3.2, Packaging	Updated the packaging of pre-filled syringe from tray to foam insert.	To accurately describe study drug packaging.
Section 6.3.3, Storage	Added the storage condition for the investigational product in case of DTP program/provision for home administration of investigational product.	To comply with study procedures as per the protocol 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.
Section 6.3.4, Special Handling	Added the special handling of the investigational product in case of DTP program/provision for home administration of investigational product.	To comply with study procedures of as per the protocol 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.
Section 6.4, Drug Accountability	Added text related to the documentation of investigational product administration in case of DTP program/provision. Added text related to shipping of used investigational product to the site in case of DTP.	To comply with study procedures as per the protocol 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.

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Section 7.1, Changes to Study Procedures Due to a Pandemic	Added new section to address the changes to study procedures 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.	To comply with study procedures as per the protocol 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.
Section 7.2, Study Schedule	Updated details regarding the study baseline visit. Updated the window for the safety follow-up visit to ±10 days from ±7 days for subjects with UC (Section 7.2.1.3) and subjects with CD (Section 7.2.2.3).	To reflect the discontinuation of ontamalimab Phase 3 clinical development program. To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.
Section 7.3.2, Treatment Response Assessments – Subjects with Ulcerative Colitis	Added note that Mayo composite score will be computed only if an endoscopy is performed. Reduced signs and symptoms to be collected from subjects.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.
Section 7.3.3.4, Crohn's Disease Memory Aid	Added information to be collected from subjects with the option of a memory aid.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.
Section 7.3.4.3, Targeted Neurological Assessment	Added text on the assessment of potential PML following unblinding of the study. Added figure on post-unblinding process for quarterly neurological assessments.	To reflect the discontinuation of ontamalimab Phase 3 clinical development program.
Section 7.3.4.6, Clinical Laboratory Evaluations	Added text to allow clinical laboratory assays to be done by local laboratory in case of issues related to COVID-19 (or other similar pandemic). Added liver function test (local laboratory) for subjects performing home administration consecutively for 3 months.	To comply with study procedures as per the protocol 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. To comply with the FDA requirements.

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Section 7.3.4.8, Electrocardiogram	Changed the ECG reading from central to local. Added details on performance of ECG in case of COVID-19-related or other pandemic-related issues.	To comply with study procedures as per the protocol due 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.
Section 7.3.4.11, Colonoscopy in Subjects at Elevated Risk of Colorectal Cancer	Added language to specify that colonoscopy is not required by the protocol.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.
Section 7.3.5, Others	Removed the sections on health-related quality-of-life assessments and healthcare resource utilization assessments.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.
Section 7.3.5.1, Pharmacodynamic Assessments Section 7.3.6, Volume of Blood to be Drawn from Each Subject	Removed laboratory assessments for serum soluble MAdCAM-1 and blood β_7^+ T cells. Removed antidrug antibody and neutralizing antibody sampling. Updated volume of blood to be drawn.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.
Section 9.4, Statistical Analysis Process	Added text to clarify that changes to analysis will be described in the statistical analysis plan.	To address the impact of COVID-19 (or other similar pandemic) on data analysis.
Section 9.5, Planned Interim Analysis, Adaptive Design, Data Monitoring Committee, and Hypersensitivity Adjudication Committee	Updated text regarding the use of a DMC until the time of unblinding. Removed text describing interim analyses and the use of a hypersensitivity adjudication committee.	To reflect the discontinuation of ontamalimab Phase 3 clinical development program.
Section 9.6, Sample Size Calculation and Power Considerations	Added text to report the discontinuation of the ontamalimab Phase 3 clinical development program. Updated sample size projection for the enrollment of subjects from induction and maintenance studies and removal of planned projection of direct-entry of subjects with UC.	Revised projections due to plan of early discontinuation of induction and maintenance studies and the removal of criteria for direct-entry of subjects with UC.
Section 9.8, Efficacy Analyses	Removed the efficacy endpoints that are no longer applicable after the implementation of Amendment 4.	To minimize the subject burden due to discontinuation of ontamalimab Phase 3 clinical development program.

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Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 9.10, Other Analyses	Removed the section on PK and PD analyses.	As there will be no PK or PD analyses due to discontinuation of ontamalimab Phase 3 clinical development program.
Section 10.2.3.2, Recording, Access, and Retention of Source Data and Study Documents	Added sentence on document retention requirement in case of DTP provision.	To comply with study procedures as per the protocol 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.
Appendices	Added Summary of Changes of Protocol Amendment 3. Removed scales and assessments no longer applicable under Amendment 4. Removed Appendix 5, Determination of Failure or Intolerance to Prior Treatment for Ulcerative Colitis.	Administrative change.

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

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

Fax
+1 484 595 8155 (Global)

Email
drugsafety@shire.com

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

North America:

PPD 24 Hour Safety Hotline: RTP +1 888 483 7729; Wilmington +1 800 201 8725

PPD 24 Hour Safety Hotline Fax: RTP +1 888 529 3580 or +1 919 654 3836;
Wilmington +1 888 488 9697 or +1 919 654 3849

Latin America:

PPD 24 Hour Safety Hotline: +55 11 4504 4801

PPD 24 Hour Safety Hotline Fax: +55 11 3958 0983

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

PPD 24 Hour Safety Hotline: +44 1223 374 240

PPD 24 Hour Safety Hotline Fax: +44 1223 374 102

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or nonmedical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Shire licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that a product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Capsule fill empty or overage • Bottle/vial fill shortage or overage • Capsule/tablet damaged/broken • Syringe/vial cracked/broken	• Syringe leakage • Missing components • Product discoloration • Device malfunction
Labeling	• Label missing • Leaflet or Instructions For Use (IFU) missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (eg, secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial • Particulate in packaging	

Please report the product quality complaint using the "Product Complaint Data Collection Form" via the email address below:

ctmcomplaint@takeda.com

Telephone number (provided for reference if needed):

1 800 828 2088

Shire, Lexington, MA (USA)

For instructions on reporting AEs related to product complaints, see Section 8.2.2.

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
β-hCG	beta-human chorionic gonadotropin
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CNS	central nervous system
CRA	clinical research associate
CRO	contract research organization
CRP	C-reactive protein
DMC	data monitoring committee
EC	ethics committee
ECCO	European Crohn's and Colitis Organisation
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOT	end of treatment
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation

$IgG_{2\kappa}$	immunoglobulin G_2 kappa
IRB	Institutional Review Board
IRT	interactive response technology
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MTX	methotrexate
NAb	neutralizing antibody
PFS	prefilled syringe
PGA	physician global assessment
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
RB	rectal bleeding
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SMT	Safety Management Team
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	*Mycobacterium tuberculosis*
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal

STUDY SYNOPSIS

Protocol number: SHP647-304	**Drug:** Ontamalimab (SHP647)
Title of the study: A Phase 3 Long-term Safety Extension Study of SHP647 in Subjects with Moderate to Severe Ulcerative Colitis or Crohn's Disease (AIDA)	
Number of subjects (total and for each treatment arm): A maximum of 451 subjects are projected for enrollment in this study.	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study will be conducted in approximately 225 sites in approximately 33 countries.	
Study period (planned): 2018 – 2023	**Clinical phase:** 3

Objectives:

Primary: To evaluate the safety and tolerability of long-term treatment with ontamalimab in subjects with moderate to severe ulcerative colitis (UC) or Crohn's disease (CD).

Secondary - 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.

Secondary - 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.

Rationale: In 2019, Takeda formally acquired Shire, the sponsor of 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 who had failed at least 1 prior treatment. Per the announcement, the induction and maintenance studies will be closed earlier than originally planned. In recognition that this could potentially cause hardships for subjects who were benefiting from this investigational treatment (ie, fulfilling treatment response criteria as defined in Section 9.8.1.1 and Section 9.8.2.1), this long-term safety extension study, which is expected to be completed in no more than 3 years (ie, by December 2023), may continue to provide active treatment to subjects already enrolled who are responding to treatment and to subjects entering from a maintenance study who have responded to treatment (ie, in the induction or maintenance studies and who meet the entry criteria). 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.

Originally, this extension study was designed to evaluate the safety and efficacy of long-term treatment with ontamalimab in subjects with moderate to severe UC or CD who: (1) completed one of the 4 multicenter, randomized, double-blind, placebo-controlled, parallel-group studies evaluating ontamalimab as an induction therapy (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) and did not meet the response criteria (clinical and/or endoscopic response/remission as appropriate) required for entry into a maintenance study (SHP647-303 or SHP647-307), or (2) were treatment failures (as defined in the respective protocols) and/or completers in one of the 2 multicenter, double-blind, randomized, placebo-controlled, parallel-group studies evaluating ontamalimab as maintenance therapy (SHP647-303 or SHP647-307). 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.

Subjects in the induction studies SHP647-301 or SHP647-302:

- As of September 2020, no subjects remain in the induction studies who would be eligible to participate in this study (SHP647-304); therefore, no additional subjects from the induction studies will enter this study under Amendment 4.

Subjects in the maintenance studies SHP647-303 or SHP647-307:

- Subjects who received and responded to active treatment in either or both of the induction or maintenance studies may be eligible to enter this study.
- Subjects who have not received ontamalimab yet (ie, received placebo in both the induction and maintenance studies) will not be eligible to enter this study.
- Subjects eligible to enter this study will be assessed for treatment response criteria according to the revised study schedule in Study SHP647-304.

Subjects currently in Study SHP647-304 (ie, enrolled prior to Amendment 4) will be assessed for treatment response as follows:

- Subjects who have already entered Study SHP647-304 may continue and will be assessed for treatment response according to the revised study schedule. If they show response to ontamalimab treatment, they may continue further in this study.
- 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 be evaluated periodically and in case of clinical worsening at an unscheduled visit during the study for treatment response. If a subject shows response to ontamalimab treatment, he or she may continue in this study either until he or she shows a loss of treatment response (ie, no longer meets response criteria) or elects to seek another treatment option, or until the end of the study.

Investigational product, dose, and mode of administration:

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

Methodology:

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, 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 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 the ongoing COVID-19 pandemic [or other similar pandemic], in which case they may qualify for the "Direct to Patient" [DTP] program) for investigational product 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 SC injections using PFSs. Subjects will undergo treatment response and safety assessments.

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 subscores. The composite score is a recommended measure consisting of the Mayo score without the physician global assessment (PGA) subscore. The clinical composite score is a measure consisting of rectal bleeding (RB) plus stool frequency 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 Simple Endoscopic Score for Crohn's Disease (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 investigational product 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.

If clinical response criteria are no longer satisfied and alternative explanations for clinical worsening (eg, infection) can be excluded, the subject will be discontinued. If necessary for assessment in the opinion of the investigator (eg, borderline treatment response results), the following evaluations may be considered:

1) Have subject return in 2 to 4 weeks for repeat assessment if loss of response criteria is still met:

   a) Perform endoscopy to determine if there is an objective benefit despite clinical symptoms; if the composite of clinical and endoscopic data meets response criteria, continue the study.

      1. Endoscopic response criterion for UC is Mayo endoscopic subscore decreased by ≥1 point as compared to the baseline value recorded upon entry into the induction studies.

2. Endoscopic response criterion for CD is SES-CD improved by >25% as compared to the baseline value recorded upon entry into the induction studies.

b) Biomarkers may be used to determine overall response criteria at the discretion of the investigator; serum CRP < upper limit of normal or fecal calprotectin <250 μg/g is considered indicative of clinical benefit.

Upon termination from the study, subjects must return for a safety visit 12 weeks after the last dose of investigational product.

Subjects who have experienced loss of response should be withdrawn from active treatment once other possible etiologies have been ruled out and appropriate clinical evaluation has been performed as suggested above. While these response criteria are offered as general guidance to the investigator, there may be additional criteria that warrant withdrawal from active treatment and the ultimate decision of withdrawal from active treatment is left to the investigator based on the assessment of disease activity, subject's clinical benefit and tolerance of the investigational product.

For subjects who are tolerating investigational product and receiving clinical benefit in the judgment of the investigator (ie, fulfilling treatment response criteria as defined in Section 9.8.1.1 and Section 9.8.2.1), study participation may continue until the subject withdraws from the study, or the investigator or sponsor decide to withdraw the subject (eg, in the interest of subject safety), or the sponsor decides to close the study, or the program is stopped completely. A subject's maximum duration of participation in this study under the current amendment is expected to be no more than 3 years (ie, a subject's participation is not planned to extend beyond 2023), subject to local or country requirements. Subjects will enter a 12-week safety follow-up period following the last dose of investigational product.

Inclusion and exclusion criteria:

Inclusion Criteria – Subjects with UC:

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must have been enrolled previously in Study SHP647-301 or SHP647-302 and are in the treatment period of Study SHP647-303, completed the ET or Week 52 visit in the maintenance study SHP647-303, had responded to ontamalimab treatment (in the induction and/or maintenance studies), and meet one of the following criteria:
    - Subjects are on placebo at the maintenance study ET or Week 52 visit: they received ontamalimab in the induction studies and fulfilled the maintenance study response entry criteria, OR
    - Subjects have received ontamalimab at the maintenance study ET or Week 52 visit:
        - 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, compared to the baseline value for induction studies, AND/OR
        - Composite score that has decreased by ≥30% and ≥3 points compared to the baseline value for induction studies.

4. Subjects receiving any treatment(s) for UC described in Section 5.2.1 are eligible provided they have been on a stable dose for the designated period of time.

Exclusion Criteria – Subjects with UC:

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

1. Subjects who had major protocol deviation(s) (as determined by the sponsor) in Study SHP647-301, SHP647-302, or SHP647-303.
2. Subjects who permanently discontinued investigational product because of an adverse event (AE), regardless of relatedness to investigational product, in Study SHP647-301, SHP647-302, or SHP647-303.
3. Subjects who are likely to require major surgery for UC.
4. Subjects are females who became pregnant during Study SHP647-301, SHP647-302, or SHP647-303, females who are lactating, females who are planning to become pregnant during the study period, or males or females of childbearing potential not agreeing to continue using appropriate contraception methods (ie, highly effective methods for female and medically appropriate methods for male study subjects) through the conclusion of study participation.
5. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
6. Subjects who, in the opinion of the investigator or the sponsor, will be uncooperative or unable to comply with study procedures.
7. Subjects who have a newly-diagnosed malignancy or recurrence of malignancy (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
8. Subjects who have developed any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal [GI] [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study.
9. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
10. Subjects with known exposure to *Mycobacterium tuberculosis* (TB) since testing at screening in Study SHP647-301 or SHP647-302 and who have been advised to require treatment for latent or active disease, but who are without a generally accepted course of treatment.
11. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are sponsor employees directly involved in the conduct of the study.
12. Subjects who are participating in other investigational studies (other than SHP647-301, SHP647-302, or SHP647-303) or plan to participate in other investigational studies during long-term extension study SHP647-304.

Inclusion Criteria – Subjects with CD:

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must have been enrolled previously in Study SHP647-305 or SHP647-306 and are in the treatment period of Study SHP647-307, completed the ET or Week 52 visit in maintenance study SHP647-307, had responded to ontamalimab treatment (in the induction and/or maintenance studies), and meet one of the following criteria:
    - Subjects are on placebo at the maintenance study ET or Week 52 visit: they received ontamalimab in the induction study and fulfilled the maintenance study response criteria, OR
    - Subjects have received ontamalimab at the maintenance study ET or Week 52 visit:
        - CDAI score that has decreased by ≥100 points at the end of treatment visit 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.
4. Subjects receiving any treatment(s) for CD described in Section 5.3.1 are eligible provided they have been on a stable dose for the designated period of time.

Exclusion Criteria – Subjects with CD:

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

1. Subjects who had major protocol deviation(s) (as determined by the sponsor) in Study SHP647-305, SHP647-306, or SHP647-307.
2. Subjects who permanently discontinued investigational product because of an AE, regardless of relatedness to investigational product, in Study SHP647-305, SHP647-306, or SHP647-307.
3. Subjects who are likely to require major surgery for CD or developed acute severe complications of CD (with or without fulfilling the treatment failure criteria in the maintenance study) that required immediate intervention (eg, need for immediate biologic treatment with proven effect) and/or CDAI score >450.
4. Subjects are females who became pregnant during Study SHP647-305, SHP647-306, or SHP647-307, females who are lactating, females who are planning to become pregnant during the study period, or males or females of childbearing potential not agreeing to continue using appropriate contraception methods (ie, highly effective methods for female and medically appropriate methods for male study subjects) through the conclusion of study participation.
5. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
6. Subjects who, in the opinion of the investigator or the sponsor, will be uncooperative or unable to comply with study procedures.
7. Subjects who have a newly-diagnosed malignancy or recurrence of malignancy (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated

with no evidence of recurrence).

8. Subjects who have developed any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study.
9. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or ECG abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
10. Subjects with known exposure to TB since testing at screening in Study SHP647-305 or SHP647-306, and who have been advised to require treatment for latent or active disease, but who are without a generally accepted course of treatment.
11. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are sponsor employees directly involved in the conduct of the study.
12. Subjects who are participating in other investigational studies (other than SHP647-305, SHP647-306, or SHP647-307) or plan to participate in other investigational studies during long-term extension study SHP647-304.

Maximum duration of subject involvement in the study:

For subjects who are tolerating investigational product and receiving clinical benefit in the judgment of the investigator (ie, fulfilling treatment response criteria as defined in Section 9.8.1.1 and Section 9.8.2.1), study participation may continue until the subject withdraws from the study, or the investigator or sponsor decide to withdraw the subject (eg, in the interest of subject safety), or the sponsor decides to close the study, or the program is stopped completely. Subjects will enter a 12-week safety follow-up period following the last dose of investigational product. A subject's maximum duration of participation in this study under the current amendment is expected to be no more than 3 years (ie, a subject's participation is not planned to extend beyond 2023), subject to local or country requirements. It is expected that the study will be completed in no more than 3 years (ie, by December 2023).

Endpoints and statistical analysis:

Analysis Sets:

The full analysis set (FAS) will consist of all subjects in the randomized set who receive at least 1 dose of investigational product in the SHP647-304 study.

The safety set will consist of all subjects who receive at least 1 dose of investigational product in the SHP647-304 study.

Primary Endpoint: The primary endpoint is the assessment of safety as measured by: incidence and severity of AEs; incidence and nature of serious infections; and actual values and change from baseline, as well as incidence of abnormalities, in laboratory tests, ECGs, and vital signs.

Safety Endpoints: All safety analyses will be performed using the safety set. Subjects will be analyzed according to the treatment they actually received. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Summaries will be presented by indication separately and also overall. Summaries may be presented by the status at entry into this study (eg, induction nonresponder, maintenance ontamalimab completer, maintenance discontinuation rollovers, etc.).

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. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, serious AEs, and deaths will be similarly summarized/listed. Adverse events of special interest will be summarized by treatment group.

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

Secondary Endpoints – Subjects with Ulcerative Colitis:

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.

Secondary Endpoints – Subjects with Crohn's Disease:

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.

All analyses will be performed using the FAS.

Secondary endpoints will be summarized by treatment group using descriptive statistics at each assessment visit. Summaries may be presented by the status at entry into the study (eg, induction nonresponder, maintenance ontamalimab completer, maintenance early discontinuation rollovers, etc.). Statistical summaries will include number of subjects and percentages, and 95% confidence intervals.

STUDY SCHEDULES

Table 1 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 1 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	

Table 1 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											

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. See Section 7.3.4.3 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.

[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.

Table 1 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											

[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 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 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

Table 2 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 2 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 7.3.4.3 for further details.

Table 2 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													

[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.
[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.
[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 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 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

Table 3 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 3 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	

Table 3 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											

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.

[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 7.3.4.3 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.

[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.

Table 3 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											

[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 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 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

Table 4 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 4 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 7.3.4.3 for further details.

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

Table 4 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													

[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.

[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 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 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

1.1.1 Ulcerative Colitis

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

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

1.1.2 Crohn's Disease

Crohn's disease (CD) is a chronic, relapsing disease marked by granulomatous inflammation of the gastrointestinal (GI) tract. Although the terminal ileum and right colon are the most commonly involved sites, CD can affect any part of the GI tract, from the mouth to the perianal region. Inflammation is typically transmural (full-thickness), segmental, and discontinuous, and symptoms are predominantly determined by the part of bowel or organ involved. Patients typically present with symptoms including abdominal pain, diarrhea, rectal bleeding (RB), which may be persistent and lead to anemia, and weight loss due to pain on eating and malabsorption. As the disease progresses, extraintestinal manifestations and associated conditions can develop, including bowel obstruction, fistulas, and stenosis, as well as painful skin ulcerations, eye pain, and arthritis.

The incidence of CD is estimated to be up to 12.7 cases per 100,000 persons per year in Europe and up to 20.2 cases per 100,000 persons per year in North America. No clear difference in incidence has been observed between men and women. Although CD can occur at any age, peak incidence has been observed in the second to fourth decades of life, with a second modest rise in incidence in the latter decades of life (Molodecky et al., 2012).

Crohn's disease is a lifelong condition with a serious effect on quality of life. The traditional approach to therapy of CD has been the step-up approach usually represented as a pyramid where, progressing from mild to severe disease, therapeutic choices proceed step by step from less potent drugs at the base of the pyramid to more potent but also more toxic drugs at the top. Current treatment primarily consists of symptomatic management with dietary modifications, 5-ASA, opiates (loperamide), systemic glucocorticoids, immunosuppressive agents (AZA/6-MP, methotrexate [MTX]), and biologic therapy with anti-TNF agents or anti-integrin agents. Despite recent advances, there is still an unmet need for a safe, effective, and durable pharmacological treatment that will induce and maintain remission.

1.2 Product Background and Clinical Information

The selectivity of lymphocyte homing to specialized lymphoid tissue and mucosal sites of the GI tract is influenced by the endothelial expression of mucosal addressin cell adhesion molecule-1 (MAdCAM-1). MAdCAM-1 is a member of the immunoglobulin super family of cell adhesion molecules and is mostly expressed on the cell surface of high endothelial venules of organized intestinal lymphoid tissue such as Peyer's patches and mesenteric lymph nodes (Briskin et al., 1997; Shyjan et al., 1996; Liaskou et al., 2011). MAdCAM-1 plays a role in gut immune surveillance, and also appears to facilitate excessive lymphocyte infiltration under conditions of chronic GI inflammation. The $\alpha_4\beta_7$ integrin is the recognized ligand for MAdCAM-1, and expression of this ligand on populations of $CD4^+$ and $CD8^+$ T cells, as well as on subsets of B cells, distinguishes them as unique gut homing lymphocytes.

Ontamalimab (previously known as PF-00547659 and SHP647) is a fully human immunoglobulin G_2 kappa ($IgG_{2\kappa}$) monoclonal antibody that binds to human MAdCAM-1 to reduce lymphocyte homing to the gut and GI inflammation. Ontamalimab binds MAdCAM-1 with high affinity and selectivity that prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM-1-expressing sites in the high endothelial venules of the GI tract.

1.3 Benefit/Risk Assessment

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

In UC induction study A7281009, decreases in fecal calprotectin were observed in all groups, including placebo; however, there were no statistically significant differences in the decrease in fecal calprotectin between any dose level of ontamalimab and placebo. Decreases in high-sensitivity CRP (hsCRP) were also observed in all 4 treatment groups; however, other than the 75 mg dose group at Week 12, no statistically significant differences were observed in active treatment versus placebo.

In the induction study A7281006 in subjects with CD, compared to placebo, nominally statistically significant decreases in fecal calprotectin were observed in the 75 mg group at Week 8 and in the 22.5 mg and 75 mg groups at Week 12. Generally, decreases from baseline in hsCRP were observed in all 4 treatment groups over the 12-week induction period. Compared to placebo, nominally statistically significant decreases in hsCRP were observed in all 3 active treatment groups (22.5 mg, 75 mg, and 225 mg) at Week 12. There was no evidence of a dose response for either of these parameters. A nominally statistically significant increase was observed in circulating β7 + central memory T lymphocytes at Weeks 8 and 12, consistent with the predicted mechanism of action.

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

GI disorders SOC followed by the infections and infestations SOC. The most common all-causality TEAE was headache, followed by abdominal pain, nasopharyngitis, UC (worsening and progression of underlying disease), and nausea, all with similar incidence between placebo- and drug-treated subjects.

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

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

Always refer to the latest version of the ontamalimab Investigator's Brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding the pharmacokinetics (PK), efficacy, and safety of ontamalimab.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Ontamalimab, a fully human $IgG_{2\kappa}$ antihuman MAdCAM-1 monoclonal antibody, was under development for the treatment of UC and CD. Ontamalimab prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM-1-expressing sites with high affinity and selectivity. Principal sites of the MAdCAM-1 expression on normal tissue include intestine, pancreas, stomach, esophagus, spleen, and to a lesser extent lung, liver, and bladder but not the CNS (Steffen et al., 1996; Pullen et al., 2009).

Although selective targeting of the MAdCAM-1 receptors is a novel approach, the basic interference of lymphocyte homing by preventing the binding of these $\alpha_4\beta_7^+$ lymphocytes to the MAdCAM-1 receptor and the resultant efficacy in UC is well established (Feagan et al., 2013). Ontamalimab is differentiated from other molecules used for the treatment of UC in that it blocks the interaction of $\alpha_4\beta_7^+$ lymphocytes to the MAdCAM-1 receptor by selectively binding to MAdCAM-1 in the gut (and related tissues) whereas other molecules only target the integrins on the infiltrating lymphocytes. Additionally, ontamalimab does not bind to the vascular cell adhesion molecule; therefore, ontamalimab is not expected to be an effective treatment for multiple sclerosis, or affect lymphocyte homing or surveillance in the CNS.

In 2019, Takeda formally acquired Shire, the sponsor of 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. Per the announcement, the induction and maintenance studies will be closed earlier than originally planned. In recognition that this could potentially cause hardships for subjects who were benefiting from this investigational treatment (ie, fulfilling treatment response criteria as defined in Section 9.8.1.1 and Section 9.8.2.1), this long-term safety extension study, which is expected to be completed in no more than 3 years (ie, by December 2023), may continue to provide active treatment to subjects already enrolled who are responding to treatment and to subjects entering from a maintenance study who have responded to active treatment (ie, in the induction or maintenance studies and who meet the entry criteria). 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.

Originally, this extension study was designed to evaluate the safety and efficacy of long-term treatment with ontamalimab in subjects with moderate to severe UC or CD who: (1) completed one of the 4 multicenter, randomized, double-blind, placebo-controlled, parallel-group studies evaluating ontamalimab as an induction therapy (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) and did not meet the response criteria (clinical and/or endoscopic response/remission as appropriate) required for entry into a maintenance study (SHP647-303 or SHP647-307), or (2) were treatment failures (as defined in the respective protocols) and/or completers in one of the 2 multicenter, double-blind, randomized, placebo-controlled, parallel-group study evaluating ontamalimab as maintenance therapy (SHP647-303 or SHP647-307). 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.

Subjects in the induction studies SHP647-301 or SHP647-302:

- As of September 2020, no subjects remain in the induction studies who would be eligible to participate in this study (SHP647-304); therefore, no additional subjects from the induction studies will enter this study under Amendment 4.

Subjects in the maintenance studies SHP647-303 or SHP647-307:

- Subjects who received and responded to active treatment in either or both of the induction or maintenance studies may be eligible to enter this study.
- Subjects who have not received ontamalimab yet (ie, received placebo in both the induction and maintenance studies) will not be eligible to enter this study.
- Subjects eligible to enter this study will be assessed for treatment response criteria according to the revised study schedule in Study SHP647-304.

Subjects currently in Study SHP647-304 (ie, enrolled prior to Amendment 4) will be assessed for treatment response as follows:

- Subjects who have already entered Study SHP647-304 may continue and will be assessed for treatment response according to the revised study schedule. If they show response to ontamalimab treatment, they may continue further in this study.

- 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 be evaluated periodically and in case of clinical worsening at an unscheduled visit during the study for treatment response. If a subject shows response to ontamalimab treatment, he or she may continue in this study either until he or she shows a loss of treatment response (ie, no longer meets response criteria) or elects to seek another treatment option, or until the end of the study.

2.2 Study Objectives

2.2.1 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.

2.2.2 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.

2.2.3 Secondary Objectives – Subjects with Crohn's Disease

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

3. STUDY DESIGN

3.1 Study Design and Flow Chart

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" [DTP] program) for investigational product 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 (PFSs). Subjects will undergo treatment response and safety assessments as outlined in the Schedules of Assessments. Assessments for Year 1 are provided in Table 1 (for subjects with UC) and Table 3 (for subjects with CD). Assessments for Year 2 through end of study, are provided in Table 2 (for subjects with UC) and Table 4 (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 subscores. 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 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 and fecal calprotectin) will be assessed every 3 months or in case there is a necessity to confirm the loss of clinical treatment response.

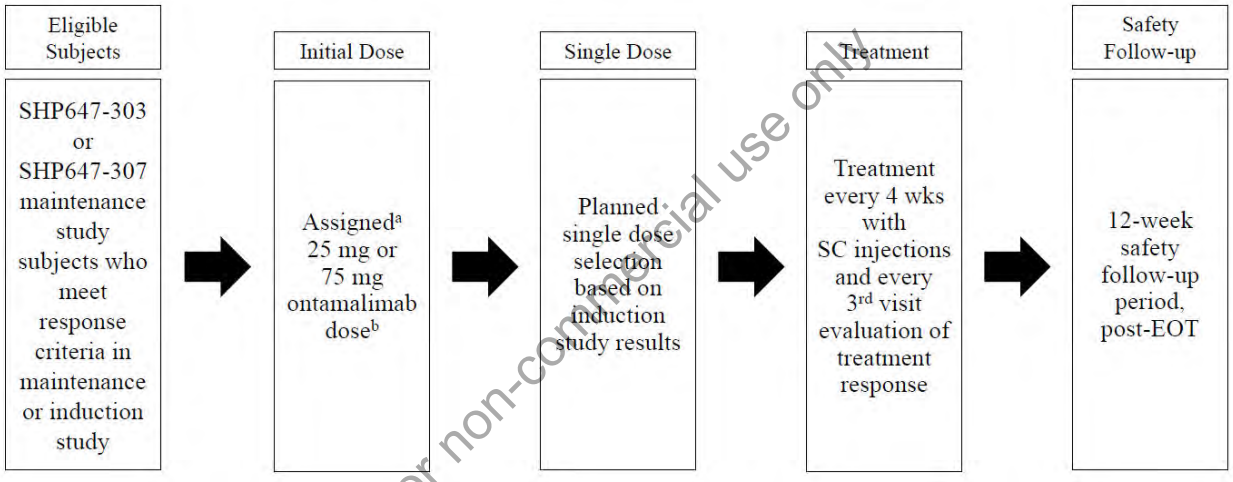
At every third visit, subjects with CD will be assessed for ongoing benefit (treatment response) using the CDAI score (treatment response defined as CDAI-100). Data on CDAI components (abdominal pain severity, very soft stool/liquid stool frequency, general well-being) will be collected from the subjects 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 (C-reactive protein 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 investigational product 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 (see Section 4.4.1 for further details).

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 Duration and Study Completion Definition

For subjects who are tolerating investigational product and receiving clinical benefit in the judgment of the investigator (ie, fulfilling treatment response criteria as defined in Section 9.8.1.1 and Section 9.8.2.1), study participation may continue until the subject withdraws from the study, or the investigator or sponsor decide to withdraw the subject (eg, in the interest of subject safety), or the sponsor decides to close the study, or the program is stopped completely. A subject's maximum duration of participation in this study under the current amendment is expected to be no more than 3 years (ie, a subject's participation is not planned to extend beyond 2023), subject to local or country requirements. Subjects will enter a 12-week safety follow-up period following the last dose of investigational product. Both the end of treatment (EOT) and 12-week safety follow-up visits are preferred to be on-site visits; however, 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, these visits may also be conducted at a subject's home, provided a qualified site staff member performs these evaluations following DTP guidance. It is expected that the study will be completed in no more than 3 years (ie, by December 2023).

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

3.3 Sites and Regions

This study will be conducted in approximately 225 sites in approximately 33 countries.

4. STUDY POPULATION

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

4.1 Eligibility Criteria – Subjects with Ulcerative Colitis

4.1.1 Inclusion Criteria

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must have been enrolled previously in Study SHP647-301 or SHP647-302 and are in the treatment period of Study SHP647-303, completed the ET or Week 52 visit in maintenance study SHP647-303, had responded to ontamalimab treatment (in the induction and/or maintenance studies), and meet one of the following criteria:
    - Subjects are on placebo at the maintenance study ET or Week 52 visit: they received ontamalimab in the induction studies and fulfilled the maintenance study response criteria, OR
    - Subjects have received ontamalimab at the maintenance study ET or Week 52 visit:
        - 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, compared to the baseline value for induction studies, and/or
        - Composite score that has decreased by ≥30% and ≥3 points compared to the baseline value for induction studies.
4. Subjects receiving any treatment(s) for UC described in Section 5.1.2.1 are eligible provided they have been on a stable dose for the designated period of time.

4.1.2 Exclusion Criteria

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

1. Subjects who had major protocol deviation(s) (as determined by the sponsor) in Study SHP647-301, SHP647-302, or SHP647-303.
2. Subjects who permanently discontinued investigational product because of an AE, regardless of relatedness to investigational product, in Study SHP647-301, SHP647-302, or SHP647-303.
3. Subjects who are likely to require major surgery for UC.
4. Subjects are females who became pregnant during Study SHP647-301, SHP647-302, or SHP647-303, females who are lactating, females who are planning to become pregnant during the study period, or males or females of childbearing potential not agreeing to continue using appropriate contraception methods (ie, highly effective methods for female and medically appropriate methods for male study subjects) through the conclusion of study participation (see Section 4.3).
5. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
6. Subjects who, in the opinion of the investigator or the sponsor, will be uncooperative or unable to comply with study procedures.
7. Subjects who have a newly-diagnosed malignancy or recurrence of malignancy (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
8. Subjects who have developed any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study.
9. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

10. Subjects with known exposure to *Mycobacterium tuberculosis* (TB) since testing at screening in Study SHP647-301 or SHP647-302 and who have been advised to require treatment for latent or active disease, but who are without a generally accepted course of treatment.
11. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are sponsor employees directly involved in the conduct of the study.
12. Subjects who are participating in other investigational studies (other than SHP647-301, SHP647-302, or SHP647-303) or plan to participate in other investigational studies during long-term extension study SHP647-304.

4.2 Eligibility Criteria – Subjects with Crohn's Disease

4.2.1 Inclusion Criteria

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must have been enrolled previously in Study SHP647-305 or SHP647-306 and are in the treatment period of Study SHP647-307, completed the ET or Week 52 visit in maintenance study SHP647-307, had responded to ontamalimab treatment (in the induction and/or maintenance studies), and meet one of the following criteria:

    - Subjects are on placebo at the maintenance study ET or Week 52 visit: they received ontamalimab in the induction study and fulfilled the maintenance study response criteria, OR
    - Subjects have received ontamalimab at the maintenance study ET or Week 52 visit:
        - CDAI score that has decreased by ≥100 points at EOT visit 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.
4. Subjects receiving any treatment(s) for CD described in Section 5.2.2.1 are eligible provided they have been on a stable dose for the designated period of time.

4.2.2 Exclusion Criteria

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

1. Subjects who had major protocol deviation(s) (as determined by the sponsor) in Study SHP647-305, SHP647-306, or SHP647-307.
2. Subjects who permanently discontinued investigational product because of an AE, regardless of relatedness to investigational product, in Study SHP647-305, SHP647-306, or SHP647-307.
3. Subjects who are likely to require major surgery for CD, or developed acute severe complications of CD (with or without fulfilling the treatment failure criteria in the maintenance study) that required immediate intervention (eg, need for immediate biologic treatment with proven effect) and/or CDAI score >450.
4. Subjects are females who became pregnant during Study SHP647-305, SHP647-306, or SHP647-307, females who are lactating, females who are planning to become pregnant during the study period, or males or females of childbearing potential not agreeing to continue appropriate contraception methods (ie, highly effective methods for female and medically appropriate methods for male study subjects) through the conclusion of study participation (see Section 4.3).
5. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
6. Subjects who, in the opinion of the investigator or the sponsor, will be uncooperative or unable to comply with study procedures.
7. Subjects who have a newly-diagnosed malignancy or recurrence of malignancy (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
8. Subjects who have developed any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study.

9. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or ECG abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
10. Subjects with known exposure to TB since testing at screening in Study SHP647-305 or SHP647-306, and who have been advised to require treatment for latent or active disease, but who are without a generally accepted course of treatment.
11. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are sponsor employees directly involved in the conduct of the study.
12. Subjects who are participating in other investigational studies (other than SHP647-305, SHP647-306, or SHP647-307) or plan to participate in other investigational studies during long-term extension study SHP647-304.

4.3 Reproductive Potential

The potential effects of ontamalimab on embryofetal or postnatal development have not been assessed in humans. Preliminary results from an enhanced pre- and postnatal development toxicity study of ontamalimab in nonhuman primates indicated that, at the dose levels tested (30 and 60 mg/kg), infant losses were increased in ontamalimab-exposed animals when compared both to control animals in the study and to the historical control animal data from the testing facility. The relevance of this finding to humans is unknown but cannot be excluded. Based on the exposure in the Phase 2 clinical study A7281009 (area under the concentration-time curve [AUC] from 0 to 672 hours [$AUC_{0\text{-}672h}$] at 6140 µg·h/mL following repeated SC administration of 75 mg SHP647 once every 4 weeks), maternal exposure (AUC) in cynomolgus monkeys within a similar duration at 30 and 60 mg/kg once every 10 days is approximately 77 times and 172 times the clinical exposure, respectively.

To minimize the risk of unintentional exposure of the embryo or fetus in the clinical study, all sexually active male and female subjects who, in the opinion of the investigator, are biologically capable of having children and with their partners are at risk of pregnancy, must agree to use an appropriate form of contraception (ie, highly effective methods for female and medically appropriate methods for male study subjects), in accordance with the package instructions/leaflet, for the duration of the active treatment period and for at least 16 weeks after the last dose of investigational product.

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

During the induction studies (SHP647-301, SHP647-302, SHP647-305, and SHP647-306) or maintenance studies (SHP647-303 and SHP647-307), the investigator or designee in consultation with the subject will confirm the subject's childbearing potential status. For subjects of childbearing potential, it must be confirmed and documented that the subject has selected the most appropriate method of contraception (ie, highly effective methods for female and medically appropriate methods for male study subjects) from the permitted list of contraception methods. Subjects must affirm the consistent and correct use of at least one of these selected methods. Regular contraception check discussions will take place at the time points specified in Table 1 and Table 2 (for subjects with UC), Table 3 and Table 4 (for subjects with CD) (ie, at each site visit) and will be documented. In addition, the subject must be instructed to call the site immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

4.3.1 Contraceptive Methods for Female Study Subjects

For subjects entering from a maintenance study, at baseline in this study, the childbearing potential of subjects must be re-established and documented if the subject's status has changed since the induction studies (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) or maintenance studies (SHP647-303 or SHP647-307) (see Section 7.3.4.7).

Sexually active females of childbearing potential must already be using an established highly effective form of contraception, and must be advised to use appropriate contraceptives throughout the study period and for 16 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the clinical study. The following highly effective contraceptive methods are considered to be methods with low user dependency:

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

- Male sterilization/vasectomized partner
- Implantable progesterone-only hormonal contraception associated with inhibition of ovulation.

Female subjects should be in one of the following categories:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥51 years of age); postmenopausal status should be confirmed by follicle-stimulating hormone (FSH) testing.
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization or has medically confirmed ovarian failure.
- Females of childbearing potential with a negative pregnancy test result at Study SHP647-304 baseline. Females of childbearing potential must agree to practice true abstinence (refrain from sexual activity that could result in pregnancy) or agree to use appropriate methods of highly effective contraception.

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

- Combined (estrogen- and progestogen-containing) hormonal contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal) stabilized for at least 30 days before Study SHP647-304 baseline
- Progestogen-only hormonal contraception associated with inhibition of ovulation plus a barrier method
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization/vasectomized partner with documented absence of sperm in the postvasectomy ejaculate
- True abstinence (see Section 4.3).

4.3.2 Contraceptive Methods for Male Study Subjects

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

Appropriate methods of contraception for male subjects are:

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

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

- Use of a highly effective method of contraception listed in Section 4.3.1 OR an acceptable method of contraception (failure rate of >1% per year)
  - Female condom with spermicide (use by female sexual partner); however, if spermicide is not available in the country, additional contraception (ie, one of those listed below) must be used in addition to a female condom
  - Intrauterine device with spermicide
  - Contraceptive sponge with spermicide
  - Intravaginal system (eg, vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide).

4.4 Withdrawal of Subjects

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

If investigational product is discontinued, regardless of the reason, the evaluations listed for the EOT visit are to be performed. All subjects who discontinue investigational product should also undergo the protocol-specified 12-week follow-up period. In the event that subjects are unable to

attend in person for the follow-up visit, all efforts should be made to collect information on AEs and concomitant medications. Comments (spontaneous or elicited) or complaints made by the subject must be recorded. The reason for termination and date of stopping investigational product must be recorded.

Subjects who discontinue will not be replaced.

4.4.1 Loss of Response

If response to investigational product 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 *C. 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.

If clinical response criteria are no longer satisfied and alternative explanations for clinical worsening (eg, infection) can be excluded, the subject will be discontinued. If necessary for assessment in the opinion of the investigator (eg, borderline treatment response results), the following evaluations may be considered:

1. Have subject return in 2 to 4 weeks for repeat assessment if loss of response criteria is still met:

    a) Perform endoscopy to determine if there is an objective benefit despite clinical symptoms; if the composite of clinical and endoscopic data meets response criteria, continue the study.

        1. Endoscopic response criterion for UC is Mayo endoscopic subscore decreased by ≥1 point as compared to the baseline value recorded upon entry into the induction studies.
        2. Endoscopic response criterion for CD is SES-CD improved by >25% as compared to the baseline value recorded upon entry into the induction studies.

    b) Biomarkers may be used to determine overall response criteria at the discretion of the investigator; serum CRP < upper limit of normal (ULN) or fecal calprotectin <250 µg/g is considered indicative of clinical benefit.

Upon termination from the study, subjects must return for a safety visit 12 weeks after the last dose of investigational product.

Subjects who have experienced loss of response should be withdrawn from active treatment once other possible etiologies have been ruled out and appropriate clinical evaluation has been performed as suggested above. While these response criteria are offered as general guidance to the investigator, there may be additional criteria that warrant withdrawal from active treatment, and the ultimate decision of withdrawal from active treatment is left to the investigator based on the assessment of disease activity, the subject's clinical benefit, and tolerance of the investigational product.

4.4.2 Subject Withdrawal Criteria

Additional reasons a subject may be withdrawn from active treatment include but are not limited to: AEs, SAEs, pregnancy, protocol deviations, and failure to return for visits.

A subject should be withdrawn from study treatment if the subject undergoes surgery for UC or CD.

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

If a subject chooses to withdraw from study participation due to personal concerns related 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 (other than a COVID-19-related or other pandemic-related AE), this should be specified as the reason for subject withdrawal in the electronic case report form (eCRF).

If a subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluation should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

4.4.3 Reasons for Withdrawal

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and source document. This includes unavoidable circumstances, such as 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.

If a subject chooses to withdraw from study participation due to personal concerns related 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 (other than a COVID-19-related or other pandemic-related AE), this should be specified as the reason for subject withdrawal in the eCRF.

Other reasons for discontinuation may include but are not limited to:

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

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

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

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior and Concomitant Treatment – Subjects with Ulcerative Colitis

5.1.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal remedies and vitamins) that is ongoing at the time of the baseline visit. It is expected that prior treatment will have been recorded during the induction study.

5.1.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product in this study and the end of the safety follow-up period, inclusive. Additional safety assessments may be required, according to concomitant therapy safety recommendations.

5.1.2.1 Permitted Treatment

Any permitted treatment may be initiated or discontinued as clinically appropriate. The following treatments for UC are permitted as concomitant medication:

- 5-ASA (mesalamine) and sulfasalazine
- Immunosuppressants (AZA, 6-MP, MTX)
- Concomitant oral glucocorticoids; however, tapering should start once subject achieves adequate treatment response and should be guided by investigator clinical judgment. The recommended tapering scheme, based on European Crohn's and Colitis Organisation (ECCO) guidelines, is shown in Table 5.

Note: If a new course of oral glucocorticoid treatment (for IBD) is required, the subject should be discontinued from the study.

Table 5 Glucocorticoid Tapering – Subjects with Ulcerative Colitis

	First Taper	Subsequent Taper
Timing	Prospectively define glucocorticoid-dependent subjects (ie, ECCO[a])	When subject is stable
Increments	• If daily dose >10 mg: Taper by 5 mg/day each 1-2 weeks • When daily dose is ≤10 mg: Taper by 2.5 mg/day each 1-2 weeks	• If daily dose is >5 mg: Taper by 2.5 mg/day each week • When daily dose is ≤5 mg: Taper by 1 mg/day each week
Action if unable to taper	Return to SHP647-304 baseline dose	

ECCO=European Crohn's and Colitis Organisation.
[a] Glucocorticoid-dependent subjects are:

- Subjects who are unable to reduce glucocorticoids below the equivalent of prednisone 10 mg/day (or budesonide below 3 mg/day) within 3 months of starting glucocorticoids, without recurrent active disease OR
- Subjects who have a relapse within 3 months of stopping glucocorticoids (Dignass et al., 2012).

Medicinal marijuana (cannabis) under a physician's prescription, obtained from a licensed pharmacy or provider may be used.

Routine nonlive vaccinations are allowed during the study.

Dietary and herbal supplements and probiotics are allowed in the study and should be recorded as concomitant medications.

Use of nicotine-containing preparations should be recorded as concomitant medication.

5.1.2.2 Prohibited Treatment

The following common treatments are excluded medications for this study. As the subjects are transferred from Study SHP647-301, SHP647-302, or SHP647-303, during which these treatments were also prohibited, no washout period is applicable.

- Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab)
- Anti-TNF treatment and other biologics with immunomodulatory properties including biosimilars
- Live (attenuated) vaccines
- Any investigational product other than ontamalimab

- Nonbiologics with immunomodulatory properties (except for AZA, 6-MP, and MTX, which are permitted)
- Leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange.

Treatments not listed in this section may be considered allowable; see Section 5.1.2.1 for further details.

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

Subjects who enter the 12-week safety follow-up period will no longer need to abstain from the medications that were prohibited during the treatment period. Other UC treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated without prior discussion with the sponsor study physician or designee, due to the long half-life of ontamalimab.

5.2 Prior and Concomitant Treatment – Subjects with Crohn's Disease

5.2.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal remedies and vitamins) that is ongoing at the time of the baseline visit. It is expected that prior treatment will have been recorded during the induction study.

5.2.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product in this study and the end of the safety follow-up period, inclusive. Additional safety monitoring may be required, according to concomitant therapy safety recommendations.

5.2.2.1 Permitted Treatment

The following treatments for CD are permitted as concomitant medication:

- Oral 5-ASA (mesalamine) and sulfasalazine
- Immunosuppressants (AZA, 6-MP, MTX)

- Concomitant oral glucocorticoids; however, tapering should start once subject achieves adequate treatment response and should be guided by investigator clinical judgment. The recommended tapering scheme, based on ECCO guidelines, is shown in Table 6. Parenteral and rectally used glucocorticoids are permitted per discretion of the investigator.

Note: If a new course of oral glucocorticoid treatment (for IBD) is required, the subject should be discontinued from the study.

Table 6 Glucocorticoid Tapering – Subjects with Crohn's Disease

	First Taper	Subsequent Taper
Timing	Prospectively define glucocorticoid-dependent subjects (ie, ECCO[a])	When subject is stable
Increments	• If daily dose >10 mg: Taper by 5 mg/day each 1-2 weeks • When daily dose is ≤10 mg: Taper by 2.5 mg/day each 1-2 weeks • When daily dose of budesonide is up to a maximum of 9 mg/day: Taper by 3 mg every 3 weeks	• If daily dose is >5 mg: Taper by 2.5 mg/day each week • When daily dose is ≤5 mg: Taper by 1 mg/day each week
Action if unable to taper	Return to SHP647-304 baseline dose	

ECCO=European Crohn's and Colitis Organisation.

[a] Glucocorticoid-dependent subjects are:

- Subjects who are unable to reduce glucocorticoids below the equivalent of prednisone 10 mg/day (or budesonide below 3 mg/day) within 3 months of starting glucocorticoids, without recurrent active disease
  OR
- Subjects who have a relapse within 3 months of stopping glucocorticoids (Dignass et al., 2012).

Antidiarrheal opiate drugs such as IMODIUM® (loperamide), LOMOTIL® (diphenoxylate hydrochloride and atropine sulfate), tincture of opium, and codeine will be recorded.

Medicinal marijuana (cannabis) under a physician's prescription, obtained from a licensed pharmacy or provider may be used.

Routine nonlive vaccinations are allowed during the study.

Dietary and herbal supplements and probiotics are allowed in the study and should be recorded as concomitant medications.

Use of nicotine-containing preparations should be recorded as concomitant medication.

5.2.2.2 Prohibited Treatment

The following common treatments are excluded medications for this study. As the subjects are transferred from Study SHP647-305, SHP647-306, or SHP647-307, during which these treatments were also prohibited, no washout period is applicable.

- Off-label usage of immunosuppressants used in transplantation or other non-established therapies for CD (eg, mycophenolate mofetil, cyclosporine, rapamycin, thalidomide, tofacitinib, or tacrolimus)
- Rectally administered 5-ASA
- Bismuth subsalicylate products
- Anti-TNF treatment and other biologics with immunomodulatory properties, including biosimilars
- Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab)
- Nonbiologics with immunomodulatory properties (except for AZA, 6-MP, and MTX, which are permitted)
- Lymphocytes apheresis or selective monocyte granulocytes apheresis
- Live (attenuated) vaccines
- Fecal microbiota transplantation
- Any investigational product other than ontamalimab.

Treatments not listed in this section may be considered allowable; see Section 5.2.2.1 for further details.

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

Parenteral nutrition is not permitted at any time during the study.

Subjects who enter the 12-week safety follow-up period will no longer need to abstain from the medications that were prohibited during the treatment period. Other CD treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated without prior discussion with the sponsor study physician or designee, due to the long half-life of ontamalimab.

5.3 COVID-19

In cases in which the subject is known to have been infected with the COVID-19 virus but does not have the disease, he or she should be actively moved to lower doses of prednisone (<20 mg/day) or transition to budesonide when feasible. Thiopurines and MTX should be temporarily withheld. The study drug should have dosing delayed for 2 weeks while the subject is monitored for the development of COVID-19.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

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

6.1.1 Blinding the Treatment Assignment

The fill volume for all syringes will be the same.

This study has been double-blind, as the purpose of the blinding was to maintain the blind in maintenance study SHP647-303 for UC subjects and SHP647-307 for CD subjects while these studies are ongoing. Due to the early discontinuation of the program, this study is planned to become unblinded after the completion of the analysis for the induction studies (SHP647-301, SHP647-302, SHP647-305, and SHP647-306) and prior to the completion of the SHP647-303 and SHP647-307 studies. Until the induction study results become available, this study will continue to be blinded (ie, unblinding will not occur until the final analysis of the induction studies is completed), 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. If neither dose is deemed efficacious, this study will be terminated.

As the treatment assignment is planned to be unblinded after the completion of the analysis for the induction studies (SHP647-301, SHP647-302, SHP647-305, and SHP647-306) and prior to the completion of the SHP647-303 and SHP647-307 studies, these two studies will be considered unblinded, and the date of study unblinding will be recorded.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

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

6.2.2 Allocation of Subjects to Treatment

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 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 investigational product 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 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 investigational product packing identification number may not be assigned to more than 1 subject.

6.2.3 Dosing

Investigational product (ontamalimab) will be administered subcutaneously every 4 weeks for the duration of the treatment period. See Section 7.3 for the timing of dosing relative to other procedures.

Investigational product should be administered in the anterolateral right or left thigh. The injection site should be rotated. If there are clinical reasons why the drug cannot be administered in the thigh, the drug may be administered in the deltoid area or abdomen with appropriate documentation.

As some subjects may enter this study having received placebo and not active treatment in the induction (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) or maintenance (SHP647-303 or SHP647-307) study, after the first administration of investigational product, the subject must be observed by a member of the study staff for at least 30 minutes (the total duration should be determined at the discretion of the investigator). For subsequent administrations, observation of the subject is at the discretion of the investigator. Injection site and allergic reaction monitoring should be completed by a member of the study staff.

Principal investigators are responsible for ensuring that all study and nonstudy personnel identified to administer investigational product are qualified, with documented training and delegation of responsibilities prior to their first investigational product administration visit at subjects' homes.

In a situation in which a subject is not able to visit the study 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, DTP investigational product administration options may be available, in accordance with local regulations (refer to DTP guidance document).

All subjects and nonstudy personnel performing the investigational product administration must receive training in order to receive DTP shipments. Training will include how to identify hypersensitivity reactions, inject the IP, and properly dispose of IP after use. Training may be in person or via telephone call. All DTP shipments will require pre-administration and post-administration calls by the site staff to assess and monitor subject's health status and safety; to review any AEs, concomitant medications, and diary assessments; and to perform the neurological questionnaire assessment by the investigator. These calls must be appropriately recorded in the source document.

The personnel that perform study procedures at the subjects' homes will be delegated, trained, and properly supervised by the principal investigator(s) of each site.

All study and nonstudy personnel will be trained on potential hypersensitivity reactions (Type I and Type III) and associated symptoms.

NOTE: DTP investigational product administration, except when performed by study personnel, is NOT ALLOWED for a subject's first dose of investigational product in this study.

Investigator-directed delays in dosing due to abnormal laboratory results or AEs or 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 should be discussed with the medical monitor to determine whether the subject should remain in the study. Dosing delays up to 8 weeks (2 doses) are allowed, and the subjects are allowed to miss a maximum of 2 doses due to COVID-related or other pandemic-related issues (see Section 5.3). Sites must receive Shire approvals for each subject meeting the missed/delayed dosing criteria.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is dispensed by qualified staff members. During the COVID-19 public health emergency (or other similar pandemic), alternative investigational product delivery to study participants may be necessary to avoid unnecessary subject visits to sites while providing needed investigational product. Additional investigational product may be dispensed during a scheduled study visit or investigational product may be shipped directly from investigational sites to participants' residences by a contracted logistics provider or distributor (DTP shipment) in compliance with national laws or temporary national emergency measures and sponsor processes.

6.2.4 Unblinding the Treatment Assignment

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.

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.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

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

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

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

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

6.3.2 Packaging

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

Changes to sponsor-supplied packaging before dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

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

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. In case of a DTP situation, the investigational product can be shipped to subject's home; please refer to DTP guidance for further details.

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

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

6.3.4 Special Handling

The investigational product should be protected from light and should not be frozen. Do not shake. In case of a DTP situation, the safety of the investigational product will be managed; it will be transported via a secured courier or study site personnel with temperature monitoring and tracking. Please refer to DTP guidance for further details.

6.4 Drug Accountability

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

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

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented in the subject's source document and/or other investigational product record. In case of a DTP situation, the investigational product administration will be documented in the drug administration visit report form (if nonstudy personnel administer the investigational product) and in the drug administration log (in case of self-administration by the subjects/caregivers/parents).

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

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

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

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

6.5 Subject Compliance

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

7. STUDY PROCEDURES

7.1 Changes to Study Procedures Due to a Pandemic

The following information provides guidance regarding changes to study procedures that may be implemented for study participants or study sites affected by a pandemic (eg, coronavirus disease [COVID-19] or other future similar unexpected public health concerns) that require physical distancing that may result in subjects missing their visits. This guidance takes references from the US Food and Drug Administration (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency – Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 02 July 2020; the European Medicines Agency (EMA) Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic, Version 3 (28 April 2020); and the EMA Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, dated 26 June 2020.

Because a pandemic (eg, COVID-19) may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical team as needed, while maintaining subject safety and confidentiality as the priority.

Procedural changes due to COVID-19 (or other similar pandemic) may include the following (refer to DTP guidance document for further details):

- Allow study sites to follow COVID-19 screening requirements per local regulations.
- Identify which study visits and procedures may be conducted in the clinic or by optional home healthcare and evaluations that may be done remotely (eg, Telehealth, Telemedicine). See Table 1, Table 2, Table 3, and Table 4 for details on subject visits that must be done with the subject present at the investigative site and visits that may be conducted at the clinic or by home healthcare visits to extend flexibility to patients during the COVID-19 public health emergency (or other similar pandemic). Home healthcare visits will be documented in the study records and eCRF.
- Allowance of more flexibility around scheduling of study visits and/or allowing some assessments to be conducted remotely (See Table 1, Table 2, Table 3, and Table 4).

- For home healthcare visits, collection of clinical laboratory samples (blood specimen collection or other diagnostic tests) may be performed by the investigator or qualified site staff who can visit the trial participant's residence, or at a local laboratory if necessary.
- Missed clinic visits or subject withdrawals due to COVID-19 (or other similar pandemic) must be recorded on the eCRF (See Section 4.4.3, Reasons for Withdrawal).
- ECG procedures: For home healthcare visits, ECGs may be performed by a qualified healthcare professional who is authorized/certified to perform such tests routinely.
- "Remote visits" via virtual communications (eg, TeleHealth application) may be performed as a safety check (AE assessment) on subject well-being, concomitant medication use, neurological assessments, etc.
- Allow transfer of study participants to investigational sites away from risk zones or closer to their home that are already participating in the trial or to new sites.
- Deviations from the protocol-specified procedures (eg, not collecting a protocol-specified specimen, such as postdose bloodwork) will be recorded as related to COVID-19 (or other similar pandemic).
- Alternative investigational product deliveries may include dispensing additional investigational product at clinic visits or DTP delivery of the investigational product from the investigational site to subjects in compliance with national laws or temporary national emergency measures (See Section 6.2.3, Dosing and Section 6.3, Labeling, Packaging, Storage, and Handling).

7.2 Study Schedule

The investigator may schedule visits (unscheduled visits) in addition to those listed on the schedules of assessments (Table 1 and Table 2 for subjects with UC and Table 3 and Table 4 for subjects with CD), in order to conduct evaluations or assessments required to protect the well-being of the subject.

7.2.1 Subjects with Ulcerative Colitis

7.2.1.1 Baseline Visit (Week 0/Day 1)

For subjects entering into Study SHP647-304 from maintenance study SHP647-303 and who completed the 52-week treatment period, procedures performed (with the exception of the treatment response evaluation) at the Week 52 visit will be used as the baseline visit (Week 0/Day 1) assessments for this extension study. For subjects entering from maintenance study SHP647-303 and who completed participation prior to Week 52, procedures performed (with the exception of the treatment response evaluation) at the ET visit will be used as the baseline visit (Week 0/Day 1) assessments for this extension study. The assessments and procedures performed during the baseline visit are specified in Table 1.

For subjects entering into Study SHP647-304 from a maintenance study, baseline of the induction study will be used as the baseline visit (Week 0/Day 1) for treatment response evaluation for this extension study.

The assessments and procedures performed during the baseline visit are specified in Table 1.

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

For eligible subjects, all relevant study information (with the exception of the treatment response evaluation) recorded for Week 12 of the induction study or Week 52 or ET of the maintenance study will be used as the baseline visit data for this extension study.

After eligibility has been confirmed and all baseline procedures and assessments have been completed, each subject will be assigned to 1 of the 2 treatment groups as described in Section 6.2.2 and the first dose of investigational product will be administered.

7.2.1.2 Treatment Period

During the treatment period in this extension study, subjects will attend study visits every 4 weeks (Weeks 4, 8, 12, 16, etc.). Assessments and procedures to be performed at each visit are specified in Table 1.

Assessments and procedures to be performed at each visit beginning in Treatment Year 2 (Week 52) are specified in Table 2.

For subjects who are tolerating investigational product and receiving clinical benefit in the judgment of the investigator, study participation may continue until the subject withdraws from the study, or the investigator or sponsor decide to withdraw the subject (eg, in the interest of subject safety), or the sponsor decides to close the study, or the program is stopped completely.

Once study treatment has ended, ie, for any of the reasons described in Section 4.4, subjects will attend the EOT visit, at which assessments and procedures will be performed as shown in Table 2. The EOT visit is preferred to be an on-site visit; however, 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, this visit may also be conducted at a subject's home, provided a qualified site staff member performs these evaluations following DTP guidance. After completion of the EOT visit, subjects will enter the safety follow-up period.

7.2.1.3 Follow-up Period

The safety follow-up period for this protocol is 12 weeks from the EOT visit for each subject. During the follow-up period, there will be a visit at the study site at 12 weeks (±10 days) post-EOT. The 12-week safety follow-up visit is preferred to be an on-site visit; however, 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, this visit may also be conducted at a subject's home, provided a qualified site staff member performs these evaluations following DTP guidance.

The assessments and procedures specified in Table 2 will be performed, including querying for SAEs, AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

7.2.2 Subjects with Crohn's Disease

7.2.2.1 Baseline Visit (Week 0/Day 1)

For subjects entering into Study SHP647-304 from maintenance study SHP647-307 and who completed the 52-week treatment period, procedures performed (with the exception of the treatment response evaluation) at the Week 52 visit will be the baseline visit (Week 0/Day 1) assessments for this extension study. For subjects entering from maintenance study SHP647-307 and who completed participation prior to Week 52, procedures performed (with the exception of the treatment response evaluation) at the ET visit will be the baseline visit (Week 0/Day 1) assessments for this extension study.

For subjects entering into Study SHP647-304 from a maintenance study, baseline of the induction study will be used as the baseline visit (Week 0/Day 1) for treatment response evaluation for this extension study.

The assessments and procedures performed during the baseline visit are specified in Table 3.

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

For eligible subjects, all relevant study information (with the exception of the treatment response evaluation) recorded for Week 16 of the induction study or Week 52 or ET of the maintenance study will be used as the baseline visit data for this extension study.

After eligibility has been confirmed and all baseline procedures and assessments have been completed, each subject will be assigned 1 of the 2 treatment groups as described in Section 6.2.2 and the first dose of investigational product will be administered.

7.2.2.2 Treatment Period

During the treatment period in this extension study, subjects will attend study visits every 4 weeks (Weeks 4, 8, 12, 16, etc.). Assessments and procedures to be performed at each visit are specified in Table 3.

Assessments and procedures to be performed at each visit beginning in Treatment Year 2 (Week 52) are specified in Table 4.

For subjects who are tolerating investigational product and receiving clinical benefit in the judgment of the investigator, study participation may continue until the subject withdraws from the study, or the investigator or sponsor decide to withdraw the subject (eg, in the interest of subject safety), or the sponsor decides to close the study, or the program is stopped completely.

Once study treatment has ended, ie, for any of the reasons described in Section 4.4, subjects will attend the EOT visit, at which assessments and procedures will be performed as shown in Table 4. The EOT visit is preferred to be an on-site visit; however, 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, this visit may also

be conducted at a subject's home, provided a qualified site staff member performs these evaluations following DTP guidance. After completion of the EOT visit, subjects will enter the safety follow-up period.

7.2.2.3 Follow-up Period

The safety follow-up period for this protocol is 12 weeks from the EOT visit for each subject. During the follow-up period, there will be a visit at the study site at 12 weeks (±10 days) post-EOT. The 12-week safety follow-up visit is preferred to be an on-site visit; however, 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, this visit may also be conducted at a subject's home, provided a qualified site staff member performs these evaluations following DTP guidance.

The assessments and procedures specified in Table 4 (for subjects with CD) will be performed, including querying for SAEs, AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

7.2.3 Additional Care of Subjects After the Study

No aftercare is planned for this study.

7.3 Study Evaluations and Procedures

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

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

- Vital signs and ECG
- Laboratory sample collection
- Endoscopy, if performed (see Sections 7.3.2.1 and 7.3.3.1)

- Investigational product administration.

Notes:

- Blood and tissue samples may be stored for up to the duration allowed by local regulations but for no longer than 25 years.
- Endoscopy is optional after the implementation of Amendment 4; if performed, the results should be recorded.

7.3.1 Demographic and Other Baseline Characteristics

For subjects entering this extension study SHP647-304 from a maintenance study, all relevant demographic and baseline characteristics recorded for the induction study (SHP647-301, SHP647-302, SHP647-305, or SHP647-306) or maintenance study (SHP647-303 or SHP647-307) will be used as the baseline characteristics for this study.

7.3.2 Treatment Response Assessments – Subjects with Ulcerative Colitis

7.3.2.1 Endoscopy

Endoscopy is optional after the implementation of Amendment 4; if performed, the results should be recorded using the Mayo endoscopic subscore. Endoscopy may be performed at the time points specified in Table 1 and Table 2 and is to consist of either flexible sigmoidoscopy or colonoscopy (if preferred) for subjects with UC or colonoscopy (if preferred) for subjects with CD. If more than 2 endoscopies/colonoscopies are needed in a year, the subject should be discontinued.

If it is necessary, bowel preparation should be conducted as per local routine. The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during the baseline endoscopy in the induction study (SHP647-301 or SHP647-302) or maintenance study (SHP647-303).

The endoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's medical record. Endoscopy results will be reviewed by a local reader.

7.3.2.2 Mayo Score

The Mayo score is a measure of UC disease activity. Mayo scores (total or partial) will be recorded at the time points specified in Table 1 and Table 2.

The total Mayo score ranges from 0 to 12 points and consists of the following 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease (see Appendix 2):

- Bowel movement frequency (0-3)
- Rectal bleeding (0-3)
- Findings of flexible sigmoidoscopy or endoscopy (0-3)
- Physician global assessment (PGA; 0-3).

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

The composite score is a recommended measure consisting of the Mayo score without the PGA subscore and ranges from 0 to 9 points. Note: After the implementation of Amendment 4, endoscopy is optional, and the composite score will be computed only if an endoscopy is performed.

The clinical composite score is a measure consisting of RB plus stool frequency 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 7.3.2.3). 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 stool frequency 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.

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 (see Appendix 2). 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 patient's recollection of abdominal discomfort and general sense of well-being and other observations (such as physical findings and the patient's performance status). The endoscopic subscore and the PGA must be performed by a physician qualified to perform endoscopy; it is recommended that the same physician performs all such assessments for a particular subject throughout the study, and that the same physician who performed the assessments during the induction study does so during the current study.

7.3.2.3 Ulcerative Colitis Memory Aid

Subjects will be asked to report the following signs and symptom data, as experienced over the previous 24 hours, with the assistance of a memory aid, which they may use for the 7 days prior to each scheduled visit:

- Stool frequency
- Rectal bleeding severity

The memory aid guidelines for subjects with UC are presented in Appendix 2.

7.3.3 Treatment Response Assessments – Subjects with Crohn's Disease

7.3.3.1 Colonoscopy

Colonoscopy is optional after the implementation of Amendment 4; if performed, the results should be recorded using the SES-CD. Colonoscopy may be performed at the time points specified in Table 3 and Table 4. If more than 2 colonoscopies are needed in a year, the subject should be discontinued.

Bowel preparation regimens typically incorporate dietary modifications along with oral cathartics. Typically, the standard dose of a bowel preparation is split between the day before and the morning of the procedure. In this study, bowel preparation and colonoscopy are to be conducted as per local routine; however, sodium phosphate based preparations should be avoided, as such regimens can produce mucosal changes that mimic IBD.

A complete colonoscopy that includes the visualization of rectum, the sigmoid colon, the left colon, the transverse colon, the right colon, the ileocecal valve, and the terminal ileum should be performed. Incomplete endoscopy caused by but not limited to a complication during endoscopy, interruption of the endoscopy for any reasons cannot be accepted as complete colonoscopy with the exception of impassable stenosis or other CD-related complications as cause of failure to complete the colonoscopy procedure.

The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during the baseline endoscopy in the induction study (SHP647-305 or SHP647-306). The colonoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's medical record. Colonoscopy results will be reviewed by a local reader.

7.3.3.2 Simple Endoscopic Activity Score for Crohn's Disease

Colonoscopy, if performed, will be evaluated by the SES-CD scoring system at the time points specified in Table 3 and Table 4.

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 when 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 that the stenosis scores cannot exceed a total of 11 (Reinisch et al., 2017).

The SES-CD is presented in Appendix 2.

7.3.3.3 Crohn's Disease Activity Index

The CDAI is a composite measure with 8 components; 3 components (abdominal pain severity, very soft stool/liquid stool frequency, and general well-being) will be self-reported by the subject, as described in Section 7.3.3.4, and 5 components will be recorded at the time points specified in Table 3 and Table 4.

The CDAI scores at visits specified in Table 3 and Table 4 will be calculated using the following:

- Components 1 to 3 from subject-reported data collected for 7 days before the visit (see Section 7.3.3.4) and
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at the visit.

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 is presented in Appendix 2.

7.3.3.4 Crohn's Disease Memory Aid

Subjects will be asked to recall clinical data for the CDAI score. They may use a memory aid to record 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 investigator will record this information in the eCRF and use it to calculate the CDAI score for that visit.

The memory aid guidelines for subjects with CD are presented in Appendix 2.

7.3.4 Safety

7.3.4.1 Medical and Medication History

For subjects entering from an induction or maintenance study, medical history, including UC or CD history, cardiac history, and smoking history, and prior medications will be collected at the screening visit of Study SHP647-301, SHP647-302, SHP647-305, or SHP647-306.

Concomitant medications and procedures will be documented throughout the SHP647-304 study at the time points specified in Table 1 and Table 2 (for subjects with UC) and in Table 3 and Table 4 (for subjects with CD).

7.3.4.2 Physical Examination (Including Weight)

Complete and targeted physical examinations and weight assessments will be performed at the times specified in Table 1 and Table 2 (for subjects with UC) and in Table 3 and Table 4 (for subjects with CD). 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. For subjects with CD, targeted physical examination includes review of the skin and mucosa, specifically perianal for fistula and oral cavity for stomatitis as part of the CDAI assessment.

Weight will be measured at the time points specified in Table 1 and Table 2 (for subjects with UC), and Table 3 and Table 4 (for subjects with CD).

The complete physical examination performed at Week 12 of induction study SHP647-301 or SHP647-302, at Week 16 of induction study SHP647-305 or SHP647-306, or at the ET or Week 52 visit of maintenance study SHP647-303 or SHP647-307, will be the baseline (Week 0/Day 1) examination of Study SHP647-304. Abnormalities identified during this visit will be documented. Any changes from the baseline visit (Week 0/Day 1) in physical examination findings that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.3.4.3 Targeted Neurological Assessment

Targeted neurological assessments to monitor for the development of signs and/or symptoms of PML will be performed at the time points specified in Table 1 and Table 2 (for subjects with UC), and Table 3 and Table 4 (for subjects with CD). Subjects will be evaluated to reveal any potential abnormalities in the following neurological domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior.

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

A step-wise approach for the proposed neurological assessment plan is provided in Table 7.

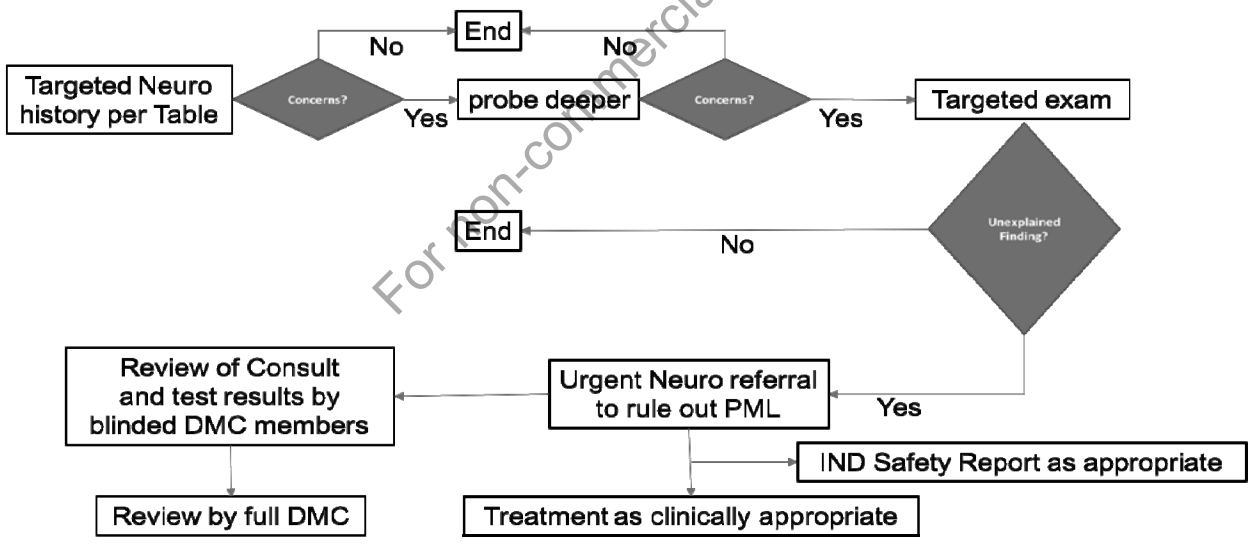
Table 7 Quarterly Neurological Assessments

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

Additionally, should there be any unexplained abnormal neurological findings, the subject is to be urgently referred to a neurologist. The sites will immediately inform the sponsor of any such occurrences. If the neurologist confirms the presence of PML, appropriate actions, including discontinuation of investigational product, will be taken. Suspected PML cases will be reviewed promptly by data monitoring committee (DMC) members with PML expertise and presented at the next scheduled DMC meeting(s). If PML is diagnosed, the treatment code will be unblinded and there will be an urgent meeting of the DMC. A flow diagram of the quarterly assessments and actions is presented in Figure 2. Any concerns from the DMC will be promptly communicated to the sponsor, investigator, and treating neurologist.

After the study is unblinded, assessment of potential PML will be conducted by independent physicians with PML expertise. If they conclude that a diagnosis of PML is likely, there will be an urgent meeting of the Safety Management Team (SMT) to review the data and make a recommendation regarding continuation of the study. Any concerns from the independent experts or the SMT will be promptly communicated to the investigator and treating neurologist.

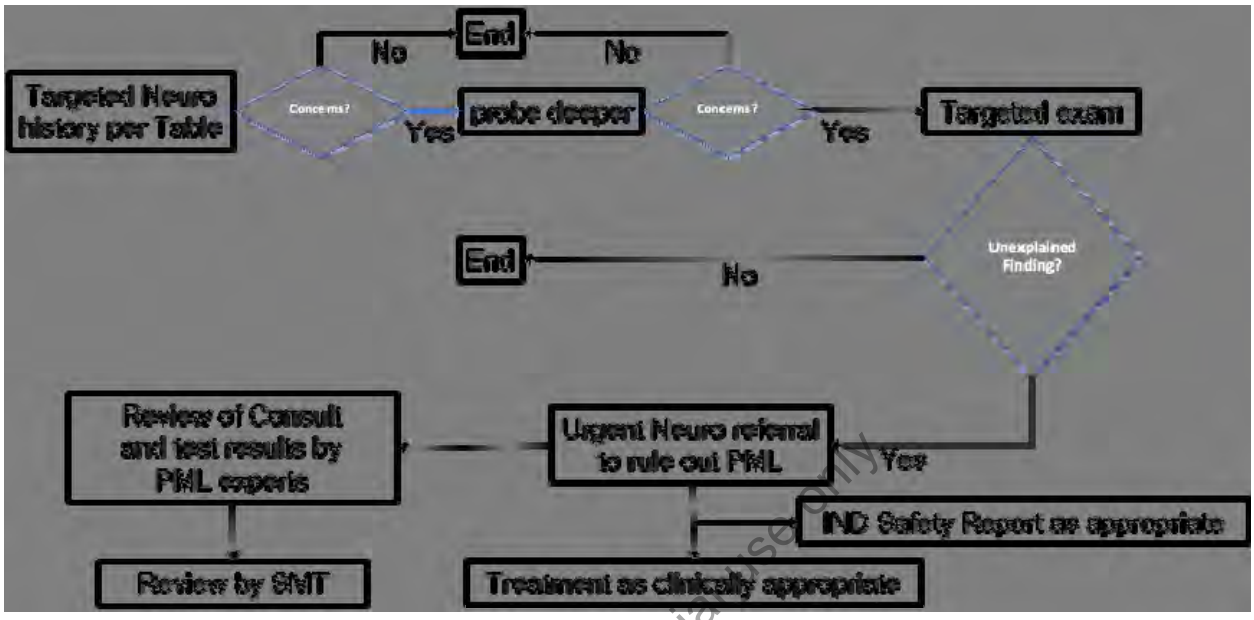
Figure 2 Flow Diagram for Quarterly Neurological Assessments



DMC=data monitoring committee; IND=investigational new drug; neuro=neurological; PML=progressive multifocal leukoencephalopathy.

After the study has been unblinded, the flow diagram will be modified as shown in Figure 3.

Figure 3 Post-unblinding Flow Diagram for Quarterly Neurological Assessments



IND=investigational new drug; neuro=neurological; PML=progressive multifocal leukoencephalopathy; SMT=Safety Management Team.

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

7.3.4.4 Adverse Event Collection

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

7.3.4.5 Vital Signs

Vital signs will be measured at the time points specified in Table 1 and Table 2 (for subjects with UC), and Table 3 and Table 4 (for subjects with CD). Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data. Vital signs include blood pressure, pulse, respiratory rate, and temperature. Vital signs should be recorded before collection of blood samples for laboratory assessments, where applicable.

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

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

Body temperature should be taken using a thermometer and reported in degrees Celsius or Fahrenheit.

Any deviations from baseline (Week 0/Day 1) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE unless documented in the subject's medical history as a pre-existing medical condition.

7.3.4.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. Clinical laboratory assays 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 (Clinical Laboratory Improvement Amendments) certificate, and the investigator must add the local laboratory as appropriate. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed at the time points specified in Table 1 and Table 2 (for subjects with UC) and in Table 3 and Table 4 (for subjects with CD):

Serum Chemistry	
• alkaline phosphatase • aspartate aminotransferase • alanine aminotransferase • total bilirubin • total protein • albumin • glucose	• blood urea nitrogen • creatinine • sodium • potassium • chloride • calcium • carbon dioxide
Hematology	
• hemoglobin • hematocrit • mean corpuscular hemoglobin • mean corpuscular hemoglobin concentration • mean corpuscular volume • erythrocyte (red blood cell) count • leukocyte (white blood cell) count	• neutrophils • lymphocytes • monocytes • eosinophils • basophils • platelet count
Urinalysis	
• glucose • protein • specific gravity • pH • nitrite	• bilirubin • ketones • hemoglobin • urobilinogen • leukocyte esterase

Diagnosis of *C. difficile* infection should be made using the central laboratory. If, for any reason, the central laboratory is not available, please see Appendix 4 for guidance regarding the diagnostic algorithms. When a subject experiences an increase in GI symptoms, which could be an exacerbation of disease, an infectious etiology must be evaluated including testing for *C. difficile* as described in Appendix 4.

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

7.3.4.7 Pregnancy Test and Follicle-stimulating Hormone Test

A urine beta–human chorionic gonadotropin (β-hCG) pregnancy test will be performed on all females of childbearing potential at the time points specified in Table 1 and Table 2 (for subjects with UC) and Table 3 and Table 4 (for subjects with CD), if pregnancy is suspected, or on withdrawal of the subject from the study.

Pregnancy tests are not required for females of nonchildbearing potential who have undergone hysterectomy or bilateral oophorectomy, have medically confirmed ovarian failure, or are medically confirmed postmenopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; postmenopausal status should be confirmed by FSH testing in females who have had 12 consecutive months of spontaneous amenorrhea and are 51 years of age or older). This does not need to be performed if postmenopausal status was confirmed by FSH in induction study SHP647-301, SHP647-302, SHP647-305, SHP647-306, or maintenance study SHP647-303 or SHP647-307.

If a female subject's status has changed to postmenopausal since the induction study (SHP647-301, SHP647-302, SHP647-305, SHP647-306) or maintenance study (SHP647-303 or SHP647-307), the childbearing potential of the subject must be re-established and documented (FSH confirmation test) at baseline of SHP647-304. Once FSH results are received, and if postmenopausal status is uncertain, the routine pregnancy testing will continue as planned for the remainder of the study. If postmenopausal status is confirmed, routine pregnancy testing is no longer required.

7.3.4.8 Electrocardiogram

A 12-lead ECG will be recorded at the time points specified in Table 1 and Table 2 (for subjects with UC) and Table 3 and Table 4 (for subjects with CD). When timing of measurements coincide, ECGs should be performed before collection of blood samples for laboratory assessments.

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

If it is not possible to perform an ECG due to a COVID-19-related or other pandemic-related issue, the investigator is to ensure that an ECG is performed at the next possible visit (scheduled or unscheduled).

7.3.4.9 Monitoring for Type I and Type III Immune Reactions

Subjects will be educated on the signs and symptoms of hypersensitivity reactions and how to respond to them. In addition, subjects will be instructed to report hypersensitivity AEs to the investigator at the time of occurrence, and to seek immediate medical care if hypersensitivity develops. At each visit, the subject will be queried for AEs of special interest (AESIs) related to hypersensitivity.

Subjects will be also instructed to report AEs such as serum sickness, vasculitis, Arthus reaction, and severe injection related reactions to the investigator, and to seek immediate medical care if these events are severe in intensity.

Subjects who experience a hypersensitivity reaction or severe or serious injection-related reaction (eg, shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs) should discontinue investigational product.

For subjects who experience an AE suggestive of the presence of circulating immune complexes formation (eg, fever, rash [including hives], arthralgia, myalgia, vasculitis, Arthus reaction, general ill feeling, itching, and swollen lymph nodes), the investigator will decide on treatment discontinuation.

Further details of hypersensitivity reactions as AESIs are provided in Section 8.1.3.1.

7.3.4.10 Evaluation of Increased Gastrointestinal Symptoms

When a subject experiences an increase in GI symptoms, which could be an exacerbation of disease, an infectious etiology must be evaluated including testing for *C. difficile* as described in Appendix 4. If the subject has undergone or is undergoing a glucocorticoid taper, the glucocorticoid dose should be increased to the pre-taper dose; when clinically stable, the taper may begin again per Table 5 (for subjects with UC), and Table 6 for subjects with CD).

Subjects should be assessed for possible treatment failure. If treatment failure is considered after infectious etiology has been ruled out or treated, and/or after increase in the glucocorticoid dose (if appropriate), then the procedures in Section 4.4.2 should be followed.

In each case, the appropriate AE (eg, infection, exacerbation) should be recorded in the subject's source document.

7.3.4.11 Colonoscopy in Subjects at Elevated Risk of Colorectal Cancer

Subjects at risk for colorectal cancer who undergo annual endoscopy may undergo a colonoscopy with all annual surveillance procedures followed (eg, excision of adenomatous polyps with pathology report included in source documents). This is not required by the protocol, but if performed, the results should be recorded. Subjects at high risk for colorectal cancer are those who meet either of the following criteria:

- Subjects with extensive colitis for ≥8 years or disease limited to left side of colon (ie, distal to splenic flexure) for ≥10 years before screening, regardless of age
- Subjects ≥50 years of age at the time of signing of the informed consent form.

7.3.5 Others

7.3.5.1 Pharmacodynamic Assessments

Predose blood and stool samples will be collected at the time points specified in Table 1 and Table 2 (for subjects with UC), and Table 3 and Table 4 (for subjects with CD) for each of the following biomarkers:

- Serum CRP
- Stool fecal calprotectin

Stool samples will be analyzed for fecal calprotectin at the time points indicated in Table 1 and Table 2 (for subjects with UC), Table 3 and Table 4 (for subjects with CD).

Details of sample collection, handling, shipment, and analysis will be provided in the laboratory manual. In case of a DTP situation, samples can be collected at subject's home or nearby clinic; please refer to DTP guidance for further details.

7.3.6 Volume of Blood to Be Drawn from Each Subject – All Subjects

For subjects entering from an induction or maintenance study, the volume of blood to be drawn from each subject is summarized in Table 8 for Treatment Year 1 and Table 9 for Treatment Year 2 through Year 3.

Table 8 Volume of Blood to Be Drawn from Each Subject – Treatment Year 1 (All Subjects)

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Hematology	2	5	10
Serum chemistry	4	5	20
FSH	2	1	2
Blood samples for biomarkers			
Serum CRP	2	2	4
Total mL			**36**

CRP=C-reactive protein; FSH=follicle-stimulating hormone.

Table 9 Volume of Blood to Be Drawn from Each Subject – Treatment Year 2 Through Year 3 (All Subjects)

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Hematology	2	4	8
Serum chemistry	4	2	8
Blood samples for biomarkers			
Serum CRP	2	2	4
Total mL			**20**

CRP=C-reactive protein.

For subjects entering from a maintenance study, during this study (after the implementation of Amendment 4) it is expected that approximately 36 mL of blood will be drawn from each subject in the first year of study participation and approximately 20 mL of blood in each year thereafter. Additionally, it is expected that an approximate total of 30 mL of blood will be drawn from each subject at the EOT visit and the safety follow-up visit at 12 weeks following the last dose of investigational product.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

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

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

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Sections 7.2.1.3 and 7.2.2.3. Where possible, a diagnosis rather than a list of symptoms should be recorded. Resolved AEs considered to be significant by the investigator that occurred in Studies SHP647-301, SHP647-302, SHP647-303, SHP647-305, SHP647-306, or SHP647-307 will be captured as part of the SHP647-304 baseline medical history, while ongoing AEs from Studies SHP647-301, SHP647-302, SHP647-303, SHP647-305, SHP647-306, or SHP647-307 will be captured as AEs in Study SHP647-304. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured in the subject's source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the subject's source document.

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

8.1.1 Severity Categorization

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

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

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

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Adverse Events of Special Interest

Adverse events of special interest will be captured and monitored during this study. Investigators will report all AESIs to the sponsor, regardless of causality, using the same timelines as described for SAE reporting (see Section 8.2.2). The following describe the AESIs and the criteria for reporting AESIs.

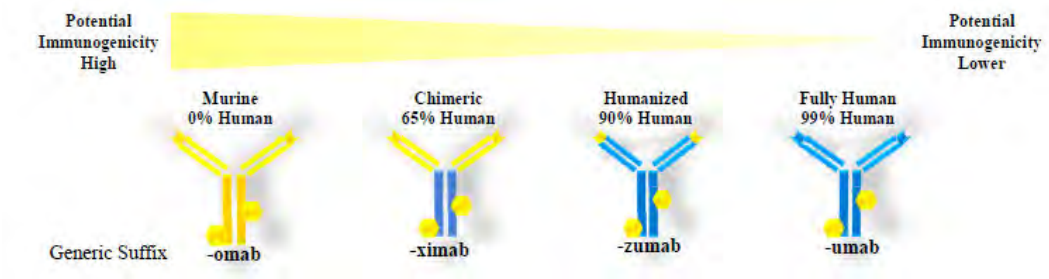
8.1.3.1 Hypersensitivity

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

It is well known that the administration of foreign proteins can cause immune responses including hypersensitivity reactions such as anaphylaxis and serum sickness. Other immune responses to foreign proteins include the development of ADAs and neutralizing antibodies (NAbs).

Monoclonal antibodies have been used in human therapeutics since the 1980s. The first monoclonal antibody approved for human use (ORTHOCLONE OKT3®), was a murine protein which caused rapid production of NAbs. Since then, much effort has been expended to reduce the immunogenicity of these useful therapeutic proteins by reducing the extent of "foreignness" from chimeric antibodies such as infliximab, to humanized antibodies such as vedolizumab, and finally to fully human antibodies such as adalimumab and ontamalimab (Isabwe et al., 2018) (see Figure 4).

Figure 4 Potential Immunogenicity of Therapeutic Monoclonal Antibodies



Ontamalimab is a fully human antibody of the immunoglobulin G2 subclass. In Phase 1 and Phase 2 clinical trials of ontamalimab, in which over 700 subjects were treated for up to 3 years, there has been no case of anaphylaxis. There have been 2 reported cases of drug hypersensitivity: serum sickness attributed to concomitant administration of penicillin; and a reaction characterized by dyspnea, facial erythema, and chest pain with onset 2 days after administration of the fifth dose of ontamalimab. The latter event mimicked a reaction that the subject had previously experienced after 4 doses of infliximab. In addition, low titer activity has been observed in ADA assays, including pretreatment samples and placebo-treated subjects, and no subject has had a 2-fold or greater increase in ADA titer. Analysis of PK and clinical parameters has shown no difference between subjects whose ADA assays results are positive as compared with those whose are negative.

Nonetheless the possibility of a hypersensitivity reaction occurring after drug exposure cannot be fully ruled out. The reactions of concern are Type I (anaphylaxis) and Type III (immune complex) reactions. The clinical presentation of anaphylactic reactions is described in Table 10.

Table 10 Clinical Criteria for Diagnosing Anaphylaxis (Type 1 Hypersensitivity)

Anaphylaxis is highly likely when below criterion and at least any one of the following criteria a and b are fulfilled:
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b) Reduced BP[a] or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

BP=blood pressure; PEF=peak expiratory flow.
[a] Low systolic blood pressure for children is defined as less than 90 mmHg from 11 to 17 years.
Source: Adapted from Sampson et al., 2006.

Type III hypersensitivity responses, including those mediated by immune complexes and T cells (delayed hypersensitivity responses in the older literature), are relatively rare with respect to therapeutic protein products and a high degree of clinical suspicion is necessary for the diagnosis (Center for Drug Evaluation and Research - Guidance for industry: Immunogenicity assessment for therapeutic protein products, 2014). Type III hypersensitivity reactions involve the formation of biologic/ADA immune complexes in the circulation which, when present in the correct stoichiometric ratio, become deposited in tissues. Once immune complexes are deposited, they can elicit complement activation and inflammation, leading to tissue damage. When immune complexes are deposited in tissues, they tend to localize in small postcapillary venules where there is loss of laminar blood flow, in sites of ultrafiltration where there is high pressure and fenestrated endothelium (eg, choroid plexus, ciliary body, synovium, and glomeruli), in sites of

turbulent blood flow (eg, coronary artery branches off aorta, aortic bifurcations, and cardiac valve leaflets), and in renal glomerular endothelium.

Signs and symptoms of immune complex deposition typically have onset 1 to 3 weeks after exposure (Warrington et al., 2018) usually improving in 7 to 10 days, with full recovery in 2 to 4 weeks and may include fever, rash (including hives), arthralgia, myalgia, vasculitis, Arthus reaction, general ill feeling, itching, and swollen lymph nodes.

8.1.4 Outcome Categorization

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

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

8.1.5 Symptoms of the Disease Under Study

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

8.1.6 Clinical Laboratory and Other Safety Evaluations

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

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

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

8.1.7 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Sections 7.2.1.3 and 7.2.2.3.

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

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum. If the pregnancy outcome is a live birth, the vital status and clinical condition of the infant should be obtained and documented at 1 year postpartum.

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

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire “Clinical Study Serious Adverse Event and Nonserious AE as Required by the Protocol Form” as well as the Shire Investigational and

Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

8.1.8 Abuse, Misuse, Overdose, and Medication Error

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

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

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

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

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

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

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

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

8.1.9 Unexpected Adverse Event

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the reference safety information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

8.1.10 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is Section 6.8 of the ontamalimab IB, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.8) unless they result in an SAE.

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

8.2.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

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

that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Sections 7.2.1.3 and 7.2.2.3 must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

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

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

In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs (ie, SUSARs) occurring during all interventional studies across the ontamalimab program.

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

8.2.8 Safety Monitoring for Potential Cases of Drug-induced Liver Injury

The following safety monitoring and stopping criteria are provided for elevated hepatic blood tests based on normal and elevated baseline alanine aminotransferase (ALT) and total bilirubin levels.

Abnormal values in ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities per Table 11 should be evaluated further to definitively determine the etiology of the abnormal laboratory values. The measurement(s) should be reconfirmed with another blood draw preferably within 48 to 72 hours of the initial finding of potential concern. Please refer to laboratory manual for further instructions.

Guidance for Dosing Interruption: Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment.

Table 11 Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment-emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
Normal baseline: ALT ≥5× ULN **Elevated baseline[a]:** ALT ≥3× baseline *or* ≥300 U/L (whichever occurs first)	Normal Patients with Gilbert's syndrome or hemolysis: No change in baseline TBL	None	Repeat ALT, AST, ALP, TBL, in 2-5 days. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered an induction study (SHP647-301, SHP647-302, SHP647-305 or SHP647-306) or maintenance study (SHP647-303 or SHP647-307) with HBcAb with or without HBsAb, would need evaluation with HBV DNA to rule out HBV reactivation.[c]
Normal baseline: ALT ≥8× ULN **Elevated baseline[a]:** ALT ≥5× baseline *or* ≥500 U/L (whichever occurs first)	Normal Patients with Gilbert's syndrome or hemolysis: No change in baseline TBL	None	Interrupt investigational product[b] Initiate close monitoring and workup for competing etiologies. Investigational product can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered an induction study (SHP647-301, SHP647-302, SHP647-305 or SHP647-306) or maintenance study (SHP647-303 or SHP647-307) with HBcAb with or without HBsAb, would need evaluation with HBV DNA to rule out HBV reactivation.[c]

Table 11 Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment-emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
Normal baseline: ALT ≥3× ULN **Elevated baseline[a]:** ALT ≥2× baseline *or* ≥300 U/L (whichever occurs first)	TBL≥2mg/dL increased over baseline *or* Patients with Gilbert's syndrome of hemolysis: Doubling of baseline direct bilirubin	None	Interrupt investigational product[b] Initiate close monitoring and workup for competing etiologies. Investigational product can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered an induction study (SHP647-301, SHP647-302, SHP647-305 or SHP647-306) or maintenance study (SHP647-303 or SHP647-307) with HBcAb with or without HBsAb, would need evaluation with HBV DNA to rule out HBV reactivation.[c]
Normal baseline: ALT ≥5× ULN **Elevated baseline[a]:** ALT ≥2× baseline *or* ≥300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain *or* Immunologic symptoms Rash Eosinophilia >5%	Interrupt investigational product[b] Initiate close monitoring and workup for competing etiologies. Investigational product can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered an induction study (SHP647-301, SHP647-302, SHP647-305 or SHP647-306) or maintenance study (SHP647-303 or SHP647-307) with HBcAb with or without HBsAb, would need evaluation with HBV DNA to rule out HBV reactivation.[c]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBV=hepatitis B virus; TBL=total bilirubin; ULN=upper limit of normal.
[a] Elevated baseline ALT defined as ALT ≥1.5× ULN.
[b] Confirmatory repeat liver-related blood tests should be performed within 2-3 days before the investigational product is interrupted.
[c] If HBV DNA positive, antivirals would need to be started as soon as possible.
Source: Adapted from Chalasani and Regev, 2016.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

9.3 Data Handling Considerations

These data will be handled in such a way that, before unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

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

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

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513, US).

Unless otherwise specified, summary tabulations will be presented by indication and treatment group. All data listings will be sorted by indication, treatment group, site, and subject number, and will include the subject's age, sex, and race. Summaries will be presented by indication separately and also overall. Summaries may be presented by the status at entry into this study (eg, induction nonresponder, maintenance ontamalimab completer, maintenance discontinuation rollovers, etc.).

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

Note: The overall impact of COVID-19 (or other similar pandemic) on data analyses is unknown at the time of the writing of this amendment; details on changes to any analyses or any additional analyses to evaluate the impact of COVID-19 (or other similar pandemic) on the study objectives will be described in the SAP.

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

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

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

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

See Section 7.3.4.3 for details on the handling of suspected PML cases in this study.

9.6 Sample Size Calculation and Power Considerations

A maximum of 451 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 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 451 subjects may be enrolled into this study.

9.7 Study Population

The full analysis set (FAS) will consist of all subjects in the randomized set who receive at least 1 dose of investigational product in the SHP647-304 study.

The safety set will consist of all subjects who receive at least 1 dose of investigational product in the SHP647-304 study.

9.8 Efficacy Analyses

Efficacy will not be formally evaluated in this study. Treatment response analyses are described below.

9.8.1 Treatment Response Analyses – Subjects with Ulcerative Colitis

Treatment response analyses will be performed using the FAS.

9.8.1.1 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.

Secondary endpoints will be summarized by treatment group using descriptive statistics at each assessment visit. Summaries may be presented by the status at entry into the study (eg, induction nonresponder, maintenance ontamalimab completer, maintenance discontinuation rollovers, etc.). Statistical summaries will include number of subjects and percentages, and 95% confidence intervals.

The detailed analyses will be described in the SAP.

9.8.2 Treatment Response Analyses – Subjects with Crohn's Disease

Treatment response analyses will be performed using the FAS.

9.8.2.1 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 treatment group using descriptive statistics at each assessment visit. Summaries may be presented by the status at entry into the study (eg, induction nonresponder, maintenance ontamalimab completer, maintenance discontinuation rollovers, etc.). Statistical summaries will include number of subjects and percentages, and 95% confidence intervals.

The detailed analyses will be described in the SAP.

9.9 Safety Analyses

The primary endpoint is the assessment of safety as measured by: incidence and severity of AEs; incidence and nature of serious infections; and actual values and change from baseline, as well as incidence of abnormalities, in laboratory tests, ECGs, and vital signs.

All safety analyses will be performed using the safety set. Subjects will be analyzed according to the treatment they actually received. Summaries will be presented by indication separately and also overall. Summaries may be presented by the status at entry into this study (eg, induction nonresponder, maintenance ontamalimab completer, maintenance early discontinuation rollovers, etc.).

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

Treatment-emergent AEs 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. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, by indication, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, SAEs, and deaths will be similarly summarized/listed. Adverse events of special interest will be summarized by treatment group.

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

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

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

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

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

The sponsor ensures that local regulatory authority requirements are met before and during the study (including annual safety reporting, ie, Development Safety Update Reports). The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

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

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

10.1.3 Public Posting of Study Information

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

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

The sponsor will upload the clinical study report to the EudraCT database and will also provide a summary of the clinical study report for submission to the competent authority of the countries concerned as required by local regulatory requirement(s). This requirement will be fulfilled within 1 year for nonpediatric studies as per guidance. The ECs will be provided with a copy of the same summary as locally required.

10.1.5 Study Suspension, Termination, and Completion

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

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

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

10.2.2 Protocol Adherence and Investigator Agreement

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

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to

the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

All data in the eCRF will have a separate source (eg, paper or electronic patient-reported outcome); no data will be recorded directly in the eCRF.

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

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

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

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

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

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

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, x-rays, etc.). Nonstudy site personnel will not disclose any personal information or personal medical information.

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

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

Sites are to ensure that all study documents related to DTP are complete, accurate, and retained at the site according to the document retention requirements.

10.2.3.3 Audit/Inspection

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

10.2.3.4 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

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

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

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

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

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

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

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

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

10.4 Privacy and Confidentiality

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

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

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

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

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

10.5 Study Results/Publication Policy

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

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

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

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

submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

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

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

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APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Protocol Amendment 4	21 Sep 2020	Global
Protocol Amendment 3	07 Nov 2019	Global
Protocol Amendment 2	17 Sep 2018	Global
Protocol Amendment 1	18 Dec 2017	Global
Original Protocol	13 Jul 2017	Global

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number	**Amendment Date**	**Global/Region/Country/Site Specific**
3	**07 Nov 2019**	**Global**

Protocol Amendment Summary and Rationale:

The main purpose of SHP647-304 Amendment 3 is to allow for direct entry of subjects with moderate to severe ulcerative colitis (UC) who had not participated previously in any of the Phase 3 induction studies (SHP647-301, SHP647-302) or maintenance study (SHP647-303). This includes UC subjects who were ineligible for an induction study due to previous treatment with ontamalimab during a Phase 1 or Phase 2 study or previous treatment with vedolizumab, or subjects who had met the eligibility criteria for induction study SHP647-301 or SHP647-302 but were unable to enroll because of an enrollment cap in their particular country.

The significant changes in SHP647-304 Protocol Amendment 3 relative to the previous edition, SHP647-304 Protocol Amendment 2, are captured below.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3**	**Amendment Date** **07 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Product Quality Complaints	Updated language regarding reporting of product quality complaints.	To align product quality complaints language with current Shire template.
Study Synopsis, Number of Subjects (total and for each treatment arm)	Updated total sample size projected for the enrollment in the study.	To reflect changes in sample size in the SHP647-301, SHP647-302, and SHP647-303 studies and revised projections for the number of subjects who may rollover from those studies, and to reflect targeted sample size for direct-entry UC subjects who may enter directly based on the completed A7281010 study and assessment of the literature.
Study Synopsis, Rationale Section 2.1, Rationale for the Study	Added language to describe UC subjects who would be entering directly.	To specify inclusion of UC subjects who had not previously participated in an induction (SHP647-301 or SHP647-302) or maintenance (SHP647-303) study.
Study Synopsis, Methodology Section 3.1, Study Design and Flowchart Section 6.2.2, Allocation of Subjects to Treatment	Revised language to reflect inclusion of direct-entry UC subjects. Updated Figure 1, Study Design Flow Chart to include direct-entry UC subjects.	To reflect inclusion of UC subjects entering directly.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3**	**Amendment Date** **07 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Study Synopsis, Methodology Section 3.1, Study Design and Flowchart Table 1, Schedule of Assessments – Treatment Year 1 (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303), footnote "m" Table 2, Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303), footnote "k" Table 3, Schedule of Assessments – Treatment Year 1 (CD Subjects, Entering from Study SHP647-305, Study SHP647-306, or Study SHP647-307), footnote "l" Table 4, Schedule of Assessments – Treatment Year 2 Through End of Study (CD Subjects, Entering from Study SHP647-305, Study SHP647 306, or Study SHP647 307), footnote "j"	Updated language to clarify that the e-diary will be available daily throughout the study.	To provide additional clarity around the collection of e-diary data.
Study Synopsis, Methodology Section 3.1, Study Design and Flowchart Section 4.4.2.1, Treatment Failure Assessment and Stopping Criteria	Added treatment failure language for direct-entry UC subjects.	To reflect inclusion of UC subjects entering directly.
Study Synopsis, Inclusion and exclusion criteria Section 4.1.2, Exclusion Criteria Section 4.2.2, Exclusion Criteria	Added the term 'highly effective methods for female and medically appropriate methods for male study subjects' in the parentheses after the term 'appropriate contraception methods'. For UC and CD subjects entering from an induction or maintenance study, added to exclusion criterion number 4 that females who are lactating also are excluded.	To clarify what is meant by appropriate contraception methods. To clarify that females who are lactating are excluded.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3**	**Amendment Date** **07 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Eligibility Criteria – Direct-entry Subjects with Ulcerative Colitis	Added inclusion and exclusion criteria for UC subjects entering directly.	To reflect inclusion of UC subjects entering directly.
Study Synopsis, Endpoints and statistical analysis Section 9.4, Statistical Analysis Process Section 9.8.1, Efficacy Analyses – Subjects with Ulcerative Colitis	Updated efficacy endpoints to reflect inclusion of direct-entry UC subjects.	To reflect inclusion of direct-entry UC subjects.
Study Synopsis, Analysis Sets Section 9.7, Study Population	Updated PD analysis set definition to include the word 'evaluable' in the definition: 'The pharmacodynamics (PD) analysis set will consist of all subjects who receive at least 1 dose of investigational product in study SHP647-304 and have at least 1 evaluable postdose PD value.'	To clarify that PD values must be evaluable, and for consistency with the PK analysis set.
Study Synopsis, Safety Endpoints Section 9.9, Safety Analyses	Updated safety endpoints to reflect inclusion of direct-entry UC subjects. Added that adverse events of special interest will be summarized by treatment group.	To reflect inclusion of direct-entry UC subjects. To include analysis of adverse events of special interest.
Table 1, Schedule of Assessments – Treatment Year 1 (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303) Table 2, Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303) Table 3, Schedule of Assessments – Treatment Year 1 (CD Subjects, Entering from Study SHP647-305, SHP647-306, or SHP647-307) Table 4, Schedule of Assessments – Treatment Year 2 Through End of Study (CD Subjects, Entering from Study SHP647-305, SHP647-306, or SHP647-307)	Added visit numbers to the Schedules of Assessments.	For clarity regarding visit numbers.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3**	**Amendment Date** **07 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Table 1, Schedule of Assessments – Treatment Year 1 (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303), footnote "j" Table 2, Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303), footnote "g" Section 7.2.2.1, Endoscopy Section 7.2.4.12, Colonoscopy in Subjects at Elevated Risk of Colorectal Cancer	Added language to specify subjects at risk for colorectal cancer must undergo annual colonoscopy with appropriate surveillance procedures followed.	To specify surveillance of subjects at elevated risk of colorectal cancer.
Table 1, Schedule of Assessments – Treatment Year 1 (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303), footnote "q" Table 2, Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303), footnote "n" Table 3, Schedule of Assessments – Treatment Year 1 (CD Subjects, Entering from Study SHP647-305, SHP647-306, or SHP647-307), footnote "p" Table 4, Schedule of Assessments – Treatment Year 2 Through End of Study (CD Subjects, Entering from Study SHP647-305, SHP647-306, or SHP647-307), footnote "m" Section 7.2.4.10, Monitoring for Hypersensitivity	Added new row in Tables 1, 2, 5, and 6, new subsection to Section 7.2.5, and language to describe monitoring for hypersensitivity.	To address Food and Drug Administration (FDA) recommendation to evaluate the risk of hypersensitivity reactions in the Phase 3 studies and aid in the collection of relevant safety data.
Table 3, Schedule of Assessments – Treatment Year 1 (UC Subjects, Direct Entry) Table 4, Schedule of Assessments – Treatment Year 2 Through End of Study (UC Subjects, Direct Entry)	Added new Schedules of Assessments tables for UC subjects entering directly.	To provide detailed procedures for UC subjects entering the study directly.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3**	**Amendment Date** **07 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 4.3, Reproductive Potential	Updated text to reflect results of an enhanced pre- and postnatal development (ePPND) toxicity study in nonhuman primates. Added language to describe UC subjects who would be entering directly. Added the term 'highly effective methods for female and medically appropriate methods for male study subjects' in parentheses after the terms 'appropriate form of contraception' and 'appropriate method of contraception'.	Updated information to reflect preliminary results from an ePPND toxicity study of ontamalimab in nonhuman primates, which indicated that, at the dose levels tested (30 and 60 mg/kg), infant losses were increased in ontamalimab-exposed animals when compared both to control animals in the study and to the historical control animal data from the testing facility. The relevance of this finding to humans is unknown but cannot be excluded. Results of the ePPND study were reported in the ontamalimab Investigator's Brochure Edition 8.0. Added to reflect inclusion of UC subjects who had not previously participated in an induction (SHP647-301 or SHP647-302) or maintenance (SHP647-303) study. To clarify what is meant by appropriate contraception methods.
Section 4.3.1, Contraceptive Methods for Female Study Subjects	Added text to specify that contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the clinical study.	To align with guidance document "Recommendations related to contraception and pregnancy testing in clinical trials" of Clinical Trial Facilitation Group.
Section 4.4.2, Subject Withdrawal Criteria	The term 'major protocol deviations' has been changed to 'protocol deviations'.	For consistency with Section 4.4.3 (Reasons for Withdrawal).
Section 5.1.2.1, Permitted Treatment	Added the statement "any permitted treatment may be initiated or discontinued as clinically appropriate."	To clarify that during the study any permitted treatment may be initiated or discontinued as clinically appropriate.
Table 5, Glucocorticoid Tapering – Subjects with Ulcerative Colitis Table 6, Glucocorticoid Tapering – Subjects with Crohn's Disease	Changed to column heading from 'Second Taper' to 'Subsequent Taper'.	To clarify that, as this is long-term study, there may be more than two tapers of glucocorticoid dosing.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3**	**Amendment Date** **07 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 5.2, Prior and Concomitant Treatment – Direct-entry Subjects with Ulcerative Colitis	Added new subsection to describe prior and concomitant treatment for UC subjects entering directly.	To reflect inclusion of UC subjects entering directly.
Section 7.1.2, Direct-entry Subjects with Ulcerative Colitis	Added new subsection to describe study schedule for UC subjects entering directly.	To reflect inclusion of UC subjects entering directly.
Section 7.2.1, Demographic and Other Baseline Characteristics Appendix 2, Scales and Assessments	Added text to describe assessment of demographics/baseline characteristics for UC subjects entering directly. Added stool frequency screening questions to Appendix 2.	To reflect inclusion of UC subjects entering directly.
Section 7.2.3, Efficacy Assessments – Direct-entry Subjects with Ulcerative Colitis	Added new subsection to describe efficacy assessments for UC subjects entering directly.	To reflect inclusion of UC subjects entering directly.
Section 7.2.4, Safety Section 7.2.5, Others	Updated the text in the subsections to describe inclusion of UC subjects entering directly.	To reflect inclusion of UC subjects entering directly.
Table 7, Quarterly Neurological Assessments	Column heading changed from 'targeted neurological history' to 'interim neurologic history and targeted neurologic examination'.	To align with language of newly proposed electronic case report form.
Section 7.2.4.6, Clinical Laboratory Evaluations Section 7.2.4.11, Evaluation of Increased Gastrointestinal Symptoms	Added text to describe evaluation of increased gastrointestinal symptoms.	To clarify that infectious etiology must be evaluated when a subject experiences an increase in gastrointestinal symptoms.
Section 7.2.5.7, Additional Clinical Laboratory Assessments – Direct-entry Subjects with Ulcerative Colitis	Added new subsection to describe additional clinical laboratory assessments as part of screening, for UC subjects entering directly.	To reflect inclusion of UC subjects entering directly.
Section 7.2.5.10, Chest X-ray (Direct-entry Subjects with Ulcerative Colitis Only)	Added new subsection to describe screening chest x-ray to be performed for UC subjects entering directly.	To reflect inclusion of UC subjects entering directly.
Section 7.2.5.12, Anti-vedolizumab Antibodies (Only for Direct-entry UC Subjects with Ulcerative Colitis Previously Treated with Vedolizumab)	Added new subsection to describe collection of a blood sample for measurement of anti-vedolizumab antibodies, for UC subjects entering directly who had received prior vedolizumab treatment.	To reflect inclusion of a baseline anti-vedolizumab antibody measurement for UC subjects entering directly who had received prior vedolizumab treatment.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3**	**Amendment Date** **07 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 7.2.6, Volume of Blood to Be Drawn from Each Subject – UC and CD Subjects	Decreased serum chemistry sample volume from 6 mL to 4 mL.	To correct the sample volume needed for the serum chemistry test.
Section 7.2.6, Volume of Blood to Be Drawn from Each Subject – UC and CD Subjects	Increased pharmacokinetic sample volume from 3 mL to 5 mL.	To correct the sample volume needed for the pharmacokinetic assessment.
Section 7.2.8, Volume of Blood to Be Drawn from Each Subject – UC Subjects Entering Directly	Added new subsection to provide blood volumes for UC subjects entering directly.	To reflect inclusion of UC subjects entering directly.
Section 8.1, Definition of Adverse Events, Period of Observation, Recording of Adverse Events Table 11, Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin	Updated the text to describe inclusion of UC subjects entering directly.	To reflect inclusion of UC subjects entering directly.
Section 8.1.3, Adverse Events of Special Interest	Added new subsection to describe classification of hypersensitivity as an adverse event of special interest.	To address FDA recommendation to evaluate the risk of hypersensitivity reactions in the Phase 3 studies and aid in the collection of relevant safety data.
Section 8.1.7, Pregnancy	Added text to specify that in cases of pregnancy, where the outcome is a live birth, the vital status and clinical condition of the infant should be obtained and documented at 1 year postpartum.	To extend the timeframe for follow-up of pregnancy outcomes for female study participants or partners of male study participants, in response to preliminary findings of the ePPND study.
Section 9.5, Planned Interim Analysis, Adaptive Design, Data Monitoring Committee, and Hypersensitivity Adjudication Committee	Added text to specify that an external hypersensitivity adjudication committee will be established to review data from subjects who experience a suspected Type I or Type III hypersensitivity reaction.	To address FDA recommendation to evaluate the risk of hypersensitivity reactions in the Phase 3 studies and aid in the collection of relevant safety data.
Section 9.6, Sample Size Calculation and Power Considerations	Updated sample size projections for UC subjects entering from an induction or maintenance study. Added targeted sample size for UC subjects entering directly.	To reflect changes in sample size in the SHP647-301, SHP647-302, and SHP647-303 studies and revised projections for the number of subjects who may rollover from those studies, and to provide targeted sample size for direct-entry UC subjects who may enter directly based on the completed A7281010 study and assessment of the literature.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3**	**Amendment Date** **07 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 9.8.1.2, Exploratory Efficacy Endpoints	For the endpoint "Change from induction study (SHP647-301 or SHP647-302) baseline, or Study SHP647-304 baseline for direct-entry subjects, in abdominal pain, diarrhea and urgency item scores, absolute stool frequency, absolute rectal bleeding, and total sign/symptom score based on subject daily e-diary entries (sum of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency) over time", revised the final part of the text in parentheses to read "(average of rectal bleeding, stool frequency, abdominal pain, diarrhea, and urgency)".	To correctly describe the scoring of patient-reported UC sign and symptom data.
Section 9.8.2.2, Exploratory Efficacy Endpoints	For the endpoint "Change from induction study (SHP647-305 or SHP647-306) baseline in abdominal pain, very soft stool/liquid stool frequency (as shown by type 6/7 on BSFS), total stool frequency, rectal urgency, rectal bleeding, nausea, vomiting, and incontinence, and total sign/symptom score based on subject daily e-diary entries (average of rectal bleeding, stool frequency, abdominal pain, very soft stool/liquid stool, and rectal urgency) over time", revised the final part of the text in parentheses to read "(average of rectal bleeding, stool frequency, abdominal pain, very soft stool/liquid stool, and rectal urgency)". For the endpoint, "Subject TSQM total scores and 4 domain scores over time", deleted reference to "total scores".	To correctly describe the scoring of patient-reported CD sign and symptom data. To correctly describe scoring for the Treatment Satisfaction Questionnaire for Medication (TSQM).
Section 9.10.1, Pharmacodynamic Analyses	Added that biomarker endpoints will be summarized by indication along with treatment group and visit.	Added for clarity.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3**	**Amendment Date** **07 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 10.1.5, Study Suspension, Termination, and Completion	To clarify that the end-of-study declaration may be made by the sponsor or alternatively its representatives.	Added for clarity.
Appendix 1, Protocol History	Added Summary of Changes for Amendment 2 relative to Amendment 1, and for Amendment 1 relative to original protocol.	For completeness, such that the Protocol History section includes the summary of changes made with all prior global amendments to this protocol.
Appendix 5, Determination of Failure or Intolerance to Prior Treatment for Ulcerative Colitis	Added new appendix section, "Determination of failure or intolerance to prior treatment for ulcerative colitis" to provide guidance as related to inclusion criterion #5 in which subjects meeting these criteria on prior conventional treatments (eg, sulfasalazine, mesalamine, glucocorticoids, immunosuppressants, or anti-TNF) may be eligible for this study.	To provide granularity regarding the eligibility of direct-entry UC subjects who demonstrated inadequate response, loss of response, or intolerance on conventional treatment.
Throughout protocol	'SHP647' was updated to 'ontamalimab" throughout the protocol.	To reflect that ontamalimab is the international nonproprietary name for SHP647.
Throughout protocol	Minor changes to wording and editorial changes.	To improve clarity, consistency, and remove redundancy of text.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **14 Sep 2018**	**Global/Region/Country/Site Specific** **Global**
Protocol Amendment Summary and Rationale: The main purpose of SHP647-304 Amendment 2 is to further clarify the rationale for the study design with regard to subjects who would enter following participation in one of the maintenance studies (SHP647-303 or SHP647-307) and have been classified as nonresponsive to treatment and met the protocol-specified definition of treatment failure. This amendment clarifies how subjects will be monitored for safety and clinical benefit, and for assessment of potential treatment failure and criteria for withdrawal of treatment in this long-term extension study. The amendment also describes the potential benefit for subjects, including for those who previously had been classified as nonresponsive to active treatment. Additionally, this amendment elevates efficacy endpoints based on clinical remission and endoscopic outcomes from "exploratory" to "secondary" to emphasize that assessment of efficacy and monitoring of clinical benefit is an important aspect of the study. The significant changes in SHP647-304 Protocol Amendment 2 relative to the previous edition, SHP647-304 Protocol Amendment 1, are captured below.		

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **14 Sep 2018**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Emergency Contact Information Section 8.2.2, Reporting Procedures Section 8.2.4, Serious Adverse Event Collection Time Frame	Replaced "Shire Global Pharmacovigilance" with "the Shire Global Drug Safety Department." Updated the fax number for serious adverse event reporting.	To provide updated and correct information.
Study Synopsis, Methodology Section 3.1, Study design and flowchart	Added language to clarify that efficacy data will be collected to monitor clinical benefit, and to provide information on treatment failure assessment as also outlined in Section 4.1.1, Treatment Failure Assessment and Stopping Criteria.	To emphasize and further describe that subjects will be monitored for clinical benefit and for assessment of potential treatment failure.
Study Synopsis, Methodology Study Synopsis, Maximum duration of subject involvement in the study Section 3.1, Study Design and Flowchart Section 3.2, Duration and Study Completion Definition	Added text to clarify that a subject's maximum duration of treatment is expected to be 7 years, subject to local or country requirements, and removed the phrase "or until SHP647 becomes available commercially, whichever occurs earlier."	To provide clarity regarding the maximum duration of study participation.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **14 Sep 2018**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Study Synopsis, Exclusion Criteria – Subjects with CD Section 4.2.2, Exclusion Criteria (Subjects with Crohn's Disease)	Revised exclusion criterion #3 (for subjects with CD) to add that subjects who developed acute severe complications of CD that required immediate intervention and/or CDAI score >450 are excluded.	To further define the criterion related to disease severity for subjects with CD.
Study Synopsis, Inclusion and exclusion criteria Section 4.1.2, Exclusion Criteria (Subjects with Ulcerative Colitis) Section 4.2.2, Exclusion Criteria (Subjects with Crohn's Disease)	Updated exclusion criterion #5 (for subjects with UC and subjects with CD) to indicate the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including male subjects are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and for 16 weeks after last dose of investigational product.	To specify the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including sperm banking or donation for male subjects and egg donation or harvest for female subjects, are excluded.
Study Synopsis, Objectives Section 2.2.2, Secondary Objectives – Subjects with Ulcerative Colitis Section 2.2.3, Secondary Objectives – Subjects with Crohn's Disease	Moved efficacy objectives related to clinical remission and endoscopic outcomes, from "exploratory" to "secondary."	To emphasize that this study will evaluate efficacy as well as safety.
Study Synopsis, Endpoints and statistical analyses Section 9.8.1, Efficacy Analyses – Subjects with Ulcerative Colitis Section 9.8.2, Efficacy Analyses – Subjects with Crohn's Disease	Moved efficacy endpoints based on clinical remission and endoscopic outcomes, from "exploratory" to "secondary."	To emphasize that this study will evaluate efficacy as well as safety.
Schedule of Assessments Table 8 Volume of Blood to Be Drawn from Each Subject – Treatment Year 1	Added PK and ADA sample collection at 2 additional time points, Week 4 and Week 12.	To obtain additional PK and ADA measurements earlier in the study to identify immunogenicity status, particularly for those subjects entering the study who are naïve to active treatment or who would be restarting active treatment after receiving placebo in the maintenance study.

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Section 1.3, Benefit/Risk Assessment	Added new section describing benefit and risk of SHP647 treatment.	To provide a summary of benefit and risk information for SHP647.
Section 2.1, Rationale for the Study	Added language to clarify the rationale for the study design, ie to offer access to active treatment to subjects who may have benefited from treatment at the end of a maintenance study, to subjects who had received placebo or an insufficient duration of active treatment in an induction study, or who may have met treatment failure criteria in a maintenance study. Added text to emphasize that efficacy data will be collected regularly for all subjects, to allow for monitoring of clinical benefit and evaluation of potential treatment failure. Added a statement (from Section 6.1.1, Blinding the Treatment Assignment) to explain the reason for the double-blind study design. Added text (from Section 6.2.2, Allocation of Subjects to Treatment) to describe the treatment allocation for entering subjects. Added reference citation (Pullen et al, 2009) to the first paragraph where the SHP647 molecule is described.	To improve clarity of the study rationale.
Section 4.4.1, Subject Withdrawal Criteria	Added pregnancy as a reason that a subject may be withdrawn from study treatment. Removed initiation of a new therapy for UC or CD as a reason that a subject should be withdrawn from study treatment.	For clarity and consistency with language in Section 8.1.6. To reflect that a new therapy may be permitted as described in Section 5.2.1 and Section 5.3.1.

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Section 4.4.1.1, Treatment Failure Assessment and Stopping Criteria	Added language that subjects will be assessed regularly for efficacy to monitor clinical benefit and for evaluation of potential treatment failure.	To improve clarity regarding assessment of potential treatment failure and criteria for withdrawal from study treatment.
Section 5.2, Concomitant Treatment – Subjects with Ulcerative Colitis Section 5.3, Concomitant Treatment – Subjects with Crohn's Disease	Added a statement that additional safety assessments may be necessary for concomitant treatments, in accordance with the safety recommendations for the treatments. This change was made with SHP647-304 Protocol Administrative Change Memo #3, dated 22 Mar 2018.	To provide correct information/guidance.
Section 5.2.1, Permitted Treatment (Subjects with Ulcerative Colitis)	Revised language to clarify tapering of glucocorticoids. Removed requirement for a stable dose of medicinal marijuana to be maintained during the study. Added that dietary and herbal supplements and probiotics should be recorded as concomitant medications.	To provide correct information and for consistency of language provided for UC and CD.
Section 5.2.2, Prohibited Treatment (Subjects with Ulcerative Colitis) Section 5.3.2, Prohibited Treatment (Subjects with Crohn's Disease)	Revised language to clarify tapering of glucocorticoids. Added text to clarify the prohibition of anti-TNF treatment or other biologics including biosimilars or nonbiologic agents with immunomodulatory properties, except for azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate, which are permitted. Added text to clarify the prohibition of leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange. Added text to specify that subjects who enter the 16-week safety follow-up period will no longer need to abstain from the medications that were prohibited during the treatment period and	To provide correct information, and for consistency of language for the UC and CD indications and alignment with the induction and maintenance study protocols. To clarify that once subjects enter the 16-week safety follow-up period, medications that were prohibited during the treatment period, including other treatments for UC or CD, will be allowed.

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	that other treatments for UC or CD will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated without prior discussion with the sponsor study physician or designee due to the long half-life of SHP647.	
Section 5.3.1, Permitted Treatment (Subjects with Crohn's Disease)	Revised language to clarify tapering of glucocorticoids. Removed requirement for antidiarrheal opiate drugs, medicinal marijuana, and dietary and herbal supplements to be at a stable dose at study entry and maintained at a stable dose during the study. Removed parenteral or rectal glucocorticoids from the list of prohibited medications.	To provide correct information and for alignment of permitted medications across UC and CD, where applicable.
Section 7.2, Study Procedures	Added language to specify that the duration of blood and tissue sample storage is dependent on local regulations.	To clarify that local regulations should be considered for duration of blood and tissue sample storage.
Section 7.2.4.6, Clinical Laboratory Evaluations	Added information on laboratory testing for *C. difficile* infection, including diagnostic algorithms.	To provide appropriate guidance regarding laboratory testing for *C. difficile* infection.
Section 7.2.5.2, Pharmacodynamic Assessments	Revised text to clarify the stool sample collection and assessment.	To improve clarity in the description of stool sample collection and assessment.
Section 8.2.8, Safety Monitoring Rules	Added new section describing safety monitoring and stopping algorithms for elevated hepatic blood tests.	To provide appropriate guidance on patients who have been enrolled with elevated liver function test values or who experience and increase in liver function test(s) during the study.
Section 9.9, Safety Analyses	Added text to clarify that the primary endpoint is assessment of safety.	To improve clarity and for alignment with language in the study synopsis.
Section 10, Sponsor's and Investigator's Responsibilities	Added a statement that compliance with the noted regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.	To clarify that the study is conducted in accordance with the ethical principles in the Declaration of Helsinki.

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Appendix 4, Guidance for Diagnosis and Treatment of Increased Gastrointestinal Symptoms	Added new Appendix 4, "Guidance for Diagnosis and Treatment of Increased Gastrointestinal Symptoms related to diagnosis and treatment of *C. difficile* infection."	To provide updated guidance for diagnosis and treatment of *C. difficile* infection.
Throughout protocol	Minor changes to wording.	To improve clarity, consistency, and remove redundancy of text.

<table>
<tr><th colspan="3">Protocol Amendment</th></tr>
<tr><th colspan="3">Summary of Change(s) Since Last Version of Approved Protocol</th></tr>
<tr><th>Amendment Number
1</th><th>Amendment Date
18 Dec 2017</th><th>Global/Country/Site Specific
Global</th></tr>
<tr><th colspan="2">Description of Change and Rationale</th><th>Section(s) Affected by Change</th></tr>
<tr><td colspan="2">Revised study title to reflect inclusion of subjects with Crohn's disease.
Now reads:
"A Phase 3 Long-term Safety Extension Study of SHP647 in Subjects with Moderate to Severe Ulcerative Colitis or Crohn's Disease (AIDA)"</td><td>Title page
Protocol signature page
Study Synopsis, Title of the study</td></tr>
<tr><td colspan="2">Updated the email address for Shire Drug Safety on the emergency contact information page:
Now reads:
Email
<s>globalpharmacovigilance</s>drugsafety@shire.com</td><td>Emergency contact information</td></tr>
<tr><td colspan="2">Updated the email address for reporting of product complaints that originate in the European Union and Rest of World. The email address now is the same for all regions.
Now reads:
<table>
<tr><th>Origin of Product Quality Complaint</th><th>E-mail Address</th></tr>
<tr><td>North and South America, the European Union, and Rest of World</td><td>PQC@shire.com</td></tr>
<tr><td><s>European Union and Rest of World</s></td><td><s>PQCROW@shire.com</s></td></tr>
</table></td><td>Product quality complaints</td></tr>
<tr><td colspan="2">Updated the projected number of subjects to reflect inclusion of subjects with CD entering from Studies SHP647-305, SHP647-306, and SHP647-307.
Now reads:
Number of subjects (total and for each treatment arm):
Approximately <s>1114</s> 2453 subjects are projected for enrollment in this study.</td><td>Study Synopsis, Number of subjects (total and for each treatment arm)</td></tr>
<tr><td colspan="2">Updated approximate number of sites and countries in which this study will be conducted.
Now reads:
This study will be conducted in approximately <s>350</s> 439 sites in approximately <s>33</s> 37 countries.</td><td>Study Synopsis, Sites and region(s)
Section 3.3, Sites and regions</td></tr>
<tr><td colspan="2">Revised planned study period to reflect inclusion of subjects with CD entering from Studies SHP647-305, SHP647-306, and SHP647-307.
Now reads:
Study period (planned):
2018 – <s>2024</s>2025</td><td>Study Synopsis, Study period (planned)</td></tr>
</table>

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Description of Change and Rationale		**Section(s) Affected by Change**
Revised language in the primary objective to reflect inclusion of subjects with CD entering from Studies SHP647-305, SHP647-306, and SHP647-307. *Now reads:* **Objectives:** **Primary:** To evaluate the safety and tolerability of long-term treatment with SHP647 in subjects with moderate to severe UC **or CD**		Study Synopsis, Objectives Section 2.2.1, Primary Objective
Revised language in the rationale to clarify that this study is double-blinded, and to reflect inclusion of subjects with CD entering from Studies SHP647-305, SHP647-306, and SHP647-307. *Now reads:* This **double-blind** extension study is designed to evaluate the safety of long-term treatment with SHP647 in subjects with moderate to severe UC **or CD** who**: 1)** completed one of the ~~two~~ **4** multicenter, randomized, double-blind, placebo-controlled, parallel group studies evaluating SHP647 as an induction therapy (SHP647-301 ~~and~~**,** SHP647-302**, SHP647-305, or SHP647-306) and did not meet the response criteria (clinical and/or endoscopic response/remission as appropriate) required for entry into a maintenance study (SHP647-303 or SHP647-307), or 2)** were treatment failures and/or completers in **one of** the **2** multicenter, double-blind, randomized, placebo-controlled, parallel-group study evaluating SHP647 as maintenance therapy (SHP647-303 **or SHP647-307**).		Study Synopsis, Rationale Section 2.1, Rationale for the Study
Revised language to reflect inclusion of subjects with CD entering from Studies SHP647-305, SHP647-306, and SHP647-307. *Now reads:* This is a Phase 3 **double-blind**, multicenter extension study designed to evaluate the long-term safety and efficacy of SHP647 in subjects with moderate to severe UC **or CD**. The study will enroll subjects from 6 separate Phase 3 studies: 2 multicenter, randomized, double-blind, placebo-controlled, parallel group studies evaluating SHP647 as an induction therapy in subjects with moderate to severe UC (SHP647-301 and SHP647-302); **2 multicenter, randomized, double-blind, placebo-controlled, parallel group studies evaluating SHP647 as an induction therapy in subjects with moderate to severe CD (SHP647-305 and SHP647-306);** 1 multicenter, double-blind, randomized, placebo-controlled, parallel-group study evaluating SHP647 as maintenance therapy in subjects with moderate to severe UC (SHP647-303)**; and 1 multicenter, double-blind, randomized, placebo-controlled, parallel-group study evaluating SHP647 as maintenance therapy in subjects with moderate to severe CD (SHP647-307).** **All subjects will receive active drug in this study.** Eligible subjects entering study SHP647-304 will be assigned to receive either 25 mg or 75 mg of SHP647 every 4 weeks. Allocation is dependent on how the subject entered into this study:		Study Synopsis, Methodology Section 3.1, Study design and flowchart

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• Subjects who completed maintenance study SHP647-303 **or SHP647-307 without treatment failure** and received either 25 mg or 75 mg of SHP647 every 4 weeks will continue to receive the same dose of SHP647 in this long-term safety extension study. **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.** • All other subjects will be randomized using a 1:1 allocation. Randomization will be stratified **by indication (UC or CD) and by the status from the study from which they are entering, as follows:** (1) **did not meet the response criteria (clinical and/or endoscopic response/remission as appropriate)** in an induction study; (2) treatment failure in a maintenance study, or (3) maintenance study completion **without treatment failure** for subjects receiving placebo, to facilitate balance of treatment assignment within each stratum. The eligibility of a subject for this study will be assessed **from** study data collected at: • **For UC subjects,** the Week 12 visit of **the** induction study **(SHP647-301 or SHP647-302),** OR the Week 52 or Early Termination visit of the maintenance study **(SHP647-303),** which will be considered and recorded as the baseline visit for this extension study. • **For CD subjects, the Week 16 visit of the induction study (SHP647-305 or SHP647-306), OR the Week 52 or Early Termination visit of the maintenance study (SHP647-307), which will be considered and recorded as the baseline visit for 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.** Subjects enrolled in this study will receive double-blind treatment every 4 weeks in the form of SC injections using pre-filled syringes. Subjects will undergo safety, efficacy, biomarker, pharmacokinetic, and health outcome assessments at these visits as outlined in the Schedules of Assessments (Table 1 **and Table 3** for assessments in Year 1, **for subjects with UC and CD, respectively;** Table 2 **and Table 4** for assessments beginning in Year 2 through End of Study, **for subjects with UC and CD, respectively).** The primary objective of this study is evaluation of the safety and tolerability of long-term treatment with SHP647. Safety will be measured by: incidence and severity of adverse events (AEs); incidence and nature of serious infections; actual values and change from baseline, as well as the		

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incidence of abnormalities, in laboratory tests, ECGs, and vital signs; and antidrug antibodies. **For subjects with UC,** patient-reported signs and symptom data (including stool frequency, rectal bleeding severity and frequency, diarrhea frequency, urgency frequency, and abdominal pain worst severity) will be collected using a daily e-diary for 10 days before each specified visit. The Mayo score is a measure of UC disease activity consisting of the following 4 subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician global assessment (PGA). The partial Mayo score consists of the Mayo score without the endoscopic subscores. The composite score is a recommended measure consisting of the Mayo score without the PGA subscore, and will be used for the exploratory efficacy endpoints. The Mayo scores and composite score will be based on subject daily e-diary entries. **For subjects with CD, patient-reported CD signs and symptom data (abdominal pain severity, very soft stool/liquid stool [as shown by BSFS type 6/7] frequency, rectal bleeding frequency, rectal urgency frequency, vomiting frequency, nausea severity, incontinence frequency, total stool frequency) will be collected using a daily e-diary for 14 days before each specified visit. 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 self-reported by the subject and will be collected as part of the daily e-diary for 14 days before each specified visit as in the schedules of assessments.**		
Combined language regarding eligibility of UC subjects of reproductive potential, from inclusion criterion no. 5 and exclusion criterion no. 4 and deleted inclusion criterion no.5 as it was redundant. *Now reads:* **Inclusion Criteria – Subjects with UC:** ~~5. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use acceptable contraception for the duration of the study.~~ **Exclusion Criteria – Subjects with UC:** 4. ~~Female subjects~~ **Subjects are females** who became pregnant during study SHP647-301, SHP647-302, or SHP647-303, ~~or~~ **females** who are planning to become pregnant during the study period**, or males or females of childbearing potential not agreeing to continue using appropriate contraception methods through the conclusion of study participation (see Section 4.3).**		Study Synopsis, Inclusion and exclusion criteria Section 4.1, Eligibility Criteria - Subjects with UC

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Added text to clarify the exclusion criterion regarding known exposure to TB since initial testing at screening in one of the induction studies. *Now reads:* 10. Subjects with known exposure to *Mycobacterium tuberculosis* (TB) since testing at screening in study SHP647-301 or SHP647-302 and who **have been advised to require treatment for latent or active disease, but** who are without a generally accepted course of treatment.		Study Synopsis, Inclusion and exclusion criteria Section 4.1, Eligibility Criteria - Subjects with UC
Added inclusion and exclusion criteria for subjects with CD entering from studies SHP647-305, SHP647-306, and SHP647-307. Added new subsections: Section 4.2.1, Inclusion Criteria and Section 4.2.2, Exclusion Criteria. *Now reads:* **Inclusion Criteria – Subjects with CD:** **Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:** 13. **Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.** 14. **Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.** 15. **Subjects must have been previously enrolled in study SHP647-305, SHP647-306, or SHP647-307, and reached 1 of the following clinical trial milestones:** • **Completed the Week 16 visit in induction study SHP647-305 or SHP647-306, and did NOT meet the efficacy criteria (clinical and/or endoscopic response/remission as appropriate) for entry into maintenance study SHP647-307.** • **Completed the Week 52 visit in maintenance study SHP647-307.** • **Withdrew early from maintenance study SHP647-307 due to treatment failure (or were considered to have failed treatment, at the time of the last visit in study SHP647-307), as defined in the SHP647-307 protocol.** 16. **Subjects receiving any treatment(s) for CD described in Section 5.3.1, are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.**		Study Synopsis, Inclusion and exclusion criteria Section 4.2, Eligibility Criteria – Subjects with Crohn's Disease

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Exclusion Criteria – Subjects with CD: **Subjects are excluded from the study if any of the following criteria are met:** 17. **Subjects who had major protocol deviation(s) (as determined by the sponsor) in study SHP647-305, SHP647-306, or SHP647-307.** 18. **Subjects who permanently discontinued investigational product because of an AE, regardless of relatedness to investigational product, in study SHP647-305, SHP647-306, or SHP647-307.** 19. **Subjects who are likely to require major surgery for CD.** 20. **Subjects are females who became pregnant during study SHP647-305, SHP647-306, or SHP647-307, females who are planning to become pregnant during the study period, or males or females of childbearing potential not agreeing to continue using appropriate contraception methods through the conclusion of study participation (see Section 4.3).** 21. **Male subjects who are planning to donate sperm and do not agree not to do so for the duration of the study and through 16 weeks after last dose of investigational product.** 22. **Subjects who, in the opinion of the investigator or the sponsor, will be uncooperative or unable to comply with study procedures.** 23. **Subjects who have a newly-diagnosed malignancy or recurrence of malignancy (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).** 24. **Subjects who have developed any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study.** 25. **Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.** 26. **Subjects with known exposure to *Mycobacterium tuberculosis* (TB) since testing at screening in Study SHP647-305 or**		

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SHP647-306 and who have been advised to require treatment for latent or active disease, but who are without a generally accepted course of treatment. 27. **Subjects who are investigational site staff members or relatives of those site staff members or subjects who are sponsor employees directly involved in the conduct of the study.** 28. **Subjects who are participating in other investigational studies (other than SHP647-305, SHP647-306, or SHP647-307) or plan to participate in other investigational studies during long-term extension study SHP647-304.**		
Revised definition of safety analysis set to reflect inclusion of subjects with CD entering from Studies SHP647-305, SHP647-306, and SHP647-307. Added definition for FAS. Revised definition of PK and PD analysis sets for clarity. *Now reads:* **Endpoints and statistical analysis:** **Analysis Sets:** The screened set will consist of all subjects who have signed an informed consent document for the SHP647-304 study. The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned **in the SHP647-304 study**. **The full-analysis set (FAS) will consist of all subjects in the randomized set who have received at least 1 dose of investigational product.** The safety set will consist of all subjects who receive at least 1 dose of investigational product in the SHP647-304 study, regardless of treatment received during the induction and maintenance studies (SHP647-301, SHP647-302, **SHP647-303, SHP647-305, SHP647-306,** and SHP647-~~303~~307). The pharmacokinetic **(PK) analysis** set will consist of all subjects ~~in the safety set for whom~~ **who receive** at least 1 **dose of SHP647 in Study SHP647-304 and have at least 1 evaluable** postdose PK ~~blood sample was collected~~**concentration value**. The pharmacodynamic **(PD)** analysis set will consist of all subjects ~~in the safety set for whom~~ **who receive at least 1 dose of SHP647 in Study SHP647-304 and have** at least 1 postdose PD ~~blood sample was collected~~ **value.** Deleted redundant text in synopsis under "Primary Endpoint." *Now reads:* **Primary Endpoint:** The primary endpoint ~~is safety assessment as~~ is assessment of safety as measured by: incidence and severity of AEs; incidence and nature of serious infections; actual values and change from		Study Synopsis, Endpoints and statistical analysis Section 9.7, Study Population

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baseline, as well as the incidence of abnormalities in laboratory tests, ECGs, and vital signs; and antidrug antibodies.		
Added further details on planned summary presentations for the safety analyses. Clarified definition of TEAE. *Now reads:* All safety analyses will be performed using the safety set. Subjects will be analyzed according to the treatment they actually received. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. **Summaries will be presented by indication separately and also overall. Summaries may be presented by the status at entry into this study (eg, induction nonresponder, maintenance SHP647 completer, etc).** … 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. The number of events, incidence, and percentage of TEAEs will be calculated overall, by SOC, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events ~~related to investigational product, AEs~~ leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.		Study Synopsis, Endpoints and statistical analysis Section 9.9, Safety Analyses
Revised titles of Table 1 and Table 2 to clarify that they apply to UC subjects. *Titles now read:* Table 1: Schedule of Assessments – Treatment Year 1 **(UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)** Table 2: Schedule of Assessments – Treatment Year 2 through End of Study **(UC Subjects, Entering from Study SHP647-301, SHP647-302, or SHP647-303)** Added 2 new schedules of assessments for subjects with CD entering from Studies SHP647-305, SHP647-306, and SHP647-307, entitled: **Table 3: Schedule of Assessments – Treatment Year 1 (CD Subjects, Entering from Study SHP647-305, Study SHP647-306, or Study SHP647-307)** **Table 4: Schedule of Assessments – Treatment Year 2 through End of Study (CD Subjects, Entering from Study SHP647-305, SHP647-306, or SHP647-307)**		Study Synopsis, Study Schedules: Table 1, Table 2, Table 3, Table 4

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Updated the header rows for the follow-up period in Table 2 to reflect that the safety follow-up visits are 8 and 16 weeks post-**EOT**, not post-last dose. This change was communicated in protocol SHP647-304 administrative change memo #1, dated 08 Aug 2017. *Now reads:* 8 wks post~~-last dose~~ **EOT** 16 wks post~~-last dose~~ **EOT**		Table 2
Deleted footnote connected to vital signs and ECG in Table 1 and Table 2, as the order of assessments is listed in Section 7.2 Study Procedures. Deleted the following (footnote "f" to Table 1 and footnote "c" to Table 2): ~~Vital signs (including blood pressure, pulse, respiratory rate, and temperature) and 12-lead ECG should be performed prior to collection of blood samples for laboratory assessments.~~ Added the following statement after the numbered footnotes to Table 2 for consistency with Table 1: **"Note: Refer to Section 7.2 for the order in which assessments should be performed. Timing of visits is relative to SHP647-304 baseline."**		Study Schedules: Table 1 and Table 2
Added new subsection to Section 1 (Introduction) to provide background on the CD indication. *New text:* **1.1.2 Crohn's Disease** **Crohn's disease (CD) is a chronic, relapsing disease marked by granulomatous inflammation of the gastrointestinal (GI) tract. Although the terminal ileum and right colon are the most commonly involved sites, CD can affect any part of the GI tract, from the mouth to the perianal region. Inflammation is typically transmural (full-thickness), segmental, and discontinuous, and symptoms are predominantly determined by the part of bowel or organ involved. Patients typically present with symptoms including abdominal pain, diarrhea, rectal bleeding, which may be persistent and lead to anemia, and weight loss due to pain on eating and malabsorption. As the disease progresses, extraintestinal manifestations and associated conditions can develop, including bowel obstruction, fistulas, and stenosis, as well as painful skin ulcerations, eye pain, and arthritis.** **The incidence of CD is estimated to be up to 12.7 cases per 100,000 persons per year in Europe and up to 20.2 cases per 100,000 persons per year in North America. No clear difference in incidence has been observed between men and women. Although CD can occur at any age, peak incidence has been observed in the second to fourth decades of life, with a second modest rise in incidence in the latter decades of life (Molodecky et al., 2012).** **Crohn's disease is a lifelong condition with a serious effect on quality of life. The traditional approach to therapy of CD has been the step-up**		Section 1.1.2, Crohn's Disease

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approach usually represented as a pyramid where, progressing from mild to severe disease, therapeutic choices proceed step by step from less potent drugs at the base of the pyramid to more potent but also more toxic drugs at the top. Current treatment primarily consists of symptomatic management with dietary modifications, 5 aminosalicylic acid (5-ASA), opiates (loperamide), systemic glucocorticoids, immunosuppressive agents (azathioprine/6-mercaptopurine, methotrexate [MTX]), and biologic therapy with anti-TNF agents or anti-integrin agents. Despite recent advances, there is still an unmet need for safe, effective, and durable pharmacological treatment that will induce and maintain remission.		
Added text in title of Section 2.2.2 Exploratory Objectives to clarify that these apply only to subjects with UC. Revised language of exploratory efficacy objectives for subjects with UC to be more specific about the efficacy measures. *Now reads:* Section 2.2.2 Exploratory Objectives – **Subjects with Ulcerative Colitis** • To evaluate the effect of long-term SHP647 treatment on clinical outcomes **(including remission over time based on composite score of patient-reported symptoms using daily diary and locally read endoscopy, Mayo-based remission over time, clinical remission over time, partial Mayo score over time, clinical response over time based on composite score, and Mayo-based clinical response over time)** • **To evaluate the effect of long-term SHP647 treatment on endpoints related to endoscopic healing** • To evaluate the effect of long-term SHP647 treatment on abdominal pain, urgency, diarrhea, and absolute stool frequency and bleeding scores. • To evaluate the effect of long-term SHP647 treatment on health-related quality of life (HRQL) **(as measured by Inflammatory Bowel Disease Questionnaire [IBDQ], Short Form-36 Health Survey [SF-36]) and European Quality of Life 5 Dimensions, 5 Levels questionnaire [EQ-5D-5L]).** • To evaluate the impact of long-term SHP647 treatment on incidence of hospitalizations and total inpatient days. • To evaluate the effect of long-term SHP647 treatment on ~~HRQL using EQ-5D and~~ work productivity **as measured by the Work Productivity and Activity Impairment Questionnaire - UC (WPAI-UC).** • To evaluate the impact of long-term SHP647 treatment on ~~patients~~**subject** satisfaction with ~~medication~~**treatment as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM).**		Section 2.2.2, Exploratory Objectives

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• To evaluate the impact of long-term SHP647 treatment on incidence of emergency department (ED) visits. • To evaluate the impact of long-term SHP647 treatment on incidence of UC-related and other surgeries. • To evaluate SHP647 pharmacokinetics during long-term treatment. • To evaluate the impact of long-term SHP647 treatment on selected biomarkers.		
Added new section to describe the exploratory objectives for subjects with CD. *New text:* **Section 2.2.3 Exploratory Objectives – Subjects with Crohn's Disease** • **To evaluate the effect of long-term SHP647 treatment on clinical outcomes (including 2-item PRO-based clinical response over time, 2-item PRO-based and CDAI-based clinical remission over time.** • **To evaluate the effect of long-term SHP647 treatment on endpoints related to endoscopic healing.** • **To evaluate the effect of long-term SHP647 treatment on abdominal pain severity, very soft stool/liquid stool frequency (as shown by type 6/7 on Bristol Stool Form Scale [BSFS]), total stool frequency, rectal urgency, rectal bleeding, nausea, vomiting, and rectal incontinence.** • **To evaluate the effect of long-term SHP647 treatment on HRQL (as measured by the IBDQ, SF-36, and EQ-5D-5L).** • **To evaluate the impact of long-term SHP647 treatment on incidence of hospitalizations and total inpatient days.** • **To evaluate the impact of long-term SHP647 treatment on incidence of CD-related and other surgeries.** • **To evaluate the effect of long-term SHP647 treatment on work productivity as measured by the WPAI-CD.** • **To evaluate the impact of long-term SHP647 treatment on subject satisfaction with treatment as measured by the TSQM.** • **To evaluate the impact of long-term SHP647 treatment on incidence of ED visits.** • **To evaluate SHP647 pharmacokinetics during long-term treatment.** • **To evaluate the impact of long-term SHP647 treatment on selected biomarkers.**		Section 2.2.3, Exploratory Objectives – Subjects with Crohn's Disease

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Revised language to reflect inclusion of subjects with CD entering from studies SHP647-305, SHP647-306, and SHP647-307. Deleted Figure 1 Overview of SHP647 Phase 3 Ulcerative Colitis Studies as it was redundant with Figure 2 Study Design Flow Chart. Updated Figure 1 (formerly Figure 2) Study Design Flow Chart to reflect inclusion of CD subjects. *Now reads:* Section 3.1, Study Design and Flow Chart This is a Phase 3 **double-blind**, multicenter extension study designed to evaluate the long-term safety and efficacy of SHP647 in subjects with moderate to severe UC **or CD**. The study will enroll subjects from 6 separate Phase 3 studies: 2 multicenter, randomized, double-blind, placebo-controlled, parallel group studies evaluating SHP647 as an induction therapy in subjects with moderate to severe UC (SHP647-301 and SHP647-302); **2 multicenter, randomized, double-blind, placebo-controlled, parallel group studies evaluating SHP647 as an induction therapy in subjects with moderate to severe CD (SHP647-305 and SHP647-306);** 1 multicenter, double-blind, randomized, placebo-controlled, parallel-group studies evaluating SHP647 as maintenance therapy in subjects with moderate to severe UC (SHP647-303)**; and 1 multicenter, double-blind, randomized, placebo-controlled, parallel-group studies evaluating SHP647 as maintenance therapy in subjects with moderate to severe CD (SHP647-307).** All subjects will receive active drug in this study. Eligible subjects entering Study SHP647-304 will be assigned to receive either 25 mg or 75 mg of SHP647 every 4 weeks. Allocation is dependent on how the subject entered into this study: • Subjects who completed maintenance study SHP647-303 **or SHP647-307 without treatment failure** and received either 25 mg or 75 mg of SHP647 every 4 weeks will continue to receive the same dose of SHP647 in this long-term safety extension study. **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 1additional week to confirm final status of the subject (treatment failure or not) before enrolling the subject to Study SHP647-304.** • All other subjects will be randomized using a 1:1 allocation. Randomization will be stratified **by indication (UC or CD) and by the status from the study from which they are entering, as follows:** (1) **did not meet the response criteria (clinical and/or endoscopic response/remission as appropriate)** in an induction study; (2) treatment failure in a maintenance study, or (3) maintenance study completion **without treatment failure** for subjects receiving placebo, to facilitate balance of treatment assignment within each	Section 3.1, Study Design and Flow Chart Figure 1 Study Design Flow Chart

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stratum. The eligibility of a subject for this study will be assessed **from** study data collected at: • **For UC subjects,** the Week 12 visit of **the** induction study **(SHP647-301 or SHP647-302),** OR the Week 52 or Early Termination visit of the maintenance study **(SHP647-303),** which will be considered and recorded as the baseline visit for this extension study. • **For CD subjects, the Week 16 visit of the induction study (SHP647-305 or SHP647-306), OR the Week 52 or Early Termination visit of the maintenance study (SHP647-307), which will be considered and recorded as the baseline visit for 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.** Subjects enrolled in this study will receive double-blind treatment every 4 weeks in the form of SC injections using pre-filled syringes. Subjects will undergo safety, efficacy, biomarker, pharmacokinetic, and health outcome assessments at these visits as outlined in the Schedules of Assessments (Table 1 **and Table 3** for assessments in Year 1, **for subjects with UC and CD, respectively;** Table 2 **and Table 4** for assessments beginning in Year 2 through End of Study, **for subjects with UC and CD, respectively).** The primary objective of this study is evaluation of the safety and tolerability of long-term treatment with SHP647. Safety will be measured by: incidence and severity of adverse events (AEs); incidence and nature of serious infections; actual values and change from baseline, as well as the incidence of abnormalities, in laboratory tests, ECGs, and vital signs; and antidrug antibodies. **For subjects with UC,** patient-reported signs and symptom data (including stool frequency, rectal bleeding severity and frequency, diarrhea frequency, urgency frequency, and abdominal pain worst severity) will be collected using a daily e-diary for 10 days before each specified visit. The Mayo score is a measure of UC disease activity consisting of the following 4 subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician global assessment (PGA). The partial Mayo score consists of the Mayo score without the endoscopic subscores. The composite score is a recommended measure consisting of the Mayo score without the PGA subscore, and will be used for the exploratory efficacy endpoints. The Mayo scores and composite score will be based on subject daily e-diary entries. **For subjects with CD, patient-reported signs and symptom data (abdominal pain severity, very soft stool/liquid stool [as shown by BSFS type 6/7] frequency, rectal bleeding frequency, rectal urgency**		

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frequency, vomiting frequency, nausea severity, incontinence frequency, total stool frequency) will be collected using a daily e-diary for 14 days before each specified visit. 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 self-reported by the subject and will be collected as part of the daily e-diary for 14 days before each specified visit as in the schedules of assessments. Figure 1: Study Design Flow Chart *Footnote to Figure 1 now reads:* EOT = End of Treatment; LTS = long-term safety; Q4W = every 4 weeks For Induction Studies SHP647-301 and SHP647-302, Treatment Period = 12 weeks. **For Induction Studies SHP647-305 and SHP647-306, Treatment Period = 16 weeks**. For Maintenance Studies SHP647-303 **and SHP647-307**, Treatment Period = 52 weeks. * Randomization will be stratified **by indication (UC or CD) and by the status from the study from which they are entering, as follows: (1) did not meet the response criteria (clinical and/or endoscopic response/remission as appropriate)** in an induction study; (2) treatment failure in a maintenance study, or (3) maintenance study completion **without treatment failure** for subjects receiving placebo, to facilitate balance of treatment assignment within each stratum. ** For subjects who are tolerating study drug and receiving clinical benefit in the judgment of the investigator, study participation may continue until ~~SHP647 becomes available commercially,~~ the subject withdraws from the study, or the investigator or sponsor decide to withdraw the subject (eg, in the interest of subject safety), or the sponsor decides to close the study**, or the program is stopped in the indication or completely.** Subjects will continue in a safety follow-up period for 16 weeks from the last dose of investigational product. **A subject's maximum duration of participation is expected to be approximately 7 years or until SHP647 becomes commercially available, whichever occurs earlier.**		
Revised expected duration of study to reflect inclusion of subjects with CD. Added statement to clarify a subject's anticipated maximum duration of treatment. *Now reads:* For subjects who are tolerating study drug and receiving clinical benefit in the judgment of the investigator, study participation may continue until ~~SHP647 becomes available commercially, the~~ subject withdraws from the study, or the investigator or sponsor decide to withdraw the subject (eg, in the interest of subject safety), or the sponsor decides to close the study, **or the program is stopped in the indication or completely**. **A subject's maximum duration of treatment is expected to be 7 years, or until SHP647 becomes available commercially, whichever occurs earlier.**		Study Synopsis, Methodology Study Synopsis, Maximum duration of subject involvement in the study Section 3.1, Study Design and Flow Chart Figure 1, Study Design Flow Chart Section 3.2, Duration and Study Completion Definition Section 7.1.2, Treatment Period

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Subjects will enter a 16-week safety follow-up period following the last dose of investigational product. The final visit will be in person at the site. A subject's maximum duration of participation is expected to be approximately ~~6~~**7** years. It is expected that the study will be completed in approximately ~~6~~**7** years.		
Revised for clarity. *Now reads:* The potential effects of SHP647 on embryofetal or postnatal development have not yet been assessed in animals or humans; these will be assessed in future studies. To minimize the risk of unintentional exposure of the embryo or fetus in the clinical study, all sexually active male and female subjects who, in the opinion of the investigator, are biologically capable of having children and with their partners are at risk of pregnancy, must agree to use an ~~acceptable~~ **appropriate** form of contraception, in accordance with the package instructions/leaflet, for the duration of the active treatment period and for at least 16 weeks after the last dose of investigational product. True abstinence is considered to be a highly effective contraception method (ie, a method that results in a failure rate of <1% per year) when it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to investigational product, and withdrawal are not ~~acceptable~~ **appropriate** methods of contraception. During the induction studies (SHP647-301**, SHP647-302, SHP647-305**, and SHP647~~-302~~**-306**) or maintenance ~~study~~**studies** (SHP647-303 **and SHP647-307),** the investigator or designee in consultation with the subject will confirm subject's childbearing potential status. For subjects of childbearing potential, it must be confirmed and documented that the subject has selected the most appropriate method of contraception from the permitted list of contraception methods. Subjects must affirm the consistent and correct use of at least 1 of ~~the~~ **these** selected methods. Regular contraception check discussions will take place at the time points specified in Table 1 and Table 2 **(for subjects with UC) and Table 3 and Table 4 (for subjects with CD)** (ie, at each site visit) and will be documented. In addition, the subject must be instructed to call the site immediately if the selected contraception method is discontinued or if pregnancy is known or suspected. **4.3.1 Contraceptive Methods for Female Study Subjects** At baseline in this study, the childbearing potential of subjects must be re-established and documented if the subject's status has changed since the induction studies (SHP647-301, SHP647-302, **SHP647-305,** or **SHP647-306**) or maintenance ~~study~~ **studies** (SHP647-303 **or SHP647-307**) (refer to Section 7.2.4.7). Sexually active females of childbearing potential must **already** be using an	Section 4.3, Reproductive Potential

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~~acceptable~~ **established highly effective** form of contraception, and must be advised to use ~~acceptable~~ **appropriate** contraceptives throughout the study period and for 16 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Female subjects should be in one of the following categories: • Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥51 years of age); postmenopausal status should be confirmed by follicle-stimulating hormone (FSH) testing. • Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks poststerilization or has medically confirmed ovarian failure. • Females of childbearing potential with a negative ~~serum pregnancy test result at screening and a negative urine~~ pregnancy test result at baseline. Females of childbearing potential must agree to **practice true abstinence (**~~abstain~~ **refrain** from sexual activity that could result in pregnancy**)** or agree to use ~~acceptable~~ **appropriate** methods of highly effective contraception. ~~Acceptable methods of~~ Highly effective contraception (ie, methods that result in a failure rate of <1% per year **when used consistently and correctly**) are: • Combined (estrogen- and progestogen-containing) hormonal contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal) stabilized for at least 30 days before ~~the screening visit (Visit 1)~~ **study SHP647-304 baseline** • Progestogen-only hormonal contraception associated with inhibition of ovulation plus a barrier method • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Male sterilization/vasectomized partner with **documented** absence of sperm in the postvasectomy ejaculate • True abstinence (~~see~~ Section 4.3). **4.3.2 Contraceptive Methods for Male Study Subjects** Contraception is required for all sexually active male subjects, who with their **female sexual** partners, must agree to use ~~1 of~~ the following ~~acceptable~~ **appropriate** methods of contraception throughout the study period and for 16 weeks following the last dose of investigational product. **Appropriate methods of contraception for male subjects are:** • Male condom with spermicide; however, if spermicide is not available in the country, additional contraception (ie, one of those	

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listed below) must be used in addition to a **male** condom • **Male sterilization with documented absence of sperm in the postvasectomy ejaculate.** **Appropriate methods for female sexual partners of male subjects are (unless the female sexual partner is sterile [surgically or documented nonsurgical sterility]):** • **Use of a highly effective method of contraception listed in Section 4.4.1 OR an acceptable method of contraception (failure rate of >1% per year):** o Female condom with spermicide (use by female sexual partner); however, if spermicide is not available in the country, additional contraception (ie, one of those listed below) must be used in addition to a **female** condom ~~o Sterile sexual partner~~ o Intrauterine device with spermicide~~(use by female sexual partner)~~ o Contraceptive sponge with spermicide~~(use by female sexual partner)~~ o Intravaginal system (eg, vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide) ~~(use by female sexual partner)~~ ~~• Oral, implantable, transdermal, or injectable hormonal contraceptive (use by female partner) plus a barrier method~~. ~~• Male sterilization with absence of sperm in the postvasectomy ejaculate.~~		
Deleted incorrect statement that total amount of investigational product taken would be recorded on withdrawal from the study. *Now reads:* If investigational product is discontinued, regardless of the reason, the evaluations listed for the End of Treatment (EOT) visit are to be performed. All subjects who discontinue investigational product should also undergo the protocol-specified 16-week follow-up period. In the event that subjects are unable to attend in person for the follow-up visits, all efforts should be made to collect information on AEs and concomitant medications. Comments (spontaneous or elicited) or complaints made by the subject must be recorded. The reason for termination and date of stopping investigational product~~, and the total amount of investigational product taken~~ must be recorded.		Section 4.4, Withdrawal of Subjects

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Updated to reflect inclusion of subjects with CD. *Now reads:* Additional reasons a subject may be withdrawn from active treatment include but are not limited to: AEs, SAEs, major protocol deviations, and failure to return for visits. A subject should be withdrawn from study treatment: • If a new therapy is initiated for UC **or CD**, or • If a subject undergoes surgery for UC **or CD**.		Section 4.4.1, Subject Withdrawal Criteria
Updated to include treatment failure definition for subjects with CD. *Now reads:* ***Subjects with UC who Enter from Study SHP647-301, SHP647-302, or SHP647-303*** Subjects **with UC** may enter the study from either an induction (SHP647-301 or SHP647-302) or maintenance study (SHP647-303), and may have received either active drug or placebo. Some subjects entered the study with clinical response, some without achieving clinical response in induction study (SHP647-301 or SHP647-302), or entered following treatment failure in maintenance study SHP647-303. To ~~assure~~ **ensure** that placebo-treated subjects **from Study SHP647-301, SHP647-302 or SHP647-303** have sufficient exposure to active drug to permit assessment of response, assessment of treatment failure should not begin prior to Week 12. Treatment failure should be assessed if there is an unexplained clinical exacerbation or unacceptably low level of clinical response. Treatment failure is determined by increased (worsened) stool frequency and rectal bleeding in subjects who have previously responded to SHP647, or failure to improve to a clinically significant degree in those who never responded, who enrolled as treatment failures, or who improved after enrolment into this trial but then experienced worsening of symptoms. • *NOTE: Other potential causes of disease exacerbation, including viral or bacterial gastroenteritis and* Clostridium difficile *infection should be ruled out by appropriate stool cultures and other laboratory tests. If a potential other cause is identified, treatment failure should not be assessed until a full course of treatment has been completed or if untreated, the infection would be expected to have resolved based on its natural history.* Subjects who have experienced treatment failure should be withdrawn from active treatment once other possible etiologies have been ruled out. All subjects who discontinue investigational product should undergo the protocol-specified 16-week follow-up period. The ultimate decision of withdrawal from the active treatment is left to the investigator based on the assessment of disease activity, subject's clinical		Section 4.4.1.1, Treatment Failure

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benefit and tolerance of the study drug. ***Subjects with CD who Enter from Study SHP647-305, SHP647-306, or SHP647-307*** **Subjects with CD may enter the study from either an induction (SHP647-305 or SHP647-306) or maintenance study (SHP647-307), and may have received either active drug or placebo. Some subjects entered the study with clinical response, some without achieving clinical response in induction study (SHP647-305 or SHP647-306), or entered following treatment failure in maintenance study SHP647-307.** **To ensure that placebo-treated subjects from Study SHP647-305, SHP647-306 or SHP647-307 have sufficient exposure to active drug to permit assessment of response, assessment of treatment failure should not begin prior to Week 16.** **Treatment failure should be assessed if there is an unexplained clinical exacerbation or unacceptably low level of clinical response.** **Treatment failure is determined by increased (worsened) abdominal pain and/or very soft stool/liquid stool frequency in subjects who have previously responded to their assigned treatment, or failure to improve to a clinically significant degree in those who never responded, who enrolled as treatment failures, or who improved after enrolment into this trial but then experienced worsening of symptoms.** • ***NOTE: Other potential causes of disease exacerbation, including viral or bacterial gastroenteritis and* Clostridium difficile *infection should be ruled out by appropriate stool cultures and other laboratory tests. If a potential other cause is identified, treatment failure should not be assessed until a full course of treatment has been completed or if untreated, the infection would be expected to have resolved based on its natural history.*** **Subjects who have experienced treatment failure should be withdrawn from active treatment once other possible etiologies have been ruled out. All subjects who discontinue investigational product should undergo the protocol-specified 16-week follow-up period. The ultimate decision of withdrawal from the active treatment is left to the investigator based on the assessment of disease activity and other relevant factors as appropriate, including need for rescue medication, need for major surgical intervention for further treatment of CD, subject's lack of clinical benefit and/or the occurrence of a treatment-related adverse event or intolerance leading to withdrawal of the study drug.**		
Added treatment failure as a reason for withdrawal from the study. *Now reads:* The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and source document.		Section 4.4.2, Reasons for Withdrawal

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Reasons for discontinuation include but are not limited to: • Adverse event • Protocol deviation • Withdrawal by subject • Lost to follow-up • **Treatment failure** • Other (if "other" is selected, the investigator must specify the reason) • Death • Physician decision • Pregnancy • Screen failure • Site terminated by sponsor • Study terminated by sponsor		
Made the following edits to the permitted treatments for clarity: Section 5.2.1 Permitted Treatment The following treatments for UC are permitted as concomitant medication: • 5-aminosalicylate (5-ASA; mesalamine) and sulfasalazine. • Immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]). • ~~The use of~~ Oral glucocorticoids ~~is permitted~~; tapering should start once subject achieves adequate treatment response and should be guided by investigator clinical judgment. The recommended tapering scheme, based on European Crohn's and Colitis Organisation (ECCO) guidelines, as shown in Table 5. Parenteral and rectally used glucocorticoids are permitted per discretion of the investigator. • … Medicinal marijuana (cannabis) under a physician's prescription, obtained from a licensed pharmacy or provider may be used **in a stable dose** during the study. Routine nonlive vaccinations are allowed during the study. Dietary and herbal supplements and probiotics are allowed in the study. Use of nicotine ~~patches~~ **-containing preparations** should be recorded as concomitant medication. Added footnote to Table 5 (Glucocorticoid Tapering – Subjects with Ulcerative Colitis) to define glucocorticoid-dependent subjects per the European Crohn's and Colitis Organisation guidelines:		Section 5.2, Concomitant Treatment – Subjects with Ulcerative Colitis Section 5.2.1, Permitted Treatment Section 5.2.2, Prohibited Treatment Table 5

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[a] Glucocorticoid dependent subjects are: **• Subjects who are unable to reduce glucocorticoids below the equivalent of prednisone 10 mg/day (or budesonide below 3 mg/day) within 3 months of starting glucocorticoids, without recurrent active disease** **OR** **• Subjects who have a relapse within of stopping glucocorticoids** (Dignass et al., 2012) Made the following edits to prohibited treatments: Section 5.2.2, Prohibited Treatment The following common treatments are excluded medications for this study. As the subjects are transferred from Study SHP647-301, SHP647-302, or SHP647-303, during which these treatments were also prohibited, no washout period is applicable. • Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab). • Anti-TNF treatment and other biologics with immunomodulatory properties. • Live (attenuated) vaccines ~~are not permitted during the study.~~ • **Any investigational product other than the study drug.** Treatments not listed in this section may be considered allowable; see Section 5.2.1 for further details. **No new nonpharmacological therapies that might affect bowel habit or GI function should be started during the study.**		
Added new section to describe permitted and prohibited concomitant treatments for subjects with CD. *New section reads:* **5.3 Concomitant Treatment – Subjects with Crohn's Disease** **Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product in this study and the end of the safety follow-up period, inclusive.** **5.3.1 Permitted Treatment** **Following treatments for CD are permitted as concomitant medication:** • **Oral 5-aminosalicylate (5-ASA; mesalamine) and sulfasalazine.** • **Immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]).** • **Oral glucocorticoids; however, tapering should start once subject achieves adequate treatment response and should be guided by investigator clinical judgment.**		Section 5.3, Concomitant Treatment – Subjects with Crohn's Disease Section 5.3.1, Permitted Treatment Section 5.3.2, Prohibited Treatment

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• **As the subjects are transferred from induction studies SHP647-305 or SHP647-306, or maintenance study SHP647-307, the maximum glucocorticoid dose is 20 mg/day of oral prednisone or equivalent (see Table 6), and 9 mg/day of budesonide. Tapering should follow the procedure shown in Table 6.** • **Note: Rectal 5-ASA and parenteral or rectal glucocorticoids are prohibited (see Section 5.3.2).** • *[Table 6 added to describe glucocorticoid tapering for subjects with CD.]* **During the glucocorticoid taper, subjects may experience worsening of CD signs or symptoms that, in the opinion of the investigator, are attributable to reduction in glucocorticoid dose. If signs or symptoms occur, the investigator can instruct the subject to revert to the preceding week's daily dosage. The signs or symptoms leading to this change (eg, increased stool frequency, increased rectal bleeding) must be recorded.** **Antidiarrheal opiate drugs such as IMODIUM® (loperamide), LOMOTIL® (diphenoxylate hydrochloride and atropine sulfate), tincture of opium, and codeine will be recorded. Subjects should be on stable doses at the time of the baseline visit (Visit 1) and for the duration of the study.** **Medicinal marijuana (cannabis) under a physician's prescription, obtained from a licensed pharmacy or provider may be used in a stable dose during the study.** **Routine nonlive vaccinations are allowed during the study.** **Dietary and herbal supplements and probiotics are allowed in the study, provided they are being taken at stable doses at the time of the baseline visit (Visit 1) and for the duration of the study. They should be recorded as concomitant medications.** **Use of nicotine-containing preparations should be recorded as concomitant medication.** **5.3.2 Prohibited Treatment** **The following common treatments are excluded medications for this study. As the subjects are transferred from induction studies SHP647-305 or SHP647-306, during which these treatments were also prohibited, no washout period is applicable.** • **Parenteral and rectally administered glucocorticoids.** • **Prednisone dose >20 mg per day or equivalent oral systemic corticosteroid dose and 9 mg/day of budesonide.** • **Off-label usage of immunosuppressants used in transplantation or other nonestablished therapies for CD (eg, mycophenolate mofetil, cyclosporine, rapamycin, thalidomide, tofacitinib, or tacrolimus).**		

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• **Rectally administered 5-ASA.** • **Bismuth subsalicylate products.** • **Anti-TNF treatment and other biologics with immunomodulatory properties including biosimilars.** • **Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab).** • **Lymphocytes apheresis or selective monocyte granulocytes apheresis.** • **Live (attenuated) vaccines.** • **Fecal macrobiota transplantation.** • **Any investigational product other than the study drug.** **Treatments not listed in this section may be considered allowable; see Section 5.3.1 for further details.** **No new nonpharmacological therapies that might affect bowel habit or GI function should be started during the study.** **Parenteral nutrition is not permitted at any time during the study.**		
Revised to include subjects with CD entering from Study SHP647-305, SHP647-306, or SHP647-307. Added language to note that if one of the doses (25 mg or 75 mg) of SHP647 is determined to be the efficacious dose, subjects may all be moved onto that dose. *Now reads:* Section 6.2.2 Allocation of Subjects to Treatment This is a double-blind study. Following the confirmation of eligibility, subjects will be allocated to receive either 25 mg or 75 mg of SHP647 SC every 4 weeks. Allocation is dependent on how the subject entered into this study: • Subjects who completed maintenance study SHP647-303 **or SHP647-307** without treatment failure and received either 25 mg or 75 mg of SHP647 every 4 weeks will continue to receive the same dose of SHP647 in this long-term safety extension study. • All other subjects will be randomized using a 1:1 allocation. Randomization will be stratified by ~~whether~~ **indication (UC or CD) and by** the ~~subjects~~**status from the study from which they** are entering~~this study following~~**, as follows:** (1) nonresponse in **an** induction study~~SHP647-301 or SHP647-302~~; (2) treatment failure in **a** maintenance study~~SHP647-303~~, or (3) maintenance study ~~SHP647-303~~ completion **without treatment failure** for subjects receiving		Section 6.2.2, Allocation of Subjects to Treatment

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placebo, to facilitate balance of treatment assignment within each stratum. 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-~~303~~**307**. The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. Individual subject treatment is automatically assigned by the IRT system. Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject. **If during the study either the 25 mg or 75 mg dose of SHP647 is determined to be the efficacious dose, ie based on emergent data from the induction and/or maintenance 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.**		
Added the following paragraph here (formerly in Section 9.6) and made edits for clarity. *Now reads:* The fill volume for all syringes will be the same. Added text to clarify blinding and unblinding of treatment assignment for subjects with CD. *Now reads:* The purpose of the blinding in this extension study is to maintain to the blind in maintenance study SHP647-303 **for UC subjects and SHP647-307 for CD subjects** while ~~it remains~~ **these studies are** ongoing. When study SHP647-303 **for UC** has completed and data are unblinded, the treatment assignment in this study **for UC subjects** does not need to remain blinded. **Similarly, when Study SHP647-307 for CD has completed and data are unblinded, the treatment assignment in this study for CD subjects does not need to remain blinded.**		Section 6.1.1, Blinding the Treatment Assignment *Now reads:* Section 9.3, Data Handling Considerations

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Updated to reflect inclusion of subjects with CD, and to note that if during the study one or the other dose of SHP647 is determined to be efficacious, subjects may be switched over to that treatment assignment. *Now reads:* This is a double-blind study. Following the confirmation of eligibility, subjects will be allocated to receive either 25 mg or 75 mg of SHP647 SC every 4 weeks. Allocation is dependent on how the subject entered into this study: • Subjects who completed maintenance study SHP647-303 **or SHP647-307** without treatment failure and received either 25 mg or 75 mg of SHP647 every 4 weeks will continue to receive the same dose of SHP647 in this long-term safety extension study. • All other subjects will be randomized using a 1:1 allocation. Randomization will be stratified by ~~whether~~ **indication (UC or CD) and by** the ~~subjects~~**status from the study from which they** are entering ~~thisstudy following~~, **as follows**: (1) nonresponse in **an** induction study~~SHP647-301 or SHP647-302;~~ (2) treatment failure in **a** maintenance study ~~SHP647-303,~~ or (3) maintenance study ~~SHP647-303~~ completion **without treatment failure** for subjects receiving placebo, to facilitate balance of treatment assignment within each stratum. 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~~303~~**-307**. The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. **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 SHP647 dose in this study. Individual** subject treatment is automatically assigned by the IRT system. Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject. **If during the study either the 25 mg or 75 mg dose of SHP647 is determined to be the efficacious dose, ie based on emergent data from the induction and/or maintenance 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.**		Section 6.2.2, Allocation of Subjects to Treatment
Edited to add studies from which subjects with CD would be entering this extension study.		Section 6.2.3, Dosing

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Now reads: As some subjects may enter this study having received placebo and not active treatment in the induction (SHP647-301**, SHP647-302, SHP647-305**, or SHP647-~~302~~**306**) or maintenance (SHP647-303 **or SHP647-307**) study, after the first administration of investigational product, the subject must be observed by a member of the study staff for at least 30 minutes (the total duration should be determined at the discretion of the investigator). For subsequent administrations, observation of the subject is at the discretion of the investigator. Injection site and allergic reaction monitoring should be completed by a member of the study staff.		
Updated to include study procedures for subjects with CD. *Now reads:* Study 7 Study Procedures The investigator may schedule visits (unscheduled visits) in addition to those listed on the schedules of assessments (Table 1 and Table 2 **for subjects with UC; Table 3 and Table 4 for subjects with CD),** in order to conduct evaluations or assessments required to protect the wellbeing of the subject. **7.1.1 Baseline Visit (Week 0/Day 1)** ***Subjects with UC, Entering from Study SHP647-301, SHP647-302, or SHP647-303*** For subjects **entering into Study SHP647-304 from** induction study SHP647-301 or SHP647-302, procedures performed at the Week 12 visit will be the baseline (Week 0/Day 1) assessments for this extension study. For subjects ~~previously enrolled in~~ **entering into Study SHP647-304 from** maintenance study SHP647-303 and who completed the treatment period, procedures performed at the Week 52 visit will be the baseline (Week 0/Day 1) assessments for this extension study. For subjects ~~previously enrolled in~~ **entering from** maintenance study SHP647-303 and who withdrew prior to completion of the treatment period, procedures performed at the Early Termination (ET) visit will be the baseline (Week 0/Day 1) assessments for this extension study. The assessments and procedures performed during the baseline visit are specified in Table 1. A screen failure is a subject who has given informed consent or assent, as applicable (and whose parents or legally authorized representatives have given informed consent, as applicable), failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria, and has not been randomized or administered investigational product. ~~The composite score and total Mayo score will be calculated at baseline of the SHP647-304 study (Week 12/Visit 6 of the induction studies, or Week 52/Visit 14 or ET visit of the maintenance study; used for Week 0/Day 1 of this extension study) before randomization.~~ For eligible subjects, all relevant study information recorded for Week 12 of the induction studies or Week 52 or ET of the maintenance study will be	Section 7, Study Procedures Section 7.1.1, Baseline Visit (Week 0/Day 1) Section 7.1.2, Treatment Period Section 7.1.3, Follow-up Period	

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used as the baseline visit data for this extension study. The health outcome assessments completed at Week 12 in the induction study or Week 52 or ET in the maintenance study should have been completed before any other baseline visit assessments performed for this extension study. After eligibility has been confirmed and all baseline procedures and assessments have been completed, each subject will be assigned 1 of the 2 treatment groups as described in Section 6.2.2 and the first dose of investigational product will be administered. ***Subjects with CD Entering from Study SHP647-305, SHP647-306, or SHP647-307*** **For subjects entering into Study SHP647-304 from induction study SHP647-305 or SHP647-306, procedures performed at the Week 16 visit will be the baseline (Week 0/Day 1) assessments for this extension study.** **For subjects entering into Study SHP647-304 from maintenance study SHP647-307 and who completed the treatment period, procedures performed at the Week 52 visit will be the baseline (Week 0/Day 1) assessments for this extension study. For subjects entering from maintenance study SHP647-307 and who withdrew prior to completion of the treatment period, procedures performed at the Early Termination (ET) visit will be the baseline (Week 0/Day 1) assessments for this extension study. The assessments and procedures performed during the baseline visit are specified in Table 3.** **A screen failure is a subject who has given informed consent or assent, as applicable (and whose parents or legally authorized representatives have given informed consent, as applicable), failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria, and has not been randomized or administered investigational product.** **For eligible subjects, all relevant study information recorded for Week 16 of the induction studies or Week 52 or ET of the maintenance study will be used as the baseline visit data for this extension study. The health outcome assessments completed at Week 16 in the induction study or Week 52 or ET in the maintenance study should have been completed before any other baseline visit assessments performed for this extension study.** **After eligibility has been confirmed and all baseline procedures and assessments have been completed, each subject will be assigned 1 of the 2 treatment groups as described in Section 6.2.2 and the first dose of investigational product will be administered.** **7.1.2 Treatment Period** During the first year (48 weeks) of treatment in this extension study, subjects will attend study visits every 4 weeks (Weeks 4, 8, 12, 16, etc). Assessments and procedures to be performed at each visit are specified in Table 1 **(for subjects with UC) and in Table 3 (for subjects with CD).** Assessments and procedures to be performed at each visit beginning in		

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Treatment Year 2 (Week 52) are specified in Table 2 **(for subjects with UC) and in Table 4 for subjects with CD**). For subjects who are tolerating study drug and receiving clinical benefit in the judgment of the investigator, study participation may continue until ~~SHP647 becomes available commercially,~~ the subject withdraws from the study, or the investigator or sponsor decide to withdraw the subject (eg, in the interest of subject safety), or the sponsor decides to close the study, or **the program is stopped in the indication or completely.** Once study treatment has ended, ie, for any of the reasons described in Section 4.4, subjects will attend the End of Treatment (EOT) visit, at which assessments and procedures will be performed as shown in Table 2 **(for subjects with UC) and in Table 4 for subjects with CD).** After completion of the EOT visit, subjects will enter the safety follow-up period. **7.1.3 Follow-up Period** The safety follow-up period for this protocol is 16 weeks from the ~~last dose of investigational product administered to~~ **EOT visit for** each subject. During the follow-up period, there will be a telephone contact at 8 weeks (±7 days) post-EOT, and a visit at the study site at 16 weeks (±7 days) post-EOT. The assessments and procedures specified in Table 2 **(for subjects with UC) and Table 4 (for subjects with CD)** will be performed, including querying for SAEs, AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).		
• Added statement that blood and tissue samples may be stored for up to but not longer than 25 years (this change was communicated in protocol administrative change memo #2, dated 14 Sep 2017). • Revised from "blood sample collection" to "laboratory sample collection" to clarify that this includes other sample collection, eg urine. • Moved investigational product administration to the last bullet point in the ordering of procedures. *Now reads:* Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator, that may make it unfeasible to perform the tests and procedures. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject. When timing of procedures and assessments coincide, the following order should be followed: • Health outcome and patient-reported questionnaires		Section 7.2, Study Evaluations and Procedures

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• Vital signs and ECG • ~~**Blood**~~ **Laboratory** sample collection • Endoscopy (see Section 7.2.2.1) • **Investigational product administration** • **Note: Blood and tissue samples may be stored for up to but not longer than 25 years.**		
Added reference to the induction and maintenance studies from which subjects with CD would enter this extension study. *Now reads:* All relevant demographic and baseline characteristics recorded for the induction studies (SHP647-301**, SHP647-302, SHP647-305,** or SHP647-~~302~~**306**) or maintenance study (SHP647-303 **or SHP647-307**) will be used as the baseline characteristics for this extension study SHP647-304.		Section 7.2.1, Demographic and Other Baseline Characteristics
Added new section to describe efficacy assessments for subjects with CD. *New section reads:* **7.2.3 Efficacy Assessments – Subjects with Crohn's Disease** **7.2.3.1 Patient reported Outcome - Crohn's Disease Diary** **Patient-reported CD signs and symptom data will be collected using a PRO-CD daily e-diary (electronic handheld device) for 14 days before visits as outlined in Table 3 and Table 4. Subjects will enter data on CD signs and symptoms items using the e-diary that will be provided to subjects at the start of the study. Compliance will be 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, <12 out of 14 diary entries), or lower than the previous visit.** **Subjects will be asked to record the following signs and symptom data, as experienced over the previous 24 hours, in the e-diary:** • **Abdominal pain severity (numeric rating scale [NRS])** • **Very soft stool/liquid stool frequency (as shown by BSFS type 6/7)** • **Total stool frequency** • **Rectal bleeding frequency** • **Rectal urgency frequency** • **Nausea severity** • **Vomiting frequency** • **Incontinence frequency** • **Abdominal pain used in CDAI** • **General well-being.**		Section 7.2.3, Efficacy Assessments – Subjects with Crohn's Disease Section 7.2.3.1, Patient reported Outcome - Crohn's Disease Diary Section 7.2.3.2, Colonoscopy Section 7.2.3.3, Simple Endoscopic Activity Score for Crohn's Disease Section 7.2.3.4, Crohn's Disease Activity Index

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The first 2 items (abdominal pain severity and very soft stool/liquid stool frequency) will be used to calculate the 2-item PRO. The 2-item PRO will be calculated using the following criteria: • **At visits without a colonoscopy, the 2-item PRO will be calculated based on the 7 most recent days during the 10 days of data collection before the visit. If fewer than 7 days are available, the 2-item PRO will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the 2-item PRO will be treated as missing.** • **At visits with a colonoscopy, the 2-item PRO will be calculated based on the 7 most recent days during the 10 days of data collection before the colonoscopy preparation. If fewer than 7 days are available, the 2-item PRO will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the 2-item PRO will be treated as missing.** **The PRO-CD daily e-diary is presented in Appendix 2.** **7.2.3.2 Colonoscopy** **Colonoscopy will be performed at the time points specified in Table 3 and Table 4.** **Bowel preparation regimens typically incorporate dietary modifications along with oral cathartics. Typically, the standard dose of a bowel preparation is split between the day before and the morning of the procedure. In this study, bowel preparation and colonoscopy are to be conducted as per local routine; however, sodium phosphate based preparations should be avoided, as such regimens can produce mucosal changes that mimic IBD.** **A complete colonoscopy should be performed that includes the visualization of rectum, the sigmoid colon, the left colon, the transverse colon, the right colon, the ileocecal valve and the terminal ileum. Incomplete endoscopy caused by but not limited to complication during endoscopy, interruption of the endoscopy for any reasons cannot be accepted as complete colonoscopy with the exception of impassable stenosis or other CD related complications as cause of failure to complete the colonoscopy procedure.** **The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during the baseline endoscopy in the induction study (SHP647-305 or SHP647-306). The colonoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's medical record. Colonoscopy results will be reviewed by a local reader.** **7.2.3.3 Simple Endoscopic Activity Score for Crohn's Disease** **Colonoscopy will be evaluated by the SES-CD scoring system at the time points specified in Table 3 and Table 4.**		

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The SES-CD score will be calculated using the subscores of each of the segments investigated and read by the local endoscopist at each of the visits when colonoscopy is performed. The baseline score will be based on the colonoscopy that was performed closest to the start time of the dose given at the end of 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 Crohn's disease index of severity. Overall, values on the SES-CD range from 0–56, with higher values indicating more severe disease. The 4 endoscopic variables are scored from 0–3 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 that the stenosis scores cannot exceed a total of 11 (Reinsich et al., 2017).** **The SES-CD is presented in Appendix 2.** **7.2.3.4 Crohn's Disease Activity Index** **The CDAI is a composite measure with 8 components; 3 components (abdominal pain severity, very soft stool/liquid stool frequency, and general wellbeing) will be self reported by the subject and will be recorded as part of the daily e-diary, as described in Section 7.2.3.1 and 5 components will be recorded at the time points specified in Table 3 and Table 4.** **The CDAI scores at visits specified in Table 3 and Table 4 will be calculated using the following:** • **Components 1 to 3 from subject-reported PRO-CD daily e-diary data collected ≥10 days before the visit using the same most recent 7 or 10 days as described for the 2-item PRO (Section 7.2.3.1) and** • **Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at the visit.**		

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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 is presented in Appendix 2.**		
Updated to add reference to subjects with CD from SHP647-305, SHP647-306, and SHP647-307. **7.2.4.1 Medical and Medication History** Medical history, including UC **or CD** history, cardiac history, and smoking history, and prior medications will be collected at the screening visit (Visit 1) of Study SHP647-301**, SHP647-302, SHP647-305,** or SHP647~~-302~~**-306**. Concomitant medications and procedures will be documented throughout the SHP647-304 study **at the time points specified in** Table 1 **and** Table 2 **(for subjects with UC) and Table 3 and Table 4 (for subjects with CD).** **7.2.4.2 Physical Examination (Including Weight)** Complete and targeted physical examinations and weight assessments will be performed at the times specified in Table 1 and Table 2 **(for subjects with UC) and Table 3 and Table 4 (for subjects with CD).** Complete physical examination includes the review of the following body systems: general appearance, skin, ~~HEENT~~ **head, eyes, ears, nose, and throat**; heart; lungs; ~~confrontational visual fields (~~eyes~~),~~ breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; back; and lymph nodes. Targeted physical examination includes the review of the following body systems: skin **(specifically including perianal for fistula and mouth for stomatitis),** heart, lungs, ~~confrontational visual fields (~~eyes~~),~~ abdomen, and examination of body systems where there are symptom complaints by the subject. **For subjects with CD, targeted physical examination includes review of the skin and mucosa, specifically perianal for fistula and oral cavity for stomatitis as part of the CDAI assessment.** Weight will be measured at the time points specified in Table 1 and Table 2 **(for subjects with UC) and Table 3 and Table 4 (for subjects with CD).** The complete physical examination performed at Week 12 of induction study SHP647-301 or SHP647-302, ~~or~~ **at Week 16 of induction study SHP647-305 or SHP647-306, or at** Week 52 or the ET visit of maintenance study SHP647-303 **or SHP647-307,** will be the baseline (Week 0/Day 1) examination of study SHP647-304. Abnormalities identified during this visit will be documented. Any changes from the baseline visit (Week 0/Day 1) in physical examination findings that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE. **7.2.4.3 Targeted Neurological Assessment** Targeted neurological assessments to monitor for the development of signs	Section 7.2.4, Safety Section 7.2.4.1, Medical and Medication History Section 7.2.4.2, Physical Examination (Including Weight) Section 7.2.4.3, Targeted Neurological Assessment

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and/or symptoms of progressive multifocal leukoencephalopathy (PML) will be performed at the time points specified in Table 1 and Table 2 **(for subjects with UC) and Table 3 and Table 4 (for subjects with CD).** Subjects will be evaluated to reveal any potential abnormalities in the following neurological domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior.		
Added reference to CD studies SHP647-305, SHP647-306, and SHP647-307. Clarified that temperature is reported in degrees Celsius or Fahrenheit. *Now reads:* Vital signs will be measured at the time points specified in Table1 and Table 2 **(for subjects with UC) and Table 3 and Table4 (for subjects with CD).** Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data. Vital signs include blood pressure, pulse, respiratory rate, and temperature. Vital signs should be recorded before ~~laboratory~~ **collection of** blood samples ~~are collected~~ **for laboratory assessments, where applicable.** Single measurements of sitting blood pressure will be recorded at each time point. Blood pressure should be determined by cuff with the subject's arm supported at the level of the heart and recorded to the nearest mmHg using the same method, the same arm (preferably the dominant arm), and the same position throughout the study. Respiratory rate will be measured with the subject in a comfortable position. The observer should hold the extremity of the subject as a distraction for the patient (ie, pretending he/she is taking the subject's radial pulse) and count the respiration for 1 minute. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius **or Fahrenheit.** Tympanic temperature may also be used. Any deviations from baseline (Week 0/Day 1) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE unless documented in the subject's medical history as a pre-existing medical condition.		Section 7.2.4.5, Vital Signs
Added reference to CD studies SHP647-305, SHP647-306, and SHP647-307. Deleted statement regarding a separate blood sample will be collected for each biomarker; this is outlined in the lab manual. **7.2.5.2 Pharmacodynamic Assessments** Predose blood samples will be collected at the time points specified in Table 1 and Table 2 **(for subjects with UC) and** Table 3 **and Table 4 (for subjects with CD)** for each of the following biomarkers: • Serum C-reactive protein (CRP)		Section 7.2.5.2, Pharmacodynamic Assessments

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• Serum soluble MAdCAM • Blood β_7^+ T cells ~~A separate blood sample will be collected for each biomarker.~~ Stool samples will be analyzed for fecal calprotectin at the time points indicated in Table 1 and Table 2 **(for subjects with UC)** and **Table 3 and Table 4 (for subjects with CD).** Details of sample collection, handling, shipment, and analysis will be provided in the laboratory manual.		
Added reference to CD studies SHP647-305, SHP647-306, and SHP647-307. Deleted reference to Patient Global Impression of Severity and Patient Global Impression of Change as these assessments are not being done in this study. **7.2.5.3 Health-related Quality of Life Assessments** Each subject will complete the Health-related Quality of Life (HRQL) assessments at the site during the visits specified in Table 1 and Table 2 **(for subjects with UC) and Table 3 and Table 4 (for subjects with CD),** using an electronic device. All health outcome and patient-reported questionnaires should be completed before any other assessments. The study site staff should check for completion of all patient-reported outcome (PRO) questionnaires. It is important to note that PRO assessments are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and PRO data collected from subjects. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded by the investigator. **Inflammatory Bowel Disease Questionnaire** The Inflammatory Bowel Disease Questionnaire (IBDQ) is a psychometrically validated PRO instrument for measuring the disease-specific quality of life in subjects with inflammatory bowel disease, including ulcerative colitis **and Crohn's disease.** The IBDQ consists of 32 items, which are grouped into 4 dimensions: bowel function, emotional status, systemic symptoms, and social function (Irvine et al., 1994). The 4 domains are scored as follows: • Bowel symptoms: 10 to 70 • Systemic symptoms: 5 to 35 • Emotional function: 12 to 84 • Social function: 5 to 35. The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better quality of life. A score of at least		Section 7.2.5.3, Health-related Quality of Life Assessments

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170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement. The IBDQ is presented in Appendix 2. **European Quality of Life 5 Dimensions, 5 Levels questionnaire** The European Quality of Life 5 Dimensions, 5 Levels (EQ-5D-5L™) is a patient completed instrument designed to assess impact on quality of life in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Brooks et al., 1991; Brooks, 2003; Kind, 1996). Additionally, scores from the 5 domains may be used to calculate a single index value. The instrument provides a simple descriptive profile and a single index value for health status, and is applicable to a wide range of health conditions and treatments. The EQ visual analog score (VAS) records the respondent's self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D-5L is presented in Appendix 2. ~~**Patient Global Impression of Severity and Patient Global Impression of Change**~~ ~~The Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) will capture the subject's global impression of change and severity over the course of the treatment period. They will be used as exploratory measures and to examine the psychometric properties of other PROs in the proposed studies.~~ ~~The PGIS and PGIC are presented in .~~ **Work Productivity and Activity Impairment Questionnaire- Ulcerative Colitis** The Work Productivity and Activity Impairment Questionnaire- Ulcerative Colitis (WPAI-UC) is a validated and self-administered 6-item instrument that is used to assess the effect of UC on the subject's ability to work and perform regular activities. The WPAI:UC is presented in Appendix 2. **Work Productivity and Activity Impairment Questionnaire- Crohn's Disease** **The Work Productivity and Activity Impairment Questionnaire-Crohn's Disease (WPAI-CD) is a validated and self-administered 6-item instrument that is used to assess the effect of CD on the subject's ability to work and perform regular activities. The WPAI-CD is presented in Appendix 2.**		
Corrected of the number of samples to be obtained for serum chemistry in Year 2 and subsequent years, to align with the Schedules of Assessments. Corrected the blood sample volumes for blood chemistry and CRP in text and in Table 8 (Treatment Year 1) and Table 9 (Treatment Year 2 and subsequent years) and the total blood volumes in text. *Now reads:* During this study, it is expected that approximately ~~72~~ **76** mL of blood will		Section 7.2.6, Volume of Blood to Be Drawn from Each Subject

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be drawn from each subject in the first year of study participation and approximately ~~63~~**54** mL of blood in each year thereafter. Additionally, it is expected that an approximate total of ~~28.5~~ **30** mL of blood will be drawn from each subject at the EOT visit and the safety follow-up visit at 16 weeks following the last dose of investigational product.		
Added reference to CD studies SHP647-305, SHP647-306, and SHP647-307. *Now reads:* All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. Where possible, a diagnosis rather than a list of symptoms should be recorded. Resolved AEs considered to be significant by the investigator that occurred in Studies SHP647-301, SHP647-302, **SHP647-303, SHP647-305, SHP647-306,** or SHP647~~-303~~ **307** will be captured as part of the SHP647-304 baseline medical history, while ongoing AEs from Studies SHP647-301, SHP647-302, **SHP647-303, SHP647-305, SHP647-306,** or SHP647~~-303~~ **307** will be captured as ~~part of SHP647-304 medical history followed throughout the SHP647-304~~ **AEs in** Study **SHP647-304**. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the subject's source document.		Section 8.1, Definition of Adverse Events, Period of Observation, Recording of Adverse Events
Added definitions of unexpected adverse event and suspected unexpected serious adverse reaction. *New sections added:* **8.1.8 Unexpected Adverse Event** **An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.** **The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.** **8.1.9 Suspected Unexpected Serious Adverse Reaction** **A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined**		Section 8.1.8, Unexpected Adverse Event Section 8.1.9, Suspected Unexpected Serious Adverse Reaction

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as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected. **The event(s) must meet all of the following:** • **Suspected adverse reaction** • **Serious** • **Unexpected** • **Assessed as related to study treatment**		
Clarified that that related, unexpected SAEs refers to SUSARs. *Now reads:* The sponsor or the CRO is responsible for notifying the relevant regulatory authorities, US central institutional review boards (IRBs), and EU central ethics committees (ECs) of related, unexpected SAEs **(ie, SUSARs).** In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs **(ie, SUSARs)** occurring during all interventional studies across the SHP647 program. The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.		Section 8.2.7, Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting
Added text to clarify unblinding following completion and unblinding of induction and maintenance studies. *Now reads:* Interim analyses may be conducted to support ~~the decision-making process during the program or for~~ submissions **before the completion of this study.** Such analyses would be conducted only after completion and unblinding of the induction and maintenance studies ~~SHP647-301, SHP647-302, and SHP647-303.~~ **in UC, SHP647-301, SHP647-302, and SHP647-303, and/or the induction and maintenance studies in CD, SHP647-305, SHP647-306, and SHP647-307. In the event that the induction and maintenance studies of one indication finishes before the other, special care will be taken to maintain the blind of the indication with ongoing induction and/or maintenance studies. Any interim analyses will be described in an SAP.** As there is no formal statistical testing, these interim analyses have no impact on the Type I error control.		Section 9.5, Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee
Added projections for number of CD subjects anticipated to enroll. *Now reads:* Approximately ~~1114~~**2453** subjects are projected to enroll into this study. No formal sample size estimation was performed on this study. It is estimated that approximately 440 subjects **with UC** who did not respond to induction treatment will enroll from Studies SHP647-301 and SHP647-302. Approximately 284 subjects who dropped out of study SHP647-303 and 390 subjects who completed study SHP647-303 will enroll. Estimates are based on Studies A7281009 and A7281010 and also		Section 9.6, Sample Size Calculation and Power Considerations

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rates from the literature (Loftus et al., 2017). **It is estimated that approximately 542 subjects with CD who did not meet efficacy criteria for entry into the maintenance study SHP647-307 following induction treatment will enroll from Studies SHP647-305 and SHP647-306. Approximately 364 subjects who discontinued from study SHP647-307 due to treatment failure and 433 subjects who completed Study SHP647-307 will enroll. Estimates are based on Studies A7281006 and A7281007 and also rates from the literature (Vermeire et al., 2017).**		
Created new subsection heading 9.8.1 Efficacy Analyses to clarify that this section applies to subjects with UC. Revised to clarify that efficacy analyses will be performed using the full analysis (not safety) set. Removed "subjects with" and "proportion of subjects with" from the efficacy endpoints for subjects with UC. *Now reads:* 9.8.1 Efficacy Analyses – **Subjects with Ulcerative Colitis** Efficacy analyses will be performed using the ~~safety~~ **full analysis** set. The exploratory efficacy endpoints are as follows: • ~~Subjects in r~~Remission based on composite score, assessed yearly and at end of study. Remission is defined as a composite score of patient-reported symptoms using daily diary and locally read endoscopy as follows: stool frequency subscore of 0 or 1 with at least a 1-point change from induction study (SHP647-301 or SHP647-302) baseline AND rectal bleeding subscore of 0 AND locally-read endoscopic subscore of 0 or 1 (modified, excludes friability). • ~~Proportion of subjects with~~ Remission, based on total Mayo score, assessed yearly and at end of study. Remission is defined as a total Mayo score ≤ 2 with no individual subscore (stool frequency, rectal bleeding, endoscopy [modified, excludes friability], and physician's global assessment) exceeding 1. • ~~Proportion of subjects with~~ Clinical remission as defined by as defined by stool frequency subscore of 0 or 1 with at least a 1-point change from induction study (SHP647-301 or SHP647-302) baseline in stool frequency subscore, and rectal bleeding subscore of 0, assessed yearly and at end of study. • ~~Proportion of subjects having~~ Partial Mayo score of ≤2 with no individual subscore >1 over time. The partial Mayo score does not include the endoscopy subscore. • ~~Proportion of subjects with~~ Clinical response based on composite score, assessed yearly and at end of study. Clinical response is defined as a decrease from induction study (SHP647-301 or	Section 9.8.1, Efficacy Analyses – Subjects with Ulcerative Colitis

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SHP647-302) baseline in the composite score of patient-reported symptoms using daily diary and locally read endoscopy of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥1 point or a subscore for rectal bleeding ≤1. • ~~Proportion of subjects with~~ Clinical response based on total Mayo score, assessed yearly and at end of study. Clinical response is defined as a decrease from induction study (SHP647-301 or SHP647-302) baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding ≥1 point or a subscore for rectal bleeding ≤1. • ~~Proportion of subjects with~~ Endoscopic remission, as defined by locally read endoscopic subscore 0 or 1 (modified, excludes friability), assessed yearly and at end of study.		
Added efficacy endpoints for subjects with CD, in new subsection 9.8.2. *New section reads:* **9.8.2 Efficacy Analyses – Subjects with Crohn's Disease** **Efficacy analyses will be performed using the full analysis set.** **The exploratory efficacy endpoints are as follows:** • **Clinical remission over time. Clinical remission is defined by 2-item PRO CD daily e-diary subscore of average worst daily abdominal pain ≤3 (based on 11-point NRS over the 7 most recent days) and average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days.** • **Enhanced endoscopic response, assessed yearly and at end of study, as measured by a decrease in SES-CD of at least 50% from induction study (SHP647-305 or SHP647-306) baseline.** • **Clinical remission over time as measured by CDAI <150.** • **Clinical remission over time as defined by the following: CD daily e-diary subscores of average worst daily abdominal pain ≤1 (based on the 4-point scale) over the 7 most recent days and average daily stool frequency ≤3 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days.** • **Both clinical remission by 2-item PRO and enhanced endoscopic response over time (composite endpoint).** • **Complete endoscopic healing at end of study, defined as SES-CD = 0-2.** • **Change from induction study (SHP647-305 or SHP647-306) baseline in abdominal pain, very soft stool/liquid**		Section 9.8.2, Efficacy Analyses – Subjects with Crohn's Disease

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stool frequency (as shown by type 6/7 on BSFS), total stool frequency, rectal urgency, rectal bleeding, nausea, vomiting, and incontinence, and total sign/symptom score based on subject daily e-diary entries (sum of rectal bleeding, stool frequency, abdominal pain, very soft stool/liquid stool, and rectal urgency) over time. • **Change from induction study (SHP647-305 or SHP647-306) baseline in IBDQ domains and total absolute scores in IBDQ over time.** • **Change from induction study (SHP647-305 or SHP647-306) baseline in SF-36, version 2, acute (physical and mental component summary scores and individual domain scores) over time.** • **Incidence of hospitalizations and total inpatient days during the study.** • **Incidence of CD-related surgeries and other surgical procedures during the study.** • **Change from induction study (SHP647-305 or SHP647-306) baseline in EQ-5D VAS scores and the EQ-5D-5L index over time.** • **Change from induction study (SHP647-305 or SHP647-306) baseline in the 4 WPAI-CD questionnaire domains over time.** • **Subject TSQM total scores and 4 domain scores over time.** • **Incidence of ED visits during the entire study period.** **Exploratory efficacy endpoints will be summarized by treatment group using descriptive statistics at each assessment visit. Summaries may be presented by the status at entry into the study (eg, induction nonresponder, maintenance SHP647 completer, etc). Continuous endpoints will be summarized by descriptive statistics and 95% confidence intervals. For categorical variables, statistical summaries will include number of subjects and percentages, and 95% confidence intervals.** **The detailed analyses will be described in the SAP.**		
Revised language for clarity. *Now reads:* All pharmacokinetic analyses will be ~~performed using~~ **based on** the ~~pharmacokinetic set~~ **PK population.**		Section 9.10.1, Pharmacokinetic Analyses

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Revised language for clarity. *Now reads:* Biomarker analyses will be ~~performed using the pharmacodynamics analysis set~~ **based on the PD population.**		Section 9.10.2, Pharmacodynamic Analyses
Added language to clarify that the sponsor will ensure that local regulatory requirements are met during the study, including annual safety reporting, ie, Development Safety Update Reports. *Now reads:* The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations. Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities. The sponsor ensures that local regulatory authority requirements are met before ~~the start of the study.~~**and during the study (including annual safety reporting, ie, Development Safety Update Reports).** The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of investigational product for shipment to the site.		Section 10.1.1, Good Clinical Practice Compliance
Added scales and assessments for subjects with Crohn's disease. *Cover page now reads:* Appendix 2 Scales and Assessments The following scales/assessments will be used in the study and are provided in this appendix. For questionnaires, language-specific validated versions will be used only. ***For subjects with UC:*** • Mayo scoring system • Patient-reported Outcome Ulcerative Colitis (PRO-UC) daily e-diary • **Work Productivity and Activity Impairment – Ulcerative Colitis** (WPAI-UC) ***For subjects with CD:*** • **Simple Endoscopic Score for Crohn's Disease (SES-CD)** • **Crohn's Disease Activity Index (CDAI)**		Appendix 2, Scales and Assessments

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• **Patient-reported Outcome Crohn's Disease (PRO-CD) daily e-diary** • **Work Productivity and Activity Impairment – Crohn's Disease (WPAI-CD)** ***For all subjects:*** • **Inflammatory Bowel Disease Questionnaire** (IBDQ) • **European Quality of Life 5 Dimensions, 5 Levels questionnaire** (EQ-5D-5L) • **Short Form-36 Health Survey** (SF-36) • TSQM		
Made edits to the Mayo Scoring System for Assessment of Ulcerative Colitis Activity. *Now reads:* **Mayo Scoring System for Assessment of Ulcerative Colitis Activity** **Stool frequency**[a] 0 = Normal number of stools for this subject 1 = 1 to 2 stools more than normal 2 = 3 to 4 stools more than normal 3 = 5 or more stools more than normal Subscore, 0 to 3 **Rectal bleeding**[b] 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood (more than just streaks) or streaks of blood with stool most of the time 3 = Blood alone passes Subscore, 0 to 3 **Findings on endoscopy**[c] 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern) 2 = Moderate disease (marked erythema, lack of vascular pattern, any friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration) Subscore, 0 to 3 **Physician's global assessment**[d] 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease Subscore, 0 to 3 The total Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Source: Schroeder et al., 1987		Appendix 2, Scales and Assessments

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[a] Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency. [b] The daily bleeding score represents the most severe bleeding of the day. [c] **Findings on endoscopy scoring represents the modified endoscopy subscore (value of 1 does not include friability).** **NOTE: Data will be collected to calculate the total Mayo score using both the modified endoscopy subscore and traditional endoscopy subscore (value of 1 including mild friability) as a sensitivity analysis and to estimate the impact of the modification on the endoscopic subscore.** [d] The physician's global assessment acknowledges the three other criteria, the subject's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status.		

APPENDIX 2 SCALES AND ASSESSMENTS

The following scales/assessments will be used in the study after the implementation of Amendment 4 and are provided in this appendix.

For subjects with UC:

- Mayo scoring system

For subjects with CD:

- Simple Endoscopic Score for Crohn's Disease (SES-CD)
- Crohn's Disease Activity Index (CDAI)

For all subjects:

- Memory aid

Mayo Scoring System for Assessment of Ulcerative Colitis Activity

Stool frequency[a]
0 = Normal number of stools for this subject
1 = 1 to 2 stools more than normal
2 = 3 to 4 stools more than normal
3 = 5 or more stools more than normal
Subscore, 0 to 3

Rectal bleeding[b]
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood (more than just streaks) or streaks of blood with stool most of the time
3 = Blood alone passes
Subscore, 0 to 3

Findings on endoscopy[c]
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern)
2 = Moderate disease (marked erythema, lack of vascular pattern, any friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Subscore, 0 to 3

Physician's global assessment[d]
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Subscore, 0 to 3

The total Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.

Source: Schroeder et al., 1987

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

[b] The daily bleeding score represents the most severe bleeding of the day.

[c] Findings on endoscopy scoring represents the modified endoscopy subscore (value of 1 does not include friability).
Note: Data will be collected to calculate the total Mayo score using both the modified endoscopy subscore and traditional endoscopy subscore (value of 1 including mild friability) as a sensitivity analysis and to estimate the impact of the modification on the endoscopic subscore.

[d] The physician's global assessment acknowledges the three other criteria, the subject's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status.

Simple Endoscopic Score for Crohn's Disease (SES-CD)

SITE WORKSHEET: Simple Endoscopic Score for Crohn's Disease (SES-CD)

Site #	Investigator	Subject ID	Visit Date (mmm dd yyyy)

Definitions of Simple Endoscopic Score for Crohn's Disease

	Simple Endoscopic Score for Crohn's Disease values			
Variable				
Size of Ulcers	None	Aphthous ulcers (Ø 0.1 to 0.5 cm)	Large ulcers (Ø 0.5 to 2 cm)	Very large ulcers (Ø >2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of Narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Endoscopy Finding	Ileum	Right Colon	Transverse Colon	Left Colon	Rectum
Presence and size of ulcers					
None	○	○	○	○	○
Apthous ulcers (Ø 0.1 to 0.5 cm)	○	○	○	○	○
Large ulcers (Ø 0.5 to 2 cm)	○	○	○	○	○
Very large ulcers (Ø > 2 cm)	○	○	○	○	○
Extent of ulcerated surface					
None	○	○	○	○	○
< 10%	○	○	○	○	○
10 – 30%	○	○	○	○	○
> 30%	○	○	○	○	○
Extent of affected surface					
Unaffected segment	○	○	○	○	○
< 50%	○	○	○	○	○
50 – 75%	○	○	○	○	○
>75%	○	○	○	○	○
Presence and type of narrowings					
None	○	○	○	○	○
Single, can be passed	○	○	○	○	○
Multiple, can be passed	○	○	○	○	○
Cannot be passed	○	○	○	○	○

Crohn's Disease Activity Index (CDAI)

Crohn's Disease Activity Index (CDAI)

Variable No.	Variable Description	Multiplier	Total
1	No. of liquid or soft stools (each day for 7 days)	X 2	
2	Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)	X 5	
3	General well-being (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)	X 7	
4	Number of listed complications [arthritis or arthralgia, iritis or uveitis, erythema nodosum or pyoderma gangrenosum or aphthous stomatitis, anal fissure or fistula or abscess, other fistula, fever over 37.8°C (100°F)]	X 20	
5	Use of diphenoxylate or loperamide for diarrhea (0 = no, 1 = yes)	X 30	
6	Abdominal mass (0 = no, 2 = questionable, 5 = definite)	X 10	
7	Hematocrit [Males: 47-Hct (%), Females: 42-Hct (%)]	X 6	
8	Body weight (1-weight/standard weight) X 100 (add or subtract according to sign)	X 1	
CDAI Score			

CDAI=Crohn's Disease Activity Index; ePRO=electronic patient-reported outcome; Hct=hematocrit.

Note: Variable 5: covers taking medication for symptomatic relief from diarrhoea, eg bulking agents, opiate, etc.
Variable 7: Absolute deviation of hematocrit is the difference in hematocrit from standard. A male subject with a hematocrit of 40% has an absolute deviation of 7. Each percentage deviation has a value of 6 points. If hematocrit subtotal is <0, enter 0;
Variable 8: is based on Metropolitan Life Tables (these are programmed into the ePRO device.

Percent deviation from standard weight is (1 - weight/standard weight) × 100; therefore, positive percent deviation represents weight loss, which adds points to the CDAI. Percentage deviation from standard weight = 1 point for each percent deviation. If body weight subtotal is less than minus 10, enter -10.

CDAI Interpretation:

- 0-149 points: Asymptomatic remission (Note: subjects requiring steroids to remain asymptomatic are not considered to be in remission but are referred to as being "steroid dependent").
- 150-220 points: Mild to moderate active CD.
- 221-450 points: Moderate to severe active CD.
- >451 points: Severely active to fulminant disease.

CDAI online estimator: http://www.ibdjohn.com/cdai/
Sources: Best et al., 1976; Best et al., 1979.

Memory Aid

Subject Reference Guide on "Memory Aid" Collection and Use

As you have noted in your consent, instead of a daily electronic diary, you may use a memory aid at each visit to track your clinical signs and symptoms for discussion with your study staff to assess your treatment response.

The memory aid can be in any form suitable to you and will not be collected by the study staff. This will assist you to verbally discuss the information about your daily disease activity for the week prior to your scheduled visit with your study staff. They will record it into your medical records/charts.

These written instructions will guide you on the needed information to be provided to your study doctor. For subjects with ulcerative colitis, the information recorded will consist of daily stool count and rectal bleeding as characterized by the Mayo subscore. For subjects with Crohn's disease, the information recorded will consist of the number of soft or loose stools, the level of abdominal pain, and sense of general well-being to calculate the CDAI (Crohn's Disease Activity Index) score.

"Memory Aid" Guidelines for Subjects with Ulcerative Colitis

Every day for the week (7 days) before each visit, you may use the memory aid to help you record the number of bowel movements you had that day and the WORST degree of blood you observed in your stool.

For the number of bowel movements: Every time you go to the toilet and pass liquid or solid material (blood, diarrhea, stool) will count as a bowel movement. You can write down the number of bowel movements you had that day. The day begins at 1 minute after midnight (12:01 AM) and ends at midnight (12:00 AM).

For blood in the stool: At the end of the day, think about the most blood you saw in any bowel movement and write down the number from the table below:

Observation	Number to Record
No blood seen	0
Streaks of blood with stool less than half of the time	1
Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
Blood alone passes	3

You may have a separate entry each day for both number of stool and blood in stool; reporting in this manner helps you track your symptoms to discuss with your study staff at your next visit.

Example 1

October 21, 2020
Number of bowel movements: Number you had (for example, **3**)
Blood in stool: If "streaks of blood less than half of the time", write **1**

October 22, 2020
Number of bowel movements: 5
Blood in stool: If "no blood seen", write **0**

Example 2

Date	**Bowel Movements**	**Blood**
October 21, 2020	3	1
October 22, 2020	5	0

"Memory Aid" Guidelines for Subjects with Crohn's Disease

Every day for the week (7 days) before each visit, you may use the memory aid to write down the number of very soft or liquid bowel movements you had that day (Type 6 or 7 from the Bristol Stool Chart), the level of abdominal pain, and your sense of general well-being.

For the number of soft or liquid bowel movements: Each time you go to the toilet and pass very soft or liquid material (Type 6 or 7 below) will count as a very soft or liquid bowel movement. Write down the number of such bowel movements you had that day. The day begins at 1 minute after midnight (12:01 AM) and ends at midnight (12:00 AM). ONLY COUNT very soft or liquid bowel movements that are Type 6 or 7 in the Bristol Stool chart:

Please rate your abdominal pain over the past 24 hours:	How would you rate your general well-being during the past 24 hours?
None	Generally well
Mild	Slightly below par
Moderate	Poor
Severe	Very poor
	Terrible

You may have a separate entry each day for level of abdominal pain, number of very soft/liquid stools, and sense of general well-being; reporting in this manner helps you track your symptoms to discuss with your study staff at your next visit.

Example 1

October 21, 2020

Number of very soft/liquid bowel movements:	Number you had (for example, **3**)
Abdominal pain:	Mild
General well-being:	Slightly below par

October 22, 2020

Number of very soft/liquid bowel movements:	1
Abdominal pain:	Mild
General well-being:	Generally well

Example 2

Date	**Very Soft/Liquid Bowel Movements**	**Abdominal Pain**	**General Well-being**
October 21, 2020	3	Mild	Slightly below par
October 22, 2020	1	Mild	Generally well

APPENDIX 3 GLUCOCORTICOID EQUIVALENT DOSES

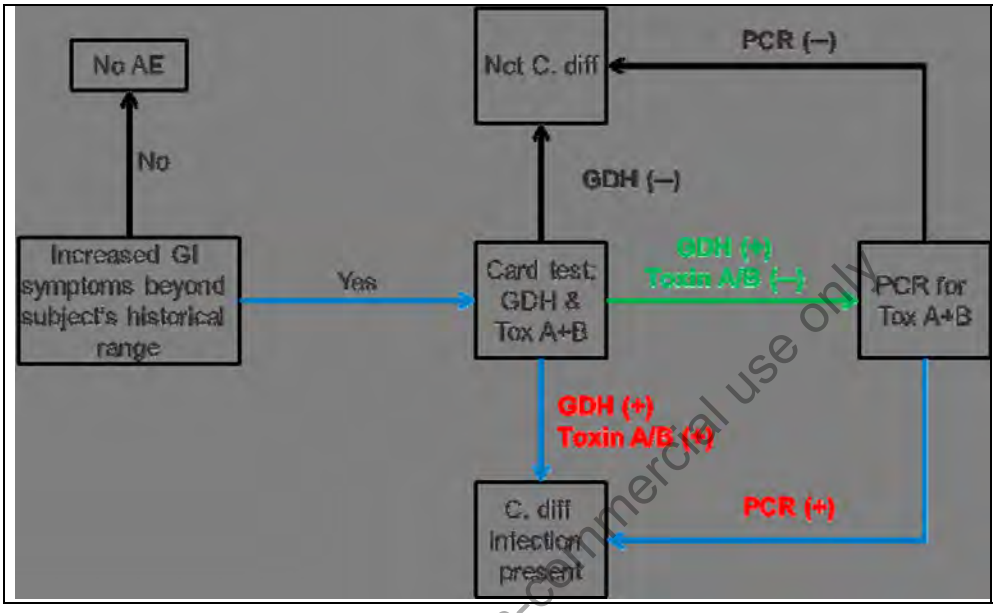
Glucocorticoid	Equivalent Dose (mg)
***Short Acting*:**	
Cortisone	25
Hydrocortisone	20
***Intermediate Acting*:**	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
***Long Acting*:**	
Betamethasone	0.6
Dexamethasone	0.75

Reference: Lacy et al., 2001-2002.

APPENDIX 4 GUIDANCE FOR DIAGNOSIS AND TREATMENT OF INCREASED GASTROINTESTINAL SYMPTOMS

If, for any reason, the central laboratory is not available, the preferred diagnostic algorithm is to use the Alere Quik Chek card test (Figure A1).

Figure A1: Algorithm for *C. difficile* Diagnosis Using the Quick Check Card Test



If the Alere Quik Chek card test is not available, then a diagnosis may be established by following either of the algorithms shown in Figure A2 (using PCR for toxin), Figure A3 (using toxigenic culture) or Figure A4 (using toxigenic culture, followed by PCR). The rationale for the method in Figure A3 is that the majority of PCR tests are expected to be negative for toxin, thus obviating the need for the test at the central laboratory. The expected turnaround time at the central laboratory for a GDH card test is expected to be shorter than that for stool culture for *C. difficile* at the local laboratory. The details of the sensitivity and specificity of these tests were reported by Khanna (Khanna et al., 2017).

When medically reasonable, treatment decisions should be deferred until an etiology has been determined. When this is not feasible, management of symptoms should be dictated by the clinical situation.

Figure A2: Alternative 1 for *C. difficile* Testing Using Local Laboratory When No Alere Quick Chek Card Test is Available

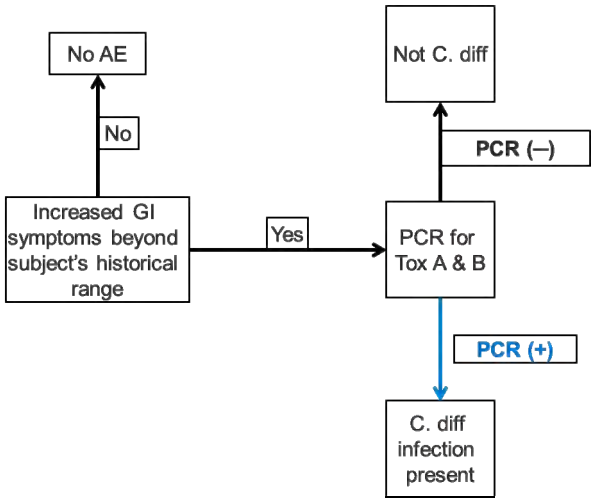


Figure A3: Alternative 2 for *C. difficile* Testing Using Local Laboratory When No Card Test is Available

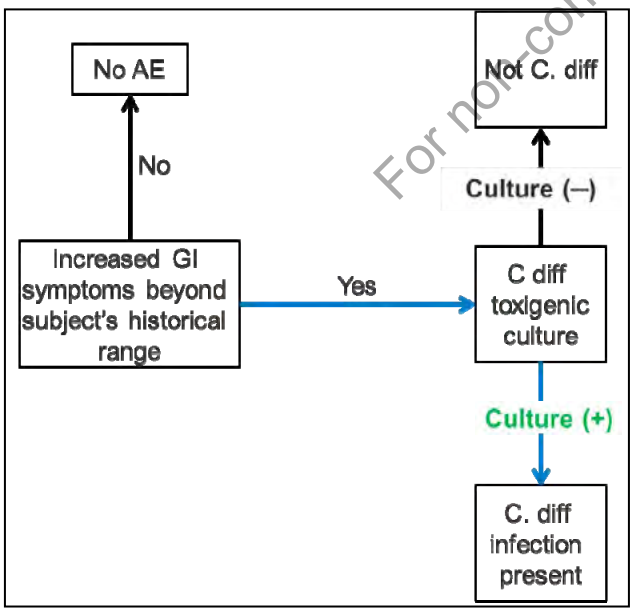
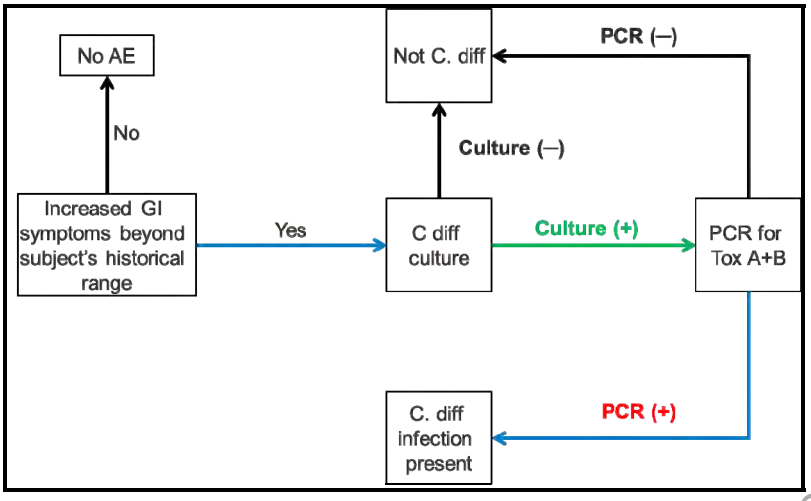


Figure A4: Alternative 3 for *C. difficile* Testing Using Local Laboratory When No Alere Quick Chek Card Test is Available



Treatment

When medically reasonable, treatment decisions should be deferred until an etiology has been determined. When this is not feasible, management of symptoms should be dictated by the clinical situation. **If management requires a prohibited treatment (eg, intravenous glucocorticoids for induction or maintenance studies), the subject should be withdrawn from treatment.**

If treatment has been deferred, once an etiology is determined (eg, *C. difficile*, disease exacerbation, Campylobacter), appropriate treatment should be promptly implemented without waiting for a scheduled visit. If the etiology is determined to be *C. difficile*, treatment guidelines conforming to the current IDSA recommendations for *C. difficile* infection (McDonald et al., 2018) or the recent expert review on *C. difficile* infection in IBD (Khanna et al., 2017) should be consulted.

If *C. difficile* infection was identified, clinical improvement should be noted within about 5 days after the start of treatment. If improvement does not occur, the etiology is most likely an IBD flare secondary to *C. difficile*, and treatment failure assessment should proceed per the protocol. Another possible explanation is primary failure of *C. difficile* therapy, which is unlikely.

If an infectious etiology other than *C. difficile* is identified, it should be managed as appropriate, with reference to current clinical guidelines (Shane et al., 2017).

If any infectious etiology is determined, the site should contact the medical monitor to make him or her aware of the diagnosis and to discuss treatment and ongoing study participation.