CLINICAL STUDY PROTOCOL

NCT Number: NCT03627091

Study Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Maintenance Therapy in Subjects With Moderate to Severe Crohn's Disease (CARMEN CD 307)

Study Number: SHP647-307

Protocol Version and Date:

Protocol Amendment 3: 17 Sep 2020

PROTOCOL: SHP647-307

TITLE:	A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Maintenance Therapy in Subjects With Moderate to Severe Crohn's Disease (CARMEN CD 307)
DRUG:	Ontamalimab (SHP647)
IND:	100,222
EUDRACT NO.:	2017-000617-23
SPONSOR:	Shire Human Genetic Therapies, Inc. ("Shire"), a wholly owned subsidiary of Takeda Pharmaceutical Company 300 Shire Way, Lexington, MA 02421 US
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted], MD
PROTOCOL HISTORY:	Protocol Amendment 3: 17 Sep 2020 Protocol Amendment 2: 22 Nov 2019 Protocol Amendment 1: 23 Aug 2018 Original Protocol: 15 Dec 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approv[redacted]

Signature:	**Date:**
[redacted] MD	21-Sep-2020 | 21:36:26 JST

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP647-307.

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Maintenance Therapy in Subjects With Moderate to Severe Crohn's Disease (CARMEN CD 307).

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 **3**	**Amendment Date** **17 Sep 2020**	**Global/Region/Country/Site Specific** **Global**

Protocol Amendment Summary and Rationale:

The main purpose of SHP647-307 Amendment 3 is to provide an update regarding the early closure of this study due to sponsor decision and to provide corresponding updates to the end of treatment procedures, including unblinding, as well as to reflect the impact of the early discontinuation of the study on the study objectives, endpoints, further assessments, and associated analyses of the data. As ontamalimab will not be further developed, most of the non-key secondary endpoints and all of the exploratory endpoints will not be analyzed, and data for the associated assessments will not be collected going forward. Due to the early termination of the ontamalimab program, the sponsor is providing an option for subjects who are responding to active treatment in this maintenance study or who are on placebo and had responded to active treatment in an induction study to continue to receive ontamalimab in the long-term safety extension study SHP647-304. Subjects already enrolled in this maintenance study and who are responding to active treatment, or who are on placebo and had responded to active treatment in an induction study, will be offered the opportunity to continue to receive ontamalimab in Study SHP647-304 provided they meet the eligibility criteria under SHP647-304 Amendment 4, which is being implemented concurrently. Subjects who received placebo in both the induction and maintenance studies will not be eligible to roll over into Study SHP647-304.

As the eligibility criteria for Study SHP647-304 depend on the blinded treatment assignment in this study, for a given subject, there is potential for the treatment assignment in this study to be unblinded at the early termination visit when assessing whether the subject may roll over into the SHP647-304 study or should proceed to the safety follow-up period. In addition, due to the early discontinuation of the SHP647 program, the SHP647-304 study is planned to be unblinded prior to the database lock for this study, which would unblind the treatment assignment in this study for a significant portion of subjects. As such, this study will be considered unblinded when the SHP647-304 study is unblinded, and the date of study unblinding will be recorded.

All subjects who discontinue investigational product and are not entering Study SHP647-304 should complete the protocol-specified safety follow-period in this study. Note that, with this amendment, 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).

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 SHP647-307 Protocol Amendment 3 relative to the previous edition, SHP647-307 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** **17 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	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).
Table 1, Schedule of Assessments	Added note to state that after the implementation of Amendment 3, the subject's next scheduled visit will be the Week 52/ET visit, which should be conducted no later than 4 weeks (±10 days) from the subject's last study visit prior to the implementation of SHP647-304 Amendment 4. [redacted] Updated footnotes 'c' and 'd' to reflect early closure of the study and issues related to COVID-19 (or other similar pandemic).	To specify that due to study closure, upon implementation of Amendment 3, the subject's next scheduled visit will be the Week 52/ET visit and to clarify timing of the Week 52/ET visit. [redacted] To reflect the discontinuation of ontamalimab Phase 3 clinical development program.
Table 1, Schedule of Assessments footnote 'j'	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 footnote 'l'	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.
Table 1, Schedule of Assessments footnote 'm'	Added footnote to specify that subjects performing home administrations consecutively for 3 months will need to perform liver function testing locally.	To comply with the FDA requirements.

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Amendment Number **3**	**Amendment Date** **17 Sep 2020**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Table 1, Schedule of Assessments footnote 'q'	Added language to clarify that, with the early termination of this study by the sponsor, colonoscopy is optional for subjects who received less than 52 weeks of treatment.	To clarify assessments to be done at the Week 52/ET visit.
Table 1, Schedule of Assessments footnote 'z'	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.
Study Synopsis, Objectives Section 2, Study Objectives and Purpose	Removed other secondary and exploratory objectives.	To reflect the discontinuation of ontamalimab Phase 3 clinical development program.
Study Synopsis, Methodology Section 3.1, Study Design and Flow Chart	Removed text regarding treatment failures. Added text on allowing continued treatment with ontamalimab for subjects benefiting. Added text on allowing study program to be stopped in case of no clinical efficacy.	To reflect the discontinuation of ontamalimab Phase 3 clinical development program.
Study Synopsis, Methodology Section 3.2, Duration and Study Completion Definition	Added text regarding COVID-19 (or other similar pandemic). Updated subject's maximum study duration from 68 weeks to 64 weeks. Added text regarding early closure of study and expected completion date of November 2021.	To reflect the discontinuation of ontamalimab Phase 3 clinical development program.
Study Synopsis, Site(s) and Region(s) Section 3.3, Sites and Regions	Updated number of countries and sites in the study.	Administrative change.
Section 4.5.1, Subject Withdrawal Criteria Section 4.5.2, Reasons for Withdrawal	Added text regarding subject withdrawal from the study due to personal concerns related to COVID-19 (or other similar pandemic).	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.

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Section(s) Affected by Change	**Description of Change**	**Rationale**
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).	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 6.2.3, 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 6.2.4, Unblinding the Treatment Assignment	Added text to describe the potential for unblinding of treatment assignment, following the end of treatment, for those subjects who had received placebo both in this study and in the induction study and who would not be eligible for entry into Study SHP647-304.	To note the potential for unblinding of treatment assignment due to the revised entry criteria for the long-term safety extension Study SHP647-304, which depends on the subject's treatment assignment in this maintenance study.
Section 6.3.2, Packaging	Updated the packaging of pre-filled syringe from tray to foam insert.	To accurately describe the packaging of study drug.
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

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		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.
Section 7, Study Procedures	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 (Section 7.1).	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 7.2.2.1, Visits 2 to 13 (Weeks 4 to 48)	Added note that, after the implementation of Amendment 3, subject's next scheduled visit will be the Week 52/ET visit.	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 7.2.2.2, Final On-treatment Visits: Visit 14, Parts 1 and 2 (Week 52/Early Termination)	Updated the window for the safety follow-up visit to ±10 days (from ±7 days). Added text on treatment failures or discontinuations from the study due to early termination. Added note that colonoscopy is not required at the ET visit.	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 7.2.3, Follow-up Period: Visit 15 (Week 64)	Updated follow-up period visit from Week 68 to Week 64 and added text regarding COVID-19 (or other similar pandemic) guidance.	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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Amendment Number **3**	**Amendment Date** **17 Sep 2020**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 7.3.3.6, 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.
Section 7.3.4, Others	[redacted]	[redacted]
Section 7.3.5, Volume of Blood to be Drawn From Each Subject Table 4, Volume of Blood to be Drawn From Each Subject	Updated the total blood volume drawn from 97 mL to 41 mL. [redacted]	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 the planned analyses 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 the planned interim analysis for related studies and that these may affect the current study. Added text that there was no planned interim analysis or adaptive design. Removed text on multiplicity concerns regarding repeated analyses.	To reflect the discontinuation of ontamalimab Phase 3 clinical development program.
Section 9.6, Sample Size Calculation and Power Considerations	Added text to clarify that the power considerations were based on a planned sample size of 983 subjects, which will not be attained.	To clarify that the planned sample size will not be attained due to early discontinuation of this study.

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Section(s) Affected by Change	**Description of Change**	**Rationale**
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, Endpoints and statistical analysis Section 9.8, Efficacy Analyses	Removed other secondary analyses and exploratory analyses. Updated text on primary efficacy endpoint measurements and secondary endpoint analyses.	Due to the early discontinuation of the study and limited sample size, previously planned analyses will no longer be conducted.
Study Synopsis, Endpoints and statistical analysis Section 9.10, Other Analyses	[redacted]	[redacted]
Section 10.1.5, Study Suspension, Termination, and Completion	Removed text regarding DMC meeting to review induction study results.	To reflect the 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.
Throughout protocol	Minor changes to wording and editorial changes.	To improve clarity, consistency, and remove redundancy of text.
Appendices	Added Summary of Changes of Protocol Amendment 2. Removed assessments no longer applicable under Amendment 2.	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
[redacted] (Global)

Email
[redacted]

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

North America:

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

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

Latin America:

PPD 24 Hour Safety Hotline: [redacted]

PPD 24 Hour Safety Hotline Fax: [redacted]

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

PPD 24 Hour Safety Hotline: [redacted]

PPD 24 Hour Safety Hotline Fax: [redacted]

PRODUCT QUALITY COMPLAINTS

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

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

Unit issues	• 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:

[redacted]

Telephone number (provided for reference if needed):

Shire, Lexington, MA (US)

[redacted]

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

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
β-hCG	beta-human chorionic gonadotropin
BSFS	Bristol Stool Form Scale
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CGHAS	Colonic Global Histologic Disease Activity Score
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CRO	contract research organization
[redacted]	[redacted]
CSF	cerebrospinal fluid
DMC	data monitoring committee
EC	ethics committee
ECCO	European Crohn's and Colitis Organisation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EIM	extra-intestinal manifestation
EMA	European Medicines Agency
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 G2 kappa
IGHAS	Ileal Global Histologic Disease Activity Score
IRB	Institutional Review Board
IRT	interactive response technology
LP	lumbar puncture
LTS	long-term safety extension
MAdCAM	mucosal addressin cell adhesion molecule
MTX	methotrexate
NAb	neutralizing antibody
NRS	numerical rating scale
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
Q4W	once every 4 weeks
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SES-CD	Simple Endoscopic Score for Crohn's Disease
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal

UC	ulcerative colitis

STUDY SYNOPSIS

Protocol number: SHP647-307	**Drug:** Ontamalimab (SHP647)
Title of the study: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Maintenance Therapy in Subjects With Moderate to Severe Crohn's Disease (CARMEN CD 307)	
Number of subjects (total and for each treatment arm): Approximately 983 subjects were planned for enrollment into the study: approximately 776 subjects from active induction treatments and approximately 207 subjects from placebo induction groups. A total of 40 subjects have been enrolled.	
Investigator(s): Multicenter study	
Site(s) and region(s): This study will be conducted in approximately 33 sites in approximately 16 countries.	
Study period (planned): 2018 to 2021	**Clinical phase:** 3

Objectives:

Coprimary: The coprimary objectives of this study are to evaluate the efficacy of ontamalimab as maintenance treatment in subjects with moderate to severe Crohn's disease (CD) based on:

- Clinical remission based on 2-item patient-reported outcome (PRO) (abdominal pain severity and very soft stool/liquid stool frequency)
- Enhanced endoscopic response based on centrally read colonoscopy.

Key Secondary:

- To evaluate the efficacy of ontamalimab as maintenance treatment on clinical remission as measured by CD Activity Index (CDAI)
- To evaluate the efficacy of ontamalimab as maintenance treatment on glucocorticoid-free clinical remission based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
- To evaluate the efficacy of ontamalimab as maintenance treatment on clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)
- To evaluate the efficacy of ontamalimab on maintenance of clinical remission among subjects in clinical remission at baseline of the SHP647-307 study based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
- To evaluate the efficacy of ontamalimab on maintenance of enhanced endoscopic response among subjects with enhanced endoscopic response at baseline of the SHP647-307 study based on centrally read colonoscopy
- To evaluate the efficacy of ontamalimab as maintenance treatment based on achieving clinical remission as well as achieving enhanced endoscopic response in the same subject
- To evaluate the effect of ontamalimab as maintenance treatment on complete endoscopic healing based on centrally read colonoscopy.

Rationale:

This study is designed to evaluate the efficacy of ontamalimab as maintenance therapy in subjects with moderate to severe CD who fulfilled the efficacy entry criteria of this study including the clinical and/or endoscopic response criteria defined in induction Study SHP647-305 or SHP647-306.

Investigational product, dose, and mode of administration:

The test product is ontamalimab (SHP647), 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.

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

Methodology:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study in subjects with moderate to severe CD who completed participation in an induction study (either SHP647-305 or SHP647-306) and fulfilled the efficacy entry criteria of this study.

This study consists of a 52-week, double-blind treatment period, followed by a 12-week safety follow-up period for subjects who either discontinue treatment early or who complete the treatment period and do not enter the long-term safety extension (LTS) study (SHP647-304).

The eligibility of a subject for the study will be assessed based on the study data collected at the Week 16 visit of the induction studies (SHP647-305 or SHP647-306), which will be considered as the baseline visit for this maintenance study.

Eligible subjects who received active treatment in one of the induction studies and fulfilled the efficacy entry criteria of this study, including achieving endoscopic and/or clinical response, will be randomized as follows: subjects who received 25 mg ontamalimab in one of the induction studies will be randomized (1:1) to receive either 25 mg ontamalimab or placebo, and subjects who received 75 mg ontamalimab in one of the induction studies will be randomized (1:1) to receive either 75 mg ontamalimab or placebo.

Eligible subjects who received placebo in one of the induction studies and fulfilled the efficacy entry criteria of this study, including achieving endoscopic and/or clinical response, will be randomized in a 2:2:1 ratio to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo, respectively) during this maintenance study.

Subjects will be stratified according to glucocorticoid use at Study SHP647-307 baseline, the subject's status of prior anti-tumor necrosis factor (TNF) treatment (naïve or experienced), and whether or not the subject achieved clinical remission by 2-item PRO or enhanced endoscopic response in the induction study.

Subjects enrolled in this study (SHP647-307) will receive double-blind maintenance treatment in the form of SC injections, using a PFS, once every 4 weeks for 52 weeks. Subjects will undergo efficacy, [redacted], and safety assessments.

Under Amendment 3, subjects who complete the double-blind treatment period, or subjects who are withdrawn from the study prior to completing the double-blind treatment period due to early closure of the study by the sponsor, may be eligible to enter the LTS study (SHP647-304) provided they meet the eligibility criteria under SHP647-304 Amendment 4. Offering treatment in the LTS study after exiting this maintenance study allows subjects who benefited from active treatment, in this study or the induction study, to potentially benefit from continued treatment at the same dose of ontamalimab or at different dose of ontamalimab if, during the course of the SHP647-304 study, one of those doses (25 mg or 75 mg) is determined to be more efficacious based on emergent data from the induction studies. However, if there is no evidence of efficacy of either of the doses in comparison to placebo in the UC/CD clinical study, the entire program may be stopped, including the LTS study. Subjects who are not entering Study SHP647-304 will enter a 12-week safety follow-up period.

Inclusion and exclusion criteria:

Inclusion criteria:

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must have completed the 16-week induction treatment period from Study SHP647-305 or SHP647-306 and met the following criteria at baseline in maintenance study SHP647-307:
   a) Meet endoscopic response criteria of a reduction in the Simple Endoscopic Score for CD (SES-CD) from induction study (SHP647-305 or SHP647-306) baseline by ≥25% at Week 16 of induction study (SHP647-305 or SHP647-306)

      OR

   b) Meet at least 1 of the following 4 criteria at baseline in maintenance Study SHP647-307, in addition to no worsening of endoscopic score as measured by SES-CD relative to induction study (SHP647-305 or SHP647-306) baseline:
      i. Achieving clinical remission as determined by meeting the criteria for clinical remission using the 2-item PRO, ie, 2-item PRO subscores of average worst daily abdominal pain ≤3 (based on 11-point numerical rating scale [NRS]) over the 7 most recent days* and average daily stool type frequency ≤2 of type 6/7 (very soft stools/liquid stools) as shown in the Bristol Stool Form Scale (BSFS) over the 7 most recent days*.
      ii. A decrease of at least 100 points in CDAI score (CDAI-100) from induction study (SHP647-305 or SHP647-306) baseline.
      iii. A decrease of ≥30% and at least 2 points from induction study (SHP647-305 or SHP647-306) baseline in the average daily worst abdominal pain over the 7 most recent days*, with the average daily stool frequency of type 6/7 (very soft stools/liquid stools) either:
      (i) not worsening from induction study (SHP647-305 or SHP647-306) baseline and/or
      (ii) meeting the criteria for clinical remission, ie, 2-item PRO subscore of 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*.
      iv. A decrease of ≥30% from induction study (SHP647-305 or SHP647-306) baseline in the average daily stool frequency of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days*, with the average daily worst abdominal pain either: (i) not worsening from induction study (SHP647-305 or SHP647-306) baseline and/or (ii) meeting the criteria for clinical remission, ie, 2-item PRO subscore of average worst daily abdominal pain ≤3 (based on 11-point NRS) over the 7 most recent days*.

      *Note: The 7 days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the criterion will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the criterion will be treated as missing.
4. Subjects receiving any treatment(s) for CD described in Section 5.2.1 are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.

Exclusion criteria:

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

1. Subjects who had major protocol deviation(s) (as determined by the sponsor) in induction study SHP647-305 or SHP647-306.
2. Subjects who permanently discontinued investigational product because of an adverse event (AE), regardless of relatedness to investigational product, in induction study SHP647-305 or SHP647-306.

3. Subjects who are likely to require surgery for CD during the study period, except minor interventions (eg, seton placement for anal fistulas).
4. Subjects are females who became pregnant during induction study SHP647-305 or SHP647-306, 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 subjects and medically appropriate methods for male subjects, as described in Section 4.4 of the protocol) 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 developed obstructive colonic stricture, or enterovesical or enterovaginal fistulae during the induction study (SHP647-305 or SHP647-306).
8. 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).
9. Subjects who have developed any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study.
10. 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.
11. Subjects with known exposure to *Mycobacterium tuberculosis* since testing at screening in induction 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.
12. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during the evaluation of the last visit in the SHP647-305 or SHP647-306 studies. If the results are considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once prior to enrollment in Study SHP647-307.
    - Alanine aminotransferase (ALT) and aspartate aminotransferase levels ≥3.0 × the upper limit of normal (ULN)
    - Total bilirubin level ≥1.5 times the ULN or >2.0 × ULN if the subject has a known documented history of Gilbert's syndrome
    - Hemoglobin level ≤80 g/L (8.0 g/dL)
    - Platelet count ≤100 × 10^9/L (100,000 cells/mm^3) or ≥1000 × 10^9/L (1,000,000 cells/mm^3)*
    - White blood cell count ≤3.5 × 10^9/L (3500 cells/mm^3)
    - Absolute neutrophil count <2 ×10^9/L (<2000 cells/mm^3)
    - Serum creatinine level >1.5 × ULN or estimated glomerular filtration rate <30 mL/min/1.73 m^2 based on the abbreviated Modification of Diet in Renal Disease Study Equation.

    *Note: if platelet count is <150,000 cells/mm^3, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.
13. 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.
14. Subjects who are participating in other investigational studies (other than induction study SHP647-305 or SHP647-306) or plan to participate in other investigational studies during Study SHP647-307.

Maximum duration of subject involvement in the study:

- Maximum duration of participation: Approximately 64 weeks
- Planned duration of treatment period: 52 weeks
- Planned duration of safety follow-up period: 12 weeks

Endpoints and statistical analysis:

Analysis Sets:

The safety set will consist of all subjects who have received at least 1 dose of investigational product in the SHP647-307 study, regardless of treatment received during the induction studies (SHP647-305 and SHP647-306).

The full analysis set (FAS) will consist of all randomized subjects who have received at least 1 dose of investigational product in the SHP647-307 study, regardless of treatment received during the induction studies (SHP647-305 and SHP647-306).

Coprimary Efficacy Endpoints:

The coprimary efficacy endpoints are:

- Clinical remission at the Week 52 visit as defined by the following: 2-item PRO subscores 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. The 7 most recent days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the endpoint will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the endpoint will be treated as missing.
- Enhanced endoscopic response at Week 52 as measured by a decrease in SES-CD of at least 50% from induction study (SHP647-305 or SHP647-306) baseline.

The number and percentage of subjects, and the estimate of the common treatment difference along with the corresponding unstratified Newcombe 95% confidence interval for each primary endpoint, will be summarized by maintenance treatment group at Week 52. Subjects with missing data at Week 52 will be considered failures and counted as nonresponders. Due to the early discontinuation of the study before full enrollment and the limited sample size, formal statistical testing will not be performed, and therefore, multiplicity adjustment is not applicable.

Key Secondary Efficacy Endpoints:

The key secondary efficacy endpoints are as follows:

- Clinical remission at the Week 52 visit as measured by CDAI <150.
- Glucocorticoid-free clinical remission at the Week 52 visit, among subjects using glucocorticoids at induction study baseline. Glucocorticoid-free clinical remission is defined as clinical remission by 2-item PRO (as defined for the coprimary endpoint; see Section 9.8.1) in addition to not requiring any treatment with glucocorticoids for at least 12 weeks prior to the Week 52 visit.
- Clinical remission at the Week 52 visit as defined by the following: CD daily electronic diary (e-diary) subscores of average 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. The 7 most recent days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the endpoint will be calculated on all available most

recent 6 or 5 days. If fewer than 5 days are available, the endpoint will be treated as missing.

- Sustained clinical remission, ie, in clinical remission at the SHP647-307 Week 52 visit, among subjects who were in clinical remission by 2-item PRO (as defined for the coprimary endpoint) at the time of baseline in Study SHP647-307.
- Sustained enhanced endoscopic response, ie, in enhanced endoscopic response at the SHP647-307 Week 52 visit, among subjects who showed enhanced endoscopic response (as defined for the coprimary endpoint) at the time of baseline in Study SHP647-307.
- Both clinical remission by 2-item PRO and enhanced endoscopic response at Week 52 (composite endpoint).
- Complete endoscopic healing at Week 52 defined as SES-CD=0-2.

The key secondary endpoints will be analyzed using the same approach as described for the coprimary endpoint. Subjects with missing key secondary endpoint data at the Week 52 visit will be considered failures and counted as nonresponders. Due to the early discontinuation of the study before full enrollment and the limited sample size, formal statistical testing will not be performed.

Safety Analyses:

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

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

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to investigational product in the SHP647-307 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 or listed. Adverse events of special interest will be summarized by treatment group.

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

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

STUDY SCHEDULE

Table 1 Schedule of Assessments

	Baseline[a]	Treatment													Follow-Up[b]
Study Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ET[c]**	**64[c]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 (Part 1)[d]** / **14 (Part 2)[d]**	**15**
Study Day	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**448**
Visit Window	**None**	**±10 days**												**±10 days**	**±10 days**
Informed consent/assent	X														
Eligibility assessment[e]	X														
Medical history[f]	IDT														
Complete physical examination[g]	IDT													X	X
Targeted physical examination[g,h]				X			X			X					
Targeted neurological assessment[i,j]	IDT			X			X			X				X	X
Vital signs	IDT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[h]	IDT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	IDT			X			X							X	
Contraception check[k]	IDT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[l]															
Hematology[h]	IDT			X			X			X				X	X
Serum chemistry[m]	IDT			X			X			X				X	X
Urinalysis	IDT			X			X			X				X	X
FSH[n]	X[j]														
Urine β-hCG[o]	IDT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA and NAb sampling	IDT			X			X			X					
CD Assessments[p] Including Endoscopic Procedure															
Colonoscopy (including biopsy)[q,r,s]	IDT													X[q]	
SES-CD	IDT													X[q,t]	
CDAI[u]	IDT			X			X			X				X	
PRO e-diary data instruction	X														
PRO-CD daily e-diary data[v]	IDT	X	X	X	X	X	X	X	X	X	X	X	X	X	
Treatment failure assessment[w]			X	X	X	X	X	X	X	X	X	X	X	X	

Table 1 Schedule of Assessments

	Baseline[a]	Treatment														Follow-Up[b]
Study Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ET[c]**		**64[c]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 (Part 1)[d]**	**14 (Part 2)[d]**	**15**
Study Day	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**		**364**	**448**
Visit Window	**None**	**±10 days**													**±10 days**	**±10 days**
Treatment Procedures																
Randomization[y]	X															
Administration of ontamalimab or placebo[y,z,aa]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hypersensitivity monitoring[bb]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedures[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[cc]			X			X							X			

ADA=antidrug antibody; β-hCG=beta-human chorionic gonadotropin; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CLIA=Clinical Laboratory Improvement Amendments; DTP=Direct-to-Patient; ECG=electrocardiogram; e-diary=electronic diary; ET=early termination; FSH=follicle-stimulating hormone; IDT=induction study (SHP647-305 or SHP647-306); LFT=liver function testing; LTS=long-term safety extension; NAb=neutralizing antibody; PRO=patient-reported outcome; SES-CD=Simple Endoscopic Score for Crohn's Disease

Note: As soon as Amendment 3 is implemented, the subject's next scheduled visit will be the Week 52/ET visit, which should be conducted no later than 4 weeks (±10 days) from the subject's last study visit prior to implementation of SHP647-304 Amendment 4.

[a] The Week 16 (Visit 7) assessment from the induction study (SHP647-305 or SHP647-306) will be used as the baseline (Day 1/Week 0) assessments for Study SHP647-307.

[b] Follow-up is not required if subject is entering the LTS study (SHP647-304) at Week 52/ET (Visit 14).

[c] Any subject who is prematurely withdrawn from the study (including for treatment failure) should return for the ET visit and then enter into the safety follow-up period if not entering the LTS study (SHP647-304). Subjects who enter the safety follow-up period will have a final visit at 12 weeks following the Week 52/ET visit. Both the Week 52/ET and 12-week safety follow-up visits are preferred to be on-site visits; however, due to the COVID-19 public health emergency (or other similar pandemic), these may also be done at a subject's home provided a qualified site staff member performs these evaluations following DTP guidance.

[d] Part 1 of Visit 14 should be scheduled within 10 days (preferably within 5 to 7 days) before Part 2; this will allow sufficient time to obtain the data from the central laboratory hematocrit test value in order to be available at Part 2 of the visit. If a central laboratory hematocrit result is available that is not older than 3 weeks, Parts 1 and 2 of Visit 14 can be performed on the same day; however, the laboratory sampling must be done before the start of colonoscopy preparation. For subjects who meet the criteria for treatment failure (as defined in Section 4.5.1), or are discontinuing prior to completing the 52-week treatment period due to early study closure, and will be entering the LTS study (SHP647-304), Part 2 of Visit 14 should be scheduled at least 2 weeks after the last dose of investigational product, to allow a sufficient time interval prior to the first dose in the LTS study.

[e] Eligibility will be assessed after the consent form is signed and after induction study SHP647-305 or SHP647-306 Week 16, Visit 7 (Part 3) procedures are completed.

[f] Medical history for induction study SHP647-305 or SHP647-306 will be used as the baseline medical history data for Study SHP647-307.

Table 1 Schedule of Assessments

	Baseline[a]	Treatment													Follow-Up[b]
Study Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52/ET[c]	64[c]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14 (Part 1)[d] / 14 (Part 2)[d]	15
Study Day	1	28	56	84	112	140	168	196	224	252	280	308	336	364	448
Visit Window	None	±10 days												±10 days	±10 days

[g] Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; eyes; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; back; and lymph nodes. Targeted physical examination includes the review of the following body systems: skin and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

[h] If it is clinically necessary, an unscheduled assessment may be performed for calculation of CDAI after Week 4 in order to evaluate treatment failure; in connection to this, blood sampling for hematocrit may be necessary if no value is available from the past 3 weeks (see Section 4.5.1). Unscheduled assessments for CDAI calculation must not be performed more than 4 times during the study.

[i] Subjects will be evaluated to reveal any potential abnormalities in the following neurological domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, cognition/behavior. See Section 7.3.3.3 for further details.

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

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

[l] 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.

[m] 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.

[n] For confirmation of postmenopausal status in females 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. If a female subject's status has changed to postmenopausal since the induction studies (SHP647-305 or SHP647-306), the FSH confirmation test will be done at baseline (Visit 1) of SHP647-307. 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.

[o] For females of childbearing potential who are not surgically sterile, do not have confirmed ovarian failure, or do not meet the definition of postmenopausal as described in the Section 4.4 and Section 7.3.3.7.

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

[q] Colonoscopy preparation will be according to local routine (see Section 7.3.2.4). Colonoscopy preparation may be done on the same day as the colonoscopy procedure. Note: For subjects discontinued from the study under Amendment 3 and prior to completion of 52 weeks of treatment, colonoscopy is not required (optional) at the ET visit.

[r] Biopsy samples from each of the segments investigated will be collected for histological evaluation (see Section 7.3.2.4).

[s] If needed, an unscheduled colonoscopy may be performed as part of treatment failure evaluation. Note: It is recommended that the unscheduled colonoscopy is performed

Table 1 Schedule of Assessments

	Baseline[a]	Treatment													Follow-Up[b]
Study Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52/ET[c]	64[c]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14 (Part 1)[d]	14 (Part 2)[d]	15
Study Day	1	28	56	84	112	140	168	196	224	252	280	308	336		364	448
Visit Window	None	±10 days													±10 days	±10 days

within 2 weeks after the visit day when either the PRO-based or the CDAI score-based criterion for treatment failure was fulfilled. If the CDAI score-based criterion is fulfilled on an unscheduled visit, then the colonoscopy is to be performed either within 2 weeks after the previous regular visit or at the next regular visit. Colonoscopy does not need to be repeated at the ET visit if performed earlier as part of treatment failure assessment and treatment failure is confirmed.

t SES-CD score at Week 52/ET will be calculated using the subscores of each of the segments investigated and centrally read for the colonoscopy performed at Week 52 (Visit 14, Part 2).

u If it is clinically necessary, an unscheduled CDAI evaluation may be performed any time after Week 4 in order to evaluate treatment failure (see Section 4.5.1). If an unscheduled CDAI evaluation is planned after an unscheduled/confirmatory colonoscopy (that did not confirm treatment failure), then the diary data cannot be utilized for CDAI calculation earlier than 1 week after the colonoscopy.

v PRO-CD daily e-diary will be available daily throughout the study. Subjects will be required to enter e-diary data every day throughout the study period; see Section 7.3.2.1 for further details. 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 e-diary entries), or lower than the previous visit.

w See Section 4.5.1 of the protocol for definition of treatment failure.

x All patient-reported questionnaires should be completed before completing any other visit assessments.

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

z 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).

aa Where applicable, specified procedures and laboratory samples should be collected before investigational product administration.

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

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

Note: See Section 7.3 for the order in which assessments should be performed. Timing of visits is relative to SHP647-307 baseline (Visit 1).

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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, extra-intestinal manifestations (EIMs) 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-aminosalicylic acid (5-ASA), opiates (loperamide), systemic glucocorticoids, immunosuppressive agents (azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]), and biologic therapy with anti-tumor necrosis factor (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 (MAdCAM). MAdCAM is a member of the immunoglobulin super family of cell adhesion molecules and is mostly expressed on the cell surface of high endothelial venules of organized intestinal lymphoid tissue such as Peyer's patches and mesenteric lymph nodes (Shyjan et al., 1996; Briskin et al., 1997; Liaskou et al., 2011). MAdCAM plays a role in gut immune surveillance, and also appears to facilitate excessive lymphocyte infiltration under conditions of

chronic GI inflammation. The $\alpha_4\beta_7$ integrin is the recognized ligand for MAdCAM, and expression of this ligand on populations of $CD4^+$ and $CD8^+$ T cells, as well as on subsets of B cells, distinguishes them as unique gut homing lymphocytes.

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

1.3 Benefit/Risk Assessment

Ontamalimab has been evaluated in Phase 1 and Phase 2 clinical studies in subjects with CD and ulcerative colitis (UC). In CD study A7281006, induction with ontamalimab did not meet the primary endpoint; no statistically significant differences were observed between the active treatment arms and the placebo arm in CD Activity Index (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 study A7281009, induction with ontamalimab at doses of 7.5 mg, 22.5 mg, or 75 mg once every 4 weeks (Q4W) resulted in statistically significantly higher proportions of subjects in remission at Week 12 based on total Mayo score (both local and central read) when compared with placebo treatment.

In 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 high-sensitivity CRP (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 (7.5 mg, 22.5 mg, and 75 mg) at Week 12. There was no evidence of a dose response for either of these parameters. A nominally statistically significant increase was observed in circulating β_7^+ central memory T lymphocytes at Weeks 8 and 12, consistent with the predicted mechanism of action. In the UC induction study A7281009, decreases in fecal calprotectin were observed in all groups, including placebo; however, there were no nominally statistically significant differences in the decrease in fecal calprotectin between any dose level of ontamalimab and placebo. Decreases in hsCRP were also observed in all 4 treatment groups; however, other than the 75 mg dose group at Week 12, no nominally significant differences were observed in active treatment vs placebo.

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

The long-term, open-label safety studies (Studies A7281007 and A7281010) were not placebo-controlled but permitted exposure to the investigational product at doses of 75 mg or 225 mg Q4W for 18 and 36 months, respectively. In Study A7281007, the most common all-causality TEAE was CD (worsening or progression), arthralgia, nasopharyngitis, and abdominal pain. In Study A7281010, the most common all-causality TEAEs were UC (worsening or progression), arthralgia, and nasopharyngitis.

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

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

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

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

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

This study is designed to evaluate the efficacy of ontamalimab as maintenance therapy in subjects with moderate to severe CD who fulfilled the efficacy entry criteria of this study including the clinical and/or endoscopic response criteria defined in induction study SHP647-305 or SHP647-306.

The CD clinical development program includes 3 completed studies: 1 Phase 1 study (A7281008) and 2 Phase 2 studies (A7281006 and A7281007).

Study A7281006 (OPERA) was a parallel, dose-ranging, randomized, double-blind, placebo-controlled study in which ontamalimab was given as 3 subcutaneous (SC) dose levels (22.5 mg, 75 mg, and 225 mg) Q4W over an 8-week period. Ontamalimab was generally safe and well tolerated and there were no deaths. Three placebo-treated subjects and 9 subjects in the 22.5 mg, 75 mg, and 225 mg ontamalimab groups discontinued treatment due to adverse events (AEs). Most TEAEs were mild or moderate in severity. Median serum concentrations of ontamalimab increased with increasing dose. Positive antidrug antibody (ADA) status did not appear to impact exposure to ontamalimab. The CDAI was the primary instrument to assess the efficacy of ontamalimab; no statistically significant differences were noted between the active treatment arms and the placebo arm. Therefore, the study did not meet its primary endpoint. However, post hoc analysis indicated increased remission rates in subjects in the 22.5 mg or 75 mg treatment arms who had higher serum concentrations of hsCRP or higher scores of SES-CD at baseline.

Study A7281008 (TOSCA) was an open-label multi-center, Phase 1 sequential cohort study that evaluated the effects of a maximum induction dose of ontamalimab on CNS immune surveillance. Subjects with inflammatory bowel disease (IBD) (including CD), with or without stoma, who failed or were intolerant to both anti-TNF and immunosuppressant therapy and who had moderate to severe active disease underwent a lumbar puncture (LP), completed induction therapy with 3 doses of 225 mg ontamalimab 4 weeks apart, and then underwent a second LP 2 (±1) weeks later. The primary endpoint was the percent change from baseline (pretreatment) in absolute lymphocyte count in cerebrospinal fluid (CSF) in subjects with IBD after receiving 3 doses of 225 mg ontamalimab. The mean percentage change from baseline in absolute lymphocytes in CSF was 61.76% with a median change of 35.2% (range: -70.2% to 267.8%). The post-treatment LP/pretreatment LP geometric mean ratio for CSF lymphocytes was 1.33 with the lower bound of the 80% confidence interval (CI)=1.13, which was greater than 0.5, supporting rejection of the null hypothesis (ie, that the percent decrease in total lymphocytes counts after treatment would be ≥50% (equivalent to the geometric mean ratio in total lymphocyte counts being ≤0.5). This result supports the hypothesis that ontamalimab does not impair trafficking of lymphocytes into the CNS and thus should not impair CNS immune surveillance.

Study A7281007 (OPERA II) was a Phase 2 open-label extension study to provide additional long-term safety data on subjects with moderate to severe CD who completed Study A7281006 or Study A7281008 and wished to continue to receive ontamalimab. Ontamalimab 75 mg (with potential dose escalation to 225 mg) SC given Q4W for 72 weeks was generally well tolerated in subjects with CD over the treatment period evaluated in this study. In subjects with positive ADA or neutralizing antibody (NAb) status, exposure to ontamalimab was not affected. Serum concentrations of ontamalimab in this study were consistent with what was predicted based on the feeder study A7281006. There were 2 deaths in the study: 1 subject died of multiple organ dysfunction syndromes in the treatment period and 1 subject died of metastatic neoplasm in the follow-up period. Neither death was reported as related to treatment with the investigational product by the investigators. The most frequently reported SAE was CD in either the treatment period or the follow-up period. The SOC with the most subjects experiencing TEAEs was GI disorders. Although Study A7281007 was not placebo controlled, the exploratory efficacy results (based on the modified Harvey Bradshaw Index) indicated that the effect of ontamalimab on disease activity was maintained over the duration of treatment.

The ontamalimab dose selection (25 mg and 75 mg) for this study is based on data from these 3 previous studies, which evaluated the activity of ontamalimab in adult patients with moderately to severely active CD based on CDAI scores between 220 and 450. The results of a post hoc analysis of remission rate by baseline elevated serum concentration of hsCRP suggested that the greatest treatment effect was at a dose of 22.5 mg. Similarly, post hoc analysis of remission rates

by endoscopic severity assessed using the SES-CD suggested best efficacy at a dose of 75 mg. Therefore, both dosage regimens 25 mg and 75 mg Q4W have been selected for the Phase 3 testing. The Phase 1 study (A7281008, TOSCA) and Phase 2 studies (A7281006, OPERA; and A7281007, OPERA II [long-term safety study]) that investigated the safety, tolerance, PK, and pharmacodynamic (PD) properties of ontamalimab support further clinical development of ontamalimab using SC administration in subjects with moderate to severe CD.

2.1.1 Rationale for Subjects Who Responded to Ontamalimab in the Induction Study and Who Could Potentially be Randomized to Placebo in the Maintenance Study

The design of the maintenance study (SHP647-307) for those who completed active treatment in the induction studies (SHP647-305 and SHP647-306) and met entry criteria is one of randomized withdrawal, whereby a subject may be randomized to continue treatment on the same dose of active treatment or switched to placebo. This design allows for the assessment of the total and multidimensional benefits of a new drug, which encompass efficacy, safety, convenience, and other factors like the durability of the effect of the drug. Having a similarly selected cohort of subjects who are treated with placebo instead of active treatment allows for such an assessment.

2.1.2 Rationale for Subjects Who Responded to Placebo in the Induction Study and Who Could Potentially be Randomized to Ontamalimab in the Maintenance Study

As one of the coprimary objectives of this study is clinical remission, rerandomizing placebo-treated subjects from the induction studies (SHP647-305 and SHP647-306) who meet entry criteria for the maintenance study (SHP647-307) allows for the greatest number of subjects to potentially be in clinical remission. Sandborn et al. (2013) demonstrated that the percentage of placebo-treated subjects in clinical remission decreases significantly over time compared with subjects on active treatment following 52 weeks of treatment with vedolizumab in a maintenance study. This finding is consistent with results from subjects with UC who followed a similar dose regimen. Rerandomizing placebo-treated subjects who qualify for the maintenance study allows for the greatest number of subjects to potentially benefit from treatment with active treatment. Additionally, randomized withdrawal of subjects on active treatment and rerandomization of placebo-treated subjects entering the maintenance study allows for a full and separate investigation of the induction of clinical remission and maintenance of clinical remission effects of any potential new treatment for CD, such as ontamalimab. Rerandomizing placebo-treated subjects allows for further investigation of long-term safety of ontamalimab.

2.2 Study Objectives

2.2.1 Coprimary Objectives

The coprimary objectives of this study are to evaluate the efficacy of ontamalimab as maintenance treatment in subjects with moderate to severe CD based on:

- Clinical remission based on 2-item patient-reported outcome (PRO) (abdominal pain severity and very soft stool/liquid stool frequency)
- Enhanced endoscopic response based on centrally read colonoscopy.

2.2.2 Secondary Objectives

2.2.2.1 Key Secondary Objectives

The key secondary objectives are as follows:

- To evaluate the efficacy of ontamalimab as maintenance treatment on clinical remission as measured by CDAI
- To evaluate the efficacy of ontamalimab as maintenance treatment on glucocorticoid-free clinical remission based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
- To evaluate the efficacy of ontamalimab as maintenance treatment on clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)
- To evaluate the efficacy of ontamalimab on maintenance of clinical remission among subjects in clinical remission at baseline of the SHP647-307 study based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
- To evaluate the efficacy of ontamalimab on maintenance of enhanced endoscopic response among subjects with enhanced endoscopic response at baseline of the SHP647-307 study based on centrally read colonoscopy
- To evaluate the efficacy of ontamalimab as maintenance treatment based on achieving clinical remission as well as achieving enhanced endoscopic response in the same subject
- To evaluate the effect of ontamalimab as maintenance treatment on complete endoscopic healing based on centrally read colonoscopy.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study in subjects with moderate to severe CD who completed their participation in an induction study (either SHP647-305 or SHP647-306) and fulfilled the efficacy entry criteria of this study.

Approximately 983 subjects were planned to be enrolled into the study: approximately 776 subjects from active induction treatments and approximately 207 subjects from placebo induction groups. The eligibility of a subject for the study will be assessed based on the study data collected at the Week 16 visit of the induction studies (SHP647-305 or SHP647-306), which will be considered as the baseline visit for this maintenance study.

This study consists of a 52-week, double-blind treatment period, followed by a 12-week safety follow-up period for subjects who either discontinue treatment early or complete the treatment period and do not enter the long-term safety extension (LTS) study (SHP647-304).

Eligible subjects who received active treatment in one of the induction studies and fulfilled the efficacy entry criteria of this study, including achieving endoscopic and/or clinical response, will be randomized as follows: subjects who received 25 mg ontamalimab in one of the induction studies will be randomized (1:1) to receive either 25 mg ontamalimab or placebo, and subjects who received 75 mg ontamalimab in one of the induction studies will be randomized (1:1) to receive either 75 mg ontamalimab or placebo.

Eligible subjects who received placebo in one of the induction studies and fulfilled the efficacy entry criteria of this study, including achieving endoscopic and/or clinical response, will be randomized in a 2:2:1 ratio to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo, respectively) during this maintenance study.

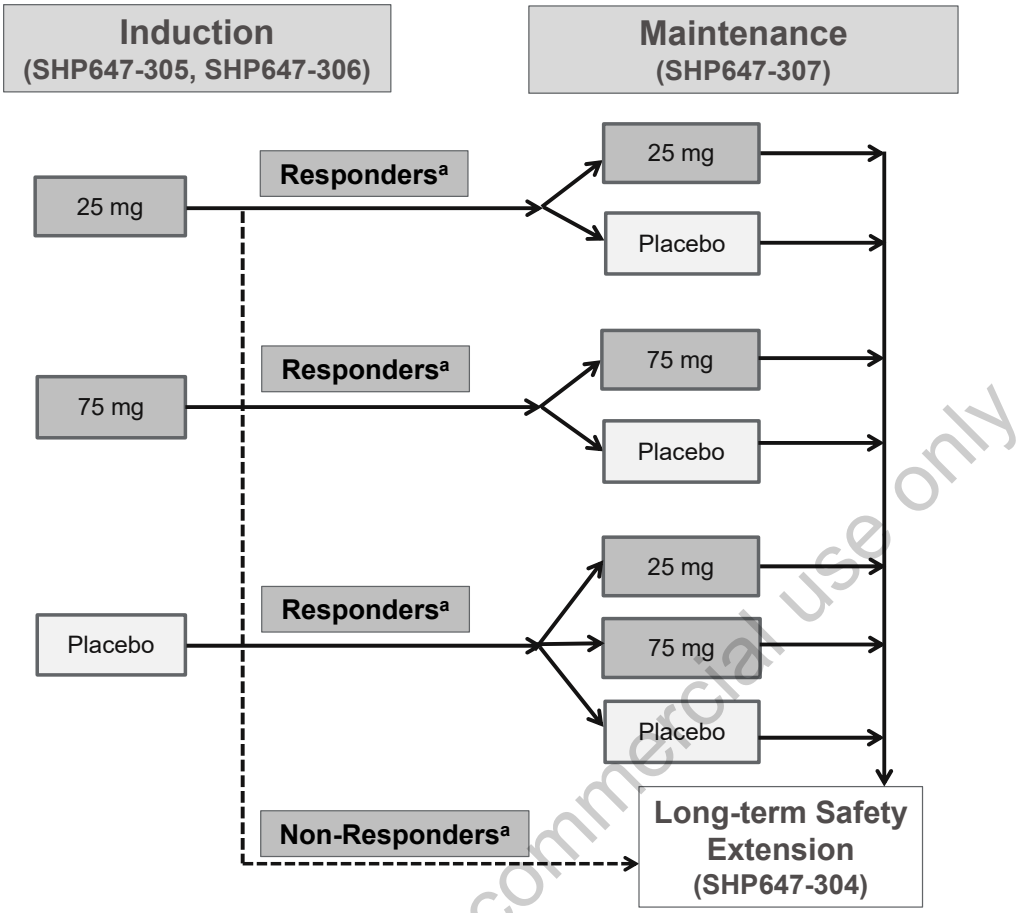
Subjects will be stratified according to glucocorticoid use at Study SHP647-307 baseline, the subject's status of prior anti-TNF treatment (naïve or experienced), and whether or not the subject achieved clinical remission by 2-item PRO or enhanced endoscopic response in the induction study.

Subjects enrolled in this study (SHP647-307) will receive double-blind maintenance treatment in the form of SC injections, using a prefilled syringe (PFS), Q4W for 52 weeks. Subjects will undergo efficacy and safety assessments as detailed in Table 1.

Under Amendment 3, subjects who complete the double-blind treatment period, or subjects who are withdrawn from the study prior to completing the double-blind treatment period due to early closure of the study by the sponsor, may be eligible to enter the LTS study (SHP647-304) provided they meet the eligibility criteria under SHP647-304 Amendment 4. Offering treatment in the LTS study after exiting this maintenance study allows subjects who benefited from active treatment, in this study or the induction study, to potentially benefit from continued treatment at the same dose of ontamalimab or at different dose of ontamalimab if, during the course of the SHP647-304 study, one of those doses (25 mg or 75 mg) is determined to be more efficacious based on emergent data from the induction studies. However, if there is no evidence of efficacy of either of the doses in comparison to placebo in the UC/CD clinical study, the entire program may be stopped, including the LTS study. Subjects who are not entering Study SHP647-304 will enter a 12-week safety follow-up period.

An overview of the ontamalimab Phase 3 CD studies is shown in Figure 1 and the overall study design is shown in Figure 2.

Figure 1 Overview of Ontamalimab Phase 3 Studies in Crohn's Disease



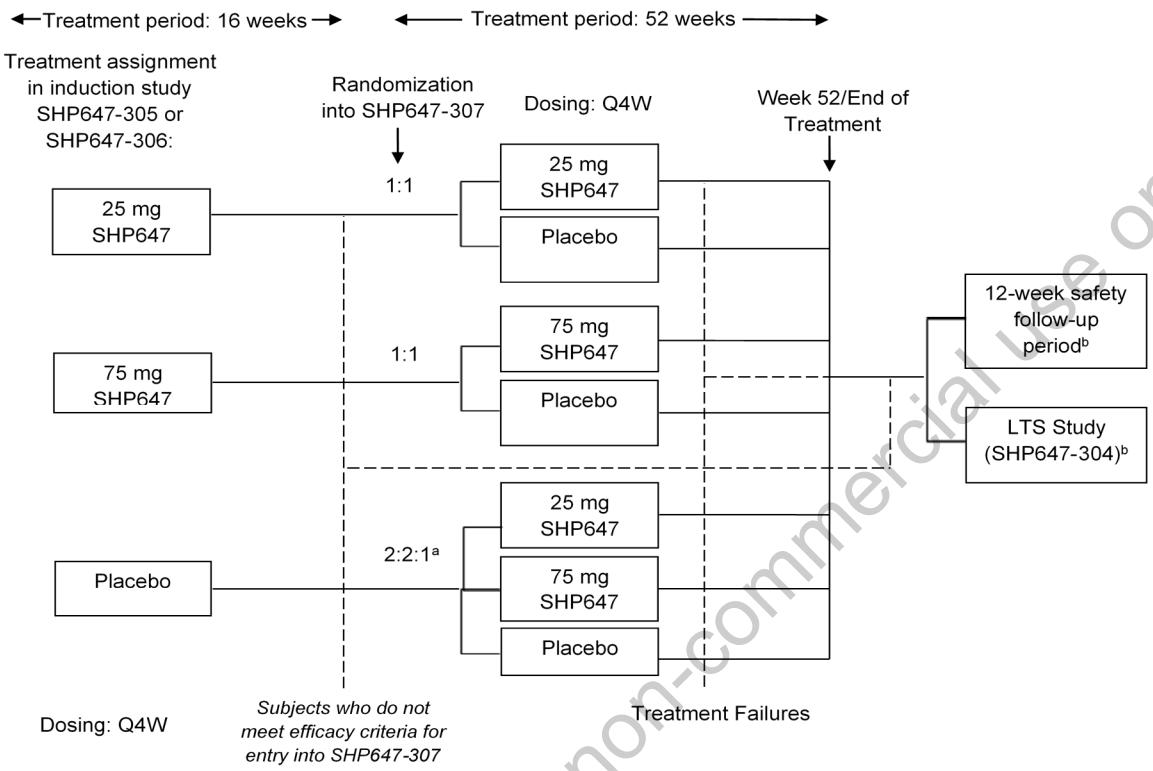
BSFS=Bristol Stool Form Scale; CDAI= Crohn's Disease Activity Index; NRS=numerical rating scale; PRO=patient-reported outcome; SES-CD=Simple Endoscopic Score for Crohn's Disease

[a] Responders are subjects who either:
(a) Meet endoscopic response criteria of a reduction in SES-CD from baseline by ≥25% at Week 16
OR
(b) Meet at least 1 of the following 4 criteria at Week 16 in addition to no worsening of endoscopic score as measured by SES-CD relative to induction study baseline (SHP647-305 or SHP647-306):

1. Subject is in clinical remission as determined by meeting the criteria for clinical remission using the 2-item PRO, ie, 2-item PRO 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.*
2. Subject has a decrease of at least 100 points in CDAI score (CDAI-100) from baseline.
3. Subject has a decrease of ≥30% and at least 2 points from baseline in the average daily worst abdominal pain over the 7 most recent days*, with the average daily stool frequency of type 6/7 (very soft stools/liquid stools) either: (i) not worsening from baseline and/or (ii) meeting the criteria for clinical remission, ie, 2-item PRO subscore of 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.*
4. Subject has a decrease of ≥30% from baseline in the average daily stool frequency of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days*, with the average daily worst abdominal pain either: (a) not worsening from baseline and/or (b) meeting the criteria for clinical remission, ie, 2-item PRO subscore of average worst daily abdominal pain ≤3 (based on 11-point NRS) over the 7 most recent days*.

*Note: The 7 most recent days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the criterion will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the criterion will be treated as missing.

Figure 2 Study Design Flow Chart



LTS=long-term safety extension; Q4W=every 4 weeks; W=week

[a] Eligible subjects who received placebo in one of the induction studies and fulfilled the efficacy entry criteria in this study will be randomized in a 2:2:1 ratio to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo, respectively).

[b] With the implementation of Amendment 3, subjects who complete the double-blind treatment period, or subjects who are withdrawn from the study prior to completing the double-blind treatment period due to early closure of the study by the sponsor, may be eligible to enter the LTS study (SHP647-304) provided they meet the eligibility criteria under SHP647-304 Amendment 4. Subjects who are not entering study SHP647-304 will enter a 12-week safety follow-up period.

3.1.1 Rationale for Coprimary Endpoints

In this study, clinical remission, as measured by a decrease below prespecified thresholds in the 2-item PRO (abdominal pain severity and very soft stool/liquid stool frequency [as shown in the Bristol Stool Form Scale (BSFS)]), and enhanced endoscopic response, as measured by a decrease in SES-CD, will be the primary instruments to assess the efficacy of ontamalimab.

Rationale for Abdominal Pain Severity

Abdominal pain is one of the most common symptoms of CD, with the cause likely to be multifactorial. In the CDAI, which was the most commonly used primary endpoint in CD studies in the past, the degree of abdominal pain was based on a 4-point scale, with scores ranging from 0 (none) to 3 (severe). However, the new standard is to use the 11-point numerical rating scale (NRS) instead for the degree of abdominal pain. The limitation is that the 4-point and the 11-point scales are not directly comparable. Numerous studies across a variety of conditions have examined cutoff scores for mild, moderate, and severe pain based on the 11-point pain NRS, with the findings across studies generally converging on a cutoff score of 4 (reflecting the maximum score indicating mild pain) and a score of 5 (reflecting the minimum score indicating moderate pain). To ensure that clinical remission criteria for abdominal pain are both clinically meaningful and fall definitively within the mild pain range on the NRS based on the literature, a remission subscore of ≤3 (a minimum improvement of at least 2 points is required for subjects who enter the study with moderate abdominal pain [subscore of ≥5]) will be used as part of the coprimary endpoints. This definition is further supported by a study conducted in a similar condition (irritable bowel syndrome) that examined the minimal clinically important difference on the 11-point NRS for abdominal pain (Spiegel et al., 2009) as well as post hoc analyses of the Phase 2 data from the ontamalimab program (Study A7281006, OPERA).

Rationale for Very Soft Stool/Liquid Stool Frequency

Diarrhea is the most common sign in the presentation of CD, affecting approximately 85% of patients with a diagnosis of CD. In the CDAI, the number of liquid or soft stools (each day for 7 days) is used with a multiplier of 2. The coprimary endpoints for clinical remission of Study SHP647-307 requires the use of a definition without any such multiplying factor and will use the BSFS for defining the very soft or liquid stools according to types 6 and 7, respectively. A retrospective study of PROs in CD based on data from randomized controlled studies using rifaximin and MTX showed that a mean daily stool frequency score of ≤1.5 had an area under the receiving operating characteristic curve of 0.79 (Khanna et al., 2015) and provided a potential cutoff for defining remission as measured by CDAI. In a recent study to select the attributes determining overall disease severity and to rank the importance of and to score these individual attributes for both CD and UC based on specialist opinion, a sample of at

least 10 loose stools per week was considered as an attribute contributing to overall disease severity in CD (Siegel et al., 2016). Based on post hoc analyses of the Phase 2 data in the ontamalimab program (Study A7281006, OPERA) and by choosing the population of subjects satisfying the moderate to severe CD inclusion criteria, various cutoffs were explored and a stool frequency ≤2.0 was found to be optimal in terms of treatment separation while still allowing for a reasonable threshold for remission. Based on these and other recent data that support this cutoff, an average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) has been chosen as the stool frequency criterion for clinical remission.

Enhanced Endoscopic Response Defined as 50% Improvement in SES-CD Score

The SES-CD was developed to meet the clinical need for a reliable, easy-to-use endoscopic scoring instrument and for its need in research for endoscopic endpoints in studies evaluating new agents for CD in the era of mucosal healing and central endoscopy reading (Koutroumpakis and Katsanos, 2016). It has been developed as an alternative to CD Endoscopic Index of Severity (CDEIS) and is simpler and therefore more suited to routine use. During the validation process, a strong correlation between SES-CD and CDEIS (r=0.920) has been seen. In addition, SES-CD correlates with clinical parameters and [redacted].

A 50% improvement in the endoscopic score will be used as a coprimary endpoint in this study as this magnitude of change is likely to be clinically relevant. Mucosal healing or "endoscopic healing" is considered to be a pivotal long-term target in the treatment of CD; however, partial endoscopic response may also provide benefits.

The benefit of endoscopic response is shown in the ACCENT-1 study (a CD clinical study evaluating infliximab in a new long-term treatment regimen), where patients who achieved complete mucosal healing (defined as complete absence of mucosal ulceration) after 1 year remained in remission for a median of 20 weeks, compared with 19 weeks for patients who achieved significant but incomplete mucosal healing and only 4 weeks for patients who experienced no healing of ulcers (D'Haens et al., 2002). The proportion of patients requiring major abdominal surgery in a single-center cohort study with infliximab was similar with complete healing or with partial healing (Schnitzler et al., 2009; Panaccione et al., 2013).

3.1.2 Rationale for Key Secondary Endpoints

Clinical Remission Defined by CDAI Score

Conventionally, a CDAI score of <150 has been used to define clinical remission. While there has been widespread use of the CDAI over a long period of time, the items do not contribute equally to the score, and symptom items reported by subjects are not specific for CD and are not sensitive for inflammation seen at colonoscopy. There has been movement away from using the

CDAI by regulatory authorities to the use of PROs and objective measures of disease such as endoscopy (Williet et al., 2014). However, for benchmarking or for comparative effectiveness purposes, CDAI endpoints are expected to be used.

Although this has been the established gold-standard for clinical remission to date, CDAI suffers from requiring complex calculations across 8 individual items including subjective elements.

Glucocorticoid-free Clinical Remission Based on Patient-reported Clinical Signs and Symptoms (2-item PRO)

First-line therapy for CD typically consists of oral budesonide for mild disease or systemically active glucocorticoids for moderate to severe disease. While systemic glucocorticoids can deliver rapid symptomatic relief and reduction of inflammation, prolonged steroid administration should be avoided given the risk of opportunistic infections and other complications (osteoporosis, growth suppression, ulcers, GI bleeding, etc.). As a result, once clinical remission has been induced, use of glucocorticoids should be tapered. Clinical remission, as defined above based on the 2-item PRO of average daily abdominal pain severity and average daily stool frequency, will be measured in subjects who are steroid-free at the end of maintenance or whose steroids use has been tapered off for a predefined period at the end of maintenance. Steroid-free is defined as not requiring any treatment with glucocorticoids at least 12 weeks prior to the Week 52 visit. The 12-week window is supported by European Crohn's and Colitis Organisation (ECCO) guidelines and the draft European Medicines Agency (EMA) guidance for CD (CPMP/EWP/2284/99 Rev. 2). The ECCO Guideline (2016) states the following, under Section 1.1.6 Pattern of relapse: "Patients are still considered steroid dependent if they relapse within 3 months of stopping steroids. Although these limits are arbitrary, they serve as guidance for clinical practice and may be used for uniformity in clinical trials." In line with this, the draft EMA guidance for CD (CPMP/EWP/2284/99 Rev. 2) states that patients can be regarded as steroid dependent if they have a relapse within 3 months of stopping steroids.

Clinical Remission Defined by Average Daily Abdominal Pain ≤1 (Based on the 4-point Scale) and Average Daily Stool Frequency ≤3 of Type 6/7

The CDAI has been the traditionally used measure to assess clinical response and clinical remission in CD. In the CDAI, the degree of abdominal pain is one of 8 variables and is used with a multiplier of 5 in the overall score. Importantly, it is based on a 4-point scale, with scores ranging from 0 (none) to 3 (severe). With the shift to the new endpoint as evident from the coprimary endpoint of clinical remission in this study, it is still important to allow for a frame of reference to the existing standard for response, based on the CDAI components. A daily average abdominal pain threshold of ≤1 will help achieve this as 1 on the 4-point scale corresponds to mild abdominal pain. Although direct mapping between the scales has not been established, this

will approximate to a score of 3 on the 11-point NRS scale, as this falls within the mild pain range on the NRS based on the literature.

Based on post hoc analyses of the Phase 2 data in the ontamalimab program, regulatory requirements, and treatment separation assumptions, a threshold for the average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) was chosen for the coprimary endpoint of clinical remission. However, given the limited data available for this endpoint, recent evidence from literature suggesting that thresholds ≤3 are likely to be quite stringent (Sandborn et al., 2017) and the refractory nature of the disease in those with moderate to severe CD, it is also important to assess the effects of treatment using a more realistic measure. Hence, for this key secondary endpoint of clinical remission, average daily stool frequency ≤3 of type 6/7 (very soft stools/liquid stools) has been chosen as the appropriate threshold.

Clinical Remission Among Subjects in Clinical Remission at Baseline of the SHP647-307 Study, Based on Patient-reported Clinical Signs and Symptoms (2-Item PRO)

Entry into the maintenance study is largely based on subjects in clinical response but not necessarily clinical remission to allow for the greatest number of subjects to have the chance to benefit from therapy during this maintenance study. However, some subjects will have achieved clinical remission at the end of the induction study. In these subjects who have started maintenance therapy while in clinical remission, it is important that this remission be maintained and stable without relapse. Hence, demonstrating clinical remission, as defined above based on the 2-item PRO of average daily abdominal pain severity and average daily stool frequency in patients who are in clinical remission at the baseline for Study SHP647-307, is an important clinical indicator of durability of treatment effect.

Enhanced Endoscopic Response Among Subjects with Enhanced Endoscopic Response at Baseline of the SHP647-307 Study

Entry into the maintenance study is largely based on subjects in clinical response or endoscopic response (at least 25% reduction in SES-CD score from baseline) to allow for the greatest number of subjects to have the chance to benefit from therapy during this maintenance study. However, some subjects will have achieved enhanced endoscopic response (at least 50% reduction in SES-CD score from baseline) at the end of the induction study. In these subjects who have started maintenance therapy with enhanced endoscopic response, it is important that this is maintained or improved even further.

Clinical Remission as Well as Enhanced Endoscopic Response in the Same Subject

Both clinical remission and endoscopic response to treatment, as defined by enhanced endoscopic response above, are important goals of treatment with ontamalimab in this maintenance study. However, the correlation between clinical improvement and endoscopic improvement is not always strong or straightforward in CD given the transmural involvement of the disease. By documenting the treatment effect on the basis of both clinical signs and symptoms as well as endoscopic improvement in the same subject, this endpoint offers possibly the most comprehensive evidence of benefit of therapy.

Complete Endoscopic Healing

Endoscopic healing will be defined in 2 ways:

- Endoscopic healing defined by SES-CD ≤4 and at least a 2-point reduction versus baseline (Visit 1) and no subscore >1 in any individual variable
- Complete endoscopic healing defined by SES-CD=0-2.

There is no uniformly accepted definition for endoscopic healing in CD and several different terminologies are used to describe the same endoscopic appearance defined by a certain endoscopic score (eg, endoscopic remission and mucosal healing). Endoscopic healing or mucosal healing is predominantly defined by the absence of mucosal ulcerations in CD during endoscopic assessment of intestinal inflammation (Atreya and Neurath, 2017). The International Organization for the study of Inflammatory Bowel Disease technical review on endoscopic indices for CD clinical studies defined complete endoscopic healing as SES-CD=0-2 (Vuitton et al., 2016). Some studies introduced SES-CD ≤4 as "endoscopic remission." The more stringent endpoint of "complete endoscopic healing" will be used as a key secondary endpoint in this study. Even in case of complete endoscopic healing, there may still be ongoing histological activity in many cases and it may not always reflect healing of all layers of the tissue, as endoscopy only addresses mucosal rather than transmural healing (Atreya and Neurath, 2017).

The importance of achieving endoscopic healing is that it may be associated with long-term symptomatic remission; longer relapse-free interval; reduced frequency of hospitalizations, complications, and surgical resections; and the potential for a significant improvement in quality of life (Peyrin-Biroulet et al., 2011).

3.2 Duration and Study Completion Definition

Each subject's final visit in this study will be the Week 52/ET visit, if continuing to the LTS study (Study SHP647-304) or at the end of the 12-week safety follow-up period if not entering Study SHP647-304. Both the Week 52/ET 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 may also be done at a subject's home provided a qualified site staff member performs these evaluations following Direct-to-Patient (DTP) guidance.

A subject's maximum duration of participation in Study SHP647-307 is expected to be approximately 64 weeks: a treatment period of 52 weeks, and a safety follow-up period of 12 weeks (if applicable). It was expected that the study would be completed in less than 4.5 years; however, due to early closure by the sponsor, the study is expected to be completed by November 2021.

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 33 sites in approximately 16 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 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 completed the 16-week induction treatment period from Study SHP647-305 or SHP647-306 and met the following criteria at baseline in maintenance study SHP647-307:
    - Meet endoscopic response criteria of a reduction in SES-CD from induction study (SHP647-305 or SHP647-306) baseline by ≥25% at Week 16 of induction study (SHP647-305 or SHP647-306)

      OR
    - Meet at least 1 of the following 4 criteria at baseline in maintenance study SHP647-307, in addition to no worsening of endoscopic score as measured by SES-CD relative to induction study (SHP647-305 or SHP647-306) baseline:
4. Achieving clinical remission as determined by meeting the criteria for clinical remission using the 2-item PRO, ie, 2-item PRO subscores of average worst daily abdominal pain ≤3 (based on 11-point NRS) over the 7 most recent days* and average daily stool type frequency ≤2 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days*.
5. A decrease of at least 100 points in CDAI score (CDAI-100) from induction study (SHP647-305 or SHP647-306) baseline.

6. A decrease of ≥30% and at least 2 points from induction study (SHP647-305 or SHP647-306) baseline in the average daily worst abdominal pain over the 7 most recent days*, with the average daily stool frequency of type 6/7 (very soft stools/liquid stools) either: (i) not worsening from induction study (SHP647-305 or SHP647-306) baseline and/or (ii) meeting the criteria for clinical remission, ie, 2-item PRO subscore of 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*.

7. A decrease of ≥30% from induction study (SHP647-305 or SHP647-306) baseline in the average daily stool frequency of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days*, with the average daily worst abdominal pain either: (i) not worsening from induction study (SHP647-305 or SHP647-306) baseline and/or (ii) meeting the criteria for clinical remission, ie, 2-item PRO subscore of average worst daily abdominal pain ≤3 (based on 11-point NRS) over the 7 most recent days*.

   *Note: The 7 days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the criterion will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the criterion will be treated as missing.

8. Subjects receiving any treatment(s) for CD described in Section 5.2.1 are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.

4.2 Exclusion Criteria

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

1. Subjects who had major protocol deviation(s) (as determined by the sponsor) in induction study SHP647-305 or SHP647-306.
2. Subjects who permanently discontinued investigational product because of an AE, regardless of relatedness to investigational product, in induction study SHP647-305 or SHP647-306.
3. Subjects who are likely to require surgery for CD during the study period, except minor interventions (eg, seton placement for anal fistulas).
4. Subjects are females who became pregnant during induction study SHP647-305 or SHP647-306, 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, as described in Section 4.4) 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 developed obstructive colonic stricture, or enterovesical or enterovaginal fistulae during the induction study (SHP647-305 or SHP647-306).
8. 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).
9. 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.
10. 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.
11. Subjects with known exposure to *Mycobacterium tuberculosis* since testing at screening in induction 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.
12. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during the evaluation of the last visit in the SHP647-305 or SHP647-306 studies. If the results are considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once prior to enrollment in Study SHP647-307.

    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥3.0 × the upper limit of normal (ULN)
    - Total bilirubin level ≥1.5 × ULN or >2.0 × ULN if the subject has a known documented history of Gilbert's syndrome
    - Hemoglobin level ≤80 g/L (8.0 g/dL)

- Platelet count ≤100 × 10^9/L (100,000 cells/mm^3) or ≥1000 × 10^9/L (1,000,000 cells/mm^3)*
- White blood cell count ≤3.5 × 10^9/L (3500 cells/mm^3)
- Absolute neutrophil count <2 × 10^9/L (<2000 cells/mm^3)
- Serum creatinine level >1.5 × ULN or estimated glomerular filtration rate <30 mL/min/1.73 m^2 based on the abbreviated Modification of Diet in Renal Disease Study Equation.

*Note: if platelet count is <150,000 cells/mm^3, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.

13. 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.
14. Subjects who are participating in other investigational studies (other than induction study SHP647-305 or SHP647-306) or plan to participate in other investigational studies during Study SHP647-307.

4.3 Restrictions

Subjects are encouraged to keep their diet habits constant throughout the study. For the purposes of this protocol, dietary supplements (such as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties) are considered to be concomitant medications (see Section 5.2).

Smoking is considered to be a risk factor for CD. Reports have shown that smoking is not only related to the onset, relapse, and exacerbation of CD, but also that smoking cessation lowers the postoperative recurrence rate (Ueno et al., 2013). Subjects should inform the investigator of any changes to their smoking habits during the study (including starting or stopping smoking). Use of nicotine patches should be recorded as concomitant medication (see Section 5.2).

4.4 Reproductive Potential

The potential effects of ontamalimab on embryofetal or postnatal development have not been assessed in humans. Preliminary results from an enhanced pre-and postnatal development toxicity study of ontamalimab in nonhuman primates indicated that, at the dose levels tested (30 and 60 mg/kg), infant losses were increased in ontamalimab-exposed animals when compared both to control animals in the study and to the historical control animal data from the testing facility. The relevance of this finding to humans is unknown but cannot be excluded. Based on the exposure in the Phase 2 clinical study A7281009 (area under the concentration-time

curve [AUC] from 0 to 672 hours [$AUC_{0\text{-}672h}$] at 6140 µg·h/mL following repeated SC administration of 75 mg ontamalimab Q4W), maternal exposure (AUC) in cynomolgus monkeys within a similar duration at 30 and 60 mg/kg once every 10 days is approximately 77 times and 172 times the clinical exposure, respectively.

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

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

During induction studies (SHP647-305 and SHP647-306), 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 (ie, at each site visit) and will be documented. In addition, the subject must be instructed to call the site immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

4.4.1 Contraceptive Methods for Female Study Subjects

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 (SHP647-305 or SHP647-306) (see Section 7.3.3.7).

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 poststerilization or has medically confirmed ovarian failure.
- Females of childbearing potential with a negative pregnancy test result at baseline (ie, Week 16 of the induction study SHP647-305 or SHP647-306; Week 0 of Study SHP647-307). 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 baseline (ie, Week 16 of the induction study SHP647-305 or SHP647-306; Week 0 of Study SHP647-307)
- Progestogen-only hormonal contraception associated with inhibition of ovulation plus a barrier method
- Intrauterine device
- Intrauterine hormone-releasing system

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

4.4.2 Contraceptive Methods for Male Study Subjects

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

Appropriate methods of contraception for male subjects are:

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

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

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

4.5 Withdrawal of Subjects

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

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 52/ET (Visit 14 Part 1 and Part 2) are to be performed. All subjects who discontinue investigational product and who are not entering the LTS study (SHP647-304) should also undergo the protocol-specified 12-week safety follow-up period. In the event that subjects are unable to attend in person for the follow-up visits, all efforts should be made to collect information on AEs and concomitant medications. Comments (spontaneous or elicited) or complaints made by the subject must be recorded. The reason for termination and date of stopping investigational product must be recorded.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

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

- Adverse events
- Serious AEs
- Meeting the criteria for treatment failure
- Pregnancy
- Protocol deviations
- Failure to return for visits.

A subject should be withdrawn from study treatment:

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

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

If a subject 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 source document.

Treatment failure is defined as meeting at least one of the following criteria:

1. Worsening of at least 30% either in abdominal pain and/or stool frequency scores over the 7 most recent days compared to the baseline values of Study SHP647-307 resulting in abdominal pain and/or stool frequency scores that are greater than or equal to the inclusion criteria thresholds (≥5 for abdominal pain and/or ≥4 for stool frequency) of the induction study.

   This criterion needs to be met on 2 successive visits.

2. Worsening of CDAI score by ≥100 points from baseline of Study SHP647-307 and CDAI>220 during one of the visits when CDAI is evaluated. This criterion needs to be met on at least 1 visit, unlike the 2 successive visits requirement that is necessary for criterion 1 above.

If it is clinically necessary, the investigator can decide to perform an unscheduled CDAI assessment based on the subject's reported symptoms and signs any time after Week 4. The unscheduled CDAI assessment can be performed no more than 4 times during the study.

Subjects who meet treatment failure criteria 1 and/or 2 will be considered treatment failures, with a need for a confirmatory colonoscopy. If needed, an unscheduled colonoscopy may be performed as part of treatment failure evaluation. Note: It is recommended that the unscheduled colonoscopy is performed within 2 weeks after the visit day when either the PRO-based or the CDAI score-based criterion for treatment failure was fulfilled. If the CDAI score-based criterion is fulfilled on an unscheduled visit, then the colonoscopy is to be performed either within 2 weeks after the previous regular visit or at the next regular visit.

Colonoscopy does not need to be repeated at the ET visit if performed earlier as part of treatment failure assessment and treatment failure is confirmed.

Treatment failure on endoscopy is defined as worsening of at least 30% on SES-CD scores and at least a 2-point increase in comparison to baseline values of Study SHP647-307 and SES-CD >6 (or ≥4 for isolated ileitis).

If the endoscopy does not confirm treatment failure, but the CDAI or PRO scores indicate treatment failure again for the next visit where CDAI is assessed (either scheduled or unscheduled) or for the next visit where PRO is assessed after the nonconfirmatory colonoscopy, then the subject will be categorized as a treatment failure without a need for further endoscopy.

Other causes of these changes, including viral or bacterial gastroenteritis and *Clostridium difficile* infection must be ruled out by appropriate stool cultures and other laboratory tests (see Appendix 4 for further information on testing for *C. difficile* infection, including diagnostic algorithms). If a potential other cause is identified, treatment failure will 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. This testing must begin once treatment failure is suspected, ie, at the first visit identified as potential treatment failure, to minimize the interval either to start treatment or to identify treatment failure.

Additionally, the investigator, in consultation with the study medical monitor, can use his/her clinical judgment to further determine if a particular subject meets criteria for treatment failure.

Subjects who do not enter the LTS study will continue into the 12-week safety follow-up period. If a subject withdraws their consent, no further evaluation should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

4.5.2 Reasons for Withdrawal

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

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.

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

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

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal remedies and vitamins) that is ongoing at the time of the baseline visit (Visit 1). It is expected that prior treatment will have been recorded during the induction study.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product in this maintenance study and the end of the 12-week safety follow-up period, inclusive.

5.2.1 Permitted Treatment

Subjects must remain on stable doses of permitted CD treatments until completion of the Week 52 visit, unless decreases are required because of AEs. Stable doses of the following treatments for CD are permitted as concomitant medication:

- Oral 5-ASA (mesalamine) and sulfasalazine
- Immunosuppressants (AZA, 6-MP, or MTX)
- Oral glucocorticoids; however, tapering is mandatory starting on Day 1. As the subjects are transferred from induction studies SHP647-305 or SHP647-306, the maximum glucocorticoid dose is 20 mg/day of oral prednisone or equivalent (Appendix 3) or 9 mg/day of budesonide. Tapering should follow the procedure shown in Table 2.

Note: Rectal 5-ASA and parenteral or rectal glucocorticoids are prohibited (see Section 5.2.2).

Table 2 Glucocorticoid Tapering

	First Taper	Second Taper
Timing	Prospectively define glucocorticoid-dependent subjects (ie, European Crohn's and Colitis Organisation)[a]	When subject is stable
Increments	• If daily dose of prednisone is >10 mg: Taper by 5 mg/day each 1–2 weeks • When daily dose of prednisone 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 of prednisone is >5 mg: Taper by 2.5 mg/day each week • When daily dose of prednisone is ≤5 mg: Taper by 1 mg/day each week
Action if unable to taper	Return to SHP647-307 baseline dose	Return to last effective dose: • If >10 mg, exit study • If ≤10 mg, remain as failure for glucocorticoid-free population.

[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).

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 as concomitant medications. Reported use of any antidiarrheal opiate medicines will assist the investigator response to Question 5 of the CDAI. Antidiarrheal opiate drugs must be taken at stable doses for the duration of the study unless dose reduction or discontinuation is required due to clinical improvement of AE. However, escalations of the dose after dose reduction, or re-initiation after drug discontinuation, is not allowed (see Section 5.2.3).

Subjects using medicinal marijuana (cannabis) under a physician's prescription, and who obtain the product from a licensed pharmacy or provider, should continue to use it under the same regimen for the duration of the study, unless otherwise instructed by the investigator or treating physician.

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 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.

Antibiotics are permitted, with the exception of antibiotics used to treat the underlying disease or any continuous antibiotic treatment (>2 weeks) immediately before Week 52 (Visit 14, Part 1).

5.2.2 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.

- Parenterally and rectally administered glucocorticoids
- Prednisone dose >20 mg/day, budesonide >9 mg/day, or other equivalent oral systemic corticosteroid dose
- Off-label usage of immunosuppressants used in transplantation or other nonestablished 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)
- Lymphocytes apheresis or selective monocyte granulocytes apheresis
- Live (attenuated) vaccines
- Fecal microbiota transplantation
- 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.

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

5.2.3 Rescue Therapy

Subjects must maintain their stable dose of background CD treatment, unless dose reduction or discontinuation is required due to associated AEs. If a subject requires initiation of a new therapy or increase in glucocorticoids for CD above the SHP647-307 baseline level, the subject should be withdrawn from study treatment and enter the safety follow-up period, and appropriate treatment should be given at the discretion of the investigator.

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

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.

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

6.1.1 Blinding the Treatment Assignment

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

6.2 Administration of Investigational Products

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, randomization, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and emergency unblinding. Please refer to the Study Manual for additional details regarding the IRT system.

6.2.2 Allocation of Subjects to Treatment

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

Subjects who fulfill all eligibility criteria and who received active treatment in the induction study (SHP647-305 or SHP647-306) will be randomized via a computer-generated randomization schedule as follows: subjects who received 25 mg ontamalimab in one of the induction studies will be randomized (1:1) to receive either 25 mg ontamalimab or placebo, and subjects who received 75 mg ontamalimab in one of the induction studies will be randomized (1:1) to receive either 75 mg ontamalimab or placebo.

Subjects who fulfill all eligibility criteria and who received placebo in the induction study will be randomized in a 2:2:1 ratio to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo, respectively) during this maintenance study.

Subjects will be stratified according to glucocorticoid use at SHP647-307 baseline, the subject's status of prior anti-TNF treatment (naïve or experienced), and whether or not the subject achieved clinical remission by 2-item PRO or enhanced endoscopic response in the induction study.

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

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

6.2.3 Dosing

Investigational product (ontamalimab or placebo) will be administered subcutaneously by qualified site personnel Q4W up to Week 52 (ie, a total of up to 13 doses of investigational product). 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. If there are clinical reasons why the investigational product cannot be administered in the thigh, the investigational product may be administered in the deltoid area or abdomen with appropriate documentation. The location of the investigational product administration will be recorded.

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

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 (see Section 10.2.1).

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 findings 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 continue with the treatment. 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

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

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

Due to early termination of the ontamalimab program, the sponsor is providing an option for subjects who are responding to active treatment in this maintenance study or who are on placebo and had responded to active treatment in an induction study to continue to receive ontamalimab in the long-term safety extension study SHP647-304. As this eligibility criterion into SHP647-304 depends on the blinded treatment assignment in this study, for these subjects, there is a potential for the treatment assignment in this study to be unblinded at the ET visit when assessing whether a subject can be a rollover into the SHP647-304 study or proceed to the safety follow-up period. The date of the ET visit will be recorded.

In addition, due to the early discontinuation of the SHP647 program, the SHP647-304 study is planned to be unblinded prior to the database lock in this study, which would unblind the treatment assignment in this study for a significant portion of subjects. As such, this study will be considered unblinded when the SHP647-304 study is unblinded, and the date of study unblinding will be recorded.

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 labeled carton.

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

6.3.3 Storage

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

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. 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 minimum/maximum thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational

product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

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

6.3.4 Special Handling

The investigational product should be protected from light and should not be frozen. Do not shake. 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, 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 requiring 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). Home healthcare visits will be documented in the study records.
- Allowance of more flexibility around scheduling of study visits and/or allowing some assessments to be conducted remotely (See Table 1).
- 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.
- Missed clinic visits or subject withdrawals due to COVID-19 (or other similar pandemic) must be recorded in the source document (See Section 4.5.2, 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 schedule of assessments (Table 1), in order to conduct evaluations or assessments required to protect the well-being of the subject.

7.2.1 Baseline Visit (Visit 1, Week 0)

Procedures performed at Week 16 (Visit 7) of the induction studies (SHP647-305 or SHP647-306) will be the baseline (Day 1/Week 0) assessments for this maintenance study. The baseline visit for this maintenance study will be on the same day as the Week 16 visit of the induction study. To be eligible for this maintenance study, subjects must have fulfilled the specific entry criteria set up in the induction study (see Section 4.1 and Section 4.2 for a full list of inclusion and exclusion criteria, respectively). 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 randomized or administered investigational product.

The results of the 2-item PRO, the endoscopic score measured by SES-CD, and CDAI score at Week 16/Visit 7 of induction study SHP647-305 or SHP647-306 will be used for Week 0/Day 1/Visit 1 of Study SHP647-307 before randomization.

For eligible subjects, all relevant study information recorded for Week 16 of the induction studies will be included in the baseline visit data for this maintenance study. All procedures that would lead to the assessment of the subject eligibility criteria for the maintenance study at Week 16/Visit 7 in the induction study should have been completed before any other baseline visit assessments performed for this maintenance study.

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

7.2.2 Treatment Period

7.2.2.1 Visits 2 to 13 (Weeks 4 to 48)

The schedule of Visits 2 to 13 during the treatment period, and the assessments and procedures to be performed at each visit, are specified in Table 1.

Note: As soon as Amendment 3 is implemented, the subject's next scheduled visit will be the Week 52/ET visit, which should be conducted no later than 4 weeks (±10 days) from the subject's last study visit prior to implementation of SHP647-304 Amendment 4.

7.2.2.2 Final On-treatment Visits: Visit 14, Parts 1 and 2 (Week 52/Early Termination)

The Week 52/ET visit consists of 2 parts.

Part 1 of Visit 14 should be scheduled within 10 days (preferably within 5 to 7 days) before Part 2; this will allow sufficient time to obtain the data from the central laboratory hematocrit test value in order to be available at Part 2 of the visit. If a central laboratory hematocrit result is available that is not older than 3 weeks, Parts 1 and 2 of Visit 14 can be performed on the same day; however, the laboratory sampling must be done before the start of colonoscopy preparation. The Week 52/ET assessments and procedures that will take place during Part 1 are specified in Table 1.

Part 2 of Visit 14 will take place on Day 364 ±10 days. The Week 52/ET assessments and procedures, including the colonoscopy that will take place during Part 2, are specified in Table 1. For subjects who meet the criteria for treatment failure (as defined in Section 4.5.1), or are discontinuing prior to completing the 52-week treatment period due to early study closure, and will be entering the LTS study (SHP647-304), Part 2 of Visit 14 should be scheduled at least

2 weeks after the last dose of investigational product, to allow a sufficient time interval prior to the first dose in the LTS study.

The Week 52/ET visit is preferred to be on-site; 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, the visit may also be done at a subject's home provided a qualified site staff member performs the evaluations following DTP guidance.

Note: For subjects discontinuing from the study due to early termination of the study by the sponsor, clinical response as measured by at least a 100-point reduction in CDAI score (CDAI-100 response) from induction study (SHP647-305 or SHP647-306) baseline will be evaluated at the ET visit as well.

Colonoscopy is **not** required (optional) at the ET visit if the subject has not completed 52 weeks of treatment due to early closure of the study (see Section 10.1.5).

After both parts of Visit 14 have been completed, the subject will either enter the LTS study (SHP647-304) or the 12-week safety follow-up period.

The Week 52 assessments and procedures will also form the ET assessments for any subjects who are withdrawn early from the study.

7.2.2.3 Unscheduled Visit to Evaluate Potential Treatment Failure With CDAI

An unscheduled visit can be performed at any time after Week 4 if the investigator decides, based on patient-reported symptoms and clinical signs, that there is a possibility of treatment failure and therefore it is necessary to calculate the CDAI before the scheduled CDAI evaluation. During this visit, the investigator performs all the physical examinations and other assessments (including blood sampling for hematocrit if there no hematocrit value is available from the past 3 weeks), reviews the relevant diary data for the past 7 days, calculates the CDAI score if every item is available, and makes the decision as to whether or not a confirmatory unscheduled colonoscopy is necessary. If the hematocrit value is not available at the time of the visit, the patient will be informed via telephone on the outcome.

7.2.2.4 Unscheduled Visit to Evaluate Potential Treatment Failure With Colonoscopy

If either the PRO treatment criterion is fulfilled at 2 consecutive scheduled assessments or the CDAI treatment failure criterion is fulfilled on at least one occasion (at either a scheduled or an unscheduled visit), the investigator will schedule a colonoscopy either within 2 weeks after the previous regular visit or, if it is not possible to do so, then for the next scheduled regular visit.

7.2.3 Follow-up Period: Visit 15 (Week 64)

Subjects who are withdrawn early from the study, or who do not enter the LTS study (SHP647-304), should enter the 12-week safety follow-up period for safety monitoring. Subjects who are proceeding to the LTS study (SHP647-304) will not enter the safety follow-up period.

For subjects who complete SHP647-307, safety follow-up will occur 12 weeks following the subject's last visit (Week 52) in the treatment period.

At the end of the 12-week safety follow-up period, there will be a visit at the site on Day 448 ±10 days (for subjects who completed the 52-week treatment period) or 12 weeks ±10 days after the ET visit (for subjects who are withdrawn early from the study), which will form the Week 64 visit (Visit 15). The final 12-week safety follow-up visit is preferred to be on-site; 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, the visit may also be done at a subject's home provided a qualified site staff member performs the evaluations following DTP guidance. The assessments and procedures specified in Table 1 will be performed, including querying for SAEs, AEs, and concomitant medications and procedures. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

7.2.4 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:

- Patient-reported questionnaires
- Vital signs and ECG
- Laboratory sample collection
- Investigational product administration
- Colonoscopy (generally performed at a separate visit (see Section 7.3.2.4).

Note: Blood and tissue samples may be stored for up to the duration allowed by local regulations, but for no longer than 25 years.

7.3.1 Demographic and Other Baseline Characteristics

All relevant demographic and baseline characteristics recorded for the induction studies (SHP647-305 or SHP647-306) will be used as the baseline characteristics for this maintenance study.

7.3.2 Efficacy

7.3.2.1 Patient-reported Outcome – Crohn's Disease Daily E-diary

Patient-reported CD signs and symptoms data will be collected using a PRO-CD daily e-diary (electronic handheld device). The e-diary will be available daily throughout the study. Subjects will be required to enter e-diary data every day throughout the study period. Subjects will enter data on CD signs and symptoms items using the e-diary, which 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 e-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 (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.

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:

- Visits 2 to 13: 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.
- Visit 14 (Part 2) and at any regular visit (Visit 3 to 13) when a confirmatory colonoscopy is performed to evaluate treatment failure: 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.

For all 2-item PRO calculations, the 7 most recent days may or may not be contiguous during the 10 days of data collection depending on days to be excluded because of missing data. The PRO-CD daily e-diary is presented in Appendix 2.

7.3.2.2 Simple Endoscopic Score for Crohn's Disease

The SES-CD will be performed at the time points specified in Table 1. The SES-CD score at Week 52/ET or at an unscheduled colonoscopy to confirm treatment failure will be calculated using the subscores of each of the segments investigated and centrally read for the colonoscopy performed.

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 (Daperno et al., 2004). 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).

A complete colonoscopy is required (including visualization of the terminal ileum except when it is not possible due to impassable stenosis or previous partial colectomy/ileocolectomy). 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).

Study videos will be scored separately by 2 central readers who are blinded to the treatment. If the central readers' scores are not in agreement, there will be a third adjudication read to select the correct read from the first 2 scores. Results of the central reading of the videos will be communicated to sites within 5 business days.

For the evaluation of efficacy, in cases where 1 or 2 segments cannot be fully evaluated by central endoscopic readers, ileocolonic segments that are evaluable during screening (Visit 1) of the induction studies (SHP647-305 and SHP647-306) and Week 52/ET of this study (SHP647-307) (matching segments approach) will be utilized.

The SES-CD is presented in Appendix 2.

7.3.2.3 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 and will be recorded as part of the daily e-diary, as described in Section 7.3.2.1 and 5 components will be recorded at the time points specified in Table 1.

The CDAI scores at Visits 4, 7, and 10 or at an unscheduled visit for treatment failure evaluation will be calculated using the following:

- Components 1 to 3 from subject-reported PRO-CD daily e-diary data collected every day. For the calculation, data from the past 7 days will be utilized in a similar way as described for the 2-item PRO (see Section 7.3.2.1) and
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at the visit.

The CDAI score at Week 52/ET (Visit 14, Part 2 after all evaluations are complete), or at any of the regular visit days (Visits 4, 7, and 10) when a treatment failure confirmatory colonoscopy is performed, will be calculated using the following:

- Components 1 to 3 from subject-reported PRO-CD daily e-diary data collected every day. For the calculation, data from the previous 7 days will be utilized before the day

of the start of colonoscopy preparation in a similar way as described for the 2-item PRO (see Section 7.3.2.1) and

- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at Part 1 and Part 2 of the Week 52/ET visit or at Visits 4, 7, and 10 when colonoscopy is performed for treatment failure evaluation.

The investigator may also perform an unscheduled CDAI assessment based on the subject's reported symptoms in order to evaluate treatment failure (see Section 4.5.1).

Change in CDAI has been used as a primary endpoint in multiple pivotal studies 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.

7.3.2.4 Colonoscopy and Histology

Colonoscopy will be performed at Visit 14, Part 2 (Table 1) or as an unscheduled visit for confirming treatment failure.

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; however, bowel preparation can be done entirely on the morning of the procedure. In this study, bowel preparation and colonoscopy are to be conducted per local routine; however, sodium phosphate-based preparations must be avoided, as such regimens can produce mucosal changes that mimic IBD.

In general, a complete colonoscopy should be performed; this includes visualization of the rectum, sigmoid colon, left colon, transverse colon, right colon, ileocecal valve, and the terminal ileum except when it is not possible after previous partial colectomy/ileocolectomy. An incomplete colonoscopy can be accepted for evaluation in exceptional cases, eg, in case of impassable stenosis or other CD-related complications as causes 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 colonoscopy in the induction study (SHP647-305 or SHP647-306). To achieve consistency in capturing and assessing endoscopic video recordings, each participating site will use an integrated hardware/software solution and associated tools for the capture and transmission of

endoscopy video recordings for central reading. Nonreadable endoscopic images, as assessed by the investigator, should not be sent for central reading. 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.

During colonoscopy at the Week 52/ET visit or at an unscheduled visit to confirm treatment failure by colonoscopy, 10 biopsies will be collected from the most inflamed area of the mucosa: 2 samples each from the ileum, the 3 segments of the colon, and the rectum except when it is not possible due to impassable stenosis or previous partial colectomy/ileocolectomy. Colonoscopy and biopsy procedures will be defined in a colonoscopy instructions manual and/or reference card(s), on which all sites will be trained. Colonoscopy results will be reviewed by a central reader.

Each biopsy will be stained with hematoxylin and eosin and then digitized for central review using the Colonic (CGHAS) and Ileal (IGHAS) Global Histologic Disease Activity Scores (see Appendix 2). Biopsies for conventional histologic assessment will be collected in formalin and shipped to the central laboratory. The central laboratory will register all biopsies and create paraffin blocks. Blocks will be batched and shipped on an agreed schedule to specialty laboratory, where tissue processing (sectioning, hematoxylin and eosin staining, and affixation to glass slides), digitalization, and uploading of images will occur. All images for a subject will be scored by the same qualified central pathologists blinded to the subject and treatment sequence information, according to the scoring modality.

Colonoscopy is **not** required (optional) at the ET visit if the subject has not completed 52 weeks of treatment due to early closure of the study.

7.3.3 Safety

7.3.3.1 Medical and Medication History

Medical history, including CD history, cardiac history, and smoking history, and prior medications will be collected at the screening visit (Visit 1) of induction study SHP647-305 or SHP647-306. Concomitant medications and procedures will be documented throughout the SHP647-307 study at the time points specified in Table 1; diarrhea medications may also be documented at unscheduled visits for the calculation of CDAI, in order to assess treatment failure (see Section 4.5.1).

7.3.3.2 Physical Examination (Including Weight)

Complete and targeted physical examinations will be performed at the time points specified in Table 1. Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; eyes; breast (optional);

abdomen; external genitalia (optional); extremities; neurologic function; back; and lymph nodes. Targeted physical examination includes the review of the following body systems: skin and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

Weight will be measured at the time points specified in Table 1.

For SHP647-307, the complete physical examination performed at Week 16 (Visit 7 [Part 3]) of induction study SHP647-305 or SHP647-306 will be used as the baseline examination. Abnormalities identified during this visit will be documented. Any changes from the baseline visit (Week 0) in physical examination findings that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

Unscheduled physical examinations and weight measurements may be performed for calculation of CDAI in order to evaluate treatment failure (see Section 4.5.1).

7.3.3.3 Targeted Neurological Assessment

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

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

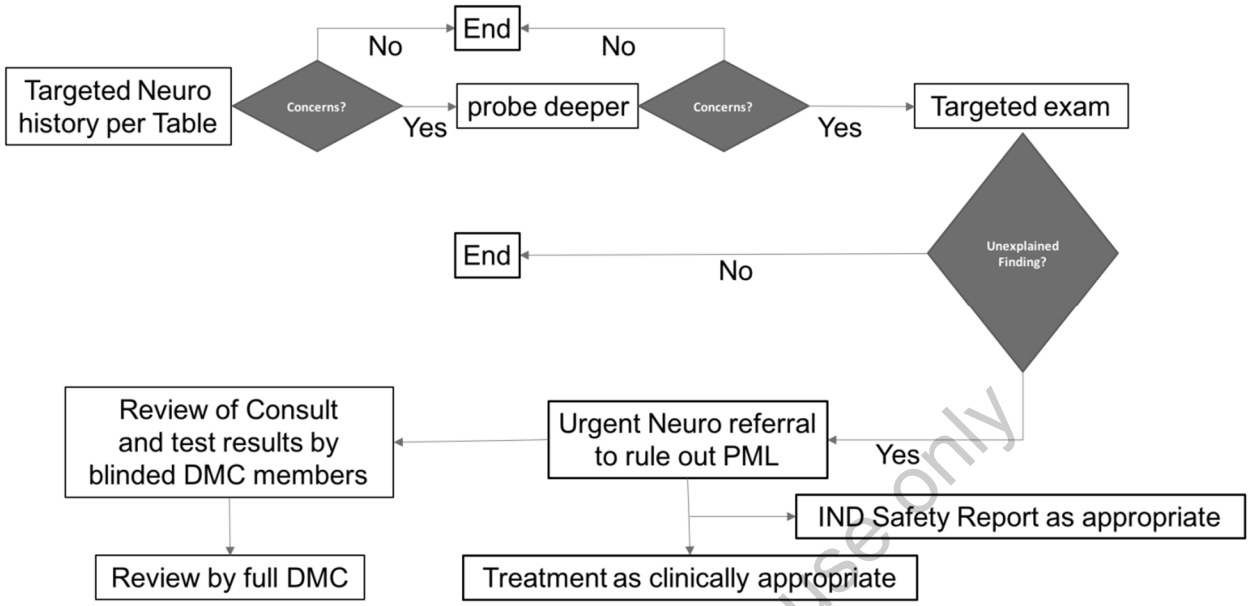
A step-wise approach for the proposed neurological assessment plan is provided in Table 3.

Table 3 Quarterly Neurological Assessments

Domain	Step 1: Interim Neurological 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 7s, proverbs; changes in activities of daily living over prior 6 months

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

Figure 3 Flow Diagram for Quarterly Neurological Assessments



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

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

7.3.3.4 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, “Have you had any health problems since your last visit?”). Adverse events are collected from the time informed consent and/or assent is signed until the end of the Week 52 visit or the end of the defined safety follow-up period stated in Section 7.2.3 (See Section 8, Adverse and Serious Adverse Events Assessment.)

7.3.3.5 Vital Signs

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

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

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

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

Any deviations from baseline (Visit 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.

7.3.3.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. 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 that are unexpected or not explained by the subject's clinical condition may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed at the time points specified in Table 1.

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

Hematocrit may be measured at unscheduled time points any time after Week 4 for calculation of CDAI in order to evaluate treatment failure (see Section 4.5.1). Unscheduled CDAI evaluation and related blood sampling for hematocrit cannot be performed more than 4 times during the study.

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 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.

7.3.3.7 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; 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 SHP647-305 or SHP647-306.

If a female subject's status has changed to postmenopausal since the induction studies (SHP647-305 or SHP647-306), the childbearing potential of the subject must be re-established and documented (FSH confirmation test) at baseline (Visit 1) of SHP647-307. 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.

7.3.3.8 Electrocardiogram

A 12-lead ECG will be recorded at the time points specified in Table 1. When timings of measurements coincide, ECGs should be performed before laboratory blood collection.

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

7.3.3.9 Antidrug Antibodies

Blood samples for measurement of ADAs and NAbs will be collected at the time points specified in Table 1. Blood samples must be collected before administration of investigational product at that visit.

7.3.3.10 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 until the adjudication committee assesses the case and finalizes recommendation of permanent discontinuation or rechallenge with investigational product.

Subjects who experience an AE suggestive of the presence of circulating immune complexes formation (eg, fever, rash [including hives], arthralgia, myalgia, vasculitis, Arthus reaction, general ill feeling, itching, and swollen lymph nodes) will have the related AEs reviewed by the adjudication committee; if the AEs are assessed as related to the formation of circulating immune complexes and not related to underlying disease, blood samples will be collected and stored at the central laboratory. Tests will be performed as confirmatory of presence of circulating immune complexes at the request of the adjudication committee.

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

7.3.3.11 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 2.

Subjects should be assessed for possible treatment failure no earlier than the Week 4 scheduled visit. 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 4.5.1 should be followed.

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

7.3.4 Others

7.3.4.1 [redacted]

[redacted]

7.3.5 Volume of Blood to Be Drawn From Each Subject

The volume of blood to be drawn from each subject is summarized in Table 4.

Table 4 Volume of Blood to Be Drawn From Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Hematology	2	5[a]	10
Serum chemistry	4	5	20
FSH	2	1	2
ADA and NAb sampling	3	3	9
Total mL			**41**

ADA=antidrug antibody; FSH=follicle-stimulating hormone; NAb=neutralizing antibody

[a] Up to 4 additional samples may be taken at unscheduled visits for measurement of hematocrit, in order to determine the Crohn's Disease Activity Index score for treatment failure assessment.

The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 41 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

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

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

All AEs are collected from the time the informed consent and/or assent is signed until Week 52 or the end of the defined follow-up period stated in Section 7.2.3. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. Resolved AEs considered to be significant by the investigator that occurred in induction studies SHP647-305 or SHP647-306 will be captured as part of the SHP647-307 baseline medical history, while ongoing AEs from Studies SHP647-305 or SHP647-306 will be captured as AEs in SHP647-307 and followed throughout the SHP647-307 study. All AEs should be captured in the subject's source document. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the subject's source document.

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

8.1.1 Severity Categorization

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

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

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

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Adverse Events of Special Interest

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

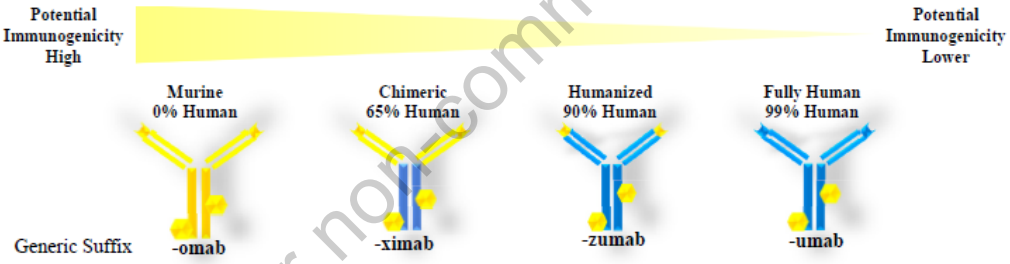
8.1.3.1 Hypersensitivity

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

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

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

Figure 4 Potential Immunogenicity of Therapeutic Monoclonal Antibodies



Ontamalimab is a fully human antibody of the immunoglobulin G2 subclass. In Phase 1 and Phase 2 clinical trials of ontamalimab, in which over 700 subjects were treated for up to 3 years, there has been no case of anaphylaxis. There have been 2 reported cases of drug hypersensitivity: serum sickness attributed to concomitant administration of penicillin; and a reaction characterized by dyspnea, facial erythema, and chest pain with onset 2 days after administration of the fifth dose of ontamalimab. The latter event mimicked a reaction that the subject had previously experienced after 4 doses of infliximab. In addition, low-titer activity has been observed in ADA assays, including in 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 assay 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 5.

Table 5 Clinical Criteria for Diagnosing Anaphylaxis (Type I Hypersensitivity)

Anaphylaxis is highly likely when the first criterion below and at least 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 BP for children is defined as less than 90 mmHg from 11 to 17 years.
Source: Adapted from Sampson et al., 2006.

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

Signs and symptoms of immune complex deposition typically have onset 1 to 3 weeks after exposure (Warrington et al., 2018) usually improving in 7 to 10 days, with full recovery in 2 to 4 weeks and may include fever, rash (including hives), arthralgia, myalgia, vasculitis, Arthus reaction, general ill feeling, itching, and swollen lymph nodes. Some of these findings, such as fever, rash, arthralgia, and myalgia, are consistent with findings associated with IBD and may therefore be very difficult to assign to a particular etiology. When such a reaction is suspected, samples for laboratory assessment will be obtained and stored. Tests will be performed if the diagnosis is confirmed and requested by the adjudication committee.

8.1.4 Outcome Categorization

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

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

8.1.5 Symptoms of the Disease Under Study

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

8.1.6 Clinical Laboratory and Other Safety Evaluations

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

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

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

8.1.7 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.2.3.

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

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

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

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

8.1.8 Abuse, Misuse, Overdose, and Medication Error

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

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

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

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

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

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

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

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

8.1.9 Unexpected Adverse Event

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

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

8.1.10 Suspected Unexpected Serious Adverse Reaction

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

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

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

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

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

8.2.2 Reporting Procedures

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

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

8.2.3 Serious Adverse Event Definition

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

- Results in death.
- Is life-threatening.
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event.
  Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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 Section 7.2.3 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

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

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

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

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

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

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

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

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities per Table 6 should be evaluated further to definitively determine the etiology of the abnormal laboratory values. The measurement(s) should be reconfirmed with another blood draw preferably within 48 to 72 hours of the initial finding of potential concern. Please refer to laboratory manual for further instructions.

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

Table 6 Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment-emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
Normal baseline ALT ≥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 the induction study (SHP647-305 or SHP647-306) 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 the induction study (SHP647-305 or SHP647-306) with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation.[c]
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 the induction study (SHP647-305 or SHP647-306) with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation.[c]

Table 6 Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment-emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
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 the induction study (SHP647-305 or SHP647-306) 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 to 3 days before the investigational product is interrupted.

[c] If HBV DNA positive antivirals would need to be started as soon as possible.

Source: Adapted from Chalasani and Regev, 2016.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol in the electronic case report form (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

Prior to the unblinding described in Section 6.2.4, data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, antibodies to investigational product, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, before unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

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

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

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

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

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

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, Data Monitoring Committee, and Hypersensitivity Adjudication Committee

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

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

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 DMC SAP.

An external hypersensitivity adjudication committee will be established to review data from subjects who experience a suspected Type I or Type III hypersensitivity reaction in order to confirm the nature and etiology of the reaction, to determine whether testing should be performed on stored blood samples, and to finalize recommendations of permanent discontinuation or rechallenge with investigational product. Further details regarding the adjudication committee can be found in the adjudication charter.

9.6 Sample Size Calculation and Power Considerations

The planned sample size for this maintenance study depends on enrollment from the induction studies (SHP647-305 and SHP647-306). Assuming that 50% of subjects receiving ontamalimab induction treatments and 40% of subjects receiving placebo induction treatment in Studies SHP647-305 and SHP647-306 will be eligible to move into this maintenance study based on Week 16 results in the induction studies, an estimated 983 subjects will be eligible to enter this maintenance study: 388 subjects from ontamalimab 25 mg induction treatment, 388 subjects from ontamalimab 75 mg induction treatment, and 207 subjects from placebo induction treatment. Expected rates at Week 16 are based on observed rates from a post hoc analysis of the A7281006 study and the literature (Sandborn et al., 2017).

Graphical methods are used to control the global family-wise Type-I error rate at the 0.05 level (2-sided) for the comparisons of the 2 ontamalimab treatment groups with the respective placebo group based on induction ontamalimab dose. Alpha is split equally at the 0.025 level (2-sided) for each of the pairwise treatment comparisons for the coprimary endpoints. Therefore, the power analysis and sample size estimation were calculated based on the chi-square test of proportions using nQuery Advisor® Version 7.0 (Statistical Solutions Ltd, Cork, Ireland) for an individual ontamalimab dose compared to placebo.

Power calculations are based on assuming a 0.025 (2-sided) significance level for each pairwise treatment comparison; 388 subjects previously treated with 25 mg ontamalimab in induction studies (1:1 allocation ratio: 194 subjects in the 25 mg ontamalimab treatment group versus 194 subjects in the placebo group) and 388 subjects previously treated with 75 mg ontamalimab in induction studies (1:1 allocation ratio: 194 subjects in the 75 mg ontamalimab treatment group versus 194 subjects in the placebo group) were planned. These numbers of subjects would yield

an approximately 92% power to detect individual pairwise treatment difference in the first coprimary efficacy endpoint, clinical remission at Week 52, of 17% (39% ontamalimab versus 22% placebo). Expected clinical remission rates by 2-item PRO at Week 52 are based on clinical remission by CDAI observed in the vedolizumab pivotal maintenance study (Sandborn et al., 2013). No adjustment for missing data is required in these sample size calculations as subjects with missing data for clinical remission by 2-item PRO at Week 52 are imputed as failures and the above rates account for these subjects.

With the 388 subjects previously treated for each ontamalimab dose in the induction studies as noted above, this number of subjects would yield an approximately 94% power to detect an individual pairwise treatment difference in the other coprimary efficacy endpoint, enhanced endoscopic response at Week 52, of 17% (35% ontamalimab versus 18% placebo). Expected enhanced endoscopic responses rates at Week 52 are based on enhanced endoscopic response rates derived from the literature (Feagan et al., 2017). No adjustment for missing data is required in these sample size calculations as subjects with missing data for enhanced endoscopic response at Week 52 are imputed as failures and the above rates account for these subjects.

The overall power for the coprimary endpoints will be approximately 87% assuming no correlation between the tests on the endpoints and approximately 89% power assuming a correlation of 0.4.

With the planned sample size of 388 subjects previously treated with 25 mg in induction studies and 388 subjects previously treated with 75 mg in induction studies, Table 7 provides the power for detecting a treatment difference between a ontamalimab treatment group and the placebo group for the key secondary endpoints.

Table 7 Power to Detect the Corresponding Treatment Effect for Key Secondary Endpoints

Key Secondary Endpoint at Week 52	Ontamalimab Premise	Placebo Premise	Power
Clinical remission by CDAI	39%	22%	0.92
Glucocorticoid-free clinical remission by 2-item PRO[a]	32%	16%	0.67
Clinical remission by abdominal pain ≤1 and stool frequency ≤3	42%	27%	0.80
Sustained clinical remission by 2-item PRO[b]	65%	45%	0.52
Sustained enhanced endoscopic response[c]	65%	40%	0.90
Clinical remission by 2-item PRO and enhanced endoscopic response	22%	10%	0.84
Complete endoscopic healing	10%	3%	0.71

CDAI=Crohn's Disease Activity Index; PRO=patient-reported outcome

[a] Based on an anticipated 53% of subjects who will be on corticosteroids at baseline of this study.

[b] Based on an anticipated 34% of subjects who will be in clinical remission by 2-item PRO at baseline of this study.

[c] Based on an anticipated 50% of subjects that will be have enhanced endoscopic response at baseline of this study.

With the early discontinuation of the study, the planned sample size of 983 subjects will not be attained, as the final number of subjects enrolled into this study is 40. Formal statistical testing will not be performed.

9.7 Study Population

The safety set will consist of all subjects who have received at least 1 dose of investigational product in the SHP647-307 study, regardless of treatment received during the induction studies (SHP647-305 and SHP647-306).

The full analysis set (FAS) will consist of all randomized subjects who have received at least 1 dose of investigational product in the SHP647-307 study, regardless of treatment received during the induction studies (SHP647-305 and SHP647-306).

9.8 Efficacy Analyses

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

9.8.1 Coprimary Efficacy Endpoints

The coprimary efficacy endpoints are:

- Clinical remission at the Week 52 visit as defined by the following: 2-item PRO subscores 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. The 7 most recent days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the endpoint will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the endpoint will be treated as missing.
- Enhanced endoscopic response at Week 52 as measured by a decrease in SES-CD of at least 50% from induction study (SHP647-305 or SHP647-306) baseline.

The number and percentage of subjects, and the estimate of the common treatment difference along with the corresponding unstratified Newcombe 95% CI for each primary endpoint, will be summarized by treatment group at Week 52. Subjects with missing data at Week 52 will be considered failures and counted as nonresponders. Due to the early discontinuation of the study before full enrollment and the limited sample size, formal statistical testing will not be performed.

Statistical Testing and Protection of the Type I Error

Due to the early discontinuation of the study before full enrollment and the limited sample size, formal statistical testing will not be performed, and therefore, multiplicity adjustment is not applicable.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- Clinical remission at the Week 52 visit as measured by CDAI <150.
- Glucocorticoid-free clinical remission at the Week 52 visit, among subjects using glucocorticoids at induction study baseline. Glucocorticoid-free clinical remission is defined as clinical remission by 2-item PRO (as defined for the coprimary endpoint; see Section 9.8.1) in addition to not requiring any treatment with glucocorticoids for at least 12 weeks prior to the Week 52 visit.
- Clinical remission at the Week 52 visit as defined by the following: CD daily e-diary subscores of average 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. The 7 most recent days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the endpoint will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the endpoint will be treated as missing.
- Sustained clinical remission, ie, in clinical remission at the SHP647-307 Week 52 visit, among subjects who were in clinical remission by 2-item PRO (as defined for the coprimary endpoint) at the time of baseline in Study SHP647-307.
- Sustained enhanced endoscopic response, ie, in enhanced endoscopic response at the SHP647-307 Week 52 visit, among subjects who showed enhanced endoscopic response (as defined for the coprimary endpoint) at the time of baseline in Study SHP647-307.
- Both clinical remission by 2-item PRO and enhanced endoscopic response at Week 52 (composite endpoint).
- Complete endoscopic healing at Week 52 defined as SES-CD=0-2.

The key secondary endpoints will be analyzed using the same approach as described for the coprimary endpoints. Subjects with missing key secondary endpoint data at the Week 52 visit will be considered failures and counted as nonresponders. Due to the early discontinuation of the study before full enrollment and the limited sample size, formal statistical testing will not be performed.

9.9 Safety Analyses

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

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

Treatment-emergent AEs are defined as AEs with start dates at the time of or following the first exposure to investigational product in the SHP647-307 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 leading to withdrawal, SAEs, and deaths will be similarly summarized or listed. Adverse events of special interest will be summarized by treatment group.

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

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

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

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) Guidelines E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

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

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

10.1.2 Indemnity/Liability and Insurance

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

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

10.1.3 Public Posting of Study Information

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

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

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

10.1.5 Study Suspension, Termination, and Completion

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

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

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

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

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

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

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

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

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

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

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

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

10.3.2 Institutional Review Board or Ethics Committee

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

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

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

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

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

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

10.4 Privacy and Confidentiality

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

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

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

approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

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

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

10.5 Study Results/Publication Policy

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

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

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

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

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

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

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APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Protocol Amendment 3	17 Sep 2020	Global
Protocol Amendment 2	22 Nov 2019	Global
Protocol Amendment 1	23 Aug 2018	Global
Original Protocol	15 Dec 2017	Global

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **22 Nov 2019**	**Global/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 complaints language with current Shire template.
Study Synopsis, Objectives, Key secondary Section 2.2.2.1, Key Secondary Objectives	Added that complete endoscopic healing will be measured by centrally read endoscopy.	For clarity.
Study Synopsis, Exclusion Criteria Section 4.2, Exclusion Criteria	Revised exclusion criterion #4 to add that lactating females are also excluded.	To clarify that lactating females are excluded.
Study Synopsis, Exclusion Criteria Section 4.2, Exclusion Criteria Section 4.4, Reproductive Potential	Added the term 'highly effective methods for female and medically appropriate methods for male study subjects' to exclusion criterion #4 in parentheses after the term 'appropriate contraception methods'. Also added after the terms 'appropriate form of contraception' and 'appropriate method of contraception' in Section 4.4.	To clarify what is meant by appropriate contraception methods.
Study Synopsis, Safety Analyses Section 9.9, Safety Analyses	Added that adverse events of special interest will be summarized by treatment group.	To include analysis of adverse events of special interest.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **22 Nov 2019**	**Global/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Table 1, Schedule of Assessments, footnote "d" Section 7.2.2.2, Final On-treatment Visits: Visit 14, Parts 1 and 2 (Week 52/Early Termination)	Revised to extend the window between Visit 14 (Part 1) and Visit 14 (Part 2) to 10 days, although 5 to 7 days is preferable. Added that Parts 1 and 2 of Visit 14 can be performed on the same day if central laboratory hematocrit result is not older than 3 weeks.	To allow sufficient time to obtain data from the central laboratory hematocrit test value in order to be available at Part 2 of the visit. To reduce the burden on the subjects.
Table 1, Schedule of Assessments, footnote "h"	Added new footnote stating that an unscheduled assessment for calculation of CDAI may be performed after Week 4 if it is clinically necessary; blood sampling for hematocrit may be necessary if there is no value available from last 3 weeks; and unscheduled assessment for CDAI must not be performed more than 4 times during the study.	To provide clarity about unscheduled assessment for calculation of CDAI in order to evaluate treatment failure.
Table 1, Schedule of Assessments, footnote "n" Section 7.3.2.4, Colonoscopy and Histology	Revised to clarify that colonoscopy preparation may be done on the same day as the colonoscopy procedure.	To reduce logistical burden around the colonoscopy requirements.
Table 1, Schedule of Assessments, footnote "p" Section 4.5.1, Subject Withdrawal Criteria	Added that colonoscopy is to be performed either within 2 weeks after the previous regular visit or the next regular visit if the CDAI based score criterion is fulfilled at an unscheduled visit.	To provide clarity around unscheduled colonoscopy with respect to CDAI score-based criterion.
Table 1, Schedule of Assessments, footnote "r"	Added new footnote stating that an unscheduled CDAI evaluation may be performed any time after Week 4 if it is clinically necessary; if an unscheduled CDAI evaluation is planned after an unscheduled/confirmatory colonoscopy, then diary data cannot be utilized for CDAI calculation earlier than 1 week after colonoscopy.	To provide clarity about unscheduled CDAI evaluation and use of diary data for CDAI calculation in order to evaluate treatment failure.
Table 1, Schedule of Assessments, footnote "s" Section 7.3.2.1, Patient-reported Outcome – Crohn's Disease Daily E-diary	Updated language to describe availability of e-diary throughout the study.	To provide additional clarity around the collection of e-diary data.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **22 Nov 2019**	**Global/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Table 1, Schedule of Assessments, footnote "x" Section 7.3.3.10, Monitoring for Type I and Type III Immune Reactions	Added new row and footnote to Table 1, new subsection to Section 7.3.3, and language to describe monitoring for hypersensitivity.	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 3.1, Study Design and Flow Chart	Added new figure (Figure 1, Overview of Ontamalimab Phase 3 Studies in Crohn's Disease).	Added for clarity.
Section 3.1.2, Rationale for Key Secondary Endpoints	Added that 'complete endoscopic healing' will be used as a key secondary point.	Added for clarity.
Section 4.4, Reproductive Potential	Updated text to reflect results of an enhanced pre-and postnatal development (ePPND) toxicity study in nonhuman primates.	To reflect preliminary results from an ePPND toxicity study of ontamalimab in nonhuman primates, which indicated that, at the dose levels tested (30 mg/kg 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 are reported in the ontamalimab Investigator's Brochure Edition 8.0.
Section 4.4.1, Contraceptive Methods for Female Study Subjects	Added text to specify that contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the clinical study.	To align with guidance document "Recommendations related to contraception and pregnancy testing in clinical trials" of Clinical Trial Facilitation Group.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **22 Nov 2019**	**Global/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 4.5.1, Subject Withdrawal Criteria	Added criteria of treatment failure as a reason of subject withdrawal.	To clarify that when treatment failure criteria are fulfilled the subject may be withdrawn from the maintenance study and either enter into the long-term safety follow-up study (Study SHP647-304), or the 16-week safety follow-up period.
	Changed the term 'protocol violations' to 'protocol deviations'.	For consistency with Section 4.5.2 (Reasons for Withdrawal).
	Removed the term '4 weeks apart' after the term '2 successive visits'.	To account for flexibility in the time between visits due to the existing visit windows.
Section 4.5.1, Subject Withdrawal Criteria Section 7.3.2.3, Crohn's Disease Activity Index	Updated to specify that the investigator may perform an unscheduled CDAI assessment based on the subject's reported symptoms.	To allow treatment failure to be assessed at unscheduled visits.
Section 7.2.2.3, Unscheduled Visit to Evaluate Potential Treatment Failure With CDAI Section 7.2.2.4, Unscheduled Visit to Evaluate Potential Treatment Failure With Colonoscopy	Added new subsections to Section 7.2.2 to describe unscheduled visits to evaluate potential treatment failure with CDAI (Section 7.2.2.3) and colonoscopy (Section 7.2.2.4).	To allow treatment failure to be assessed at unscheduled visits.
Section 7.3.2.1, Patient-reported Outcome – Crohn's Disease Daily E-diary	Changed the term 'very soft stools/liquid stools' to 'very soft stool/liquid stool frequency'.	For consistency with other sections.
	Updated text so that the method for calculating 2-item PRO at Visit 14 (Part 2) also applies to any regular visit (Visit 3 to 13) when a confirmatory colonoscopy is performed to evaluate treatment failure.	To allow evaluation of treatment failure.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **22 Nov 2019**	**Global/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 7.3.2.2, Simple Endoscopic Score for Crohn's Disease	Updated text so that the method for calculation of the SES-CD score at week 52/ET also applies to unscheduled colonoscopy. Added reference citation to Daperno et al., 2004. Added the term ileocolectomy along with partial colectomy.	To allow evaluation of treatment failure at unscheduled visits. To provide additional information regarding the Simple Endoscopic Score for Crohn's Disease (SES-CD). For consistency with other sections.
Section 7.3.2.3, Crohn's Disease Activity Index	Text updated in relation to calculation of CDAI scores at an unscheduled visit for treatment failure evaluation; at any of the regular visit days when a treatment failure confirmatory colonoscopy is performed, and at any of the visits when colonoscopy is performed for treatment failure evaluation.	To allow evaluation of treatment failure.
Section 7.3.2.4, Colonoscopy and Histology	Sentence updated to read as 'colonoscopy will be performed at Visit 14, Part 2 or as an unscheduled visit for confirming treatment failure.'	To allow colonoscopy for the assessment of treatment failure at unscheduled visit.
Section 7.3.3.1, Medical and Medication History Section 7.3.3.2, Physical Examination (Including Weight) Section 7.3.3.6, Clinical Laboratory Evaluations	Updated to specify that diarrhea medications, physical examination, weight, and hematocrit may be determined at unscheduled time points for calculation of CDAI.	To allow treatment failure to be assessed between scheduled visits as well.
Table 3, Quarterly Neurological Assessments	Column heading changed from 'targeted neurological history' to 'interim neurologic history and targeted neurologic examination'.	To align with language of newly proposed electronic case report form.
Section 7.3.3.6, Clinical Laboratory Evaluations Table 4, Volume of Blood to Be Drawn From Each Subject	Added that unscheduled CDAI evaluation and related blood sampling for hematocrit cannot be performed more than 4 times during the study.	To clarify the maximum number of unscheduled CDAI evaluations and related blood samples for hematocrit for treatment failure assessment.
Section 7.3.3.6, Clinical Laboratory Evaluations Section 7.3.3.11, Evaluation of Increased Gastrointestinal Symptoms	Added new subsection (Section 7.3.3.11) to Section 7.3.3 to describe evaluation of increased gastrointestinal symptoms.	To clarify that infectious etiology must be evaluated when a subject experience an increase in gastrointestinal symptoms.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **22 Nov 2019**	**Global/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 7.3.5, Volume of Blood to be Drawn from Each Subject	Decreased serum chemistry sample volume from 6 mL to 4 mL. [redacted]	To correct the sample volume needed for the serum chemistry test and [redacted]
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 time frame 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 Statistical Power	Updated power considerations for complete endoscopic healing.	To accurately reflect the power considerations for complete endoscopic healing.
Section 9.8.3, Exploratory [redacted] Endpoints	[redacted]	[redacted]

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **22 Nov 2019**	**Global/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 10.1.5, Study Suspension, Termination, and Completion	Added text to specify that designated meeting of the DMC will take place after completion of the induction studies for the review of the safety and efficacy results of the induction studies for the recommendation to the sponsor whether to continue or discontinue with the maintenance study or long-term study. Clarified that the end-of-study declaration may be made by the sponsor or alternatively its representatives.	To provide clarity around continue or discontinue with the maintenance study or long-term study after the completion of the induction studies. To improve clarity.
Appendix 2, Scales and Assessments	Updated the example SES-CD worksheet.	To provide the scoring values for the SES-CD endoscopic variables and clarify how the scores are recorded for each ileocolonic segment.
Throughout protocol	Minor changes to wording.	To improve clarity, consistency, and remove redundancy of text.

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1**	**Amendment Date** **17 Aug 2018**	**Global/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Emergency Contact Information	Updated the global fax number for serious adverse event reporting.	To provide updated emergency contact information.
Study Synopsis, Inclusion and exclusion criteria Section 4.1, Inclusion Criteria	Updated inclusion criterion #3b (ii) to indicate that subjects must have a decrease of at least 100 points in CDAI score (CDAI-100) from induction study baseline.	To align with what has been used in more recent clinical trials for evaluating response.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #7 to indicate that subjects who developed enterovesical or enterovaginal fistulae during the induction study (SHP647-305 or SHP647-306) would be excluded.	To specify the exclusion of subjects who developed such fistulae during the induction study.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #12 to indicate that subjects meeting the following lab criteria would be excluded: • ALT or AST ≥3×ULN • Total bilirubin level ≥1.5 times the ULN (>2 times the ULN if subject has a known documented history of Gilbert's syndrome) Added note to exclusion criterion #12 to specify that, if platelet count is <150,000 cells/mm^3, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.	To align criteria with FDA guidelines.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #5 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, Methodology Section 3.1, Study Design and Flow Chart Figure 2, Study Design Flow Chart	Added a statement to note that subjects who are withdrawn early from the study due to fulfilling the criteria for treatment failure also may be eligible to enter the long-term safety (LTS) study, SHP647-304, and to provide rationale for this.	To clarify the subject population that may be eligible to enter the LTS study and provide rationale for offering the opportunity for treatment in LTS to subjects who meet the criteria for "treatment failure" in this study.

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1**	**Amendment Date** **17 Aug 2018**	**Global/Country/Site Specific** **Global**
Study Synopsis, Key Secondary Endpoints Section 3.1.2, Rationale for Key Secondary Efficacy Endpoints Section 9.8.2.1, Key Secondary Efficacy Endpoints	Updated the second key secondary efficacy endpoint definition to include the stipulated window for not requiring any treatment with glucocorticoids (at least 12 weeks prior to the Week 52 visit).	To clarify the endpoint definition for glucocorticoid-free clinical remission (based on ECCO and EMA guidances).
Section 1.3, Benefit and Risk Assessment	Added new section describing risks and benefits of ontamalimab treatment.	To provide updated risk and benefit information for ontamalimab.
Section 4.5.1, Subject Withdrawal Criteria Schedule of Assessments, footnote "n"	Added a note to specify that if an unscheduled colonoscopy is needed for treatment failure evaluation, it is strongly encouraged that the colonoscopy is performed within 2 weeks after the visit day when either the PRO-based or the CDAI score-based criterion for treatment failure was fulfilled.	To specify the recommended time frame within which the unscheduled colonoscopy should be performed, if needed as part of treatment failure evaluation.
Section 4.5.1, Subject Withdrawal Criteria	Added pregnancy to the list of reasons a subject may be withdrawn from study treatment.	For clarity and consistency with language in Section 8.1.6.
Section 5.2.1, Permitted Treatment	Added language to specify that any antidiarrheal opiate drugs must be taken at stable doses for the duration of the study unless dose reduction or discontinuation is required due to clinical improvement or adverse event, and that escalation of the dose after dose reduction, or re-initiation after drug discontinuation, is not allowed.	To clarify that concomitant antidiarrheal opiate drugs are permitted if taken at stable doses for the duration of the study, with dose reduction or discontinuation allowed only if required due to clinical improvement or adverse event.
Section 6.2.3, Dosing	Add language to specify that a total of up to 13 doses of investigational product (IP) will be administered in this study.	To clarify the total number of doses of IP to be administered in this study.
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 7.2.3.6, Clinical Laboratory Evaluations	Added language to state that diagnosis of *C. difficile* infection should be made using the central laboratory and to note that guidance regarding diagnostic algorithms, if the central laboratory is not available, is provided in Appendix 4.	To provide guidance regarding laboratory testing for *C. difficile* infection.

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1**	**Amendment Date** **17 Aug 2018**	**Global/Country/Site Specific** **Global**
Section 7.2.3.5, Vital Signs	Removed language that specified measuring body temperature orally with a digital thermometer or by using tympanic temperature.	To clarify how body temperature should be obtained.
Section 8.2.8, Safety Monitoring Rules	Added new section and table describing safety monitoring and stopping criteria for elevated hepatic blood tests.	To provide appropriate guidance on patients who have been enrolled with elevated liver function test values or who experience and increase in liver function test(s) during the study.
Section 10, Sponsor's and Investigator's Responsibilities	Added a statement that compliance with the noted regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.	To clarify that the study is conducted in accordance with the ethical principles in the Declaration of Helsinki.
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 appropriate guidance for diagnosis and treatment of *C. difficile* infection.
Throughout protocol	Minor changes to wording.	To improve clarity, consistency, and remove redundancy of text.

APPENDIX 2 SCALES AND ASSESSMENTS

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

- Simple Endoscopic Score for Crohn's Disease
- Crohn's Disease Activity Index
- Colonic Global Histologic Disease Score and Ileal Global Histologic Disease Score
- Patient-reported Outcome – Crohn's Disease Daily E-diary

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 (dd mmm yyyy)

Definitions of Simple Endoscopic Score for Crohn's Disease

Score / Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (∅ 0.1 to 0.5 cm)	Large ulcers (∅ 0.5 to 2 cm)	Very large ulcers (∅ >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

	Ileum	Right colon	Transverse colon	Left colon	Rectum	**Total**
Presence and size of ulcers (0–3)						
Extent of ulcerated surface (0–3)						
Extent of affected surface (0–3)						
Presence and type of narrowing(s) (0–3)						
					SES-CD =	

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: This variable covers taking medication for symptomatic relief from diarrhea, eg, bulking agents, opiates 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: This variable 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 -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 refered to as being "steroid dependent")
- 150-220 points: Mild to moderate active Crohn's disease
- 221-450 points: Moderate to severe active Crohn's disease
- >451 points: Severely active to fulminant disease.

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

Colonic Global Histologic Disease Score (CGHAS) and Ileal Global Histologic Disease Score (IGHAS)

Scoring system for histological abnormalities in Crohn's disease mucosal biopsy specimens

Epithelial damage	0, Normal 1, Focal pathology 2, Extensive pathology
Architectural changes	0, Normal 1, Moderately disturbed (<50%) 2, Severely disturbed (>50%)
Infiltration of mononuclear cells in the lamina propria	0, Normal 1, Moderate increase 2, Severe increase
Infiltration of polymorphonuclear cells in the lamina propria	0, Normal 1, Moderate increase 2, Severe increase
Polymorphonuclear cells in epithelium	1, In surface epithelium 2, Cryptitis 3, Crypt abscess
Presence of erosion and/or ulcers	0, No 1, Yes
Presence of granuloma	0, No 1, Yes
No. of biopsy specimens affected*	0, None (0 of 6) 1, ≤33% (1 or 2 of 6) 2, 33%–66% (3 or 4 of 6) 3, >66% (5 or 6 of 6)

Note: Each topic is scored independently. Moderate increase is defined as up to twice the number of cells that can normally be expected; severe increase is defined as more than twice the normal number of cells.
* The score for "No. of biopsy specimens affected" will be adapted to 10 biopsies; details will be provided in the statistical analysis plan.
Reference: D'Haens et al., 1998

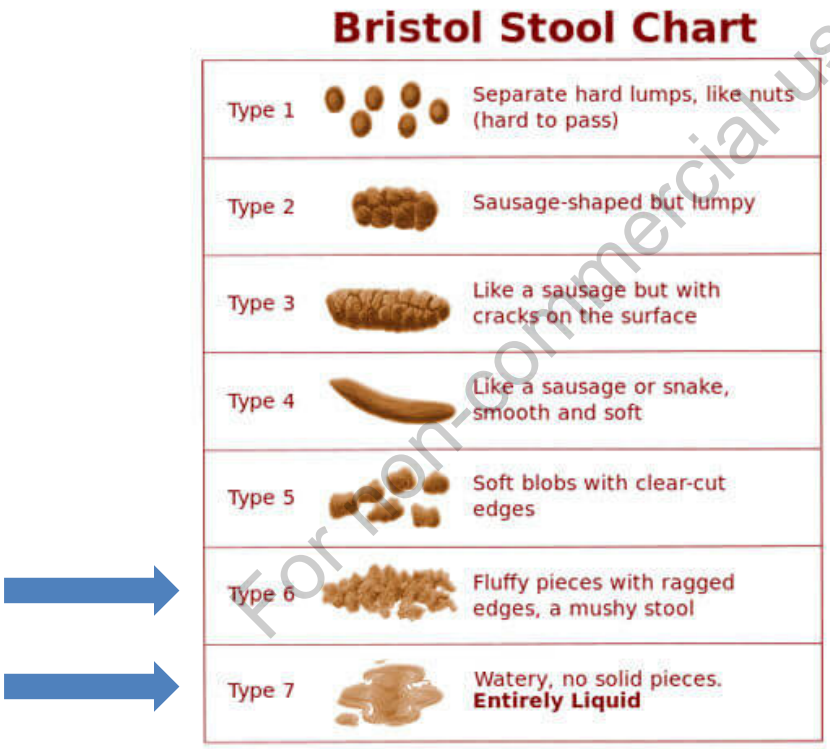
Patient-reported Outcomes – Crohn's Disease Daily E-diary Version 1

1. Please rate your worst abdominal pain over the past 24 hours.
   0 1 2 3 4 5 6 7 8 9 10

   No pain Worst imaginable pain

2. Please indicate how often you had a bowel movement over the past 24 hours. A bowel movement is defined as a trip to the toilet and passing stool (liquid, soft or solid), passing blood only, passing blood and mucus, or passing mucus only.
   Enter number of bowel movements passed: _____

The next question asks about the number of liquid or very soft stools you had in the past 24 hours. Liquid or very soft stools are defined as Type 6 and Type 7 in the chart below.



3. You indicated you had X bowel movements in the past 24 hours. Of these, how many were liquid or very soft?
   Enter number of liquid or very soft bowel movements: _____

4. You indicated you had X bowel movements in the past 24 hours. Of these, how many had blood, either in the stool, the toilet bowel, or on the toilet paper?
   Enter number of bowel movements with blood: _____

5. You indicated you had X bowel movements in the past 24 hours. How many of these involved urgency (having to suddenly rush to the toilet to make it on time)?
   Enter number of bowel movements with urgency: _____

6. Please rate your worst feeling of nausea (feeling sick to your stomach or like you might throw up) over the past 24 hours.
   None

   Mild

   Moderate

   Severe

7. How many vomiting episodes did you have in the past 24 hours? An episode includes one or multiple heaves (including dry heaves) in quick succession followed by a break in vomiting.
   Enter number of vomiting episodes: _____

8. How many bowel incontinence episodes (losing control of your bowels before reaching the toilet) did you have in the past 24 hours?
   Enter number of bowel incontinence episodes: _____

9. Please rate your abdominal pain over the past 24 hours.
   None

   Mild

   Moderate

   Severe

10. How would you rate your general well-being over the past 24 hours?
    Generally well

    Slightly below par

    Poor

    Very poor

    Terrible

APPENDIX 3 GLUCOCORTICOID EQUIVALENT DOSES

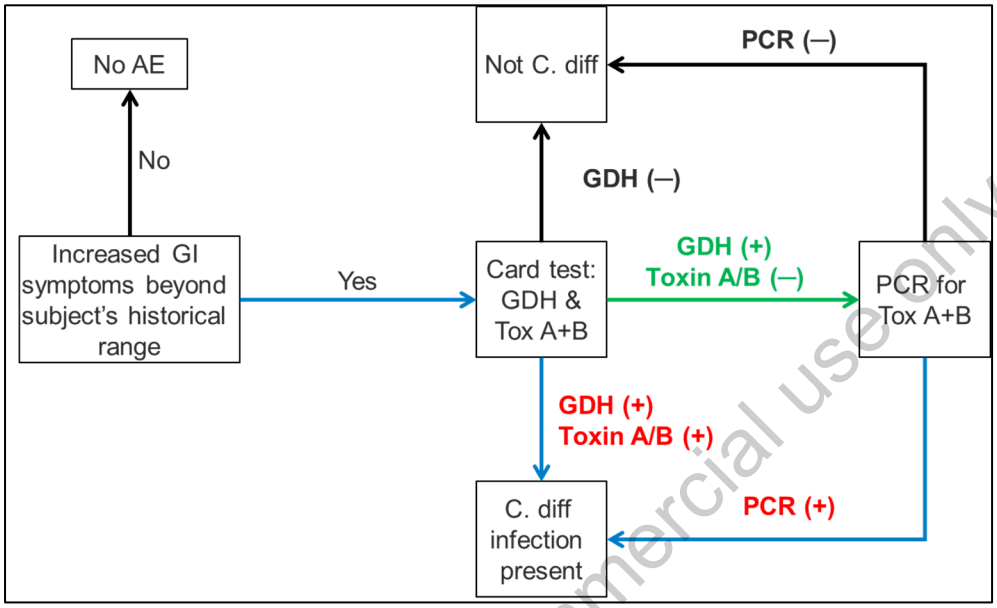
Glucocorticoid	Equivalent Dose (mg)
***Short Acting*:**	
Cortisone	25
Hydrocortisone	20
***Intermediate Acting*:**	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
***Long Acting*:**	
Betamethasone	0.6
Dexamethasone	0.75

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 polymerase chain reaction [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

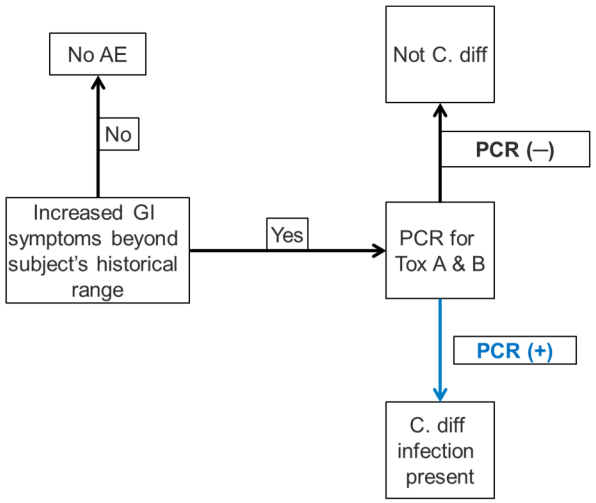


Figure A3 Alternative 2 for *C. difficile* Testing Using Local Laboratory When No Card Test is Available

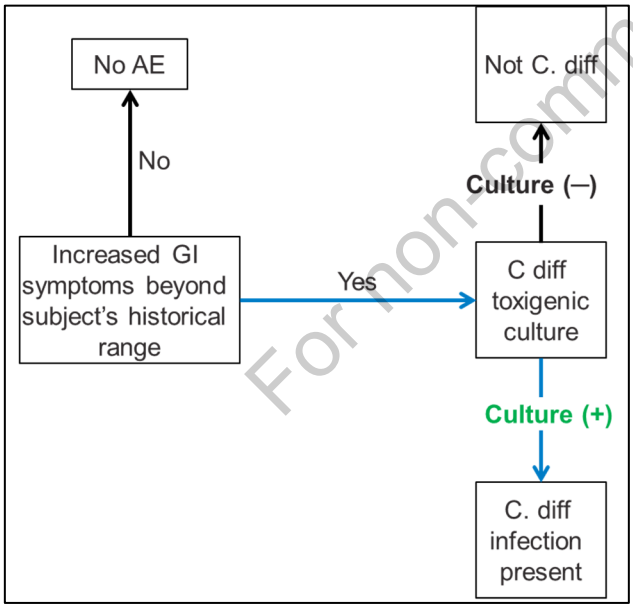
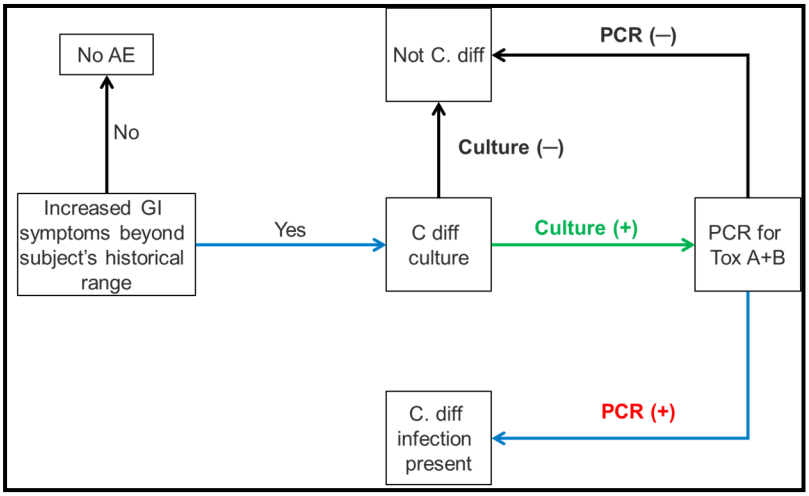


Figure A4 Alternative 3 for *C. difficile* Testing Using Local Laboratory When No Alere Quick Chek Card Test is Available



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 Infectious Diseases Society of America recommendations for *C. difficile* infection (McDonald et al., 2018) or the recent expert review on *C. difficile* infection in IBD (Khanna et al., 2017) should be consulted.

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

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

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