STATISTICAL ANALYSIS PLAN

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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

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Version 1.1: 13 Jan 2021

STATISTICAL ANALYSIS PLAN

SHP647
PHASE 3

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)

PROTOCOL IDENTIFIER: SHP647-307

Study Sponsor(s): Shire Human Genetic Therapies, Inc. ("Shire"), a wholly owned subsidiary of Takeda Pharmaceutical Company
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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	15 Oct 2020	Final
1.1	13 Jan 2021	Start and End dates of Tables 7,8,9 changed to use Study Day midpoints

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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
BLQ	below the limit of quantification
BSFS	Bristol Stool Form Scale
CI	confidence interval
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
[redacted]	[redacted]
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
EOT	end of treatment
FAS	full analysis set
HEOR	Health Economics and Outcomes Research
IRT	interactive response technology
IP	investigational product
LTS	long-term safety extension
NAb	neutralizing antibody
NRS	numerical rating scale
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MNT	maintenance
PCI	potentially clinically important
[redacted]	[redacted]
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous/subcutaneously
SES-CD	Simple Endoscopic Score for Crohn's Disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety, as well as descriptive summaries of [redacted] data and Health Economics and Outcomes Research (HEOR) data, as described in Protocol Amendment 3 dated 17 Sep 2020 (original protocol dated 15 Dec 2017). Specifications for tables, figures, and listings are contained in a separate document. The analysis plans for [redacted] and HEOR patient-reported outcome (PRO) validation, if performed, are prepared separately.

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

2. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

2.1 Objectives

2.1.1 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 PRO (abdominal pain severity and very soft stool/liquid stool frequency)
- Enhanced endoscopic response based on centrally read colonoscopy.

2.1.2 Secondary Objectives

The key secondary objectives are as follows:

- To evaluate the efficacy of ontamalimab as maintenance treatment on clinical remission as measured by Crohn's Disease 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.

2.2 Estimands

The primary and key secondary estimands are described in Table 1.

Table 1: List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable**	**C: Strategy for Addressing Intercurrent Event**	**D: Population-level Summary**
Primary	1st coprimary estimand is the effect of ontamalimab compared to placebo at Week 52 in impact on clinical remission.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Clinical remission at the Week 52 visit, defined by 2-item PRO without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects in clinical remission at the Week 52 visit between each active treatment group (ontamalimab 25 mg, ontamalimab 75 mg) and placebo
Primary	2nd coprimary estimand is the effect of ontamalimab compared to placebo at Week 52 in impact on enhanced endoscopic response.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Enhanced endoscopic response at the Week 52 visit, defined by a decrease in SES-CD of at least 50% from induction study (SHP647-305 or SHP647-306) baseline without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with enhanced endoscopic response at the Week 52 visit between each active treatment group (ontamalimab 25 mg, ontamalimab 75 mg) and placebo

Table 1: List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable**	**C: Strategy for Addressing Intercurrent Event**	**D: Population-level Summary**
Key Secondary	1st key secondary estimand is the effect of ontamalimab compared to placebo at Week 52 in impact on clinical remission as measured by CDAI.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Clinical remission at the Week 52 visit, defined by CDAI score of <150 without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects in clinical remission at the Week 52 visit between each active treatment group (ontamalimab 25 mg, ontamalimab 75 mg) and placebo
Key Secondary	2nd key secondary estimand is the effect of ontamalimab compared to placebo at Week 52 in impact on glucocorticoid-free clinical remission.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Glucocorticoid-free clinical remission at the Week 52 visit, among subjects using glucocorticoids at induction study baseline, defined by 2-item PRO in addition to not requiring any treatment with glucocorticoids for at least 12 weeks prior to the Week 52 visit without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with glucocorticoid-free clinical remission at the Week 52 visit between each active treatment group (ontamalimab 25 mg, ontamalimab 75 mg) and placebo

Table 1: List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable**	**C: Strategy for Addressing Intercurrent Event**	**D: Population-level Summary**
Key Secondary	3rd key secondary estimand is the effect of ontamalimab compared to placebo at Week 52 in impact on clinical remission as defined by CD daily e-diary subscores.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Clinical remission at the Week 52 visit, defined by CD daily electronic diary subscores of average daily abdominal pain ≤1 (based on the 4-point scale) and average daily stool frequency ≤3 of type 6/7 over the 7 most recent days without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with clinical remission at the Week 52 visit between each active treatment group (ontamalimab 25 mg, ontamalimab 75 mg) and placebo
Key Secondary	4th key secondary estimand is the effect of ontamalimab compared to placebo at Week 52 in impact on sustained clinical remission.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Sustained clinical remission at the Week 52 visit, defined by in clinical remission by 2-item PRO at both Week 52 and baseline without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with sustained clinical remission at the Week 52 visit between each active treatment group (ontamalimab 25 mg, ontamalimab 75 mg) and placebo

Table 1: List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable**	**C: Strategy for Addressing Intercurrent Event**	**D: Population-level Summary**
Key Secondary	5th key secondary estimand is the effect of ontamalimab compared to placebo at Week 52 in impact on sustained enhanced endoscopic response.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Sustained enhanced endoscopic response at the Week 52 visit, defined by a decrease in SES-CD of at least 50% from induction study (SHP647-305 or SHP647-306) baseline, at both Week 52 and baseline of the SHP647-307 study without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with sustained enhanced endoscopic response at the Week 52 visit between each active treatment group (ontamalimab 25 mg, ontamalimab 75 mg) and placebo
Key Secondary	6th key secondary estimand is the effect of ontamalimab compared to placebo at Week 52 in impact on clinical remission with enhanced endoscopic response.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Clinical response at the Week 52 visit, defined as meeting both clinical remission by 2-item PRO and enhanced endoscopic response, defined by a decrease in SES-CD of at least 50% from induction study (SHP647-305 or SHP647-306)	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with clinical remission with endoscopic response at the Week 52 visit between each active treatment group (ontamalimab 25 mg, ontamalimab

Table 1: List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable**	**C: Strategy for Addressing Intercurrent Event**	**D: Population-level Summary**
			baseline, without discontinuation		75 mg) and placebo
Key Secondary	7th key secondary estimand is the effect of ontamalimab compared to placebo at Week 52 in impact on complete endoscopic healing.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Complete endoscopic healing at the Week 52 visit, defined as SES-CD=0-2 without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with complete endoscopic healing at the Week 52 visit between each active treatment group (ontamalimab 25 mg, ontamalimab 75 mg) and placebo

2.3 Endpoints

2.3.1 Coprimary Endpoints

The coprimary efficacy endpoints are as follows:

- 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 numerical rating scale [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 Bristol Stool Form Scale (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.

2.3.2 Key Secondary 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) 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.

3. STUDY DESIGN

3.1 General Description

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.

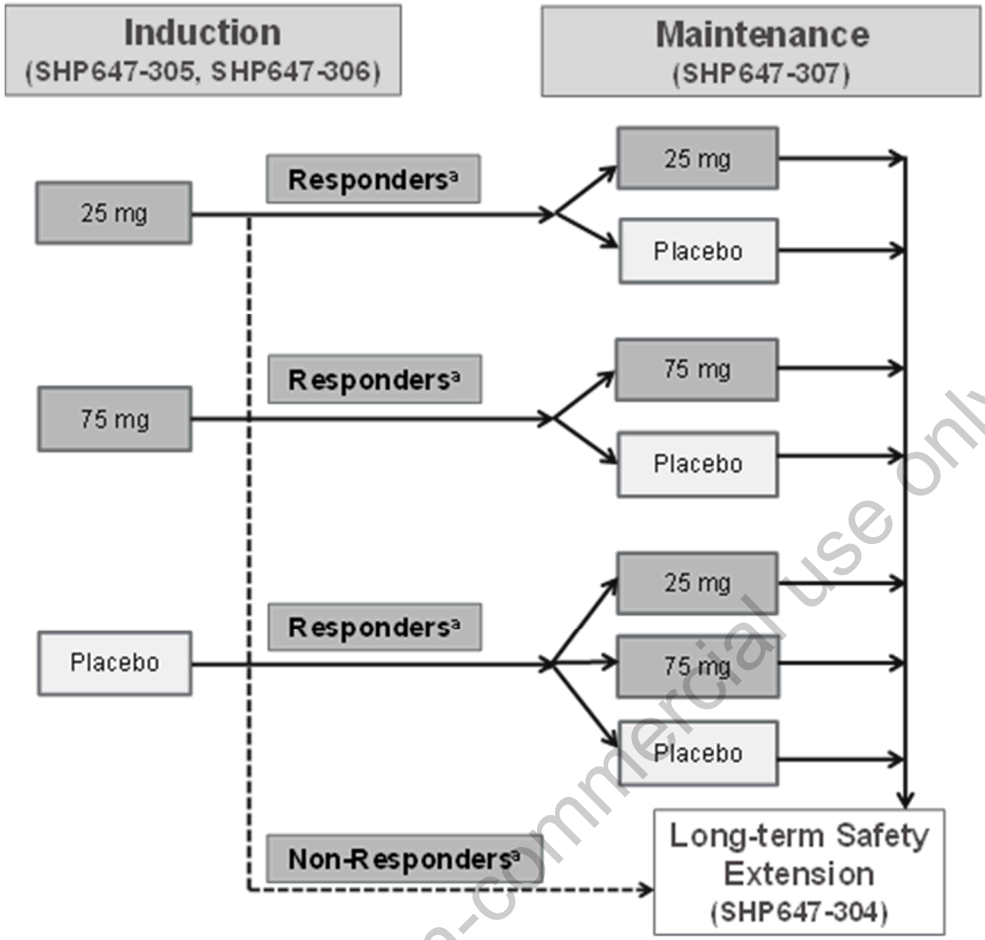
Subjects will be stratified according to glucocorticoid use at Study SHP647-307 baseline, the subject's status of prior anti-TNF treatment (naïve or experienced), and whether or not the subject achieved clinical remission by 2-item PRO or enhanced endoscopic response in the induction study.

Subjects enrolled in this study (SHP647-307) will receive double-blind maintenance treatment in the form of subcutaneous (SC) injections, using a prefilled syringe, every 4 weeks for 52 weeks. Subjects will undergo efficacy and safety assessments, as detailed in Table 13. Prior to Amendment 3, [redacted], [redacted], and health outcome assessments were also collected, as detailed in Table 12.

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 a different dose of ontamalimab if during the course of the SHP647-304 study, 1 of those doses (25 mg or 75 mg) is determined to be more efficacious based on emergent data from the UC induction studies. However, if there is no clinical sign of efficacy of either of the doses in comparison to placebo in the UC clinical studies, 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 SHP647 Phase 3 Studies in Crohn's Disease



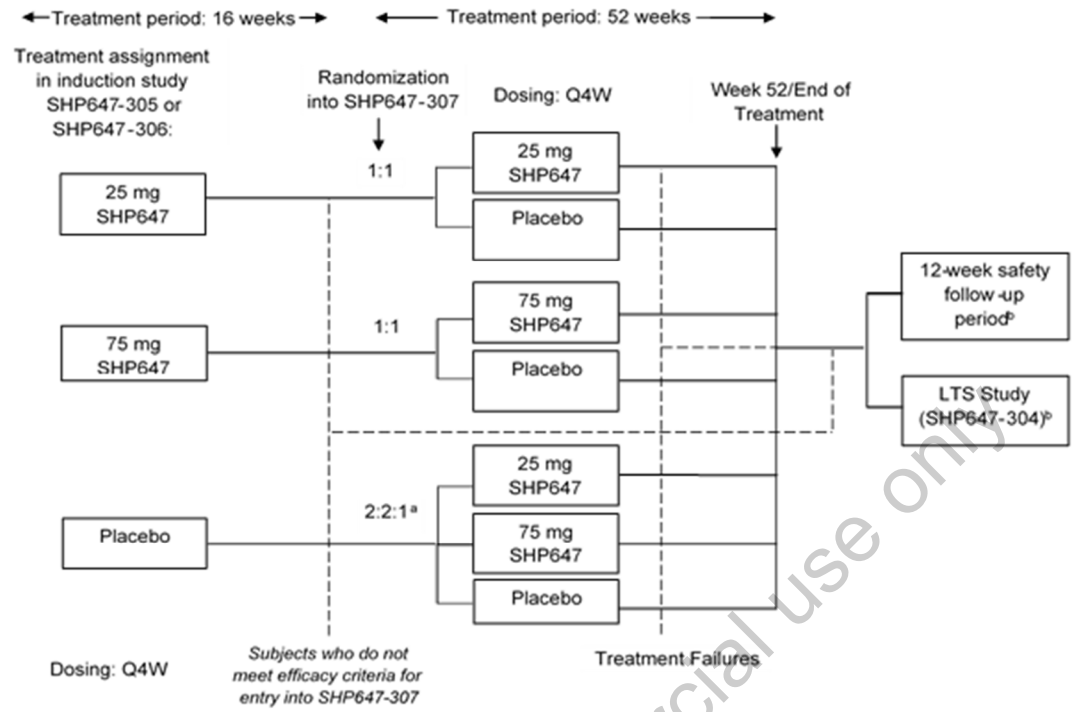
BSFS=Bristol Stool Form Scale; CDAI=Crohn's Disease Activity Index; NRS=numerical rating scale; PRO=patient-reported outcome; SES-CD=Simple Endoscopic Score for Crohn's Disease

[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-70) 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 Chat



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.

3.2 Randomization

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 (IP) 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 IP packing identification number may not be assigned to more than 1 subject.

3.3 Blinding

This is a double-blind, placebo-controlled study. All investigational and reference product (ontamalimab 25 mg, ontamalimab 75 mg, or placebo) will appear identical to protect the study blind.

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

be made available to quality assurance representatives for the purposes of conducting independent drug audits.

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 the early termination of the ontamalimab program, the sponsor is providing an option for subjects who had responded to active treatment (in this maintenance study or in the induction study) to continue to receive ontamalimab in the LTS study SHP647-304. As this eligibility criterion for 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 early termination 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 early termination 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.

3.4 Sample Size 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 (FWER) 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 .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 .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 response 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 ontamalimab in induction studies and 388 subjects previously treated with 75 mg ontamalimab in induction studies, Table 2 provides the power for detecting a treatment difference between an ontamalimab treatment group and the placebo group for the key secondary endpoints.

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.

Table 2: 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 who will have enhanced endoscopic response at baseline of this study.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed an informed consent document for the SHP647-307 study, regardless of treatment received during the induction studies (SHP647-305 and SHP647-306).

4.2 Randomized Set

The Randomized Set will consist of all subjects in the Screened Set for whom a SHP647-307 randomization number has been assigned, regardless of treatment received during the induction studies (SHP647-305 and SHP647-306).

4.3 Safety Set

The Safety Set will consist of all subjects who have received at least 1 dose of IP in the SHP647-307 study, regardless of treatment received during the induction studies (SHP647-305 and SHP647-306). Analysis will be performed according to the treatment regimen actually received regardless of the randomized treatment regimen.

4.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who have received at least 1 dose of IP in the SHP647-307 study, regardless of treatment received during the induction studies (SHP647-305 and SHP647-306). Analyses will be performed according to the randomized treatment regimen regardless of the treatment regimen actually received.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

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

The number and percentage of subjects who completed and prematurely discontinued during the treatment and follow-up periods will be presented for each treatment group, ontamalimab all doses, and overall for the Safety Set. Reasons for premature discontinuation from the treatment and follow-up periods as recorded on the termination page of the electronic case report form (eCRF) will be summarized (number and percentage) by treatment group, ontamalimab all doses, and overall for the Safety Set. The number and percentage of subjects who continued to the follow-up period and who continued to the SHP647-304 study will be presented for each treatment group, ontamalimab all doses, and overall for the Safety Set.

The number and percentage of subjects who completed and prematurely discontinued the study will be presented for each treatment group, ontamalimab all doses, and overall for the Safety Set. Subjects who complete 52 weeks of treatment and roll over to the SHP647-304 study or enter and complete the safety follow-up period will be considered to have completed the study. Reasons for premature discontinuation from the study are derived from reasons for premature discontinuation from the treatment and follow-up periods. For subjects who discontinued from treatment, the reasons for discontinuation from treatment will be presented regardless of the status of the safety follow-up period. For subjects who completed the 52 weeks of treatment and discontinued from the safety follow-up period, the reasons for discontinuation from the safety follow-up period will be presented. All subjects who prematurely discontinued during the treatment period, follow-up period, and study will be listed with their primary reason for discontinuation and duration of exposure for the Safety Set.

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

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for each treatment group, ontamalimab all doses, and overall for the Safety Set and FAS. All demographic and baseline characteristics will be listed for the Safety Set.

Subject's age is from the induction study (SHP647-305 or SHP647-306), which is calculated as the difference between the date of birth and the date of informed consent in the induction study. If day of birth is missing, then the day will be imputed as 1; if both the day and month of birth are missing, then the day will be imputed as 1 and the month will be imputed as 1 (January). The following demographic characteristics will be summarized in the following order in the tables: age, age category (<18, 18 to <65, and ≥65; <35 and ≥35), sex (Male, Female), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown), region (North America, Western Europe, Eastern Europe, Asia [Japan/South Korea], ROW [Africa/Australia/Latin America/Middle East]) (refer to Appendix 16.3), race (American Indian or Alaska Native, Asian [Japanese, Korean, Other], Black or African American, White, Native Hawaiian or Other Pacific Islander, and Other), Japanese Ancestry (Currently living in Japan, Born in Japan and currently living outside of Japan for less than 5 years, and Other), and Korean Ancestry (Currently living in Korea, Born in Korea and currently living outside of Korea for less than 5 years, and Other).

Baseline is defined as the last assessment prior to the first administration of the IP in the induction study (SHP647-305 or SHP647-306) unless otherwise specified. Maintenance (MNT; SHP647-307) baseline is defined as the value for the assessment collected at the Week 16 visit of the induction study. The following baseline characteristics will be summarized:

- Weight,
- Height,
- Body Mass Index (BMI),
- CD Disease Duration (years) and CD Disease Duration Category (<1 year, ≥1 to <3 years, ≥3 to <7 years, and ≥7 years),
  Note: CD disease duration is defined as the number of years from the date of CD diagnosis to the date of informed consent in the induction study (SHP647-305 or SHP647-306).

- CD Disease Location (Small Intestine alone, Colon and/or Rectum alone, Ileo-colitis, Perianal, and Other),
- Bowel Resection Performed Previously (Yes, No, and Unknown),
- Average Worst Abdominal Pain Score Based on 11-point Scale (0 to 10) at Baseline,
- Average Worst Abdominal Pain Score Based on 11-point Scale (0 to 10) at MNT Baseline,
- Average Abdominal Pain Score Based on 4-point Scale (0 to 3) at Baseline,
- Average Abdominal Pain Score Based on 4-point Scale (0 to 3) at MNT Baseline,
- Average Very Soft Stool/Liquid Stool Frequency at Baseline,
- Average Very Soft Stool/Liquid Stool Frequency at MNT Baseline,
- CDAI Score at Baseline,
- CDAI Score at MNT Baseline,
- SES-CD at Baseline (≥17 and <17) (actual status),
- SES-CD at MNT Baseline (≥17 and <17).

The following CD medication history/use will be summarized where "randomization status" refers to SHP647-307 randomization stratification and "actual status" refers to the actual information collected in the CRF at MNT baseline:

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

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

The following outcomes from the induction study will be summarized:

- Actual Treatment Received in Induction Study (Placebo, Ontamalimab 25 mg, Ontamalimab 75 mg),
- Remission Status at MNT Baseline (both randomized and actual status) (Yes, No),
- Clinical Response at MNT Baseline (Yes, No),
- Clinical Remission at MNT Baseline (Yes, No),
- Endoscopic Response at MNT Baseline (Yes, No),
- Clinical Remission by CDAI Score at MNT Baseline (Yes, No),
- Enhanced Endoscopic Response at MNT Baseline (Yes, No),
- Complete Endoscopic Healing at MNT Baseline (Yes, No).

5.3 Smoking History

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

5.4 Medical History

Medical history will be collected at the Screening Visit (Visit 1) in the induction study (SHP647-305 or SHP647-306) and baseline visit in the SHP647-307 study and will be listed for the Safety Set.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 2016 or newer. The induction study medical history will be summarized by the number and percentage of subjects in each treatment group and ontamalimab all doses, system organ class (SOC), and preferred term.

Cardiovascular history will be collected at the Screening Visit (Visit 1) in the induction study (SHP647-305 or SHP647-306) and will be summarized by treatment group and ontamalimab all doses for the Safety Set. Cardiovascular history will be listed for the Safety Set.

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

5.5 Prior Medications

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

Prior medication is defined as any medication with the start date prior to the date of the first dose of IP in the SHP647-307 study, and which is ongoing at the date of the baseline visit in SHP647-307 study. Incomplete medication dates will be imputed as described in Section 12.5.3.

All prior medications will be listed for the Safety Set.

5.6 Concomitant Therapies, Procedures, and Medications

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

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of IP in the SHP647-307 study and continuing after the first dose of IP in the SHP647-307 study, or with a start date between the dates of the first dose of IP in the SHP647-307 study and end of treatment (EOT) date, inclusive. Medication that starts after the first dose of SHP647-304 IP will be collected in SHP647-304 database and will not be considered as concomitant medication in SHP647-307. Incomplete medication dates will be imputed as described in Section 12.5.3. Any medication with a start date between the dates of the first dose of IP and EOT date in SHP647-307, inclusive, or with a start date after the EOT date (post-treatment) in SHP647-307 will be considered a post-treatment concomitant medication.

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

All concomitant medications, medical/surgical procedures, and therapies occurring during the SHP647-307 study will be listed for the Safety Set.

5.7 Exposure to Investigational Product

Investigational product (ontamalimab or placebo) will be administered SC every 4 weeks (from Weeks 0 to Week 48). Exposure to IP in the SHP647-307 study will be summarized by presenting the number of subjects who had 1 injection, 2 injections, 3 injections, etc. Number of injections received will be summarized by treatment group and ontamalimab all doses. The administration records by visit will be listed for the Safety Set.

Exposure to IP in the SHP647-307 study for the Safety Set will be summarized in terms of treatment duration, which is calculated as the number of days from the date of first dose of IP taken in the SHP647-307 study to the date of the last dose of IP taken in the SHP647-307 study + 29 days. Subject years of exposure is calculated as (Date of last dose of IP in the SHP647-307 study – date of first dose of IP in the SHP647-307 study + 29)/365.25. Total subject years of exposure is calculated by summing the subject years of exposure for all subjects within each column.

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented to describe the exposure to IP in each treatment group and ontamalimab all doses.

5.8 Measurements of Treatment Compliance

Compliance for the treatment period is defined as the total number of SC injections administered from the start of treatment in the SHP647-307 study until EOT in the SHP647-307 study divided by the number of injections expected to be taken during that time period, times 100. Percentage compliance will be summarized by treatment group and ontamalimab all doses. Compliance will be listed for the Safety Set.

5.9 Protocol Deviations

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

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

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

6. EFFICACY ANALYSES

All efficacy analyses will be based on the FAS unless stated otherwise. Baseline for all efficacy analyses is defined as the last observed value for the efficacy assessment prior to taking the first dose of IP (based on dates or date/times) in the induction study (SHP647-305 or SHP647-306) unless otherwise specified. Maintenance baseline for all efficacy analyses is defined as the value for the efficacy assessment collected at the Week 16 visit of the induction study.

The collected data shown in Table 12 but removed from Table 13 will be listed for the FAS including Inflammatory Bowel Disease Questionnaire questions, Short Form-36 Health Survey form, hospitalizations, CD-related surgeries and other surgical procedures, [redacted]

All efficacy analyses will be conducted according to the randomized treatment, regardless of the treatment actually received.

All confidence intervals (CIs) will be 2-sided 95% CIs.

For continuous endpoints, descriptive summary statistics will be presented for each treatment group at each scheduled visit and will include the following: n, mean, median, standard deviation, minimum, and maximum. For binary endpoints, number and percentage of subjects in each category will be summarized by treatment group at each scheduled visit.

Due to the early discontinuation of the study before full enrollment and the limited sample size, planned efficacy analyses have been updated.

6.1 Analyses of Primary Efficacy Endpoints

The coprimary efficacy endpoints are clinical remission at the Week 52 visit and endoscopic response at Week 52.

Clinical remission at the Week 52 visit is 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. Subjects with missing data at Week 52 or who discontinue before Week 52 will be considered failures.

Enhanced endoscopic response at Week 52 is measured by a decrease in SES-CD of at least 50% from induction study (SHP647-305 or SHP647-306) baseline. Subjects with missing data at Week 52 or who discontinue before Week 52 will be considered nonresponders.

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 or who discontinue before Week 52 will be considered 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.

6.1.1 Sensitivity Analyses of Primary Efficacy Endpoints

There are no sensitivity analyses of the coprimary endpoints planned for this study as a result of the early discontinuation.

6.2 Analyses of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are listed in Section 2.3.2. For each key secondary efficacy endpoint, descriptive summary statistics including unstratified Newcombe 95% CI will be presented for each treatment group. Subjects with missing key secondary endpoint data at the Week 52 visit will be considered failures and counted as nonresponders. The collected data related to the key secondary efficacy endpoints at each scheduled visit will be listed for the FAS.

6.2.1 Sensitivity Analyses of Key Secondary Efficacy Endpoints

There are no sensitivity analyses of key secondary endpoints planned for this study as a result of the early discontinuation.

6.3 Analyses of Other Secondary Efficacy Endpoints

Not applicable.

6.3.1 Sensitivity Analyses of Other Secondary Efficacy Endpoints

Not applicable.

6.4 Multiplicity Adjustment

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

6.5 Analyses of Exploratory Endpoint(s)

[redacted].

6.6 Subgroup Analyses

Not applicable.

7. SAFETY ANALYSIS

All safety analyses will be performed using the Safety Set. Safety variables include adverse events (AEs), clinical laboratory variables, vital signs, electrocardiogram (ECG) variables, anti-drug antibody (ADA) and neutralizing antibody (NAb) variables, and neurological variables. For each safety variable, the last value collected prior to the first dose of double-blind IP in the induction study (SHP647-305 or SHP647-306) will be used as baseline for all analyses of that safety variable. Maintenance baseline for all safety analyses is defined as the value for the safety assessment collected at the Week 16 visit of the induction study (SHP647-305 or SHP647-306). A final on-treatment assessment will be defined as the last valid assessment obtained after MNT baseline and through the EOT visit.

7.1 Adverse Events

Adverse events will be coded using MedDRA Version 19.1 2016.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to IP in the SHP647-307 study.

An overall summary of the number of subjects with TEAEs will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to IP,

related serious AEs (SAEs), TEAEs leading to study discontinuation, TEAEs leading to study medication discontinuation, and TEAEs leading to death.

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

The most common TEAEs (incidence ≥2% in any treatment group) will be summarized by preferred term in each treatment group and ontamalimab all doses in descending order of frequency by ontamalimab all doses.

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

7.1.1 Adverse Events of Special Interest and Other Potential Risk

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

7.1.1.1 Hypersensitivity

Potential hypersensitivity reactions such as serum sickness, vasculitis, or Arthus reactions to ontamalimab will be regarded as adverse events of special interest (AESI). An external hypersensitivity adjudication committee is established to review reported hypersensitivity events and adjudicate whether the event was a hypersensitivity event, which type (Type I or Type III) of event it was, and recommendations of permanent discontinuation or re-challenge with IP. Reported hypersensitivity events, adjudicated hypersensitivity events, and study drug recommendation will be summarized by treatment group and ontamalimab all doses.

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

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values (in conventional units) and changes from induction study (SHP647-305 or SHP647-306) baseline at each assessment time point for quantitative variables will be presented for each treatment group and ontamalimab all doses for the following clinical laboratory variables. The number and percentage of subjects for qualitative variables in urinalysis will be presented by treatment group and ontamalimab all doses in the Safety Set.

Serum chemistry

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

Hematology

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

Urinalysis

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

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 3. The number and percentage of subjects with post-MNT baseline PCI values will be tabulated by treatment group. The percentages will be calculated relative to the number of subjects with at least 1 post-MNT baseline assessment. The numerator is the total number of subjects with at least 1 post-MNT baseline PCI value. A supportive listing of subjects with post-MNT baseline PCI values will be provided including the subject number, site, induction study (SHP647-305 or SHP647-306) baseline, MNT baseline, and post-MNT baseline values.

Figures will be presented for hematology and chemistry to show the changes in laboratory parameters over time. Data will be presented as box-and-whisker plots for each treatment group (placebo, ontamalimab 25 mg, and ontamalimab 75 mg) at each visit, with 1 laboratory parameter per page.

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

All laboratory data will be listed for the Safety Set.

Table 3: Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Age Range	Sex	Outlier Criteria[a]	
			Low	High
Hematology				
Hemoglobin	All		<8 g/dL	NA
Hematocrit	All		<32%	NA
Mean Corpuscular Hemoglobin (MCH)	All		<LLN	>ULN
Mean Corpuscular Hemoglobin Concentration (MCHC)	All		<LLN	>ULN

Table 3: Criteria for Potentially Clinically Important Laboratory Tests

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

Table 3: Criteria for Potentially Clinically Important Laboratory Tests

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

LLN=lower limit of normal provided by the laboratory; NA=not applicable; ULN=upper limit of normal provided by the laboratory.

[a] If criteria in both directions are shown for a single parameter, then abnormalities in each direction are summarized separately.

7.3 Pregnancy Test and Follicle-stimulating Hormone Test

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

7.4 Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, body weight, respiratory rate, and temperature) and their changes from induction study (SHP647-305 or SHP647-306) baseline at each post-baseline visit and at the end of the study will be presented for each treatment group and ontamalimab all doses.

For pulse rate, a post-MNT baseline value is considered as a PCI value if its meets both criteria for observed value and change from induction study (SHP647-305 or SHP647-306) baseline. For systolic/diastolic blood pressure, a post-MNT baseline value is considered as a PCI value if it meets criteria for observed value or change from induction study (SHP647-305 or SHP647-306) baseline. For weight and BMI, post-MNT baseline value is considered as a PCI value if it meets criteria for change from induction study (SHP647-305 or SHP647-306) baseline. The PCI criteria are listed in Table 4. The number and percentage of subjects with PCI post-MNT baseline values will be tabulated by treatment group and ontamalimab all doses. The percentages will be calculated relative to the number of subjects with available induction study (SHP647-301 or SHP647-302) baseline values and at least 1 post-MNT baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-MNT baseline vital sign value. A supportive listing of subjects with post-MNT baseline PCI values will be provided including the subject number, site, induction study (SHP647-305 or SHP647-306) baseline, MNT baseline, and post-MNT baseline values.

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

Table 4: Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Systolic blood pressure (mmHg)	High	≥180	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤50	Decrease of ≥15
Pulse rate (beats per minute)	High	≥120	Increase of ≥15
	Low	≤50	Decrease of ≥15
Weight (kg)	High	-	Increase of ≥7%
	Low	-	Decrease of ≥7%
BMI (kg/m^2)	High	-	Increase of ≥10%
	Low	<18	Decrease of ≥10%
Temperature (°C)		NA	NA

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

7.5 Electrocardiogram (ECG)

A central ECG reader will be used. Descriptive statistics for ECG variables (eg, heart rate, PR interval, QRS interval, QT interval, and QTc interval using both Bazett and Fridericia corrections) and their changes from induction study (SHP647-305 or SHP647-306) baseline at each assessment time point will be presented by treatment group. Electrocardiogram interpretation will be summarized by visit. A shift table from induction study (SHP647-305 or SHP647-306) baseline to each visit for ECG interpretation results will be presented for each treatment group and ontamalimab all doses.

Electrocardiogram variable values will be considered PCI if they meet or exceed the upper limit values listed in Table 5. The number and percentage of subjects with available induction study (SHP647-301 or SHP647-302) baseline values and post-MNT baseline PCI values will be tabulated by treatment group and ontamalimab all doses. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-MNT baseline assessment. The numerator is the total number of subjects with at least 1 post-MNT baseline PCI value.

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

Table 5: Criteria for Potentially Clinically Important ECG Values

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

ECG=electrocardiogram

7.6 Other Safety Data

7.6.1 Targeted Neurological Assessment

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

7.6.2 Immunogenicity

Presence of ADAs will be listed and summarized by visit for each treatment group and ontamalimab all doses.

Anti-drug antibodies will be classified into pre-existing, treatment-induced responses, and treatment-boosted responses. Pre-existing is defined as a signal detected prior to treatment. Treatment-induced responses are defined as a negative pretreatment sample with at least 1 positive sample at a subsequent time point. Treatment-boosted responses are defined as positive pretreatment samples that are boosted to a higher level following drug administration. Those categories will be listed and summarized by treatment group and ontamalimab all doses.

Neutralizing antibodies will be tested on ADA-positive subjects, and samples will be defined as NAb-positive or negative. Presence of NAbs will be listed and summarized for all ADA-positive subjects by visit for each treatment group and ontamalimab all doses.

Anti-drug antibody prevalence will also be calculated and summarized by treatment group and ontamalimab all doses. Anti-drug antibody prevalence is the proportion of study population having drug-reactive antibodies (ADA) at any time point (including pre-existing antibodies) during the study.

Anti-drug antibody incidence will be calculated and summarized by treatment group and ontamalimab all doses. Anti-drug antibody incidence is the proportion of study population found to have seroconverted or boosted their ADA (including pre-existing ADA) at any point during the study period.

Listings of positive immunogenicity results and individual subject immunogenicity data will be presented.

7.6.3 Contraception Check

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

7.6.4 Physical Examination

Complete and targeted physical examinations will be performed at the time points specified in Table 13. Physical examination results will be listed for the Safety Set.

8. [redacted]

8.1 [redacted]

[redacted]

8.2 [redacted]

[redacted]

8.3 [redacted]

[redacted]

8.4 [redacted]

[redacted]

9. [redacted]

9.1 [redacted]

[redacted]

10. OTHER ANALYSES

10.1 Coronavirus Pandemic

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

11. INTERIM ANALYSIS/DATA MONITORING (REVIEW) COMMITTEE

A data monitoring committee (DMC) was set up to review the safety during the course of the study. The DMC will not review efficacy data until the time of unblinding.

There is no interim analysis planned for the SHP647-307 study.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

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

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

'ONTA' is the acronym of ontamalimab that will be used in output treatment presentation.

12.2 Definition of Visit Windows

Assessments will be assigned to visits based upon the date on which the assessment took place regardless of the completed CRF page. Assessments will be mapped to visits as outlined in Table 6, Table 7, Table 8, Table 9, Table 10.

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

Study day will be calculated as follows:

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

- If the assessment date is before the date of first dose of IP:
  Study day = assessment date – first dosing date

Table 6: Visit Windows (Study Day Based) – PRO and Vital Signs Assessments

Visit	Planned Study Day	Start Day of Window	End Day of Window
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	182
Week 28	196	183	210
Week 32	224	211	238
Week 36	252	239	266
Week 40	280	267	294
Week 44	308	295	322
Week 48	336	323	350
Week 52	364	351	EOT date
Follow-up	EOT date + 84	EOT date + 1	EOF date

EOF=end of follow-up; EOT=end of treatment; PRO=patient-reported outcome
Note: PRO is not collected in the follow-up period.

Table 7: Visit Windows (Study Day Based) – Safety Lab, CDAI, and Neurological Testing

Visit	Planned Study Day	Start Day of Window	End Day of Window
Week 12	84	2	126
Week 24	168	127	210
Week 36	252	211	308
Week 52	364	309	EOT date
Follow-up	EOT date + 84	EOT date + 1	EOF date

CDAI=Crohn's Disease Activity Index; EOF=end of follow-up; EOT=end of treatment
Note: Lab tests are collected at the Week 52 Part 1 visit. CDAI assessments and neurological test are collected at the Week 52 Part 2 visit. CDAI assessments are not collected in the follow-up period.

Table 8: Visit Windows (Study Day Based) – ADA Assessments

Visit	Planned Study Day	Start Day of Window	End Day of Window
Week 12	84	2	126
Week 24	168	127	210
Week 36	252	211	EOT date

ADA=anti-drug antibody; EOT=end of treatment

Table 9: Visit Windows (Study Day Based) – ECG Assessments

Visit	Planned Study Day	Start Day of Window	End Day of Window
Week 12	84	2	126
Week 24	168	127	266
Week 52	364	267	EOT date

ECG=electrocardiogram; EOT=end of treatment

Note: ECG assessments are collected at the Week 52 Part 1 visit.

Table 10: Visit Windows (Study Day Based) – SES-CD Assessments

Visit	Planned Study Day	Start Day of Window	End Day of Window
Week 52	364	2	EOT date

EOT=end of treatment; SES-CD=Simple Endoscopic Score for Crohn's Disease.
Note: SES-CD are collected at the Week 52 Part 2 visit.

12.3 Derived Efficacy Endpoints

12.3.1 Patient-reported Outcome – Crohn's Disease (PRO-CD) Daily E-diary

Patient-reported CD clinical signs and symptoms data will be collected daily using a PRO-CD daily e-diary (electronic handheld device).

Subjects will be asked to record the following signs and symptoms 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.

Note: In the instrument, if total stool frequency is entered as 0, then the questions of very soft stool/liquid stool frequency, rectal bleeding frequency, and rectal urgency frequency are skipped. These skipped items will be considered as 0 for analysis purposes.

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.

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

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).

The calculation of the total score requires a complete colonoscopy (including visualization of the terminal ileum except when it is not possible due to impassable stenosis or previous partial colectomy/ileocolectomy).

The SES-CD score is the sum of the subscores of each of the segments investigated and centrally read from the colonoscopies performed at MNT baseline and Week 52/ET (Visit 14, Part 2) of the SHP647-307 study, respectively.

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), Week 16/ET of the induction studies (SHP647-305 and SHP647-306), and Week 52/ET of this study (SHP647-307) (matching segments approach) will be utilized.

12.3.3 Crohn's Disease Activity Index (CDAI)

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, and 5 components will be recorded at the time points specified in Table 13.

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.
- 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.
- 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 CDAI is the sum of all variable values times the corresponding multiplier in Table 11.

Table 11: Crohn's Disease Activity Index (CDAI)

Variable No.	Variable Description	Multiplier
1	Number of liquid or soft stools (each day for 7 days)	× 2
2	Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)	× 5
3	General well-being (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)	× 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))	× 20
5	Use of diphenoxylate or loperamide for diarrhea (0 = no, 1 = yes)	× 30
6	Abdominal mass (0 = no, 2 = questionable, 5 = definite)	× 10
7	Hematocrit [Males: 47-HCT (%), Females: 42-HCT (%)]	× 6
8	Body weight (1-weight/standard weight) × 100 (add or subtract according to sign)	× 1

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 referred 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.

12.4 Repeated or Unscheduled Assessments of Safety Parameters

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

Table 7, Table 8, Table 9, Table 10.

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

12.5 Handling of Missing, Unused, and Spurious Data

12.5.1 Missing Date of End of Treatment

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

12.5.2 Missing Date of Crohn's Disease Diagnoses

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

12.5.3 Missing Date Information for Prior or Concomitant Medications

The induction study (SHP647-305 or SHP647-306) imputed dates will be used for prior medications for those collected in the induction study.

For prior or concomitant medications collected in the SHP647-307 study, including rescue medications, incomplete (ie, partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, the start date will be imputed first.

12.5.3.1 Incomplete Start Date

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

12.5.3.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP in the SHP647-307 study will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the date of the first dose of IP in the SHP647-307 study, then 31 December will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of IP in the SHP647-307 study, then 01 January will be assigned to the missing fields.

12.5.3.1.2 Missing Month Only

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

12.5.3.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IP in the SHP647-307 study, then the day of the date of the first dose of IP in the SHP647-307 study will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of IP in the SHP647-307 study or if both years are the same but the month is before the month of the date of the first dose of IP in the SHP647-307 study, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the first dose of IP in the SHP647-307 study or if both years are the same but the month is after the month of the date of the first dose of IP in the SHP647-307 study, then the first day of the month will be assigned to the missing day.

12.5.3.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of IP in the SHP647-307 study is missing, then it will be replaced with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

12.5.3.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of IP in the SHP647-307 study, then the day and month of the date of the last dose of IP in the SHP647-307 study will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the date of the last dose of IP in the SHP647-307 study, then 31 December will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the date of the last dose of IP in the SHP647-307 study, then 01 January will be assigned to the missing fields.

12.5.3.2.2 Missing Month Only

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

12.5.3.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP in the SHP647-307 study, then the day of the date of the last dose of IP in the SHP647-307 study will be assigned to the missing day.

- If either the year is before the year of the date of the last dose of IP in the SHP647-307 study or if both years are the same but the month is before the month of the date of the last dose of IP in the SHP647-307 study, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the last dose of IP in the SHP647-307 study or if both years are the same but the month is after the month of the date of the last dose of IP in the SHP647-307 study, then the first day of the month will be assigned to the missing day.

12.5.4 Missing Date Information for Adverse Events

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

12.5.4.1 Incomplete Start Date

The same rules as in Section 12.5.3.1 will be followed.

12.5.4.2 Incomplete Stop Date

Not applicable.

12.5.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of IP in the SHP647-307 study, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be presented in data listings.

12.5.6 Missing Relationship to Investigational Product for Adverse Events

If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP in the SHP647-307 study, a causality of "Related" will be assigned. The imputed values for relationship to double-blind IP will be used for incidence summaries, while the actual values will be presented in data listings.

12.5.7 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, a character string being reported for a numerical variable, the appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

13. ANALYSIS SOFTWARE

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

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Not applicable.

15. REFERENCES

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16. APPENDICES

16.1 Schedule of Activities Prior to Amendment 3

Table 12: Schedule of Assessments Prior to Amendment 3

	Baseline[a]	Treatment													Follow-Up[b]	
Study Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ET[c]**	**60[c]**	**68[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**	**16**
Study Day	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**	**476**
Visit Window	**None**	**±7 days**												**±7 days**	**±7 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]	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[j]	IDT	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Laboratory Assessments																
Hematology[h]	IDT			X			X			X				X		X
Serum chemistry	IDT			X			X			X				X		X
Urinalysis	IDT			X			X			X				X		X
FSH[k]	X[j]															
Urine β-hCG[l]	IDT	X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]	IDT			X			X							X		
	IDT			X			X							X		
	IDT			X			X							X		
	IDT			X			X							X		
	IDT			X			X			X				X		
ADA and NAb sampling	IDT			X			X			X				X		
CD Assessments[m] Including Endoscopic Procedure																
Colonoscopy (including biopsy)[n,o,p]	IDT													X		
SES-CD	IDT													X[q]		
CDAI[r]	IDT			X			X			X				X		
PRO e-diary data instruction	X															
PRO-CD daily e-diary data[s]	IDT	X	X	X	X	X	X	X	X	X	X	X	X	X		
Treatment failure assessment[t]			X	X	X	X	X	X	X	X	X	X	X	X		
Health Assessment[u]																

	Baseline[a]	Treatment													Follow-Up[b]	
Study Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ET[c]**	**60[c]**	**68[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**	**16**
Study Day	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**	**476**
Visit Window	**None**	**±7 days**												**±7 days**	**±7 days**	
IBDQ	IDT			X			X							X		
[redacted]	IDT			X			X							X		
Hospitalizations, inpatient days, [redacted] (HRUA)	IDT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]	IDT			X			X							X		
[redacted]	IDT			X			X							X		
[redacted]	IDT			X			X							X		
SF-36, version 2, acute form	IDT			X			X							X		
[redacted]	IDT													X		
Treatment Procedures																
Randomization[v]	X															
Administration of ontamalimab or placebo[v,w]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hypersensitivity monitoring[x]	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[y]			X			X							X			

ADA=antidrug antibody; β-hCG=beta-human chorionic gonadotropin; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; [redacted]; ECG=electrocardiogram; [redacted]; e-diary=electronic diary; [redacted]; ET=early termination; FSH=follicle-stimulating hormone; HRUA=Healthcare Resource Utilization Assessment; IBDQ=Inflammatory Bowel Disease Questionnaire; IDT=induction study (SHP647-305 or SHP647-306); LTS=long-term safety extension; [redacted]; NAb=neutralizing antibody; [redacted]; PRO=patient-reported outcome; SES-CD=Simple Endoscopic Score for Crohn's Disease; SF-36=Short Form-36 Health Survey; [redacted]

[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 an ET visit and then enter into the safety follow-up period if not entering the LTS study (SHP647-304). For subjects participating in the 16-week safety follow-up period (not entering the LTS study), the Week 60 visit will routinely be conducted by telephone; however, as an exception, the visit can be performed as a study site visit if preferred. The Week 68 visit will take place at the study site.
Note: For subjects who are withdrawn early from the study, the 2 safety follow-up visits will take place 8 weeks ±7 days and 16 weeks ±7 days after the subject's last visit in the treatment period.

[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.

[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.

	Baseline[a]	Treatment														Follow-Up[b]	
Study Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ET[c]**		**60[c]**	**68[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**	**16**
Study Day	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**		**364**	**420**	**476**
Visit Window	**None**	**±7 days**													**±7 days**	**±7 days**	

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

[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 Protocol 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, and cognition/behavior. See Section 7.2.3.3 of the protocol for further details.

[j] 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 of the protocol for further details.

[k] 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.

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

[m] 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.

[n] Colonoscopy preparation will be according to local routine (see Protocol Section 7.2.2.4). Colonoscopy preparation may be done on the same day as the colonoscopy procedure.

[o] Biopsy samples from each of the segments investigated will be collected for histological evaluation (see Protocol Section 7.2.2.4).

[p] 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.

[q] 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).

[r] If it is clinically necessary, an unscheduled CDAI evaluation may be performed any time after Week 4 in order to evaluate treatment failure (see Protocol 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.

[s] 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 7.2.2.1 of the protocol 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.

[t] See Section 4.5.1 of the protocol for definition of treatment failure.

	Baseline[a]	Treatment													Follow-Up[b]	
Study Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52/ET[c]	60[c]	68[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	16
Study Day	1	28	56	84	112	140	168	196	224	252	280	308	336	364	420	476
Visit Window	None	±7 days												±7 days	±7 days	

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

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

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

[x] 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.

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

Note: See Section 7.2 of the protocol for the order in which assessments should be performed. Timing of visits is relative to SHP647-307 baseline (Visit 1).

16.2 Schedule of Activities Under Amendment 3

Table 13: Schedule of Assessments Under Amendment 3

Study Week	Baseline[a]	Treatment													Follow-Up[b]	
	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						

Study Week	**Baseline[a]**	**Treatment**														**Follow-Up[b]**
	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**
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	X	
Treatment failure assessment[w]			X	X	X	X	X	X	X	X	X	X	X	X	X	
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; ECG=electrocardiogram; e-diary=electronic diary; ET=early termination; FSH=follicle-stimulating hormone; IDT=induction study (SHP647-305 or SHP647-306); 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 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 situation, these may also be done at a subject's home provided a qualified site staff 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 Protocol 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 the first dose in the LTS study.

Study Week	Baseline[a]	Treatment														Follow-Up[b]
	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

[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.

[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 Protocol 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, and cognition/behavior. See Section 7.3.3.3 of the protocol 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 of the protocol for further details.

[l] Clinical laboratory assays (LFT) can also be performed by the local laboratory in case of issues related to the COVID-19 pandemic and if deemed necessary by the investigator to confirm the subject's safety. In such case, the investigative site must obtain the local laboratory's normal ranges as well as CLIA (Clinical Laboratory Improvement Amendments) 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 Section 4.4 and Section 7.3.3.7 of the protocol.

[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 Protocol 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 Protocol 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 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.

Study Week	Baseline[a]	Treatment														Follow-Up[b]
	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

[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 Protocol 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 of the protocol 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, 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 of the protocol for the order in which assessments should be performed. Timing of visits is relative to SHP647-307 baseline (Visit 1).

16.3 Geographic Regions

Table 14: Geographic Regions

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

Table 14: Geographic Regions

Country	Region
Canada	North America
United States	North America

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