STATISTICAL ANALYSIS PLAN

NCT Number: NCT03559517

Study Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects With Moderate to Severe Crohn's Disease (CARMEN CD 305)

Study Number: SHP647-305

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STATISTICAL ANALYSIS PLAN

SHP647
PHASE 3

A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Crohn's Disease (CARMEN CD 305)

PROTOCOL IDENTIFIER: SHP647-305

Study Sponsor(s):	Shire Human Genetic Therapies, Inc. ("Shire") 300 Shire Way, Lexington, MA, 02421, USA
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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	27 Aug 2020	Original Document

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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
[redacted]	[redacted]
ET	early termination
EOT	end of treatment
FAS	full analysis set
HEOR	Health Economics and Outcomes Research
[redacted]	[redacted]
IBDQ	Inflammatory Bowel Disease Questionnaire
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
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
SF-36	Short Form-36 Health Survey

SOC	system organ class
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
[redacted]	[redacted]
WHO	World Health Organization
[redacted]	[redacted]

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, and Health Economics and Outcomes Research (HEOR) data, as well as descriptive summaries of [redacted] data, as described in Protocol Amendment 2 dated 22 Nov 2019 (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 and Crohn's disease. The planned analyses reflect the planned early discontinuation of this study.

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

- Inducing clinical remission based on 2-item PRO (abdominal pain severity and very soft stool/liquid stool frequency)
- Inducing endoscopic response based on centrally read colonoscopy.

2.1.2 Secondary Objective(s)

The key secondary objectives are as follows:

- To evaluate the efficacy of ontamalimab in inducing clinical remission as measured by Crohn's Disease Activity Index (CDAI)
- To evaluate the efficacy of ontamalimab in inducing enhanced endoscopic response based on centrally read colonoscopy
- To evaluate the efficacy of ontamalimab in inducing clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)
- To evaluate the efficacy of ontamalimab in inducing clinical response based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
- To evaluate the efficacy of ontamalimab in inducing clinical remission based on patient-reported clinical signs and symptoms (as measured by 2-item PRO) as well as inducing endoscopic response based on centrally read colonoscopy in the same subject
- To evaluate the efficacy of ontamalimab in inducing endoscopic healing based on centrally read colonoscopy.

2.1.3 Other Secondary Objectives

The other secondary objectives are as follows:

- To evaluate the safety and tolerability of ontamalimab
- To evaluate the effect of ontamalimab induction treatment on other clinical outcomes (clinical response defined by CDAI, or clinical remission over time, or change from baseline in frequency in CD-related clinical parameters)
- To evaluate the effect of ontamalimab induction treatment on other endoscopic outcomes
- To evaluate the effect of ontamalimab on health-related quality of life (HRQL) (as measured by the Inflammatory Bowel Disease Questionnaire [IBDQ] and the Short Form-36 Health Survey [SF-36])

- To evaluate the effect of ontamalimab on incidence of hospitalizations and total inpatient days
- To evaluate the impact of ontamalimab on incidence of CD-related and other surgeries.

2.1.4 Exploratory Objective(s)

The exploratory objectives are as follows:

- [redacted]

2.2 Estimand(s)

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 16 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 16 visit without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects in clinical remission at the Week 16 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 16 in impact on endoscopic response.	16- to 80-year-old adolescents and adults with CD defined through inclusion and exclusion criteria as stated in the protocol	Endoscopic response at the Week 16 visit, defined by at least 25% decrease in SES-CD from baseline without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with endoscopic response at the Week 16 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 16 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 16 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 16 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 16 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 16 visit, defined by at least 50% decrease in SES-CD from baseline without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with enhanced endoscopic response at the Week 16 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 16 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 16 visit, defined by 2-item PRO subscores of average daily pain ≤1 and average daily stool frequency ≤3 of type 6/7 without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with clinical remission at the Week 16 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 16 in impact on clinical 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 16 visit, defined as meeting at least 1 of the 2 criteria on 2-item PRO mentioned in Section 2.3.2 without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with clinical response at the Week 16 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 16 in impact on clinical remission with 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 16 visit, defined as meeting both clinical remission by 2-item PRO and endoscopic response, defined by at least 25% in SES-CD, without discontinuation	Composite: intercurrent events captured in variable definition	Difference in proportions of subjects with clinical remission with endoscopic response at the Week 16 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 16 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 16 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 16 visit between each active treatment group (ontamalimab 25 mg, ontamalimab 75 mg) and placebo

2.3 Endpoints

2.3.1 Primary Endpoints

The coprimary efficacy endpoints are as follows:

- Clinical remission at the Week 16 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.
- Endoscopic response at Week 16 as measured by a decrease in Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 25% from baseline.

2.3.2 Key Secondary Endpoints

The key secondary efficacy endpoints are as follows:

- Clinical remission at the Week 16 visit as measured by a CDAI score of <150.
- Enhanced endoscopic response at Week 16 as measured by a decrease in SES-CD of at least 50% from baseline.
- Clinical remission at the Week 16 visit as defined by the following: 2-item PRO 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.
- Clinical response at the Week 16 visit as measured by the 2-item PRO and defined as meeting at least 1 of the following 2 criteria:
    - 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:

      (a) Not worsening from baseline

      and/or

      (b) 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*

- 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 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.

- Clinical remission with endoscopic response, ie, both clinical remission by 2-item PRO (based on 11-point NRS) and endoscopic response, as measured by a decrease in SES-CD of at least 25% at Week 16 (composite endpoint)
- Complete endoscopic healing at Week 16 defined as SES-CD=0-2.

2.3.3 Other Secondary Endpoints(s)

Other secondary endpoints are as follows:

- Clinical response at the Week 16 visit as measured by at least a 100-point reduction in the CDAI from baseline (CDAI-100 response)
- Clinical response at the Week 16 visit as measured by at least a 70-point reduction in the CDAI from baseline (CDAI-70 response)
- Clinical remission over time, as measured by the 2-item PRO
- Change from baseline in total stool frequency, rectal bleeding frequency, rectal urgency frequency, nausea severity, vomiting frequency, and rectal incontinence frequency scores; and total sign/symptom score based on subject daily electronic diary (e-diary) entries
- Endoscopic healing at Week 16 as measured by SES-CD ≤4 and at least 2-point reduction versus baseline and no subscore >1 in any individual variable
- Change from baseline in IBDQ domain and total (absolute) scores over time
- Change from baseline in SF-36, version 2, acute (physical and mental component summary scores and individual domain scores) over time
- Incidence of all cause hospitalizations and total inpatient days
- Incidence of CD-related surgeries and other surgical procedures during the entire study period.

2.3.4 Exploratory Endpoint(s)

The exploratory endpoints are as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

2.3.5 [redacted]

[redacted]

2.3.6 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. STUDY DESIGN

3.1 General Description

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of ontamalimab in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.

A total of 1032 subjects (387 subjects in the 25 mg ontamalimab treatment group, 387 subjects in the 75 mg ontamalimab treatment group, and 258 subjects in the placebo group) are planned for enrollment into the study (Figure 1). Subjects must be at least 16 years of age and no more than 80 years of age at the time of signing the informed consent/assent form.

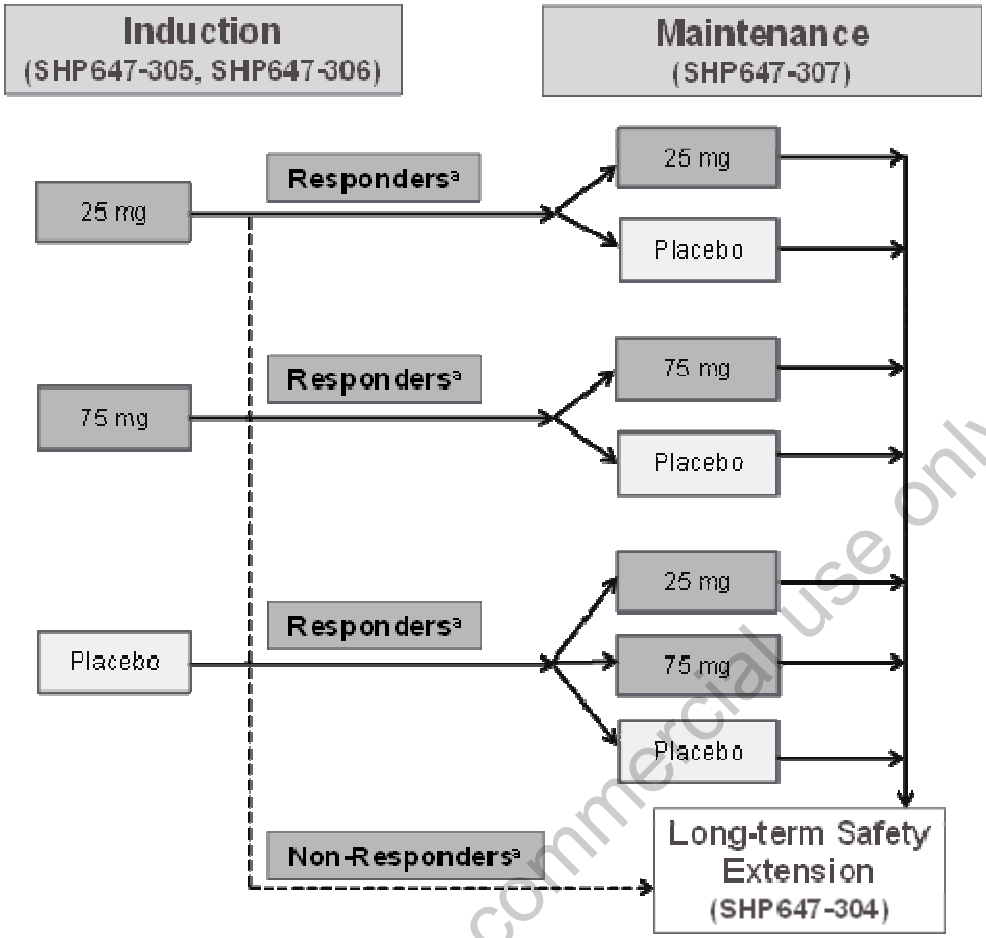
The study consists of a screening period up to 6 weeks and a 16-week treatment period. After the screening period, eligible subjects will be randomized to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo) in a 3:3:2 ratio. Randomization will be stratified based upon the subject's status of prior anti-tumor necrosis factor (TNF) treatment (naïve or experienced), glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline), and SES-CD at baseline (SES-CD ≥17 or SES-CD <17). Subjects will receive subcutaneous (SC) injections of ontamalimab or placebo, using a prefilled syringe (PFS), on Week 0/Day 1 (Visit 2), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12 (Visit 6). Subjects will undergo efficacy, [redacted] safety, and health outcome assessments at these visits as detailed in Table A1.

At the end of the 16-week treatment period, subjects will be offered the opportunity to participate in either a double-blind maintenance study (SHP647-307; for subjects who fulfill the entry criteria) or a long-term safety extension (LTS) study (SHP647-304; for subjects who do not fulfill the entry criteria for Study SHP647-307) as shown in Figure 1. Subjects who withdraw early from the 16-week treatment period or who do not wish to enter the maintenance study (SHP647-307) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period. Only those subjects who complete the full course of investigational product (IP) treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

An interim analysis for the coprimary endpoints was planned after approximately the first 50% of all randomized subjects in both the SHP647-305 and SHP647-306 studies have either completed the studies or have prematurely withdrawn from the studies. The sample size was planned to be reassessed as part of this interim analysis. Due to the early discontinuation of this study, no interim analysis will be conducted.

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

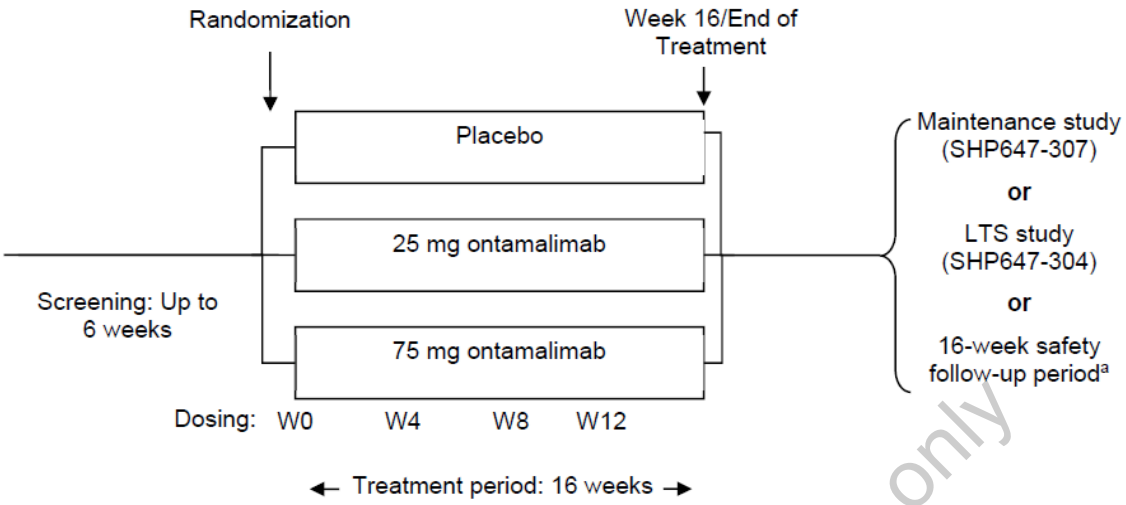
OR

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

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

Figure 2 Study Design Flow Chat



LTS=long-term safety extension; W=week
[a] Subjects who withdraw early from the 16-week treatment period or who do not wish to enter the maintenance study (SHP647-307) or LTS study (SHP647-304) will continue into a 16-week safety follow-up period.

3.2 Randomization

The actual treatment given to individual subjects is determined by a randomization schedule.

Eligible subjects will be randomized in a ratio of 3:3:2 via a computer-generated randomization schedule to receive SC injections of 25 mg ontamalimab, 75 mg ontamalimab, or placebo, respectively. The randomization will be performed centrally and stratified by status of prior anti-TNF therapy (2 strata: naïve versus experienced), glucocorticoid use at baseline (2 strata: on glucocorticoids at baseline versus not on glucocorticoids at baseline), and SES-CD at baseline (2 strata: SES-CD ≥17 at baseline versus SES-CD <17 at baseline).

To ensure that the allocation of subjects with prior anti-TNF therapy exposure is similar to that observed in previous studies, the percentage of subjects with prior exposure to treatment with anti-TNF therapy exposure will be capped at 60% of the sample population. There will be no cap on the number of anti-TNF naïve subjects randomized.

Subject numbers are assigned to all eligible subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number will be assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to IP allocated to the subject, once eligibility has been determined. Individual subject treatment will be automatically assigned by the interactive response technology (IRT) system.

Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as

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

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

3.4 Sample Size and Power Considerations

Graphical methods are used to control the global family-wise Type I error rate at the .05 level (2-sided) for the comparisons of the 2 ontamalimab treatment groups with the placebo group. Alpha is initially 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 made based on assuming a .025 (2-sided) significance level for each pairwise treatment comparison, 1720 subjects will be screened to randomize 1032 subjects in a 3:3:2 allocation ratio: 387 subjects in the 25 mg ontamalimab treatment group, 387 subjects in the 75 mg ontamalimab treatment group, and 258 subjects in the placebo group. These numbers of subjects would yield an approximately 93% power to detect individual pairwise treatment difference in the first coprimary efficacy endpoint, clinical remission by 2-item PRO at Week 16, of 10% (17.5% ontamalimab versus 7.5% placebo). Expected clinical remission rates by 2-item PRO at Week 16 are based on observed rates from a post hoc analysis of the A7281006 study

and placebo remission rates from literature (Sandborn et al., 2017). 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 16 are imputed as failures and the above rates account for these subjects.

With the 1032 subjects in allocation noted above, this number of subjects would yield an approximately 94% power to detect individual pairwise treatment difference in the other coprimary efficacy endpoint, endoscopic response at Week 16, of 12.5% (27.5% ontamalimab versus 15% placebo). Expected endoscopic response rates at Week 16 are based on observed rates from a post hoc analysis of the A7281006 study and also endoscopic response rates from literature (Sandborn et al., 2017). No adjustment for missing data is required in these sample size calculations as subjects with missing data for endoscopic response at Week 16 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 90% assuming a correlation of 0.4.

With the sample size of 1032 subjects, Table 2 provides the power for detecting a treatment difference between an ontamalimab treatment group and the placebo group for the key secondary endpoints.

Table 2 Power to Detect the Corresponding Treatment Effect for Key Secondary Endpoints

Key Secondary Endpoint at Week 16	Ontamalimab Premise	Placebo Premise	Power
Clinical remission by CDAI	26.5%	15%	0.90
Enhanced endoscopic response	25%	13%	0.94
Clinical remission by abdominal pain ≤1 and stool frequency ≤3	24%	14%	0.81
Clinical response by 2-item PRO	52.5%	40%	0.81
Clinical remission by 2-item PRO and endoscopic response	11%	4.5%	0.77
Complete endoscopic healing	6%	2%	0.58

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

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed an informed consent document.

4.2 Randomized Set

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

4.3 Safety Set

The Safety Set will consist of all subjects who have received at least 1 dose of IP. 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 subjects in the randomized set who have received at least 1 dose of IP. Analysis will be performed according to the randomized treatment regimen regardless of the treatment regimen actually received.

[redacted]

[redacted]

[redacted]

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, FAS, [redacted], and [redacted]) 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, [redacted], and [redacted] sets. 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 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 SHP647-307 or -304 studies 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 16 weeks of treatment and roll over to the 307/304 studies 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 16 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 by 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 calculated as the difference between the date of birth and the date of informed consent. 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-<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 2), 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 IP unless otherwise specified. The following baseline characteristics will be summarized:

- Weight,
- Height,
- Body Mass Index (BMI),
- CD Disease Duration 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.

- Average Worst Abdominal Pain Score (0 to 10),
- Average Abdominal Pain Score (0 to 4),
- Average Very Soft Stool/Liquid Stool Frequency,
- CDAI Score at Baseline,
- [redacted]
- CD Disease Location (Small Intestine alone, Colon and/or Rectum alone, Ileo-colitis, Perianal, and Other),
- Bowel Resection Performed Previously (Yes, No, and Unknown),
- SES-CD at Baseline (≥17 and <17) (both randomized status and actual status),
- Isolated Ileitis at Baseline (Yes, No)
- [redacted]

The following CD medication history/use will be summarized:

- Anti-TNF Experienced (Naïve and Experienced) (both randomized status and actual status),

- Anti-TNF Failure (Yes vs No),
- Anti-TNF Failure Times (Anti-TNF Naive, Anti-TNF Experienced without Failure, Failed 1 Anti-TNF Therapy, Failed 2 Anti-TNF Therapies, Failed 3 or more Anti-TNF Therapies),
- Glucocorticoid Use at Baseline (Yes vs. No) (both randomized status and actual status),
- Glucocorticoid Use at Baseline (Systemic and Topical, Systemic Only, Topical Only, None),
- Systemic Glucocorticoid Dose at Baseline,
- Systemic Glucocorticoid Dose at Baseline Category (≤10 mg, >10 mg),
- Immunosuppressant Use at Baseline (Yes vs. No),
- Immunosuppressant Experienced (Yes vs. No),
- 5-ASA Use at Baseline (Yes vs. No),
- 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 AND Immunosuppressant Use at Baseline (Both Glucocorticoid and Immunosuppressant Use, Only Glucocorticoid Use, Only Immunosuppressant Use, Neither Glucocorticoid nor Immunosuppressant Use).

5.3 Smoking History

Smoking history will be summarized for each treatment group and ontamalimab all doses and will be listed for the Safety Set.

5.4 Medical History

Medical history will be collected at the screening visit (Visit 1), including CD history and cardiac history, 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. The number and percentage of subjects will be summarized by each treatment group and ontamalimab all doses, system organ class (SOC), and preferred term. Medical history will be listed for the Safety Set. General medical history will be listed for the Safety Set.

Cardiovascular history information will be summarized by each treatment group and ontamalimab all doses. Cardiovascular history will be listed for the Safety Set.

CD history will be listed for the Safety Set.

5.5 Prior Therapies, Procedures and Medications

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

Prior medication is defined as any medication with the start date prior to the date of the first dose of IP. Incomplete medication dates will be imputed as described in Section 12.5.3.

Prior medications for Indication Under Study 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.

All prior medications, medical/surgical procedures, and therapies 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 and continuing after the first dose of IP, or with a start date between the dates of the first dose of IP and end of treatment (EOT) date, inclusive. Medication that starts after the first dose of SHP647-307/304 IP will be collected in SHP647-307/304 database and will not be considered as concomitant medication in SHP647-305. 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, inclusive, or with a start date after the EOT date (post-treatment) 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 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 (Weeks 0, 4, 8, and 12). Exposure to IP will be summarized by presenting the number of subjects who had 1 injection, 2 injections, 3 injections, or 4 injections. Number of injections received will be summarized in each treatment group and ontamalimab all doses. The administration records by visit will be listed for the Safety Set.

Exposure to IP 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 to the date of the last

dose of IP taken +29 days. Subject years of exposure is calculated as (Date of last dose of IP in this study – date of first dose of IP in this study +29)/365.25. Total subject years of exposure is calculated by summing of each subject years of exposure within each column.

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented to describe the exposure to IP by 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 until the end of treatment 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 for 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) unless otherwise specified.

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 by 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. Full details of the changes to the planned analyses are located in Section 14.

6.1 Analyses of Primary Efficacy Endpoints

The coprimary efficacy endpoints are clinical remission at the Week 16 visit and endoscopic response at Week 16.

Clinical remission at Week 16 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 16 or who discontinue before Week 16 will be considered failures.

The endoscopic response at Week 16 is defined as a decrease in SES-CD of at least 25% from baseline. Subjects with missing data at Week 16 or who discontinue before Week 16 will be considered non-responders.

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 16.

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 by treatment group at each scheduled visit.

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

The other secondary efficacy endpoints are listed in Section 2.3.3. Summaries for these endpoints will not be performed as a result of the early discontinuation. The collected data related to the other secondary efficacy endpoints will be listed for the Full Analysis Set.

6.3.1 Sensitivity Analyses of Other Secondary Efficacy Endpoints

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

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)

The exploratory efficacy endpoints are listed in Section 2.3.4. [redacted]

6.6 Subgroup Analyses

The subgroup analyses will not be conducted due to the early discontinuation of the study.

7. SAFETY ANALYSIS

All safety analyses will be performed using the Safety Set. Safety variables include 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 will be used as baseline for all analyses of that safety variable. A final on-treatment assessment will be defined as the last valid assessment obtained after baseline and through the end of the treatment 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 investigational product.

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 presented 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 for 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, each 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), and recommendations of permanent discontinuation or re-challenge with investigational product. Reported hypersensitivity events, adjudicated hypersensitivity events and study drug recommendation will be summarized by treatment group and for 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; 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 baseline at each assessment time point for quantitative variables will be presented by treatment group and for ontamalimab all doses for the following clinical laboratory variables.

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-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-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline PCI value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, and baseline and post-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 baseline category to each visit will be presented by treatment group and for 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
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+

Table 3 Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Age Range	Sex	Outlier Criteria[a]	
			Low	High
Glucose	All		NA	NA
Blood	All		NA	NA
Ketones	All		NA	NA
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 baseline at each post-baseline visit and at the end of the study will be presented by treatment group and for ontamalimab all doses.

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. The PCI criteria are listed in Table 4. The number and percentage of subjects with PCI post-baseline values will be tabulated by each treatment group and ontamalimab all doses. The percentages will be calculated relative to the number of subjects with at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, and baseline and post-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 baseline at each assessment time point will be presented by treatment group. ECG interpretation will be summarized by visit. A shift table from baseline to Week 16 for ECG interpretation results will be presented by treatment group and for ontamalimab all doses.

ECG 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 post-baseline PCI values will be tabulated by treatment group and for ontamalimab all doses. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-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 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 for each treatment group and for 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 for ontamalimab all doses.

Anti-drug antibody prevalence will also be calculated and summarized for each 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 for each treatment group and for 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 Stool Microbiology

Stool microbiology will be performed at the screening visit (Visit 1) or at any time a subject experience an increase in Gastrointestinal symptoms. Stool microbiology data will be listed for the Safety Set.

7.6.5 Physical Examination

Complete and targeted physical examinations will be performed at the time points specified in Table A1. Physical examination results will be listed for the Safety Set.

[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.

11. INTERIM ANALYSIS/DATA MONITORING (REVIEW) COMMITTEE

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

An interim analysis for the coprimary endpoints was planned after approximately the first 50% of all randomized subjects in both the SHP647-305 and SHP647-306 studies have either completed the studies or have prematurely withdrawn from the studies. The sample size was planned to be reassessed as part of this interim analysis. Due to the early discontinuation of this study, no interim analysis was conducted.

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, and Table 10.

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

Study day will be calculated as follows:

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

Table 6 Visit Windows (Study Day Based) – PRO, CDAI, and SES-CD

Visit	Planned Study Day	Start Day of Window	End Day of Window
Baseline	1	ICF date	≤1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	>98	EOT date

CDAI=Crohn's Disease Activity Index; EOT=end of treatment; ICF=informed consent form; PRO=patient-reported outcome; SES-CD=Simple Endoscopic Score for Crohn's Disease
Note: CDAI and PRO assessment are not collected during Week 2
To accommodate the schedule of the endoscopy/colonoscopy for the SES-CD prior to the Week 16 visit only, the start day of the analysis window will be extended to >88.

Table 7 Visit Windows (Study Day Based) – ADA Assessments

Visit	Planned Study Day	Start Day of Window	End Day of Window
Baseline	1	ICF date	≤1
Week 2	14	2	20
Week 4	28	21	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	>98	EOT date
Follow-up	EOT date + 112	EOT date + 1	EOF date

ADA=anti-drug antibody; EOF=end of follow-up; EOT=end of treatment; ICF=informed consent form

Table 8 Visit Windows (Study Day Based) – [redacted]

Visit	Planned Study Day	Start Day of Window	End Day of Window
Baseline	1	ICF date	≤1
Week 12	84	71	98
Week 16	112	>98	EOT date

EOT=end of treatment; ICF=informed consent form; [redacted]

Table 9 Visit Windows (Study Day Based) – Safety Lab and Vital Sign Assessments

Visit	Planned Study Day	Start Day of Window	End Day of Window
Baseline	1	ICF date	≤1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	>98	EOT date
Follow-up	EOT date + 112	EOT date + 1	EOF date

EOF=end of follow-up; EOT=end of treatment; ICF=informed consent form

Table 10 Visit Windows (Study Day Based) – ECG and Neurological Testing

Visit	Planned Study Day	Start Day of Window	End Day of Window
Baseline	1	ICF date	≤1
Week 16	112	2	EOT date
Follow-up	EOT date + 112	EOT date + 1	EOF date

ECG=electrocardiogram; EOF=end of follow-up; EOT=end of treatment; ICF=informed consent form
Note: ECG does not have scheduled assessments in the follow-up period.

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) starting during the screening period; however, collection of the daily e-diary data must begin at least 10 days before colonoscopy preparation.

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, 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:

- Screening: 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 7 out of the 10 most recent days are not available, then the 2-item PRO cannot be calculated for the subject at screening. Note that the subject must be confirmed as meeting the PRO subscore requirements at screening before a colonoscopy is performed.
- Visits 4, 5, and 6: 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 7 (Part 3): 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 screening (Visit 1, Part 2) and Week 16 (Visit 7, Part 2), 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) and Week 16/ET (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 A1.

The CDAI score at screening (Visit 1, Part 2) will be calculated using the following:

- Components 1 to 3 from subject-reported PRO-CD daily e-diary data collected >10 days before the start of colonoscopy preparation using the same most recent 7 of 10 days as described for the 2-item PRO
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected during screening (Visit 1) Part 1.
  Note: Hematology samples should be repeated if more than 3 weeks have elapsed before the day of colonoscopy to be able to use the hematocrit central laboratory results for the CDAI score calculation at screening. Hematocrit must not be older than 3 weeks before the day of colonoscopy.

The CDAI scores at Visits 4, 5, and 6 will be calculated using the following:

- Components 1 to 3 from subject-reported PRO-CD daily e-diary data collected >10 days before the visit using the same most recent 7 or 10 days as described for the 2-item PRO
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at the visit.

The CDAI score at the Week 16/ET visit will be calculated at Visit 7, Part 3 (after all evaluations are complete), using the following:

- Components 1 to 3 from subject-reported PRO-CD daily e-diary data collected >10 days before the start of colonoscopy preparation using the same most recent 7 or 10 days 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 3 of the Week 16/ET visit, where assessed.

The CDAI is the sum of all variables' 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, and Table 10.

If a subject has more than 1 assessment mapped into a given study visit with non-missing results, the assessment closest to the planned visit will be used for analysis. However, all post-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 the 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

For prior or concomitant medications, including rescue medications, incomplete (i.e, partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, the start date will be imputed first.

12.5.3.1 Incomplete Start Date

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

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP 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, 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, then 01 January will be assigned to the missing fields.

Missing Month Only

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

Missing Day Only

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

12.5.4 Incomplete Stop Date

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

Missing Day and Month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of IP, then the day and month of the date of the last dose of IP 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, 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, then 01 January will be assigned to the missing fields.

Missing Month Only

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

Missing Day Only

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

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

12.5.5 Missing Date Information for Adverse Events

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

12.5.5.1 Incomplete Start Date

The same rules as in Section 12.5.3.1 will be followed.

12.5.5.2 Incomplete Stop Date

Not applicable.

12.5.6 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, 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.

12.5.7 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, 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.

12.5.8 Character Values of Clinical Laboratory Variables

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

13. ANALYSIS SOFTWARE

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

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The following changes to the analysis specified in Protocol Amendment 2 dated 22 Nov 2019 have been made.

- Concomitant medications in the protocol are defined as any medications taken between the first dose of IP and the end of the safety follow-up period. For the purposes of analysis, these medications have been separated into concomitant medications that include medications taken during the treatment period and concomitant post-treatment medications that include medications taken after the treatment period ends.

- Due to the early discontinuation of the study before full enrollment and the resulting limited sample-size, planned analyses listed in the protocol were updated as follows:

  -Removed Per-protocol Set and Completers Set from study population for statistical analysis sets., these analysis sets were originally planned for sensitivity/supplementary analyses that will no longer be performed.

  - The analyses for coprimary and key secondary endpoints will be presented with descriptive statistics including unstratified CIs for the treatment difference. Originally planned inferential statistical testing and stratified CIs are not performed. As such, the control of multiplicity is no longer applicable

  - Sensitivity/supplementary analyses for coprimary and key secondary efficacy endpoints will not be performed.

  - Subgroup analyses for coprimary and key secondary efficacy endpoints will not be performed.

  - [redacted]

  - The interim analysis to reassess the sample size was not performed as enrollment did not reach the planned 50% of the target sample size.

- Added COVID-19 section.

15. REFERENCES

Best, W. R., Becktel, J. M. & Singleton, J. W. 1979. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology,* 77, 843-6.

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

Daperno, M., D'Haens, G., Van Assche, G., Baert, F., Bulois, P., Maunoury, V., Sostegni, R., Rocca, R., Pera, A., Gevers, A., Mary, J. Y., Colombel, J. F. & Rutgeerts, P. 2004. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc,* 60, 505-12.

Sandborn, Feagan, Panes, D'Haens, Colombel, Zhou, Huang, Enejosa, Pangan & Lacerda 2017. Safety and Efficacy of ABT-494 (Upadacitinib), an Oral Jak1 Inhibitor, as Induction Therapy in Patients with Crohn's Disease: Results from Celest. *Gastroenterology,* 152, S1308-S1309.

Appendix 1 Schedule of Activities

Table A1 Schedule of Assessments

Study Procedure	Screening[a]		Baseline	Treatment							Follow-up	
	Weeks -6 to -1		Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12	Week 16/ET[b]			Week 24[c]	Week 32[c]
Visit Number	1 (Part 1)[a]	1 (Part 2)[a]	2	3	4	5	6	7 (Part 1)[b]	7 (Part 2)[b]	7 (Part 3)[b]	8	9
Study Day	-42 to 0		1	14±3	28±3	56±3	84±3			112±3	168±7	224±7
Informed consent/assent	X											
Eligibility assessment	X		X							X[d]		
Demographics and medical history[e]	X											
Complete physical examination[f]	X									X		X
Targeted physical examination[f]		X	X		X	X	X					
Targeted neurological assessment[g]	X									X		X
Vital signs	X		X		X	X	X			X		X
Height	X											
Weight	X		X		X	X	X			X		X
12-lead ECG	X		X							X		
Chest x-ray[h]	X											
Contraception check[i]	X		X	X	X	X	X			X		X
Laboratory Assessments												
Hematology	X[j,k]		X		X	X	X	X				X
Serum chemistry	X[j]		X		X	X	X	X				X
Urinalysis	X[j]		X		X	X	X	X				X
Stool microbiology[l]	X[j]											
HBsAg, HBcAb, HCVAb[m]	X[j]											
HIV testing per local regulation[n]	X											
FSH[o]	X[j]											
Serum β-hCG[p]	X[j]											
Urine β-hCG[p]			X		X	X	X			X		X
TB test (PPD or QuantiFERON-TB Gold Plus)[q]	X											
JCV antibody banked sample[r]			X									
[redacted]			X				X	X				
[redacted]			X				X	X				
[redacted]			X				X	X				
[redacted]			X				X	X				
[redacted]			X	X	X	X	X	X				

Table A1 Schedule of Assessments

Study Procedure	Screening[a]		Baseline	Treatment							Follow-up	
	Weeks -6 to -1		Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12	Week 16/ET[b]			Week 24[c]	Week 32[c]
Visit Number	1 (Part 1)[a]	1 (Part 2)[a]	2	3	4	5	6	7 (Part 1)[b]	7 (Part 2)[b]	7 (Part 3)[b]	8	9
Study Day	-42 to 0		1	14±3	28±3	56±3	84±3			112±3	168±7	224±7
ADA and NAb sampling			X	X	X	X	X	X				X
Endoscopic Procedure												
Colonoscopy (including biopsy)[s]		X							X			
CD Assessments												
CDAI[t]		X			X	X	X			X		
PRO-CD daily e-diary data instruction	X											
PRO-CD daily e-diary data[u]	X	X	X	X	X	X	X	X	X	X		
SES-CD[v]			X							X		
Health Assessment[w]												
IBDQ			X			X	X			X		
[redacted]			X			X	X			X		
Hospitalizations, inpatient days, [redacted] (HRUA)					X	X	X			X		X
[redacted]					X	X	X			X		
[redacted]			X		X	X	X			X		
[redacted]			X							X		
SF-36, version 2, acute			X			X	X			X		
[redacted]			X							X		
Treatment Procedures												
Randomization[x]			X									
Administration of ontamalimab or placebo[x, y]			X		X	X	X					
Hypersensitivity monitoring[z]			X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Prior medications	X											
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool collection kit for stool sample[aa]	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;

Table A1 Schedule of Assessments

Study Procedure	Screening[a]		Baseline	Treatment							Follow-up	
	Weeks -6 to -1		Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12	Week 16/ET[b]			Week 24[c]	Week 32[c]
Visit Number	1 (Part 1)[a]	1 (Part 2)[a]	2	3	4	5	6	7 (Part 1)[b]	7 (Part 2)[b]	7 (Part 3)[b]	8	9
Study Day	-42 to 0		1	14±3	28±3	56±3	84±3			112±3	168±7	224±7

FSH=follicle-stimulating hormone; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCVAb=hepatitis C virus antibody; HIV=human immunodeficiency virus; HRUA=Healthcare Resource Utilization Assessment; IBDQ=Inflammatory Bowel Disease Questionnaire; IGRA= interferon-gamma release assay; JCV=John Cunningham virus; LTS=long-term safety extension; [redacted]; NAb=neutralizing antibody; [redacted]; PML=progressive multifocal leukoencephalopathy; PPD=purified protein derivative; PRO=patient-reported outcome; SES-CD=Simple Endoscopic Score for CD; SF-36 v2=Short Form-36 Health Survey, version 2; TB=tuberculosis; [redacted]

[a] Screening assessments will take place over more than 1 day (at least 2 visits will be necessary to complete the screening evaluations, including colonoscopy).

[b] Subjects who withdraw early during the treatment period should return for the ET visit and then enter into the safety follow-up period. The Week 16 (Visit 7) and ET visits consist of 3 parts:

- Part 1 of Visit 7 can either be done on the same day as Part 2 or be done up to 3 days before Part 2. If Parts 1 and 2 are done on the same day, blood samples must be taken before starting the colonoscopy preparation.
- Part 2 of Visit 7 must be completed within 10 days (preferably within 5 to 7 days) before Part 3; this will allow sufficient time to obtain the data from the centrally read colonoscopy.
- Part 3 of Visit 7 will take place on Day 112 ±3 days.

[c] Subjects NOT entering the maintenance study (SHP647-307) or LTS study (SHP647-304) at the completion of the Week 16 visit will need to complete the safety follow-up assessments. The Week 24 (Visit 8) 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 32 (Visit 9) visit will take place at the study site.

[d] The outcome of Visit 7, Part 3 is used to assess eligibility to enroll subjects in the maintenance (SHP647-307) or LTS (SHP647-304) studies. Please refer to the respective protocols for further details.

[e] Medical history will include CD history, cardiac history, and smoking history.

[f] 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.

[g] 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. Subjects with any unexplained positive item at screening that is suggestive of PML should be excluded. See Section 7.2.3.3 of the protocol for further details.

[h] A chest x-ray performed up to 12 weeks before screening (Visit 1) may be used if available; the official reading must be located in the subject's source documentation.

[i] 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.

Table A1 Schedule of Assessments

Study Procedure	Screening[a]		Baseline	Treatment							Follow-up	
	Weeks -6 to -1		Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12	Week 16/ET[b]			Week 24[c]	Week 32[c]
Visit Number	1 (Part 1)[a]	1 (Part 2)[a]	2	3	4	5	6	7 (Part 1)[b]	7 (Part 2)[b]	7 (Part 3)[b]	8	9
Study Day	-42 to 0		1	14±3	28±3	56±3	84±3			112±3	168±7	224±7

[j] Screening laboratory test results, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results of repeated tests must be reviewed for eligibility before the screening colonoscopy procedure.

[k] Hematology samples should be repeated if more than 3 weeks have elapsed before the day of colonoscopy to be able to use the hematocrit central laboratory results for the CDAI score calculation at screening.

Note: Hematocrit must NOT be older than 3 weeks before the day of colonoscopy.

[l] Diagnosis of *Clostridium difficile* infection should be made using the central laboratory. If for any reason the central laboratory is not available, see Appendix 5 of the protocol for guidance regarding alternate diagnostic algorithms. When a subject experiences an increase in gastrointestinal symptoms, which could be an exacerbation of disease, an infectious etiology must be evaluated including testing for *C. difficile* as described in Appendix 5 of the protocol.

[m] Subjects who test negative for HBsAg but positive for HBcAb without HBV DNA may be considered eligible. For subjects who test positive for HBcAb and negative for HBsAg, a blood sample should be taken for HBV DNA. Blood for HBV DNA reflex testing is collected for required subjects only. If HBV DNA is positive, these subjects will not be eligible.

[n] Testing may be performed at the site's local laboratory in accordance with country requirements, or at the central laboratory. Documentation of a negative HIV test result within 6 months prior to screening will be accepted.

[o] For confirmation of postmenopausal status in females who have had 12 consecutive months of spontaneous amenorrhea and are ≥51 years of age.

[p] Female subjects of childbearing potential; serum pregnancy test at screening (Visit 1) and urine pregnancy test at all other time points.

[q] A documented negative IGRA or PPD test within 12 weeks before screening (Visit 1) is acceptable provided that an IGRA result or PPD official reading and method is located in the source documentation.

[r] A serum sample will be collected and banked. It may be analyzed if a subject shows neurological symptoms suggestive of PML.

[s] Colonoscopy preparation will be according to local routine (see Protocol Section 7.2.2.4). Colonoscopy must be performed during the screening period, preferably within 5 to 7 days but no later than 10 days before baseline (Visit 2), to allow for adequate e-diary data collection for the 2-item PRO and CDAI scores and to obtain the centrally read endoscopic subscore to verify the subject's eligibility. Colonoscopy preparation may be done on the same day as the colonoscopy procedure. During the colonoscopy at screening (Visit 1, Part 2) and Week 16/ET, 10 biopsies will be collected from the most inflamed area of the mucosa; 2 samples each from the ileum, the 3 segments of the colon, and the rectum except when it is not possible due to impassable stenosis or previous partial colectomy/ileocolectomy. If the calculated CDAI scores is <220 or >450, or the PRO scores are outside the eligibility thresholds, the subject will be considered a screen failure and should not proceed with the colonoscopy preparation and/or the colonoscopy.

[t] The CDAI score at screening (Visit 1, Part 2) includes subject-reported PRO-CD daily e-diary data collected ≥10 days before the start of colonoscopy preparation.

The CDAI score at Visits 4, 5, and 6 includes subject-reported PRO-CD daily e-diary data collected ≥10 days before the visit.

The CDAI score at the Week 16/ET visit will be calculated at Visit 7, Part 3 (after all evaluations are complete) and includes subject-reported PRO-CD daily e-diary data collected ≥10 days before the start of colonoscopy preparation.

Note: All required components (including subject-reported PRO-CD daily e-diary data collected ≥10 days before the start of colonoscopy preparation and ≤3 weeks of central

Table A1 Schedule of Assessments

Study Procedure	Screening[a]		Baseline	Treatment							Follow-up	
	Weeks -6 to -1		Week 0/ Day 1	Week 2	Week 4	Week 8	Week 12	Week 16/ET[b]			Week 24[c]	Week 32[c]
Visit Number	1 (Part 1)[a]	1 (Part 2)[a]	2	3	4	5	6	7 (Part 1)[b]	7 (Part 2)[b]	7 (Part 3)[b]	8	9
Study Day	-42 to 0		1	14±3	28±3	56±3	84±3			112±3	168±7	224±7

hematocrit results) should be available to calculate the CDAI scores. See Section 7.2.2.3 of the protocol for further details.

[u] Patient-reported CD clinical signs and symptoms will be collected daily using a PRO-CD daily e-diary (electronic handheld device) starting during the screening period; however, collection of the daily e-diary data must begin at least 10 days before colonoscopy preparation. Subjects should be provided with the e-diary to take home on their first visit. Compliance will be assessed by the site staff, and the subject should be retrained on the appropriate use of the e-diary when compliance is below 80% (eg, <23 out of 28 e-diary entries). If at least 70% compliance cannot be achieved after repeated instructions during the screening period, noncompliant subjects will be automatically noneligible as they will not fulfill inclusion criterion 1 (see Protocol Section 4.1). If 7 out of the 10 most recent days are not available, then the 2-item PRO cannot be calculated for the subject at screening.

[v] The SES-CD score at baseline (Visit 2) and at Week 16/ET will be calculated using subscores of each of the segments investigated and centrally read from the colonoscopies performed at screening (Visit 1, Part 2) and Week 16 (Visit 7, Part 2), respectively.

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

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

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

[z] Beginning at Visit 2, 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.

[aa] 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 baseline (Visit 2).

Appendix 2 Geographic Regions

Table A2 Geographic Regions

Country	Region
Japan	Asia
Croatia	Eastern Europe
Czech Republic	Eastern Europe
Lithuania	Eastern Europe
Poland	Eastern Europe
Romania	Eastern Europe
Russia	Eastern Europe
Serbia	Eastern Europe
Austria	Western Europe
Germany	Western Europe
Italy	Western Europe
Netherlands	Western Europe
United Kingdom	Western Europe
Australia	ROW
Brazil	ROW
Israel	ROW
New Zealand	ROW
South Africa	ROW
United States	North America

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