CLINICAL STUDY PROTOCOL

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

Protocol Version and Date:

Original Protocol: 15 Dec 2017
Amendment 1: 21 Aug 2018
Amendment 2: 22 Nov 2019

PROTOCOL: SHP647-305

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)
DRUG:	SHP647
IND:	100,222
EUDRACT NO.:	2017-000575-88
SPONSOR:	Shire Human Genetic Therapies, Inc. ("Shire") 300 Shire Way, Lexington, MA 02421 US
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted] MD
PROTOCOL HISTORY:	Original Protocol: 15 Dec 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted] **Date:** [redacted]

[redacted] MD, [redacted]

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP647-305.

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).

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

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

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

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

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

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

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Nonserious Adverse Events (AEs) Required by the Protocol Form within 24 hours to Shire Global Drug Safety. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor by fax or e-mail using the details below.

Fax
[redacted] (North America)
[redacted] (Global)

Email
[redacted]

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

Pharmaceutical Product Development North America:

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

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

Pharmaceutical Product Development Latin America:

24 Hour Safety Hotline: [redacted]

24 Hour Safety Hotline Fax: [redacted]

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

24 Hour Safety Hotline: [redacted]

24 Hour Safety Hotline Fax: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.2.2.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	**E-mail Address**
North and South America, the European Union, and Rest of World	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (US)
[redacted]

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
β-hCG	beta-human chorionic gonadotropin
ADA	antidrug antibodies
AE	adverse event
AZA	azathioprine
BSFS	Bristol Stool Form scale
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
[redacted]	[redacted]
CI	confidence interval
CMH	Cochran-Mantel Haenszel
CNS	central nervous system
[redacted]	[redacted]
CSF	cerebrospinal fluid
CRO	contract research organization
DMC	data monitoring committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
[redacted]	[redacted]
EMA	European Medicines Agency
[redacted]	[redacted]
ET	early termination
EU	European Union
FAS	full-analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FWER	family-wise type I error rate
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody

HIPAA	Health Insurance Portability and Accountability Act
HRQL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
$IgG_{2\kappa}$	immunoglobulin G2 kappa
[redacted]	[redacted]
IGRA	interferon-gamma release assay
IRB	Institutional Review Board
IRT	interactive response technology
LP	lumbar puncture
LTS	long-term safety extension
[redacted]	[redacted]
MTX	methotrexate
NAb	neutralizing antibody
NRS	numerical rating scale
PCR	polymerase chain reaction
[redacted]	[redacted]
PFS	prefilled syringe
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
PRO	patient-reported outcome
Q4W	once every 4 weeks
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36	Short Form-36 Health Survey

SUSAR	serious unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent AE
TNF	tumor necrosis factor
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
[redacted]	[redacted]

STUDY SYNOPSIS

Protocol number: SHP647-305	**Drug:** SHP647
Title of the study: 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)	
Number of subjects (total and for each treatment arm): A total of 1032 subjects (387 subjects in the 25 mg SHP647 treatment group, 387 subjects in the 75 mg SHP647 treatment group, and 258 subjects in the placebo group) are planned for enrollment into the study.	
Investigator(s): Multicenter study.	
Site(s) and region(s): It is anticipated that the study will be conducted in approximately 19 countries. Regions will include North America; Europe, the Middle East, and Africa; Latin America; and Asia Pacific. Approximately 210 sites will be utilized.	
Study period (planned): 2018 to 2021	**Clinical phase:** 3

Objectives:

Coprimary: The coprimary objectives of this study are to evaluate the efficacy of SHP647 in subjects with moderate to severe Crohn's disease (CD) in:

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

Key secondary:

- To evaluate the efficacy of SHP647 in inducing clinical remission as measured by CD Activity Index CDAI
- To evaluate the efficacy of SHP647 in inducing enhanced endoscopic response based on centrally read colonoscopy
- To evaluate the efficacy of SHP647 in inducing clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)
- To evaluate the efficacy of SHP647 in inducing clinical response based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
- To evaluate the efficacy of SHP647 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 SHP647 in inducing endoscopic healing based on centrally read colonoscopy.

Other secondary:

- To evaluate the safety and tolerability of SHP647
- To evaluate the effect of SHP647 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 SHP647 induction treatment on other endoscopic outcomes
- To evaluate the effect of SHP647 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 SHP647 on incidence of hospitalizations and total inpatient days
- To evaluate the impact of SHP647 on incidence of CD-related and other surgeries.

Rationale:

This study is designed to evaluate the efficacy and safety of SHP647 in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.

The CD clinical development program includes 3 completed studies: 1 Phase 1 study (A7281008) and 2 Phase 2 studies (A7281006 and A7281007). The SHP647 dose selection (25 and 75 mg) for this study is based on data from these 3 previous studies, which evaluated the activity of SHP647 in adult patients with moderately to severely active CD based on CDAI scores between 220 and 450. The Phase 1 study (A7281008, TOSCA) and Phase 2 studies (A7281006, OPERA; and A7281007, OPERA II [long-term safety study]) that investigated the safety, tolerance, pharmacokinetics, and pharmacodynamic properties of SHP647 support further clinical development of SHP647 using subcutaneous (SC) administration in subjects with moderate to severe CD.

Investigational product, dose, and mode of administration:

The test product is SHP647 (a fully human immunoglobulin G2 kappa antihuman mucosal address in cell adhesion molecule [MAdCAM] monoclonal antibody), which will be provided as a sterile aqueous buffered solution for SC administration in a glass prefilled syringe (PFS) with a fixed needle. Each PFS contains 1 mL of SHP647 solution at an appropriate concentration to provide the intended dose of drug (25 or 75 mg). Additional information is provided in the current SHP647 investigator's brochure (IB).

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain SHP647.

Methodology:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of SHP647 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 SHP647 treatment group, 387 subjects in the 75 mg SHP647 treatment group, and 258 subjects in the placebo group) are planned for enrollment into the study. 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 SHP647, 75 mg SHP647, or placebo) in a 3:3:2 ratio. Randomization will be stratified based upon the subject's status of prior antitumor necrosis factor (TNF) treatment (naïve or experienced), glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline), and Simple Endoscopic Score for CD (SES-CD) at baseline (SES-CD ≥17 or SES-CD <17). Subjects will receive SC injections of SHP647 or placebo, using a 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], [redacted], safety, and health outcome assessments at these visits.

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). 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 treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

A planned interim analysis for the coprimary endpoints will take place 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 will be reassessed as part of this interim analysis.

Inclusion and exclusion criteria:

Inclusion criteria:

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and assent as applicable to participate in the study.
3. Subjects must be between ≥16 and ≤80 years of age at the time of the signing of the informed consent/assent form. Note: Subjects <18 years of age must weigh ≥40 kg and must have body mass index ≥16.5 kg/m^2.
4. Subjects must have active moderate to severe ileal (terminal ileum), ileocolic, or colonic CD at baseline (Visit 2) as defined by:
    a. CDAI score between 220 and 450 (inclusive) **AND**
    b. Presence of ulcerations that are characteristic to CD, as determined by a colonoscopy performed during screening, and as defined by the SES-CD >6 (SES-CD ≥4 for isolated ileitis) **AND**
    c. Meeting the following subscores in the 2-item PRO:
        i. Average of the abdominal pain subscores ≥5 (average worst daily pain on the 11-point numerical rating scale [NRS]) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous) **AND/OR**
        ii. Average of the daily stool frequency subscore ≥4 of type 6/7 (very soft stools/liquid stools) as shown in the Bristol Stool Form Scale (BSFS) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous).
5. Subjects must have a documented diagnosis (endoscopic with histology) of CD for ≥3 months before screening. Documented diagnosis is defined as:
    - A biopsy report to confirm the histological diagnosis **AND**
    - A report documenting disease duration based upon prior colonoscopy.

    Note: If a biopsy report is not available in the source document at the time of screening, the histology report of the biopsy performed mandatorily during the screening colonoscopy should be consistent with the CD diagnosis. If the histology diagnosis is not clear at this time point, the subject should not be randomized.
6. Subjects must be willing and able to undergo a colonoscopy during screening after all other inclusion criteria have been met.
7. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or mesalamine (5-aminosalicylic acid [5-ASA]), glucocorticoids, immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]), or anti-TNF. Subjects who have had an inadequate response to sulfasalazine or mesalamine should have also failed at least 1 other conventional treatment such as glucocorticoids.
8. Subjects receiving any treatment(s) for CD described in Section 5.2.1 of the protocol are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
9. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception for the duration of the study.

Exclusion criteria:

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

1. Subjects with indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of ulcerative colitis.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)

Maximum duration of subject involvement in the study:

- Planned duration of screening period: Up to 6 weeks
- Planned duration of treatment period: 16 weeks
- Planned duration of follow-up period: 16 weeks.

Endpoints and statistical analysis:

Analysis sets:

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

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

The per-protocol set will consist of all subjects in the FAS who do not have protocol deviations that may affect the coprimary efficacy endpoints.

The completer set will consist of all subjects in the FAS who have completed the Week 16 assessment for this study.

[redacted]

[redacted]

Coprimary efficacy endpoints:

The coprimary efficacy endpoints are:

- 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 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.
- Endoscopic response at Week 16 as measured by a decrease in SES-CD of at least 25% from baseline.

The coprimary efficacy endpoints, clinical remission at the Week 16 visit and endoscopic response at the Week 16 visit, will each be compared for each active treatment group (25 mg or 75 mg SHP647) to the placebo group using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use, and SES-CD at baseline for each of the stages of the study (stage 1 includes subjects whose primary efficacy data are used in the interim analysis and stage 2 includes all other subjects. Note: classification of stage 1 and stage 2 is based on the time of randomization rather than the time of study completion or termination). Subjects with missing data at the Week 16 visit will be considered failures and counted as nonresponders.

Weighted inverse normal p-value combination methods are used to combine the p-values from stage 1 and stage 2 through the following formula:

$$C(p_1, p_2) = 1 - \Phi[w_1 \Phi^{-1}(1-p_1) + w_2 \Phi^{-1}(1-p_2)]$$

Where p_1, p_2 are the p-values computed from the CMH chi-square test for each stage, $w_i^2 = n_i/(n_1 + n_2)$, n_1 and n_2 are the preplanned stage-wise sample sizes that are fixed at the time of the interim analysis based on an original total sample size, and Φ denotes the cumulative distribution function of the standard normal distribution (Bretz, et al., 2009a). Given that there is no possibility of stopping early for efficacy, that any potential stopping for futility of either or both doses of SHP647 is nonbinding, and that weights are prespecified, the test statistic $C(p_1, p_2)$ can be compared against the nominal alpha level to assess statistical significance (Chang, 2008).

The coprimary endpoints will each be tested by the following hypothesis:

$$H_0: \delta = 0$$
$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata. The common treatment difference is a weighted average of the stratum-specific treatment differences.

The global family-wise type I error rate (FWER) for the statistical tests of the coprimary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al. (2009b) will be utilized to propagate α from the coprimary endpoints to the key secondary endpoints and between the 2 SHP647 treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the coprimary endpoints (P) and alpha is propagated in a hierarchical manner to each of the 6 key secondary endpoints (K1–K6) within a pairwise treatment comparison. In order to pass alpha between the coprimary endpoints and the first key secondary endpoint, both coprimary endpoints must attain statistical significance.

Key secondary efficacy 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 worst daily abdominal pain ≤1 (based on the 4-point scale) over the 7 most recent days and average daily stool frequency ≤3 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days. 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 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.

The key secondary endpoints will be analyzed using the same approach as described for the coprimary endpoints. Subjects with missing key secondary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.

Other secondary efficacy endpoints:

- 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 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.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods:

- Binary endpoints will be compared between each active treatment group and the placebo group using a CMH chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use at baseline, and SES-CD at baseline. The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% CI using the method of Yan and Su (2010) and the p-value computed from CHM test will be provided. Subjects with missing binary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.
- Continuous endpoints that are only measured at baseline and the Week 16 visit will be analyzed using an analysis of covariance model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (Visit 2) (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% confidence intervals (CIs) for least squares mean treatment differences will be provided.
- Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation. The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

Safety analyses:

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

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

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events and percentage of TEAEs will be calculated by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, serious AEs, and deaths will be similarly summarized or listed.

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

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

STUDY SCHEDULE

Table 1: Schedule of Assessments

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]											
FSH[n]	X[j]											
Serum β-hCG[o]	X[j]											
Urine β-hCG[o]			X		X	X	X			X		X
TB test (PPD or QuantiFERON-TB Gold/TB Plus)[p]	X											

Table 1: 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
JCV antibody banked sample[q]			X									
[redacted]			X				X	X				
[redacted]			X				X	X				
[redacted]			X				X	X				
[redacted]			X				X	X				
[redacted]			X	X	X	X	X	X				
ADA and NAb sampling			X	X	X	X	X	X				X
Endoscopic Procedure												
Colonoscopy (including biopsy)[r]		X							X			
CD Assessments												
CDAI[s]		X			X	X	X			X		
PRO-CD daily e-diary data instruction	X											
PRO-CD daily e-diary data[t]	X	X	X	X	X	X	X	X	X	X		
SES-CD[u]			X							X		
Health Assessment[v]												
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		

Table 1: 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
Treatment Procedures												
Randomization[w]			X									
Administration of SHP647 or placebo[w, 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[y]	X					X	X					

Ab=antibody; ADA=antidrug antibodies; β-hCG=beta-human chorionic gonadotropin; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; [redacted]; ECG=electrocardiogram; [redacted]; ET=early termination; FSH=follicle-stimulating hormone; GDH=glutamate dehydrogenase; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HCV RNA=hepatitis C virus ribonucleic acid; HRUA=Healthcare Resource Utilization Assessment; IBD=inflammatory bowel disease; IBDQ=Inflammatory Bowel Disease Questionnaire; JCV=John Cunningham virus; LTS=long-term safety extension; [redacted]; NAb=neutralizing antibody; PCR=polymerase chain reaction; PGA=physician's global assessment; [redacted]; PML=progressive multifocal leukoencephalopathy; PPD=purified protein derivative; PRO=patient-reported outcomes; 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 should be scheduled 1 to 3 day(s) before Part 2; this will allow for blood samples to be taken before starting the colonoscopy preparation and before the colonoscopy procedure at Part 2 of the visit (Section 7.2.2.4)
- Part 2 of Visit 7 should be scheduled preferably 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 (SHP647-304) study 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.

Table 1: 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

[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 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 for further details.

[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] The detection of *Clostridium difficile* by toxigenic stool culture (stool culture followed by detection of toxin) is considered the gold standard for the diagnosis of the colonization or infection with pathogenic *C. difficile*. Comparable sensitivity may be achieved by direct testing of stool via point-of-use rapid membrane enzyme immunoassay card for both *C. difficile* toxin A and B and GDH antigen on a card. Use of the card for point-of-care screening is encouraged where permitted by local regulation; any samples showing a positive result with this method should be sent for toxigenic stool culture. Molecular techniques such as PCR for detection of toxin RNA are also acceptable alternatives. Refer to the laboratory manual for further guidance and instruction for *C. difficile* screening.

[m] If a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if the subject tests positive for antibody to hepatitis B surface antigen (also referred as anti-HBsAg) reflex testing. HCV RNA PCR reflex testing may be performed if the subject is HCVAb positive.

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

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

[p] A documented negative PPD test within 12 weeks before baseline (Visit 2) is acceptable provided that an interferon-gamma release assay official reading and method or test is located in the source documentation.

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

Table 1: 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

[r] Colonoscopy preparation will be according to local routine. Colonoscopy must be performed during the screening period within 5 to 7 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. 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. If the calculated CDAI scores is <220 or >450, the subject will be considered a screen failure and should not proceed with the colonoscopy preparation and/or the colonoscopy.

[s] 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 hematocrit results) should be available to calculate the CDAI scores. See Section 7.2.2.3 for further details.

[t] Patient-reported CD clinical signs and symptoms will be collected daily using a PRO-CD daily e-diary (electronic handheld device) starting from the first screening visit; however, collection of the daily e-diary data must begin at least 14 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 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 (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.

[u] 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.

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

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

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

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

Note: See Section 7.2 for the order in which assessments should be performed. Timing of visits is relative to baseline (Visit 2).

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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

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

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

1.2 Product Background and Clinical Information

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

SHP647 (previously known as PF-00547659) is a fully human immunoglobulin G2 kappa (IgG_{2k}) monoclonal antibody that binds to human MAdCAM to reduce lymphocyte homing to the gut and GI inflammation. SHP647 binds MAdCAM with high affinity and selectivity that prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM expressing sites in the high endothelial venules of the GI tract.

Always refer to the latest version of the SHP647 investigator's brochure (IB) for the overall risk/benefit assessment and the most accurate and current information regarding the pharmacokinetics, efficacy, and safety of SHP647.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

SHP647, a fully human $IgG_{2\kappa}$ antihuman MAdCAM monoclonal antibody, is under development for the treatment of CD. SHP647 prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM-expressing sites with high affinity and selectivity. Principal sites of MAdCAM expression on normal tissue include intestine, pancreas, stomach, esophagus, spleen, and to a lesser extent lung, liver, and bladder but not the central nervous system (CNS) (Steffen et al., 1996).

Although selective targeting of the MAdCAM receptors is a novel approach, the basic interference of lymphocyte homing by preventing the binding of these $\alpha_4\beta_7^+$ lymphocytes to the MAdCAM receptor and the resultant efficacy in CD is well established (Sandborn et al., 2013). SHP647 is differentiated from other molecules targeting the $\alpha_4\beta_7$-MAdCAM mediated lymphocyte trafficking used for the treatment of CD in that SHP647 blocks the interaction of $\alpha_4\beta_7^+$ lymphocytes with the MAdCAM receptor by selectively binding to MAdCAM on the endothelial cells surface in the gut (and related tissues) while the other molecules target the integrins on the infiltrating lymphocytes. Additionally, SHP647 does not bind to the vascular cell adhesion molecule (VCAM); therefore, SHP647 is not expected to affect lymphocyte homing or surveillance in the CNS or to be an effective treatment for multiple sclerosis.

This study is designed to evaluate the efficacy and safety of SHP647 in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.

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

Study A7281006 (OPERA) was a parallel, dose-ranging, randomized, double-blind, placebo-controlled study in which SHP647 was given as 3 subcutaneous (SC) dose levels (22.5, 75, and 225 mg) once every 4 weeks (Q4W) over an 8-week period. SHP647 was generally safe and well tolerated and there were no deaths. Three placebo-treated subjects and 9 subjects in the 22.5, 75, and 225 mg SHP647 groups discontinued treatment due to adverse events (AEs). Most treatment-emergent AEs (TEAEs) were mild or moderate in severity. Median serum concentrations of SHP647 increased with increasing dose. Positive antidrug antibodies (ADA) status did not appear to impact exposure to SHP647. The CD Activity Index (CDAI) was the primary instrument to assess the efficacy of SHP647; no statistically significant differences were noted between the active treatment arms and the placebo arm. Therefore, the study did not meet its primary endpoint. However, post hoc analysis indicated increased remission rates in subjects in the 22.5 mg or 75 mg treatment arms who had higher serum concentrations of high-sensitivity C-reactive protein (hsCRP) or higher scores of Simple Endoscopic Score for CD (SES-CD) at baseline.

Study A7281008 (TOSCA) was an open-label multi-center, Phase 1 sequential cohort study that evaluated the effects of a maximum induction dose of SHP647 on CNS system immune surveillance.

Subjects with inflammatory bowel disease (IBD) (including CD), with or without stoma, who failed or were intolerant to both anti-TNF and immunosuppressant therapy and who had moderate to severe active disease underwent a lumbar puncture (LP), completed induction therapy with 3 doses of 225 mg SHP647 4 weeks apart, and then underwent a second LP 2 (±1) weeks later. The primary endpoint was the percent change from baseline (pretreatment) in absolute lymphocyte count in cerebrospinal fluid (CSF) in subjects with IBD after receiving 3 doses of 225 mg SHP647. The mean percentage change from baseline in absolute lymphocytes in CSF was 61.76% with a median change of 35.2% (range: -70.2% to 267.8%). The post-treatment LP/pretreatment LP geometric mean ratio for CSF lymphocytes was 1.33 with the lower bound of the 80% confidence interval (CI)=1.13, which was greater than 0.5, supporting rejection of the null hypothesis (ie, that the percent decrease in total lymphocytes counts after treatment would be ≥50% (equivalent to the geometric mean ratio in total lymphocyte counts being ≤0.5). This result supports the hypothesis that SHP647 does not impair trafficking of lymphocytes into the CNS and thus should not impair CNS immune surveillance.

Study A7281007 (OPERA II) was a Phase 2 open-label extension study to provide additional long-term safety data on subjects with moderate to severe CD who completed Study A7281006 or Study A7281008 and wished to continue to receive SHP647. SHP647 75 mg (with potential dose escalation to 225 mg) SC given every 4 weeks for 72 weeks was generally well tolerated in subjects with CD over the treatment period evaluated in this study. In subjects with positive ADA or neutralizing antibody (NAb) status, exposure to SHP647 was not affected. Serum concentrations of SHP647 in this study were consistent with what was predicted based on the Feeder Study A7281006. There were 2 deaths in the study: 1 subject died of multiple organ dysfunction syndromes in the treatment period and 1 subject died of metastatic neoplasm in the follow-up period. Neither death was reported as related to treatment with the study drug by the investigators. The most frequently reported serious adverse event (SAE) was CD in either the treatment period or the follow-up period. The system organ class with the most subjects experiencing TEAEs was GI disorders. Although Study A7281007 was not placebo controlled, the exploratory efficacy results (based on the modified Harvey Bradshaw Index) indicated that the effect of SHP647 on disease activity was maintained over the duration of treatment.

The SHP647 dose selection (25 and 75 mg) for this study is based on data from these 3 previous studies, which evaluated the activity of SHP647 in adult patients with moderately to severely active CD based on CDAI scores between 220 and 450. The results of a post hoc analysis of remission rate by baseline elevated serum concentration of hsCRP suggested that the greatest treatment effect was at a dose of 22.5 mg. Similarly, post hoc analysis of remission rates by endoscopic severity assessed using the Simple Endoscopic Score for CD (SES-CD) suggested best efficacy at a dose of 75 mg. Therefore, both dosage regimens 25 and 75 mg Q4W have been selected for the Phase 3 testing. The Phase 1 study (A7281008, TOSCA) and Phase 2 studies (A7281006, OPERA; and A7281007, OPERA II [long-term safety study]) that investigated the safety, tolerance, pharmacokinetics, and pharmacodynamic properties of SHP647 support further clinical development of SHP647 using SC administration in subjects with moderate to severe CD.

2.2 Study Objectives

2.2.1 Coprimary Objectives

The coprimary objectives of this study are to evaluate the efficacy of SHP647 in subjects with moderate to severe CD in:

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

2.2.2 Secondary Objectives

2.2.2.1 Key Secondary Objectives

The key secondary objectives are as follows:

- To evaluate the efficacy of SHP647 in inducing clinical remission as measured by CDAI
- To evaluate the efficacy of SHP647 in inducing enhanced endoscopic response based on centrally read colonoscopy
- To evaluate the efficacy of SHP647 in inducing clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)
- To evaluate the efficacy of SHP647 in inducing clinical response based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
- To evaluate the efficacy of SHP647 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 SHP647 in inducing endoscopic healing based on centrally read colonoscopy.

2.2.2.2 Other Secondary Objectives

The other secondary objectives are as follows:

- To evaluate the safety and tolerability of SHP647
- To evaluate the effect of SHP647 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 SHP647 induction treatment on other endoscopic outcomes
- To evaluate the effect of SHP647 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 SHP647 on incidence of hospitalizations and total inpatient days
- To evaluate the impact of SHP647 on incidence of CD-related and other surgeries.

2.2.3 Exploratory Objectives

The exploratory objectives are as follows:

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

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of SHP647 in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.

At study initiation, a total of 1032 subjects (387 subjects in the 25 mg SHP647 treatment group, 387 subjects in the 75 mg SHP647 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.

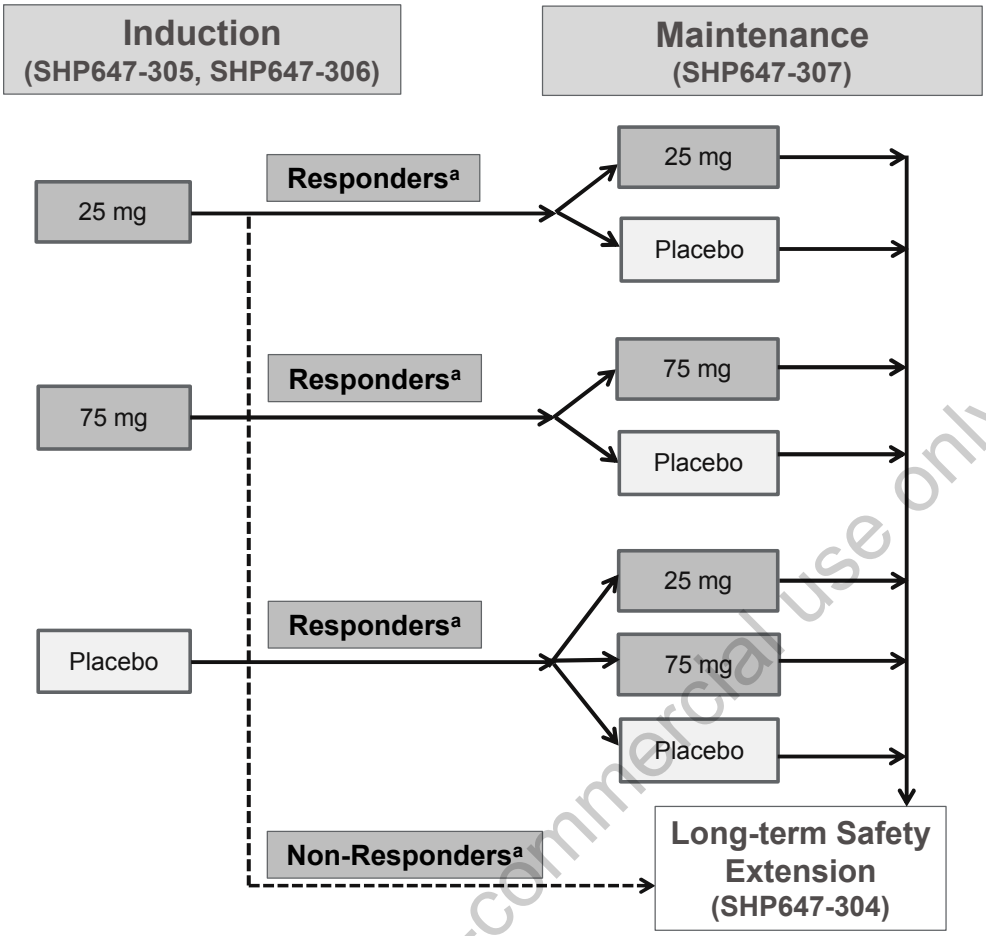
The study consists of a screening period up to 6 weeks and a 16-week treatment period. After the screening period, eligible subjects will be randomized to receive 1 of 3 treatments (25 mg SHP647, 75 mg SHP647, or placebo) in a 3:3:2 ratio. Randomization will be stratified based upon the subject's status of prior anti-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 SC injections of SHP647 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], [redacted] safety, and health outcome assessments at these visits and at the time points specified in Table 1.

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 treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

A planned interim analysis for the coprimary endpoints will take place 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 will be reassessed as part of this interim analysis. See Section 9.5 for further details of the planned interim analysis.

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; CD=Crohn's disease; CDAI= CDAI=Crohn's Disease Activity Index; NRS=numerical rating scale; PRO=patient-reported outcomes; 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.*

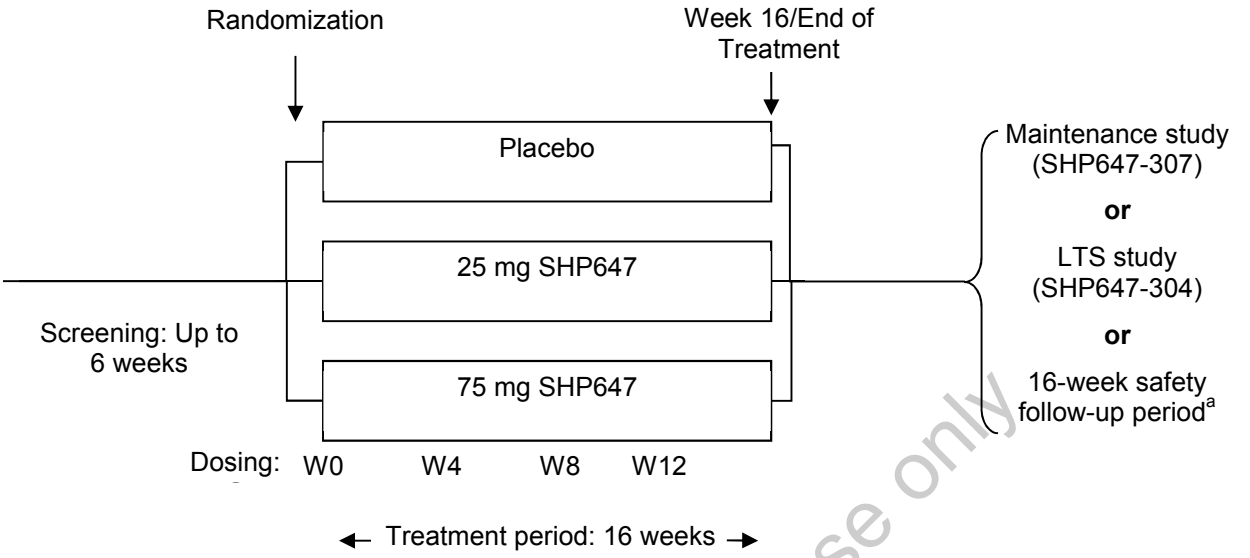
2. Subject has a decrease of at least 70 points in CDAI score (CDAI-70) from baseline.

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

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

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

Figure 2: Study Design Flow Chart



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.

Note: A planned interim analysis for the coprimary endpoints will take place 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.

3.1.1 Rationale for Coprimary Endpoints

In this study, clinical remission, as measured by a decrease below prespecified thresholds in the 2-item PRO (abdominal pain severity and very soft stool/liquid stool frequency [as shown in the Bristol Stool Form Scale, BSFS]), and enhanced endoscopic response, as measured by a decrease in SES-CD, will be the primary instruments to assess the efficacy of SHP647.

Rationale for Abdominal Pain Severity

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

This definition is further supported by a study conducted in a similar condition (irritable bowel syndrome) that examined the minimal clinically important difference on the 11-point NRS for abdominal pain (Spiegel et al., 2009) as well as post hoc analyses of the Phase 2 data from the SHP647 program (Study A7281006, OPERA).

Rationale for Very Soft Stool/Liquid Stool Frequency

Diarrhea is the most common sign in the presentation of CD, affecting approximately 85% of patients with a diagnosis of CD. In the CDAI, the number of liquid or soft stools (each day for 7 days) is used with a multiplier of 2. The coprimary endpoints for clinical remission in studies SHP647-305 and SHP647-306 requires the use of a definition without any such multiplying factor and will use the BSFS for defining the very soft or liquid stools according to types 6 and 7, respectively. A retrospective study of PROs in CD based on data from randomized controlled studies using rifaximin and methotrexate showed that a mean daily stool frequency score of ≤1.5 had an area under the receiving operating characteristic curve of 0.79 (Khanna et al., 2015) and provided a potential cutoff for defining remission as measured by CDAI. In a recent study to select the attributes determining overall disease severity and to rank the importance of and to score these individual attributes for both CD and UC based on specialist opinion, a sample of at least 10 loose stools per week was considered as an attribute contributing to overall disease severity in CD (Siegel et al., 2016). Based on post hoc analyses of the Phase 2 data in the SHP647 program (Study A7281006, OPERA) and by choosing the population of subjects satisfying the moderate to severe CD inclusion criteria, various cutoffs were explored and a stool frequency ≤2.0 was found to be optimal in terms of treatment separation while still allowing for a reasonable threshold for remission. Based on these and other recent data that support this cutoff, an average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) has been chosen as the stool frequency criterion for clinical remission.

Endoscopic Response

Endoscopic response is defined in 2 ways:

- 25% reduction in SES-CD score (“endoscopic response”)
- 50% reduction in SES-CD score (“enhanced endoscopic response”).

“Endoscopic response” will be used as a coprimary endpoint and “enhanced endoscopic response” will be used as a key secondary endpoint in this study as these magnitudes of changes are likely to be clinically relevant.

Mucosal healing or “endoscopic healing” is considered to be a pivotal long-term target in the treatment of CD; however, partial healing or endoscopic response may also provide benefits. Endoscopic response can be an important indicator that the mucosal inflammation has decreased as an effect of the investigational product. Some treatments may result in a partial initial response, even though at a later stage a complete response may occur. Median duration of remission after 1 year treatment with infliximab was similar in subjects achieving complete absence of mucosal ulcer to subjects who achieved significant but incomplete mucosal healing (D'Haens et al., 2002).

The benefit of endoscopic response was also shown in the SONIC study; the presence of endoscopic response (defined in that study as at least a 50% decrease in endoscopic score at Week 26 of treatment) identified subjects most likely to be in corticosteroid-free clinical remission at Week 50 (Ferrante et al., 2013). The proportion of patients requiring major abdominal surgery in a single-center cohort study with infliximab was similar with complete healing or with partial healing. (Schnitzler et al., 2009; Panaccione et al., 2013). Subjects with such a treatment response should be identified by endoscopic assessment in order not to misclassify them as nonresponders and underestimate the response to the treatment.

3.1.2 Rationale for Key Secondary Endpoints

Clinical Remission Defined by CDAI Score

Conventionally, a CDAI score of <150 has been used to define clinical remission. While there has been widespread use of the CDAI over a long period of time, the items do not contribute equally to the score, and symptom items reported by subjects are not specific for CD and are not sensitive for inflammation seen at colonoscopy. There has been movement away from using the CDAI by regulatory authorities to the use of PROs and objective measures of disease such as endoscopy (Williet et al., 2014). However, for benchmarking or for comparative effectiveness purposes, CDAI endpoints are expected to be used.

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

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

The CDAI has been the traditionally used measure to assess clinical response and clinical remission in CD. In the CDAI, the degree of abdominal pain is one of 8 variables and is used with a multiplier of 5 in the overall score. Importantly, it is based on a 4-point scale, with scores ranging from 0 (none) to 3 (severe). With the shift to the new endpoint as evident from the coprimary endpoint of clinical remission in this study, it is still important to allow for a frame of reference to the existing standard for response, based on the CDAI components. A daily average abdominal pain threshold of ≤1 will help achieve this as 1 on the 4-point scale corresponds to mild abdominal pain. Although direct mapping between the scales has not been established, this will approximate to a score of 3 on the 11-point NRS scale, as this falls within the mild pain range on the NRS based on the literature.

Based on post hoc analyses of the Phase 2 data in the SHP647 program, regulatory requirements, and treatment separation assumptions, a threshold for the average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) was chosen for the coprimary endpoint of clinical remission. However, given the limited data available for this endpoint, recent evidence from literature suggesting that thresholds ≤3 are likely to be quite stringent (Sandborn et al., 2017), and the refractory nature of the disease in those with moderate to severe CD, it is also important to assess the effects of treatment using a more realistic measure. Hence, for this key secondary endpoint of clinical remission, average daily stool frequency ≤3 of type 6/7 (very soft stools/liquid stools) has been chosen as the appropriate threshold.

Clinical Response

The goal of measuring clinical remission is to have a sensitive clinical measure to assess the complete absence of symptoms or the stabilization of noninflammatory symptoms. However, as response and remission are considered to be on a continuum of improvement or response to treatment, clinical remission is generally the chosen measurement over clinical response. Therefore, clinical remission is used as coprimary endpoint and clinical response is used as a key secondary endpoint in this study.

Clinical response is defined in Section 9.8.2.1. For both clinical response criteria, an additional requirement is that the symptom not being used to assess clinical response (ie, abdominal pain severity or very soft stool/liquid stool frequency) must remain unchanged/not worsen from the baseline score, or meet the criteria for clinical remission for that item of the 2-item PRO (either a 2-item PRO subscore of average daily stool frequency ≤2 of type 6/7 [very soft stools/liquid stools] as shown in the BSFS or average worst daily abdominal pain ≤3 [based on 11-point NRS] over the 7 most recent days).

The rationale for needing to meet at a minimum clinical response definition for either abdominal pain severity or very soft stool/liquid stool frequency (and not necessarily both) is based on the supposition that a lack of improvement in 1 of these symptoms is not necessarily an indicator of eventual lack of response (as assessed by the stricter clinical remission criterion). Based on Phase 2 data, it has been observed that the magnitude of placebo response rate can be higher for abdominal pain than for stool frequency. Therefore, the additional criterion of at least a 2-point decrease in abdominal pain severity from baseline is required for assessing clinical response for abdominal pain. Overall, the definition of clinical response used for this study has been chosen to allow for the maximal pool of subjects to be assessed for the effect of treatment and, if appropriate, the continuation of therapy in the maintenance study (SHP647-307).

Composite Score Endpoint of Both Clinical Remission by 2-item PRO and Endoscopic Response at Week 16

In theory, as the degree of inflammation decreases due to the effect of treatment, both clinical signs and symptoms of CD as well as endoscopic appearance can improve. However, in any given subject, the rates of clinical improvement and endoscopic improvement may not be the same. There are reasons for this discrepancy when evaluating clinical and endoscopic improvement in the same time period, including clinical symptoms not being well correlated to the mucosal inflammation. Due to the transmural feature of the disease, symptoms can correspond to the inflammation in some of the other gut layers as well. Previous clinical studies and clinical observations indicate that the improvement of clinical signs and symptoms and the improvement in endoscopic appearance may not go hand in hand. Significant clinical improvement can precede significant endoscopic improvement. The healing process of the gut mucosa may take a long time and may depend on the baseline severity of the endoscopic appearance, which may not be in line with the actual baseline severity of the symptoms. Therefore, when evaluating clinical remission together with endoscopic endpoints, improvement in endoscopic scores could be more relevant than evaluating mucosal healing in the induction phase.

For these reasons, the key secondary composite endpoint (which takes into account both clinical and endoscopic response to treatment in the same subject) consists of the evaluation of the clinical remission together with the endoscopic response.

Complete Endoscopic Healing

Endoscopic healing will be defined in 2 ways:

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

- Complete endoscopic healing defined by SES-CD=0-2.

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

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

3.2 Duration and Study Completion Definition

Each subject's final visit in this study may be at the end of the treatment period (Week 16), if continuing to Study SHP647-307 or SHP647-304, or at the end of the safety follow-up period (Week 32), if not continuing to either of these studies. In either case, the final visit will be in person at the site. A subject's maximum duration of participation is expected to be approximately 38 weeks: a screening period of up to 6 weeks, a treatment period of 16 weeks, and a safety follow-up period of 16 weeks (if applicable). It is expected that the study will be completed in approximately 3 years.

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

3.3 Sites and Regions

It is anticipated that the study will be conducted in approximately 19 countries. Regions will include North America; Europe, the Middle East, and Africa; Latin America; and Asia Pacific. Approximately 210 sites will be utilized.

4. STUDY POPULATION

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

4.1 Inclusion Criteria

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and assent as applicable to participate in the study.
3. Subjects must be between ≥16 and ≤80 years of age at the time of the signing of the informed consent/assent form. Note: Subjects <18 years of age must weigh ≥40 kg and must have body mass index ≥16.5 kg/m^2.
4. Subjects must have active moderate to severe ileal (terminal ileum), ileocolic, or colonic CD at baseline (Visit 2) as defined by:
    a. CDAI score between 220 and 450 (inclusive) **AND**
    b. Presence of ulcerations that are characteristic to CD, as determined by a colonoscopy performed during screening, and as defined by the SES-CD >6 (SES-CD ≥4 for isolated ileitis) **AND**
    c. Meeting the following subscores in the 2-item PRO:
        i. Average of the abdominal pain subscores ≥5 (average worst daily pain on the 11-point NRS) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous) **AND/OR**
        ii. Average of the daily stool frequency subscore ≥4 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous).
5. Subjects must have a documented diagnosis (endoscopic with histology) of CD for ≥3 months before screening. Documented diagnosis is defined as:
    - A biopsy report to confirm the histological diagnosis **AND**
    - A report documenting disease duration based upon prior colonoscopy.

    Note: If a biopsy report is not available in the source document at the time of screening, the histology report of the biopsy performed mandatorily during the screening colonoscopy should be consistent with the CD diagnosis. If the histology diagnosis is not clear at this time point, the subject should not be randomized.

6. Subjects must be willing and able to undergo a colonoscopy during screening after all other inclusion criteria have been met.
7. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or mesalamine (5-ASA), glucocorticoids, immunosuppressants (AZA, 6-MP, or MTX), or anti-TNF. Subjects who have had an inadequate response to sulfasalazine or mesalamine should have also failed at least 1 other conventional treatment such as glucocorticoids.
8. Subjects receiving any treatment(s) for CD described in Section 5.2.1 of the protocol are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
9. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception (as described in Section 4.4) for the duration of the study.

4.2 Exclusion Criteria

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

1. Subjects with indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of ulcerative colitis.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with presence of enterovesical (ie, between the bowel and urinary bladder) or enterovaginal fistulae.
5. Subjects with current symptomatic diverticulitis or diverticulosis.
6. Subjects with obstructive colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for CD during the treatment period.
7. Subjects with past medical history of multiple small bowel resections resulting in clinically significant short bowel syndrome.
8. Subjects requiring total parenteral nutrition.
9. Subjects with past medical history of bowel surgery resulting in an existing or current stoma. Subjects who had a j-pouch are excluded as a j-pouch could result in a stoma.
10. Subjects have had prior treatment with SHP647 (formerly PF-00547659).
11. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.

12. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than AZA, 6-MP, or MTX) or continuous antibiotics (>2 weeks) for the treatment of CD within 30 days before baseline (Visit 2).
13. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
14. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).
15. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
16. Subjects have received lymphocytes apheresis or selective monocyte granulocytes apheresis within 60 days before baseline (Visit 2).
17. Subjects have received enteral nutrition treatment within 30 days before baseline (Visit 2).
18. Subjects have received parenteral or rectal glucocorticoids or rectal 5-ASA within 14 days before screening colonoscopy.
19. Subjects have taken >20 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 14 days before baseline (Visit 2) or have taken ≥40 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 6 weeks before baseline (Visit 2).
20. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before screening (Visit 1).
21. Subjects have received a live (attenuated) vaccine within 30 days before baseline (Visit 2).
22. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis [subjects with *C. difficile* infection at screening may be allowed retest after treatment], evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before baseline (Visit 2).
23. Subjects with abnormal chest x-ray or other imaging findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray, computed tomography scan, etc., performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation).
24. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) who have not completed a generally accepted full course of treatment before baseline (Visit 2) are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon-gamma release assay (IGRA) performed.

Subjects who have no history of previously diagnosed active or latent TB are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before baseline (Visit 2). If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

- An IGRA is strongly recommended for subjects with a prior bacillus Calmette-Guérin vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON-TB Gold/TB Plus In-Tube Test.
- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent tuberculosis, a positive test on repeat will exclude the subject. Subjects with a history of active or latent tuberculosis infection must follow instructions for "Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met" in this criterion.
- Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray, taken within the 3 months before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
- A chest x-ray performed within 3 months before screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.

25. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
26. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on the targeted neurological assessment during the screening period (Section 7.2.3.3).
27. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
28. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
    - Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.
    - Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
    - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening (Visit 1).
    - History of significant cerebrovascular disease within 24 weeks before screening (Visit 1).
29. Subjects who have had significant trauma or major surgery within 4 weeks before screening (Visit 1), or with any major elective surgery scheduled to occur during the study.
30. Subjects with evidence of or suspected liver disease, liver injury due to methotrexate or primary sclerosing cholangitis.
31. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Note: If a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if the subject tests positive for antibody to hepatitis B surface antigen (also referred as anti-HBsAg) reflex testing.
32. Subjects with positive hepatitis C antibody (HCVAb) with confirmation by HCV-ribonucleic acid (RNA) polymerase chain reaction (PCR) reflex testing.
33. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening (Visit 1). Note: Screening laboratory tests, if the results are 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 must be reviewed for eligibility prior to the screening colonoscopy procedure.

- Alanine aminotransferase and aspartate aminotransferase levels ≥2.5 times the upper limit of normal (ULN)
- Total bilirubin level ≥1.5 times the ULN (except where attributed to elevation in unconjugated bilirubin in subjects with documented diagnosis of Gilbert's syndrome)
- Hemoglobin level ≤80 g/L (8.0 g/dL)
- Platelet count ≤100 × 10^9/L (100,000 cells/mm^3) or ≥1000 × 10^9/L (1,000,000 cells/mm^3)
- White blood cell count ≤3.5 × 10^9/L (3500 cells/mm^3)
- Absolute neutrophil count <2 × 10^9/L (2000 cells/mm^3)
- Serum creatinine level >1.5 times the ULN or estimated glomerular filtration rate <30 mL/min/1.73m^2 based on the abbreviated Modification of Diet in Renal Disease Study Equation.

34. Subjects with a known infection with human immunodeficiency virus, as documented in their medical history.
35. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse.
36. Subjects using marijuana (cannabis) or related products for recreational purposes, who have a known dependency per the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (including urine drug screen and medical history).
37. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
38. Female subjects who are planning to become pregnant during the study period.
39. Male subjects who are planning to donate sperm and do not agree not to do so for the duration of the study and through 16 weeks after last dose of investigational product.
40. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

4.3 Restrictions

- For the purposes of this protocol, dietary supplements (such as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties) are considered to be concomitant medications (Section 5.2).

- Smoking is considered to be a risk factor for CD. Reports have shown that smoking is not only related to the onset, relapse, and exacerbation of CD, but also that smoking cessation lowers the postoperative recurrence rate (Ueno et al., 2013). Subjects should inform the investigator of any changes to their smoking habits during the study (including starting or stopping smoking). Use of nicotine patches should be recorded as concomitant medication (Section 5.2.1).

4.4 Reproductive Potential

The potential effects of SHP647 on embryofetal or postnatal development have not yet been assessed in animals or humans; these will be assessed in future studies. To minimize the risk of unintentional exposure of the embryo or fetus in the clinical study, all sexually active male and female subjects who, in the opinion of the investigator, are biologically capable of having children and with their partners are at risk of pregnancy, must agree to use an appropriate form of contraception, in accordance with the package instructions/leaflet, for the duration of the active treatment period and for at least 16 weeks after the last dose of investigational product.

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

During the screening visit, the investigator or designee in consultation with the subject will confirm the subject's childbearing potential status. For subjects of childbearing potential, it must be confirmed and documented that the subject has selected the most appropriate method of contraception from the permitted list of contraception methods. Subjects must affirm the consistent and correct use of at least one of these selected methods. Regular contraception check discussions will take place at the time points specified in Table 1 (ie, at each site visit) and will be documented. In addition, the subject must be instructed to call the site immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

4.4.1 Contraceptive Methods for Female Study Subjects

Sexually active females of childbearing potential must already be using a highly effective form of contraception, and must be advised to use appropriate contraceptives throughout the study period and for 16 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert.

Female subjects should be in one of the following categories:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥51 years of age); postmenopausal status should be confirmed by follicle-stimulating hormone (FSH) testing.
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks poststerilization or has medically confirmed ovarian failure.

- Females of childbearing potential with a negative serum pregnancy test result at screening and a negative urine pregnancy test result at baseline (Visit 2). Females of childbearing potential must agree to practice true abstinence (refrain from sexual activity that could result in pregnancy) or agree to use appropriate methods of highly effective contraception.

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

- Combined (estrogen- and progestogen-containing) hormonal contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal) stabilized for at least 30 days before the screening visit (Visit 1)
- Progestogen-only hormonal contraception associated with inhibition of ovulation plus a barrier method
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization/vasectomized partner with documented absence of sperm in the postvasectomy ejaculate
- True abstinence (Section 4.4).

4.4.2 Contraceptive Methods for Male Study Subjects

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

Appropriate methods of contraception for male subjects are:

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

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

- Use of a highly effective method of contraception listed in Section 4.4.1 **OR** an acceptable method of contraception (failure rate of >1% per year):
    - Female condom with spermicide (use by female sexual partner); however, if spermicide is not available in the country, additional contraception (ie, one of those listed below) must be used in addition to a female condom
    - Intrauterine device with spermicide

- Contraceptive sponge with spermicide
- Intravaginal system (eg, vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide).

4.5 Withdrawal of Subjects

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

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 16/early termination (ET) (Visit 7) are to be performed. All subjects who discontinue treatment with investigational product should also undergo the protocol-specified 16-week safety follow-up period. In the event that subjects are unable to attend in person for the follow-up visits, all efforts should be made to collect information on AEs and concomitant medications. Comments (spontaneous or elicited) or complaints made by the subject must be recorded. The reason for termination and date of stopping investigational product must be recorded.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

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

- AEs
- SAEs
- Protocol violations
- Failure to return for visits.

A subject should be withdrawn from study treatment:

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

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

If a subject withdraws their consent, no further evaluation should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

4.5.2 Reasons for Withdrawal

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

Reasons for discontinuation include but are not limited to:

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

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

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

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal remedies and vitamins) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the first dose of investigational product. Use of biologics for indications other than CD during the 90 days before screening must also be recorded.

Subjects must have had an inadequate response to, or lost response to, or had intolerance to at least 1 conventional treatment such as sulfasalazine or 5-ASA, glucocorticoids, immunosuppressants (AZA, 6-MP, or MTX), or anti-TNF.

Inadequate response:	The subject experiences continued disease activity despite treatment with an adequate therapeutic dose and treatment course (dictated by the product label and international CD therapeutic guidelines)
Loss of response:	The subject experiences relapse after an initial clinical response or remission
Intolerance:	The subject has a history of having experienced an unacceptable or dose limiting toxicity associated with the use of the agent.

All prior and concomitant CD-specific treatments will be recorded. The subject's entire history of biologic CD-specific treatments will be recorded.

5.2 Concomitant Treatment

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

5.2.1 Permitted Treatment

Subjects must remain on stable doses of permitted CD treatments until completion of the Week 16 visit, unless decreases are required because of AEs. Stable doses of the following treatments for CD are permitted as concomitant medication:

- Oral sulfasalazine or 5-ASA, providing that the dose is stable for at least 2 weeks before baseline (Visit 2)
- Immunosuppressants (AZA, 6-MP, or MTX), providing that the dose is stable for at least 8 weeks before baseline (Visit 2)
- Oral glucocorticoids (prednisone or equivalent [Appendix 3] up to a maximum of 20 mg/day or budesonide up to a maximum of 9 mg/day), providing that the dose is stable for at least 2 weeks before baseline (Visit 2). After baseline (Visit 2), a stable dose of 20 mg/day prednisone or equivalent oral systemic corticosteroid dose is allowed. Steroids may be decreased due to AEs.

Note: Rectal 5-ASA and parenteral or rectal glucocorticoids are prohibited from within 14 days before screening colonoscopy.

Antidiarrheal opiate drugs such as IMODIUM® (loperamide), LOMOTIL® (diphenoxylate hydrochloride and atropine sulfate), tincture of opium, and codeine will be recorded. Subjects must be using such products in a stable regimen for at least 2 weeks before randomization at baseline (Visit 2). Reported use of any antidiarrheal opiate medicines will assist the investigator response to Question 5 of the CDAI.

Subjects using medicinal marijuana (cannabis) under a physician's prescription, and who obtain the product from a licensed pharmacy or provider, should continue to use it under the same regimen for the duration of the study, unless otherwise instructed by the investigator or treating physician. Such subjects must be using the product, in a stable regimen, for at least 3 months before screening.

Routine nonlive vaccinations are allowed during the study.

Dietary and herbal supplements and probiotics are allowed in the study, provided they are being taken at stable doses at the time of the baseline visit (Visit 2) and for the duration of the study. They should be recorded as concomitant medications.

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

Antibiotics are permitted, with the exception of antibiotics used to treat the underlying disease or any continuous antibiotic treatment exceeding 2 weeks within 30 days before starting PRO-CD daily e-diary data collection in the screening period or before Week 16 (Visit 7, Part 1).

5.2.2 Prohibited Treatment

Table 2 details the minimum required number of days before baseline (Visit 2) for common prior treatments that are excluded medications for this study.

Table 2: Common Excluded Treatments

	Excluded without any timeframe	Minimum Required Number of Days Before Baseline (Visit 2)			
Treatment		**14 days**	**30 days**	**60 days**	**90 days**
SHP647 (PF-00547659) in a previous study	X				
Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab)	X				
Parenteral and rectal glucocorticoids		X[a]			
Rectal 5-ASA		X[a]			
Investigational products			X[b]		
Live (attenuated) vaccine			X		

Table 2: Common Excluded Treatments

	Excluded without any timeframe	Minimum Required Number of Days Before Baseline (Visit 2)			
Treatment		**14 days**	**30 days**	**60 days**	**90 days**
Nonbiologics with immunomodulatory properties[c]			X		
Anti-TNF treatment				X	
Lymphocytes apheresis or selective monocyte granulocytes apheresis				X	
Biologics with immunomodulatory properties (other than anti-TNFs) including biosimilars					X

5-ASA=5-aminosalicylate; TNF=tumor necrosis factor.

[a] The minimum required number of days before baseline (Visit 2) for rectal 5-ASA and parenteral or rectal glucocorticoids is defined as 14 days before screening colonoscopy (Section 4.2, exclusion criterion 18).

[b] Or 5 half-lives if longer.

[c] Off-label usage of immunosuppressants used in transplantation or other nonestablished therapies for CD (eg, mycophenolate mofetil, cyclosporine, rapamycin, thalidomide, tofacitinib, or tacrolimus)

Treatments not listed in Table 2 may be considered allowable; see Section 5.2.1 for further details.

In addition to the treatment listed in Table 2, the following common treatments are excluded medications for this study:

- Prednisone dose >20 mg/day, budesonide >9 mg/day, or other equivalent oral systemic corticosteroid dose
- Bismuth subsalicylate products
- Fecal macrobiota transplantation.

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

Enteral nutrition is not permitted from within 30 days of baseline (Visit 2) or at any time during the study.

5.2.3 Rescue Therapy

Subjects must maintain their stable dose of background CD treatment, unless dose reduction or discontinuation are required due to associated AEs. If a subject requires initiation of a new therapy or increase in glucocorticoids for CD above the SHP647-305 or SHP647-306 baseline (Visit 2), the subject should be withdrawn from study treatment and enter the safety follow-up period, and appropriate treatment should be given at the discretion of the investigator.

Subjects who enter the safety follow-up period will no longer need to abstain from the medications that were prohibited during the baseline (Visit 2) and treatment periods. High-dose glucocorticoids and other CD treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated during the safety follow-up period without prior discussion with the sponsor study physician or designee due to the long half-life of SHP647.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is SHP647 (a fully human IgG_{2k} antihuman MAdCAM monoclonal antibody), which will be provided as a sterile aqueous buffered solution for SC administration in a glass PFS with a fixed needle. Each PFS contains 1 mL of SHP647 solution at an appropriate concentration to provide the intended dose of drug (25 or 75 mg). Additional information is provided in the current SHP647 IB.

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain SHP647.

6.1.1 Blinding the Treatment Assignment

The placebo syringes and solution will match the SHP647 syringes in appearance. The fill volume for all syringes will be the same.

6.2 Administration of Investigational Products

6.2.1 Interactive Response Technology for Investigational Product Management

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

6.2.2 Allocation of Subjects to Treatment

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

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 SHP647, 75 mg SHP647, 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 $\geq$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 investigational product allocated to the subject, once eligibility has been determined. Individual subject treatment will be automatically assigned by the IRT system.

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

6.2.3 Dosing

Investigational product (SHP647 or placebo) will be administered subcutaneously by qualified site personnel Q4W (Weeks 0, 4, 8, and 12). See Section 7.2 for the timing of dosing relative to other procedures.

Investigational product should be administered in the anterolateral right or left thigh. If there are clinical reasons why the investigational product cannot be administered in the thigh, the investigational product may be administered in the deltoid area or abdomen with appropriate documentation. The location of the investigational product administration will be recorded.

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

Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is dispensed by qualified staff members.

6.2.4 Unblinding the Treatment Assignment

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

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

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

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

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

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

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

6.3.2 Packaging

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

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

6.3.3 Storage

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

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified minimum/maximum thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range.

Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

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

6.3.4 Special Handling

The investigational product should be protected from light and should not be frozen. Do not shake.

6.4 Drug Accountability

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

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

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented in the subject's source document and/or other investigational product record.

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

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

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

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

6.5 Subject Compliance

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

7. STUDY PROCEDURES

7.1 Study Schedule

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of assessments (Table 1), in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

7.1.1 Screening Period

7.1.1.1 Screening Visit (Visit 1)

Subjects will be screened within 6 weeks before the first dose of investigational product to determine eligibility to participate in the study and to perform the other assessments and procedures specified in Table 1. Each subject or subject's parent or legally authorized representative must participate in the informed consent process and provide written informed consent/assent before any assessments or procedures specified in the protocol are performed. Screening assessments will take place over more than 1 day (at least 2 visits will be necessary to complete the screening evaluations, including colonoscopy).

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

A subject may be rescreened if their condition has changed and they may potentially be eligible. Subjects may be rescreened 1 time only. Note: Screening laboratory tests, 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.

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.

Collection of the daily e-diary data must begin at least 14 days before colonoscopy preparation. Colonoscopy preparation will be according to local routine.

Colonoscopy must be performed on all subjects after the majority of other eligibility criteria (eg, laboratory values and 2-item PRO and CDAI scores) are met. It must be performed during the screening period within 5 to 7 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 (Section 7.2.2.4). If the calculated CDAI scores is <220 or >450, the subject will be considered a screen failure and should not proceed with the colonoscopy preparation and/or the colonoscopy. All colonoscopies will be evaluated using the SES-CD (Appendix 2).

If a subject has had the following procedures performed as a part of standard medical care within 12 weeks before screening (Visit 1), these procedures do not need to be repeated as a part of screening:

- Chest x-ray
- Documented negative PPD test or IGRA for TB.

7.1.1.2 Baseline Visit (Visit 2, Week 0)

The baseline visit (Visit 2) will take place on Day 1 (Week 0). The assessments and procedures specified in Table 1 will be performed.

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

Results of the baseline laboratory tests are not required for investigational product administration but must be reviewed as soon as possible thereafter.

7.1.2 Treatment Period

7.1.2.1 Visits 3, 4, 5, and 6 (Weeks 2, 4, 8, and 12)

Visits 3, 4, 5, and 6 are scheduled to take place on Day 14 ±3 days (Week 2), Day 28 ±3 days (Week 4), Day 56 ±3 days (Week 8), and Day 84 ±3 days (Week 12), respectively. The assessments and procedures specified in Table 1 will be performed.

7.1.2.2 Final On-treatment Visit: Visit 7, Parts 1, 2, and 3 (Week 16/Early Termination)

The Week 16/ET visit (Visit 7) consists of 3 parts.

Part 1 of Visit 7 should be scheduled 1 to 3 day(s) before Part 2; this will allow for blood samples to be taken before starting the colonoscopy preparation and before the colonoscopy procedure at Part 2 of the visit. The Week 16/ET assessments and procedures that will take place during Part 1 are specified in Table 1.

Part 2 of Visit 7 should be scheduled preferably within 5 to 7 days before Part 3; this will allow sufficient time to obtain the data from the centrally read colonoscopy. The Week 16/ET assessments and procedures that will take place during Part 2 are specified in Table 1.

Part 3 of Visit 7 will take place on Day 112 ±3 days. The Week 16/ET assessments and procedures that will take place during Part 3 are specified in Table 1.

At Part 3 of Visit 7, after review of CD assessments, health outcome assessments, and safety assessments, it will be determined whether the subject should enroll in the maintenance (SHP647-307) or LTS (SHP647-304) studies or enter the follow-up period of this study. Entry into the maintenance or LTS studies is dependent upon whether the subject fulfills the efficacy entry criteria of the maintenance study (SHP647-307), including achieving endoscopic and/or clinical response, and whether the subject agrees to participate.

The Week 16 assessments and procedures will also form the ET assessments for any subjects who are withdrawn early or discontinued from the study.

7.1.3 Follow-up Period

Subjects who are withdrawn early from the study, or who do not enter either the maintenance or LTS studies, should enter the 16-week safety follow-up period for safety monitoring.

During the safety follow-up period, the Week 24 visit (Visit 8) will take place on Day 168 ±7 days, or 8 weeks ±7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study. This visit will routinely be conducted by telephone; however, as an exception, the visit can be performed as a study site visit if preferred.

At the end of the safety follow-up period, there will be a visit at the site on Day 224 ±7 days, or 16 weeks ±7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study; this visit will form the Week 32 visit (Visit 9). The assessments and procedures specified in Table 1 will be performed, including querying for SAEs, AEs, and concomitant medications and treatments. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (Section 8.1).

Subjects who are proceeding to the maintenance or LTS studies will not enter the safety follow-up period.

7.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

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

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

- Health outcome and patient-reported questionnaires
- Vital signs and ECG
- Laboratory sample collection
- Investigational product administration
- Colonoscopy is performed at a separate visit (Section 7.2.2.4).

Note: Blood and tissue samples may be stored for up to, but for no longer than, 25 years.

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics will be recorded at screening (Visit 1).

7.2.2 Efficacy

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

Patient-reported CD clinical signs and symptom data will be collected daily using a PRO-CD daily e-diary (electronic handheld device) starting from the first screening visit; however, collection of the daily e-diary data must begin at least 14 days before colonoscopy preparation. Subjects will enter data on CD signs and symptoms items using the e-diary, which will be provided to subjects at the start of the study. Compliance will be assessed by site staff at each visit. The site staff will instruct the subject on the appropriate use of the e-diary when compliance is below 80% (eg, <23 out of 28 e-diary entries). If 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 (Section 4.1).

Subjects will be asked to record the following signs and symptom data, as experienced over the previous 24 hours, in the e-diary:

- Abdominal pain severity (numeric rating scale [NRS])
- Very soft stool/liquid stool frequency (as shown by BSFS type 6/7)
- Total stool frequency
- Rectal bleeding frequency
- Rectal urgency frequency
- Nausea severity
- Vomiting frequency
- Incontinence frequency
- Abdominal pain used in CDAI
- General wellbeing.

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.
- Visits 3, 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.
The PRO-CD daily e-diary is presented in Appendix 2.

7.2.2.2 Simple Endoscopic Score for Crohn's Disease

The SES-CD will be performed at the time points specified in Table 1. The SES-CD score at 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.

The SES-CD is a simple scoring system based on 4 endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of affected surface, and presence and severity of stenosis [narrowing]) measured in the same 5 ileocolonic segments as the CD index of severity. Overall, values on the SES-CD range from 0 to 56, with higher values indicating more severe disease. The 4 endoscopic variables are scored from 0 to 3 in each bowel segment (ileum, right/transverse/left colon, and rectum):

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

A complete colonoscopy is required (including visualization of the terminal ileum).
The maximum stenosis score in a segment distal to another evaluable segment cannot exceed 2, so that the stenosis scores cannot exceed a total of 11 (Reinisch et al., 2017).

Evidence of active inflammation and ulceration is required at screening (Visit 1), in the form of a centrally read score of at least 1 in one or more ileocolonic segments in the Presence of Ulcers component of the SES-CD, as well as a total score of >6.

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

For the evaluation of efficacy, in cases where 1 or 2 segments cannot be fully evaluated by central endoscopic readers, ileocolonic segments that are evaluable during screening (Visit 1) and Week 16/ET (matching segments approach) will be utilized.

The SES-CD is presented in Appendix 2.

7.2.2.3 Crohn's Disease Activity Index

The CDAI is a composite measure with 8 components; 3 components (abdominal pain severity, very soft stool/liquid stool frequency, and general wellbeing) will be self-reported by the subject and will be recorded as part of the daily e-diary, as described in Section 7.2.2.1 and 5 components will be recorded at the time points specified in Table 1.

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 (Section 7.2.2.1) and
- 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 (Section 7.2.2.1) and
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at the visit.

The CDAI score at 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 (Section 7.2.2.1) and
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at Part 1 and Part 3 of the Week 16/ET visit, where assessed.

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

The CDAI is presented in Appendix 2.

7.2.2.4 Colonoscopy and Histology

Colonoscopy will be performed at the time points specified in Table 1.

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

In general, a complete colonoscopy should be performed; this includes visualization of the rectum, sigmoid colon, left colon, transverse colon, right colon, ileocecal valve, and the terminal ileum. At screening, an incomplete colonoscopy will not be accepted; only a few exceptions will be evaluated on a case by case basis (eg. presence of impassable narrowing without any clinical signs of bowel obstruction and when the same time the investigated segments provide the SES-CD score required for inclusion). Similarly, a complete colonoscopy is the aim at Week 16/ET, with the exception of the presence of impassable stenosis or other CD-related complications as cause of failure to complete the colonoscopy procedure.

The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during colonoscopy. To achieve consistency in capturing and assessing endoscopic video recordings, each participating site will use an integrated hardware/software solution and associated tools for the capture and transmission of endoscopy video recordings for central reading. Nonreadable endoscopic images, as assessed by the investigator, should not be sent for central reading. The colonoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's medical record.

During 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. Colonoscopy and biopsy procedures will be defined in a colonoscopy instructions manual and/or reference card(s), on which all sites will be trained. Colonoscopy results will be reviewed by a central reader.

[redacted]
(Appendix 2). Biopsies for conventional histologic assessment will be collected in formalin and shipped to the central laboratory. The central laboratory will register all biopsies and create paraffin blocks. Blocks will be batched and shipped on an agreed schedule to specialty laboratory, where tissue processing (sectioning, hematoxylin and eosin staining, and affixation to glass slides), digitalization, and uploading of images will occur. All images for a subject will be scored by the same qualified central pathologists blinded to the subject and treatment sequence information, according to the scoring modality.

7.2.3 Safety

7.2.3.1 Medical and Medication History

Medical history will be documented at screening (Visit 1), including CD history, cardiac history, and smoking history. Prior and concomitant medications and procedures will also be documented at the time points specified in Table 1.

7.2.3.2 Physical Examination (Including Height and Weight)

Complete and targeted physical examinations will be performed at the time points specified in Table 1. Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; eyes; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; back; and lymph nodes. Targeted physical examination includes the review of the following body systems: skin and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

Weight will be measured at the time points specified in Table 1. Height will be measured at screening (Visit 1) only.

Changes after the screening visit that are deemed clinically significant in the opinion of the investigator will be recorded as an AE.

7.2.3.3 Targeted Neurological Assessment

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

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

Subjects with any unexplained positive neurological assessment item at screening that is suggestive of PML should be excluded from enrollment in the study (exclusion criterion 25, Section 4.2).

The neurological assessment plan is summarized in Table 3.

Table 3: Neurological Assessment Plan

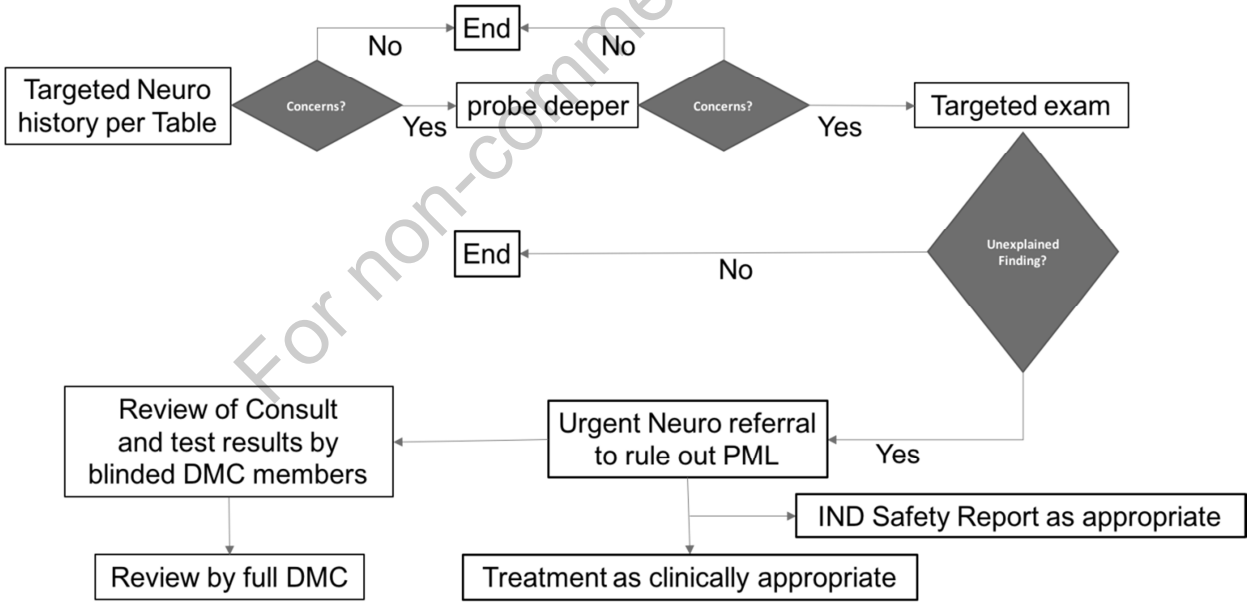
Domain	Step 1: Targeted Neurological History	Step 2: If Abnormal Response
Vision	Diplopia or visual/visual field loss	Perform visual field assessment
Motor	Major motor weakness (eg, legs, arms)	Test leg strength (hopping, foot tapping), finger tapping, pronator drift and bilateral muscle strength
Tactile sensation	Paresthesia, anesthesia in any domain (peripheral, central)	Pinprick test
Coordination/Cerebellar	Clumsiness, difficulty with walking, writing, or fine motor skills, etc.	Finger-nose, heel-shin, heel-toe walk, writing sample, draw a clock

Table 3: Neurological Assessment Plan

Domain	Step 1: Targeted Neurological History	Step 2: If Abnormal Response
Speech	Dysarthria, expressive aphasia	Naming objects, repeat multipart phrase, observe for dysarthria or aphasia
Verbal comprehension	Agnosia, receptive aphasia	Test to follow routine commands, eg, close eyes, touch finger to ear
Cognition/Behavior	New onset of difficulties with memory or thinking, important changes in behavior	Recall 3 objects over 1 minute, serial 7s, proverbs. Changes in activities of daily living over prior 6 months

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

Figure 3: Flow Diagram for Quarterly Neurological Assessments



DMC=Data Monitoring Committee; IND=investigational new drug; Neuro=neurological; PML=progressive multifocal leukoencephalopathy.

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

7.2.3.4 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent and/or assent is signed until the end of the study or the defined follow-up period stated in Section 7.1.3 (Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.3.5 Vital Signs

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

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

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

Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius or Fahrenheit. Tympanic temperature may also be used.

Any deviations from baseline (Visit 2) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE, unless documented in the subject's medical history as a pre-existing medical condition.

7.2.3.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant.

Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

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

Serum chemistry

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

Hematology

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

Virology

- hepatitis B surface antigen (HBsAg)
- hepatitis B core antibody (HBcAb)
- hepatitis B surface antibody (also referred as anti-HBsAg) if HBsAg is negative and HBcAb is positive
- hepatitis C virus antibody (HCVAb)
- HCV ribonucleic acid polymerase chain reaction if HCVAb is positive

Urinalysis

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

Virology test results must be confirmed as negative before enrollment in the study; if a virology test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor but will not be collected in the electronic case report form (eCRF) database.

Stool microbiology will be performed at the screening visit (Visit 1). The detection of *Clostridium difficile* by toxigenic stool culture (stool culture followed by detection of toxin) is considered the gold standard for the diagnosis of the colonization or infection with pathogenic *C. difficile*. Comparable sensitivity may be achieved by direct testing of stool via point-of-use rapid membrane enzyme immunoassay card for both *C. difficile* toxin A and B and glutamate dehydrogenase antigen on a card. Use of the card for point-of-care screening is encouraged where permitted by local regulation; any samples showing a positive result with this method should be sent for toxigenic stool culture. Molecular techniques such as PCR for detection of toxin RNA are also acceptable alternatives. Refer to the laboratory manual for further guidance and instruction for *C. difficile* screening.

A TB test (PPD or QuantiFERON-TB Gold/TB Plus) will be performed at the screening visit (Visit 1). A documented negative PPD test within 12 weeks before baseline (Visit 2) is acceptable provided that an IGRA official reading and method or test is located in the source documentation.

A serum sample will be collected and banked for John Cunningham virus antibody testing at baseline (Visit 2). It may be analyzed if a subject shows neurological symptoms suggestive of PML.

All laboratory assessments should be performed at central laboratories, with the exception of the following assessments: stool microbiology (local or central laboratory) and TB test (PPD or QuantiFERON-TB Gold/TB Plus) (refer to laboratory manual for details).

7.2.3.7 Pregnancy Test and Follicle-stimulating Hormone Test

A beta-human chorionic gonadotropin (β-hCG) pregnancy test will be performed on all females of childbearing potential at the time points specified in Table 1; if pregnancy is suspected; or on withdrawal of the subject from the study. A serum pregnancy test will be performed at the screening visit (Visit 1); all other pregnancy tests will be urine tests.

Pregnancy tests are not required for females of nonchildbearing potential who have undergone hysterectomy or bilateral oophorectomy, have medically confirmed ovarian failure, or are medically confirmed postmenopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; postmenopausal status should be confirmed by FSH testing in females who have had 12 consecutive months of spontaneous amenorrhea and are 51 years of age or older).

7.2.3.8 Electrocardiogram

A 12-lead ECG will be recorded at the time points specified in Table 1.

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

7.2.3.9 Chest X-ray

A chest x-ray will be performed during screening (Visit 1). If a subject has had a chest x-ray performed as a part of standard medical care within 12 weeks before screening (Visit 1), it does not need to be repeated as a part of screening. The official reading must be located in the subject's source documentation.

7.2.3.10 Antidrug Antibodies and Neutralizing Antibodies

A blood sample for measurement of ADA and NAb will be collected at the time points specified in Table 1. Blood samples must be collected before administration of investigational product.

7.2.4 Others

7.2.4.1 [redacted]

[redacted]

7.2.4.2 [redacted]

[redacted]

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

[redacted]

[redacted]

7.2.4.3 Health-related Quality of Life Assessments

Each subject will complete the HRQL assessments at the site during the visits specified in Table 1, using an electronic device. All health outcome and patient-reported questionnaires should be completed before any other assessments. The study site staff should check for completion of all PRO questionnaires.

It is important to note that PRO assessments are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and PRO data collected from subjects. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded by the investigator.

Inflammatory Bowel Disease Questionnaire

The IBDQ is a psychometrically validated PRO instrument for measuring the disease-specific HRQL in subjects with inflammatory bowel disease, including CD. The IBDQ consists of 32 items, which are grouped into 4 domains: bowel, systemic, emotional, and social function (Irvine et al., 1994). The 4 domains are scored as follows:

- Bowel function: 10 to 70
- Systemic function: 5 to 35
- Emotional function: 12 to 84
- Social function: 5 to 35.

The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better HRQL. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement.

The IBDQ is presented in Appendix 2.

[redacted]

The [redacted] is presented in Appendix 2.

[redacted]

The [redacted] and [redacted] are presented in Appendix 2.

[redacted]

Short Form-36 Health Survey (Version 2, Acute Form)
The SF-36 is a generic quality-of-life instrument that has been widely used to assess HRQL of subjects. Generic instruments are used in general populations to assess a wide range of domains applicable to a variety of health states, conditions, and diseases. The SF-36 consists of 36 items that are aggregated into 8 multi-item scales (physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional, and mental health), with scores ranging from 0 to 100 (Ware and Sherbourne, 1992). Higher scores indicate better HRQL.

[redacted]

7.2.4.4 Healthcare Resource Utilization Assessments

Hospitalizations, inpatient days, and [redacted] will be recorded at the time points specified in Table 1. Information regarding Crohn's disease-related and other surgeries will be collected from subjects during the treatment period.

7.2.5 Volume of Blood to Be Drawn From Each Subject

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

Table 4: Volume of Blood to Be Drawn From Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Hematology	2	7	14
Serum chemistry	6	7	42
HBsAg	2	1	2
HBcAb	2	1	2
HCV Ab	2	1	2
FSH	2	1	2
Serum β-hCG[a]	2	1	2
TB test (QuantiFERON-TB Gold/TB Plus or PPD)	3	1	3
JCV antibody banked sample	3.5	1	3.5
[redacted]			
[redacted]	2	3	6
[redacted]	5	3	15

Table 4: Volume of Blood to Be Drawn From Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
[redacted]	4	3	12
[redacted]	3	6	18
ADA and NAb sampling	3	7	21
Total (mL)			**144.5**

Ab=antibody; ADA=antidrug antibodies; β-hCG=beta-human chorionic gonadotropin; [redacted]; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HCV=hepatitis C virus; JCV=John Cunningham virus; [redacted]; NAb=neutralizing antibody; PPD=purified protein derivative; TB=tuberculosis.

[a] β-hCG testing for female subjects only.

[c] If a catheter is used, the first mL is to be discarded; then take 4 mL into appropriate tube for [redacted]. A total of 5 mL of blood drawn has been used in determination of sample volume.

The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 144.5 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

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

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

All AEs are collected from the time the informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured in the subject's source document. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the subject's source document.

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

8.1.1 Severity Categorization

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

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

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

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Outcome Categorization

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

- Fatal
- Not recovered/Not resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown.

8.1.4 Symptoms of the Disease Under Study

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

8.1.5 Clinical Laboratory and Other Safety Evaluations

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

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

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

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

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

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

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

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

8.1.7 Abuse, Misuse, Overdose, and Medication Error

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

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

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

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

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

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

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

There is no specific antidote for overdose with SHP647. Treatment should be symptomatic and supportive.

8.1.8 Unexpected Adverse Event

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

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

8.1.9 Suspected Unexpected Serious Adverse Reaction

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

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

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

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is Section 6.8 of the SHP647 IB, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to Shire Global Drug Safety and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (Section 8.1.7) unless they result in an SAE.

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

8.2.3 Serious Adverse Event Definition

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

- Results in death
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs.

For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).

- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an ED or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3 and must be reported to Shire Global Drug Safety and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

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

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

In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs (ie, SUSARs) occurring during all interventional studies across the SHP647 program.

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

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

9.3 Data Handling Considerations

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

9.4 Statistical Analysis Process

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

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

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

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

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

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

A planned interim analysis for the coprimary endpoints will take place 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. Recruitment will not pause for this interim analysis. The purpose of the unblinded interim analysis is to reassess the appropriateness of the premises used for the coprimary endpoints when the study was designed. There is no possibility to stop early for overwhelming efficacy as the studies must continue in order to enroll an appropriate number of subjects in the SHP647-307 study. The reassessment of sample size will be performed using conditional power methods. Results at the interim analysis may be futile for one or both of the SHP647 doses and lead to the discontinuation of that dose for CD or the SHP647 CD program. Full details of the interim analysis, the guidelines for increasing the sample size, and futility rules to stop a dose will be included in a prespecified interim analysis SAP. The interim analysis SAP will be finalized before the interim analysis is conducted.

The planned interim analysis will be conducted by an external independent statistical group and given to the independent Interim Analysis Review Committee; the individuals involved in the day-to-day conduct of the study will not be involved in the interim analysis nor have access to the results of the interim analysis. The sponsor will only be notified by the Interim Analysis Review Committee of recommendations to modify the SHP647 CD program according to the guidelines specified in the interim analysis SAP.

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

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

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

9.6 Sample Size Calculation and Power Considerations

Graphical methods are used to control the global family-wise type I error rate (FWER) at the .05 level (2-sided) for the comparisons of the 2 SHP647 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 was calculated based on the chi-square test of proportions using nQuery Advisor® Version 7.0 (Statistical Solutions Ltd, Cork, Ireland) for an individual SHP647 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 SHP647 treatment group, 387 subjects in the 75 mg SHP647 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% SHP647 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% SHP647 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 5 provides the power for detecting a treatment difference between a SHP647 treatment group and the placebo group for the key secondary endpoints.

Table 5: Power to Detect the Corresponding Treatment Effect for Key Secondary Endpoints

Key Secondary Endpoint at Week 16	SHP647 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.

9.7 Study Population

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

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

The per-protocol set will consist of all subjects in the FAS who do not have protocol deviations that may affect the coprimary efficacy endpoints.

The completer set will consist of all subjects in the FAS who have completed the Week 16 assessment for this study.

The PK set will consist of all subjects who have received at least 1 dose of investigational product and who have at least 1 evaluable postdose PK concentration value.

The pharmacodynamic (PD) set will consist of all subjects who have received at least 1 dose of investigational product and who have at least 1 evaluable postdose PD value.

9.8 Efficacy Analyses

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

9.8.1 Coprimary Efficacy Endpoints

The coprimary efficacy endpoints are:

- Clinical remission at the Week 16 visit as defined by the following: 2-item PRO subscores of average worst daily abdominal pain ≤3 (based on 11-point NRS) over the 7 most recent days and average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days. The 7 most recent days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the endpoint will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the endpoint will be treated as missing.
- Endoscopic response at Week 16 as measured by a decrease in SES-CD of at least 25% from baseline.

The coprimary efficacy endpoints, clinical remission at the Week 16 visit and endoscopic response at the Week 16 visit, will each be compared for each active treatment group (25 mg or 75 mg SHP647) to the placebo group using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use, and SES-CD at baseline for each of the stages of the study (stage 1 includes subjects whose primary efficacy data are used in the interim analysis and stage 2 includes all other subjects. Note: classification of stage 1 and stage 2 is based on the time of randomization rather than the time of study completion or termination). Subjects with missing data at the Week 16 visit will be considered failures and counted as nonresponders.

Weighted inverse normal p-value combination methods are used to combine the p-values from stage 1 and stage 2 through the following formula:

$$C(p_1, p_2) = 1 - \Phi[w_1 \Phi^{-1}(1-p_1) + w_2 \Phi^{-1}(1-p_2)]$$

Where p_1, p_2 are the p-values computed from the CMH chi-square test for each stage, $w_i^2 = n_i/(n_1 + n_2)$, n_1 and n_2 are the preplanned stage-wise sample sizes that are fixed at the time of the interim analysis based on an original total sample size, and Φ denotes the cumulative distribution function of the standard normal distribution (Bretz et al., 2009a). Given that there is no possibility of stopping early for efficacy, that any potential stopping for futility of either or both doses of SHP647 is nonbinding, and that weights are prespecified, the test statistic $C(p_1, p_2)$ can be compared against the nominal alpha level to assess statistical significance (Chang and Chow, 2008).

The coprimary endpoints will each be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata. The common treatment difference is a weighted average of the stratum-specific treatment differences.

The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% CI using the method of Yan and Su (2010) and the p-value computed from the p-value combination method will be presented for each active treatment group to placebo comparison for each endpoint.

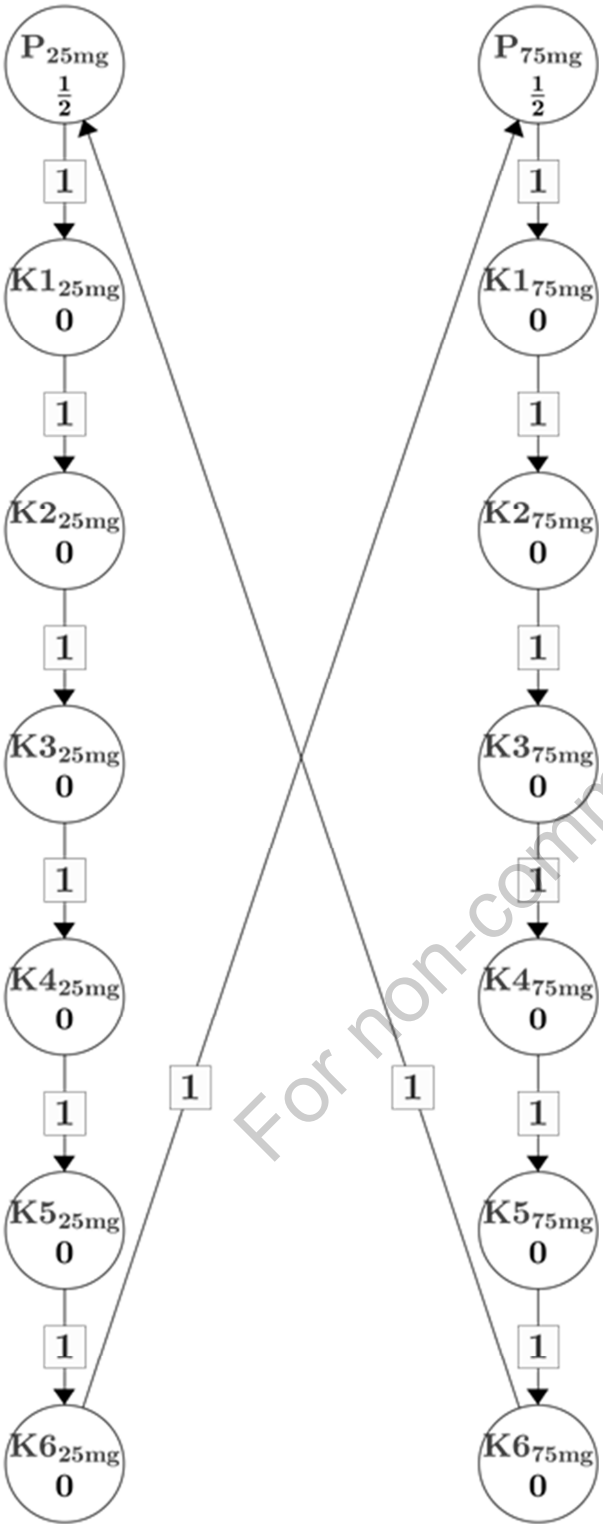
Sensitivity analyses to explore the impact of missing data on the coprimary efficacy endpoints and key secondary endpoints will be conducted. These analyses may compare imputations of the missing values which favor placebo (eg, worst case) and/or imputations which favor active treatment (eg, best case). In addition, imputation methods based on informative missingness and other missing data mechanisms may be performed. Additional sensitivity analyses will also be conducted using the per-protocol set and the completer set. Additional analyses may be developed in the SAP. All sensitivity analyses will be described in the SAP.

Prespecified subgroup analyses are planned for the coprimary endpoints including, but not limited to gender, prior anti-TNF treatment, glucocorticoid use at baseline, SES-CD at baseline, region, age group, randomization stratum, and other important subgroups. A full list of important subgroups will be described in the SAP. Within subgroups, efficacy endpoints will be compared for each active treatment group (25 mg SHP647 and 75 mg SHP647) with the placebo group using a chi-square test. The estimate of the treatment difference, along with the corresponding Newcombe (hybrid-score) 95% CI and chi-square test p-value, will be presented.

Statistical Testing and Protection of the Type I Error

The global FWER for the statistical tests of the coprimary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al. (2009b) will be utilized to propagate α from the coprimary endpoints to the key secondary endpoints and between the 2 SHP647 treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the coprimary endpoints (P) and alpha is propagated in a hierarchical manner to each of the 6 key secondary endpoints (K1–K6) within a pairwise treatment comparison. In order to pass alpha between the coprimary endpoints and the first key secondary endpoint, both coprimary endpoints must attain statistical significance. A graphical visualization of the α propagation is presented in Figure 4.

Figure 4: Visualization of Multiple Testing Strategy



K=key secondary endpoint; P=coprimary endpoints.

Only p-values that are significant according to this graphical approach are inferential and statistically significant. All other p-values are descriptive.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- Clinical remission at the Week 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 worst daily abdominal pain ≤1 (based on the 4-point scale) over the 7 most recent days and average daily stool frequency ≤3 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days. 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 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.

Similar to the coprimary endpoints, the 6 key secondary endpoints will all be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

The key secondary endpoints will be analyzed using the same approach as described for the coprimary endpoints. Subjects with missing key secondary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.

9.8.2.2 Other Secondary Efficacy Endpoints

The 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 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.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods:

- Binary endpoints will be compared between each active treatment group and the placebo group using a CMH chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use at baseline, and SES-CD at baseline.

The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% CI using the method of Yan and Su (2010) and the p-value computed from CHM test will be provided. Subjects with missing binary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.

- Continuous endpoints that are only measured at baseline and the Week 16 visit will be analyzed using an analysis of covariance model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences will be provided.
- Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation. The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

9.8.3 Exploratory Efficacy Endpoints

The exploratory endpoints are as follows:

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

Exploratory efficacy endpoints will be summarized with descriptive statistics and presented by treatment group using the same approach described as for the other secondary endpoints. See Section 9.8.2.2 for an overview of the planned analyses. Full details for the analysis of exploratory efficacy endpoints will be included in the SAP.

9.9 Safety Analyses

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

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

Treatment-emergent AEs are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events and percentage of TEAEs will be calculated by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, serious AEs, and deaths will be similarly summarized or listed.

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

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

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

9.10 Other Analyses

9.10.1 [redacted]

[redacted]

9.10.2 [redacted]

[redacted]

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

[redacted]

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

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

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

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

10.1.2 Indemnity/Liability and Insurance

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

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

10.1.3 Public Posting of Study Information

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

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

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

10.1.5 Study Suspension, Termination, and Completion

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

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

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

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

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

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

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

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

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

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

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

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

10.2.3.3 Audit/Inspection

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

10.2.3.4 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and/or assent from all study subjects before any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP.

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

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

10.3.2 Institutional Review Board or Ethics Committee

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

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

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

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

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

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

10.4 Privacy and Confidentiality

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

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

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP647; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

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

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

10.5 Study Results/Publication Policy

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

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish before release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications.

To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

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

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

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

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

11. REFERENCES

[redacted]

Atreya, R. and Neurath, M. F. 2017. Current and Future Targets for Mucosal Healing in Inflammatory Bowel Disease. *Visceral Medicine,* 33, 82-88.

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

Bretz, F., Koenig, F., Brannath, W., Glimm, E. and Posch, M. 2009a. Adaptive designs for confirmatory clinical trials. *Statistics in Medicine,* 28, 1181-1217.

Bretz, F., Maurer, W., Brannath, W. and Posch, M. 2009b. A graphical approach to sequentially rejective multiple test procedures. *Stat Med,* 28, 586-604.

Briskin, M., Winsor-Hines, D., Shyjan, A., Cochran, N., Bloom, S., Wilson, J., McEvoy, L. M., Butcher, E. C., Kassam, N., Mackay, C. R., Newman, W. and Ringler, D. J. 1997. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol,* 151, 97-110.

[redacted]

Chang, M. and Chow, S. C. 2008. Adaptive design methods in clinical trials - a review. *Orphanet journal of rare diseases,* 3, 11.

D'Haens, G., Noman, M., Baert, F. and et al. 2002. Endoscopic healing after infliximab treatment for Crohn's disease provides a longer time to relapse [abstract]. *Gastroenterology,* 122, Abstract 104936.

D'Haens, G. R., Geboes, K., Peeters, M., Baert, F., Penninckx, F. and Rutgeerts, P. 1998. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology,* 114, 262-267.

Ferrante, M., Colombel, J., Sandborn, W., Reinisch, W., Mantzaris, G., Kornbluth, A., Rachmilewitz, D., Lichtiger, S., D'Haens, G., Van der Woude, C., Danese, S., Diamond, R., Oortwijn, A., Tang, K., Miller, M., Cornillie, F. and Rutgeerts, P. 2013. Validation of Endoscopic Activity Scores in Patients With Crohn's Disease Based on a Post Hoc Analysis of Data From SONIC. *Gastroenterology,* 145, 978-0131.

Irvine, E., Feagan, B. G., Rochon, J., Archambault, A., Fedorak, R. N. and Groll, A. 1994. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of IBD. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology,* 106, 287-296.

Khanna, R., Zou, G., D'Haens, G., Feagan, B. G., Sandborn, W. J., Vandervoort, M. K., Rolleri, R. L., Bortey, E., Paterson, C., Forbes, W. P. and Levesque, B. G. 2015. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. *Alimentary Pharmacology & Therapeutics,* 41, 77-86.

[redacted]

Lacy, C., Armstrong, L., Goldman, M. and Lance, L. 2001-2002. *Drug Information Handbook,* Cleveland, OH, LexiComp, Inc.

Liaskou, E., Karikoski, M., Reynolds, G. M., Lalor, P. F., Weston, C. J., Pullen, N., Salmi, M., Jalkanen, S. and Adams, D. H. 2011. Regulation of mucosal addressin cell adhesion molecule 1 expression in human and mice by vascular adhesion protein 1 amine oxidase activity. *Hepatology,* 53, 661-72.

Molodecky, N. A., Soon, I. S., Rabi, D. M., Ghali, W. A., Ferris, M., Chernoff, G., Benchimol, E. I., Panaccione, R., Ghosh, S., Barkema, H. W. and Kaplan, G. G. 2012. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology,* 142, 46-54.e42; quiz e30.

Panaccione, R., Colombel, J.-F., Louis, E., Peyrin-Biroulet, L. and Sandborn, W. J. 2013. Evolving Definitions of Remission in Crohn's Disease. *Inflammatory Bowel Diseases,* 19, 1645-1653.

Peyrin-Biroulet, L., Ferrante, M., Magro, F., Campbell, S., Franchimont, D., Fidder, H., Strid, H., Ardizzone, S., Veereman-Wauters, G., Chevaux, J.-B., Allez, M. and Dane 2011. Results from the 2nd Scientific Workshop of the ECCO (I): Impact of mucosal healing on the course of inflammatory bowel disease. *Journal of Crohn's and Colitis,* 5, 477-483.

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

Sandborn, Feagan, Panes, D'Haens, Colombel, Zhou, Huang, Enejosa, Pangan and 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.

Sandborn, W. J., Feagan, B. G., Rutgeerts, P., Hanauer, S., Colombel, J. F., Sands, B. E., Lukas, M., Fedorak, R. N., Lee, S., Bressler, B., Fox, I., Rosario, M., Sankoh, S., Xu, J., Stephens, K., Milch, C. and Parikh, A. 2013. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med,* 369, 711-21.

Schnitzler, F., Fidder, H., Ferrante, M., Noman, M., Arijs, I., Van Assche, G., Hoffman, I., Van Steen, K., Vermeire, S. v. and Rutgeerts, P. 2009. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease Supported by an unrestricted scientific grant from Centocor. Fabian Schnitzler received a research grant by ECCO (European Crohn's and Colitis Organisation). *Inflammatory Bowel Diseases,* 15, 1295-1301.

Shyjan, A. M., Bertagnolli, M., Kenney, C. J. and Briskin, M. J. 1996. Human mucosal addressin cell adhesion molecule-1 (MAdCAM-1) demonstrates structural and functional similarities to the alpha 4 beta 7-integrin binding domains of murine MAdCAM-1, but extreme divergence of mucin-like sequences. *J Immunol,* 156, 2851-7.

Siegel, C. A., Whitman, C. B., Spiegel, B. M. R., Feagan, B., Sands, B., Loftus, E. V., Panaccione, R., D'Haens, G., Bernstein, C. N., Gearry, R., Ng, S. C., Mantzaris, G. J., Sartor, B., Silverberg, M. S., Riddell, R., Koutroubakis, I. E., O'Morain, C., Lakatos, P. L., McGovern, D. P. B., Halfvarson, J., Reinisch, W., Rogler, G., Kruis, W., Tysk, C., Schreiber, S., Danese, S., Sandborn, W., Griffiths, A., Moum, B. and Gasche, C. 2016. Development of an index to define overall disease severity in IBD. *Gut*, gutjnl-2016-312648.

Spiegel, B., Bolus, R., Harris, L. A., Lucak, S., Naliboff, B., Esrailian, E., Chey, W. D., Lembo, A., Karsan, H., Tillisch, K., Talley, J., Mayer, E. and Chang, L. 2009. Measuring irritable bowel syndrome patient-reported outcomes with an abdominal pain numeric rating scale. *Aliment Pharmacol Ther,* 30, 1159-70.

Steffen, B. J., Breier, G., Butcher, E. C., Schulz, M. and Engelhardt, B. 1996. ICAM-1, VCAM-1, and MAdCAM-1 are expressed on choroid plexus epithelium but not endothelium and mediate binding of lymphocytes in vitro. *Am J Pathol,* 148, 1819-38.

Ueno, F., Matsui, T., Matsumoto, T., Matsuoka, K., Watanabe, M. and Hibi, T. 2013. Evidence-based clinical practice guidelines for Crohn's disease, integrated with formal consensus of experts in Japan. *Journal of Gastroenterology,* 48, 31-72.

Vuitton, L., Marteau, P., Sandborn, W. J., Levesque, B. G., Feagan, B., Vermeire, S., Danese, S., D'Haens, G., Lowenberg, M., Khanna, R., Fiorino, G., Travis, S., Mary, J. Y. and Peyrin-Biroulet, L. 2016. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut,* 65, 1447-1455.

Ware, J. E., Jr. and Sherbourne, C. D. 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care,* 30, 473-83.

Williet, N., Sandborn, W. and Peyrin–Biroulet, L. 2014. Patient-Reported Outcomes as Primary End Points in Clinical Trials of Inflammatory Bowel Disease. *Clinical Gastroenterology and Hepatology,* 12, 1246-1256.e6.

Yan, X. and Su, X. 2010. Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions. *Stat Biopharm Res,* 2, 329-35.

12. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	15 Dec 2017	Global

APPENDIX 2 SCALES AND ASSESSMENTS

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

- Simple Endoscopic Score for Crohn's Disease
- Crohn's Disease Activity Index
- Colonic Global Histologic Disease Score and Ileal Global Histologic Disease Score
- Patient-reported Outcome Crohn's Disease daily e-diary
- Inflammatory Bowel Disease Questionnaire
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Short Form-36 Health Survey
- [redacted]

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

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

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

Definitions of Simple Endoscopic Score for Crohn's Disease

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

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

Crohn's Disease Activity Index (CDAI)

Crohn's Disease Activity Index (CDAI)

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

CDAI=Crohn's Disease Activity Index; ePRO=electronic patient-reported outcome; Hct=hematocrit.
Note: Variable 5: 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 CD
- 221-450 points: Moderate to severe active CD
- >451 points: Severely active to fulminant disease.

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

[redacted]

[redacted]

[redacted]

Reference: D'Haens et al., 1998

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

1. Please rate your worst abdominal pain over the past 24 hours.

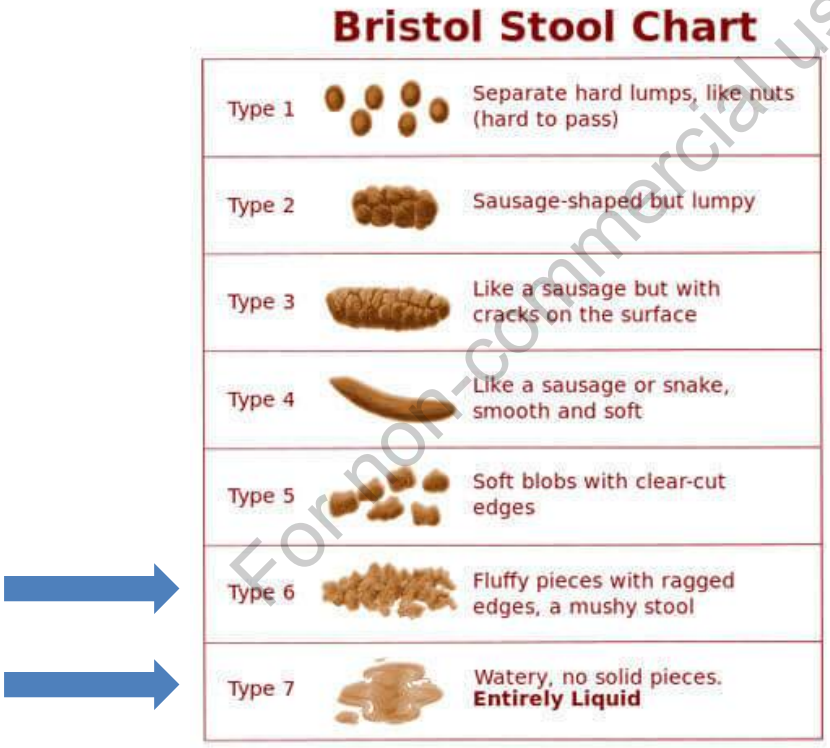
   0 1 2 3 4 5 6 7 8 9 10

   No pain Worst imaginable pain

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

   Enter number of bowel movements passed: _____

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



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

   Enter number of liquid or very soft bowel movements: _____

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

   Enter number of bowel movements with blood: _____

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

   Enter number of bowel movements with urgency: _____

6. Please rate your worst feeling of nausea (feeling sick to your stomach or like you might throw up) over the past 24 hours.

   None

   Mild

   Moderate

   Severe

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

   Enter number of vomiting episodes: _____

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

   Enter number of bowel incontinence episodes: _____

9. Please rate your abdominal pain over the past 24 hours.

   None

   Mild

   Moderate

   Severe

10. How would you rate your general wellbeing over the past 24 hours?

    Generally well

    Slightly below par

    Poor

    Very poor

    Terrible

Inflammatory Bowel Disease Questionnaire (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks.

You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last 2 weeks? Please indicate how frequent your bowel movements have been during the last 2 weeks by picking one of the options from:

    1. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
    2. EXTREMELY FREQUENT
    3. VERY FREQUENT
    4. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    5. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    6. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    7. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from:

    1. NO ENERGY AT ALL
    2. VERY LITTLE ENERGY
    3. A LITTLE ENERGY
    4. SOME ENERGY
    5. A MODERATE AMOUNT OF ENERGY
    6. A LOT OF ENERGY
    7. FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem. Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:

    1. A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
    2. A LOT OF DIFFICULTY
    3. A FAIR BIT OF DIFFICULTY
    4. SOME DIFFICULTY
    5. A LITTLE DIFFICULTY
    6. HARDLY ANY DIFFICULTY
    7. NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from:

    1. A MAJOR PROBLEM
    2. A BIG PROBLEM
    3. A SIGNIFICANT PROBLEM
    4. SOME TROUBLE
    5. A LITTLE TROUBLE
    6. HARDLY ANY TROUBLE
    7. NO TROUBLE

18. Overall, in the last 2 weeks, how much a problem have you had maintaining or getting to, the weight you would like to be at. Please choose an option from:

    1. A MAJOR PROBLEM
    2. A BIG PROBLEM
    3. A SIGNIFICANT PROBLEM
    4. SOME TROUBLE
    5. A LITTLE TROUBLE
    6. HARDLY ANY TROUBLE
    7. NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from:

    1. NONE OF THE TIME
    2. A LITTLE OF THE TIME
    3. SOME OF THE TIME
    4. A GOOD BIT OF THE TIME
    5. MOST OF THE TIME
    6. ALMOST ALL OF THE TIME
    7. ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from:

    1. NO SEX AS A RESULT OF BOWEL DISEASE
    2. MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
    3. MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
    4. SOME LIMITATION AS A RESULT OF BOWEL DISEASE
    5. A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
    6. HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
    7. NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from:

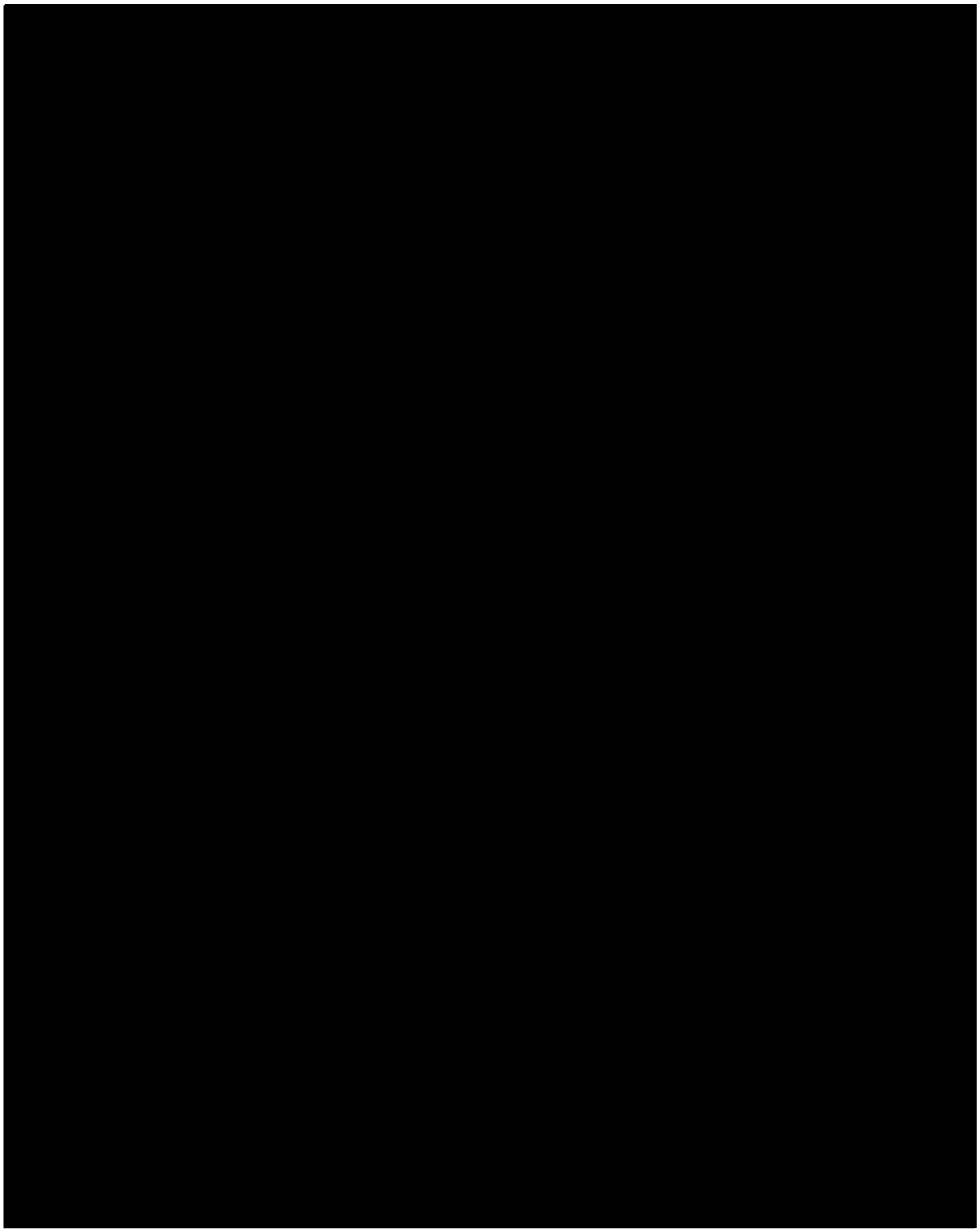
    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from:

    1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
    2. GENERALLY DISSATISFIED, UNHAPPY
    3. SOMEWHAT DISSATISFIED, UNHAPPY
    4. GENERALLY SATISFIED, PLEASED
    5. SATISFIED MOST OF THE TIME, HAPPY
    6. VERY SATISFIED MOST OF THE TIME, HAPPY
    7. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

[redacted]

[redacted]



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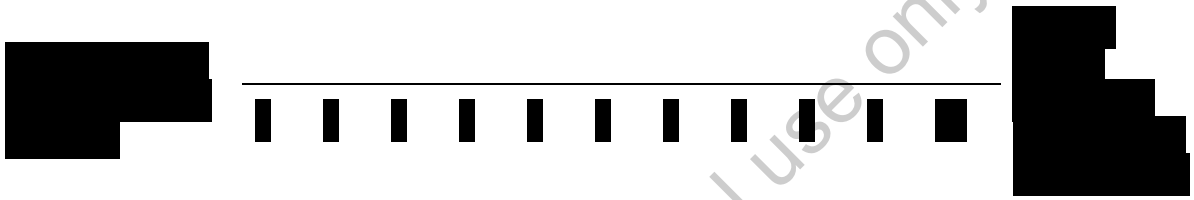

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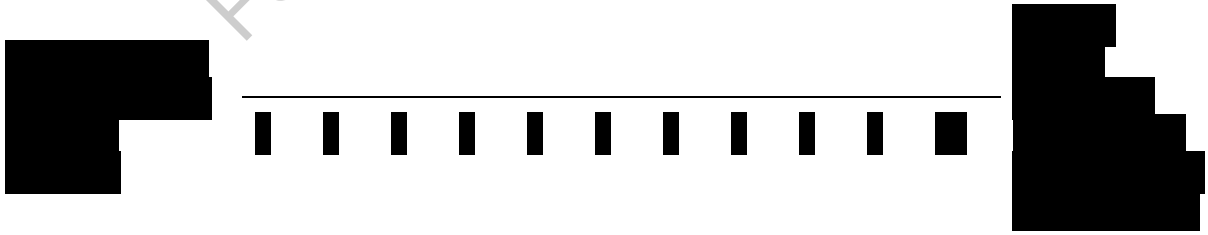

[redacted]

Short Form-36 Health Survey (Version 2), Acute Form

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past week</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 3 GLUCOCORTICOID EQUIVALENT DOSES

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

Reference: Lacy et al., 2001-2002.

PROTOCOL: SHP647-305

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)
DRUG:	SHP647
IND:	100,222
EUDRACT NO.:	2017-000575-88
SPONSOR:	Shire Human Genetic Therapies, Inc. ("Shire") 300 Shire Way, Lexington, MA 02421 US
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted] MD
PROTOCOL HISTORY:	Protocol Amendment 1: 21 Aug 2018 Original Protocol: 15 Dec 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted] MD, [redacted]	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP647-305.

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).

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

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

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

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

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

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

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 21 Aug 2018**	**Global/Country/Site Specific Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Emergency contact information	Updated global fax number for Shire Global Drug Safety	To provide updated emergency contact information
Study Synopsis, Inclusion and exclusion criteria Section 4.1, Inclusion Criteria	Updated inclusion criterion #4c to indicate that subjects must have abdominal pain subscores ≥2 on the 4-point severity scale (used in the CDAI), in addition to abdominal pain subscores ≥5 on the 11-point numerical rating scale.	To collect additional data for abdominal pain at study entry using the 0-3 CDAI severity scale.
Study Synopsis, Inclusion and exclusion criteria Section 4.1, Inclusion Criteria Section 5.1, Prior Treatment	Updated inclusion criterion #7 to add hyperlink to Section 5.1 in which "inadequate response to, lost response to, or intolerance to at least 1 conventional treatment" (eg, sulfasalazine, mesalamine, glucocorticoids, immunosuppressants, or anti-TNF) is defined.	To cross-reference section where prior treatments are defined.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #1 to indicate that subjects with non-steroidal anti-inflammatory drug-induced colitis will be excluded.	To further define the exclusion of subjects with colitis.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #24 to clarify that subjects with a history of *Mycobacterium tuberculosis* (TB) infection who have not completed a generally accepted full course of treatment before baseline will also be excluded.	To further define the exclusion of subjects with any history of positive TB.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #30 to indicate that subjects with cirrhosis with or without decompensation will be excluded.	To further define the exclusion of subjects with compromised liver function.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Moved exclusion of subjects with primary sclerosing cholangitis from exclusion criterion #30 to new criterion #31.	To further define the exclusion of subjects with compromised liver function.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #32 to indicate that subjects with negative HBsAg but positive HBcAb may be eligible if no presence of HBV DNA is confirmed.	To clarify that subjects with positive HBcAb, without HBV DBA, may be eligible for the study.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #33 to indicate that subjects with chronic hepatitis C (HCV) without evidence of HCVRNA within 12 weeks of baseline may be considered eligible.	To clarify that subjects with chronic HCV, without HCVRNA, may be eligible for the study (in case of spontaneous viral clearance or previously treated and cured).

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 21 Aug 2018**	**Global/Country/Site Specific Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #34 to indicate that subjects meeting the following lab criteria would be excluded: • ALT or AST ≥3×ULN • Total bilirubin ≥1.5×ULN or >2×ULN if the subject has a known documented history of Gilbert's syndrome Added note to exclusion criterion #34 to specify that, if platelet count is <150,000 cells/mm^3, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.	To align criteria with FDA guidelines.
Study Synopsis, Inclusion and exclusion criteria Table 1, Schedule of Assessments, footnote 'n' Section 4.2, Exclusion Criteria	Added new exclusion criterion #35 to clarify that documentation of HIV status should be performed within 6 months of screening.	To clarify the timing of acceptable documentation of HIV status.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #36 to include exclusion of subjects with abuse of medicinal marijuana. Deleted former exclusion criterion #36 related to medicinal marijuana dependency.	To indicate that subjects with medicinal marijuana abuse would be excluded.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #39 to indicate the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and for 16 weeks after last dose of investigational product.	To specify the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including sperm banking or donation for male subjects and egg donation or harvest for female subjects, are excluded.
Section 1.3, Benefit/Risk Assessment	Added new section describing risk and benefits of SHP647 treatment.	To provide updated risk and benefit information for SHP647.
Section 3.1.1, Rationale for Coprimary Endpoints	Added text describing results from recent trial with upadacitinib and from Phase 2 OPERA study with SHP647 as supporting rationale for the coprimary endpoint of endoscopic response.	To provide additional supporting rationale for the co-primary endpoint of endoscopic response.
Table 1, Schedule of Assessments: footnote 'l' Section 7.2.3.6, Clinical Laboratory Evaluations Appendix 5	Updated SOA footnote 'l' and added Appendix 5 to clarify that diagnosis of *C. difficile* infection should be made using the central laboratory. Added diagnostic algorithms and relevant information related to *C. difficile* testing and diagnosis.	To provide appropriate guidance regarding laboratory testing for *C. difficile* infection.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 21 Aug 2018**	**Global/Country/Site Specific Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Table 1, Schedule of Assessments: footnote 'n'	Added new row to SOA and footnote 'n' to indicate HIV tests may be performed at local laboratories (per local requirements), or centrally, if documentation of a negative HIV test within 6 months of screening is unavailable.	To clarify the timing of acceptable documentation of HIV status.
Section 4.5.1, Subject Withdrawal Criteria	Added pregnancy to the list of reasons a subject may be withdrawn from study treatment.	For clarity and consistency with language in Section 8.1.6.
Section 5.2.1, Permitted Treatment	Added language to specify that any antidiarrheal opiate drugs must be taken at stable doses for the duration of the study unless dose reduction or discontinuation is required due to clinical improvement or adverse event, and that escalation of the dose after dose reduction, or re-initiation after drug discontinuation, is not allowed.	To clarify that concomitant antidiarrheal opiate drugs are permitted if taken at stable doses for the duration of the study, with dose reduction or discontinuation allowed only if required due to clinical improvement or adverse event.
Section 7.2, Study Procedures	Added language to specify that the duration of blood and tissue sample storage is dependent on local regulations.	To clarify that local regulations should be considered for duration of blood and tissue sample storage.
Section 7.2.3.6, Clinical Laboratory Evaluations	Added HIV and HBV DNA samples to virology table.	To reflect new eligibility criteria regarding HIV testing and HBV DNA reflex testing.
Section 7.2.5, Volume of Blood to be Drawn from Each Subject	Added 2 new rows to Table 4 for collection of HBV DNA and HIV samples. Increased TB test sample volume by 1 mL.	To reflect changes in eligibility criteria regarding HIV testing and HBV DNA reflex testing and to correct the sample volume needed for the TB test.
Section 8.2.8, Safety Monitoring Table 5	Added new section and table describing safety monitoring and stopping criteria for elevated hepatic blood tests.	To provide appropriate guidance on subjects who have been enrolled with elevated liver function test or who have elevated liver function test(s) during the study.
Section 10, Sponsor's and Investigator's Responsibilities	Added a statement that compliance with the noted regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.	To clarify that the study is conducted in accordance with the ethical principles in the Declaration of Helsinki.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 21 Aug 2018**	**Global/Country/Site Specific Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Appendix 4, Determination of Failure or Intolerance to Prior Treatment for Crohn's Disease	Added new appendix section, "Determination of Inadequate Response/Loss of Response or Intolerance to Prior Treatment for Crohn's Disease" to provide guidance as related to inclusion criterion #7 in which subjects meeting these criteria on prior conventional treatments (eg, sulfasalazine, mesalamine, glucocorticoids, immunosuppressants, or anti-TNF) may be eligible for this study.	To provide additional granularity regarding the eligibility of subjects who demonstrated inadequate response, loss of response, or intolerance on conventional treatment.
Appendix 5, Guidance for Diagnosis and Treatment of Increased Gastrointestinal Symptoms	Added new Appendix 5, "Guidance for Diagnosis and Treatment of Increased Gastrointestinal Symptoms related to diagnosis and treatment of *C. difficile* infection.	To provide updated treatment guidance for subjects diagnosed with *C. difficile* infection.
Throughout protocol	Minor changes to wording.	To improve clarity, consistency, and remove redundancy of text.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Nonserious Adverse Events (AEs) Required by the Protocol Form within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor by fax or e-mail using the details below.

Fax
[redacted] (Global)

Email
[redacted]

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

Pharmaceutical Product Development North America:

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

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

Pharmaceutical Product Development Latin America:

24 Hour Safety Hotline: [redacted]

24 Hour Safety Hotline Fax: [redacted]

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

24 Hour Safety Hotline: [redacted]

24 Hour Safety Hotline Fax: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.2.2.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	**E-mail Address**
North and South America, the European Union, and Rest of World	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (US)
[redacted]

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
β-hCG	beta-human chorionic gonadotropin
ADA	antidrug antibodies
AE	adverse event
AZA	azathioprine
BSFS	Bristol Stool Form scale
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
[redacted]	[redacted]
CI	confidence interval
CMH	Cochran-Mantel Haenszel
CNS	central nervous system
[redacted]	[redacted]
CSF	cerebrospinal fluid
CRO	contract research organization
DMC	data monitoring committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
[redacted]	[redacted]
EMA	European Medicines Agency
[redacted]	[redacted]
ET	early termination
EU	European Union
FAS	full-analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FWER	family-wise type I error rate
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HCVRNA	hepatitis C ribonucleic acid
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus

HRQL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
$IgG_{2\kappa}$	immunoglobulin G2 kappa
[redacted]	[redacted]
IGRA	interferon-gamma release assay
IRB	Institutional Review Board
IRT	interactive response technology
LP	lumbar puncture
LTS	long-term safety extension
[redacted]	[redacted]
MTX	methotrexate
NAb	neutralizing antibody
NRS	numerical rating scale
PCR	polymerase chain reaction
[redacted]	[redacted]
PFS	prefilled syringe
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
PRO	patient-reported outcome
Q4W	once every 4 weeks
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's disease
SF-36	Short Form-36 Health Survey
SOC	system organ class
SUSAR	serious unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent AE
TNF	tumor necrosis factor
[redacted]	[redacted]
UC	ulcerative colitis
ULN	upper limit of normal

US	United States
VCAM	vascular cell adhesion molecule
[redacted]	[redacted]

STUDY SYNOPSIS

Protocol number: SHP647-305	**Drug:** SHP647
Title of the study: 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)	
Number of subjects (total and for each treatment arm): A total of 1032 subjects (387 subjects in the 25 mg SHP647 treatment group, 387 subjects in the 75 mg SHP647 treatment group, and 258 subjects in the placebo group) are planned for enrollment into the study.	
Investigator(s): Multicenter study.	
Site(s) and region(s): It is anticipated that the study will be conducted in approximately 19 countries. Regions will include North America; Europe, the Middle East, and Africa; Latin America; and Asia Pacific. Approximately 210 sites will be utilized.	
Study period (planned): 2018 to 2021	**Clinical phase:** 3

Objectives:

Coprimary: The coprimary objectives of this study are to evaluate the efficacy of SHP647 in subjects with moderate to severe Crohn's disease (CD) in:

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

Key secondary:

- To evaluate the efficacy of SHP647 in inducing clinical remission as measured by CD Activity Index CDAI
- To evaluate the efficacy of SHP647 in inducing enhanced endoscopic response based on centrally read colonoscopy
- To evaluate the efficacy of SHP647 in inducing clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)
- To evaluate the efficacy of SHP647 in inducing clinical response based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
- To evaluate the efficacy of SHP647 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 SHP647 in inducing endoscopic healing based on centrally read colonoscopy.

Other secondary:

- To evaluate the safety and tolerability of SHP647
- To evaluate the effect of SHP647 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 SHP647 induction treatment on other endoscopic outcomes
- To evaluate the effect of SHP647 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 SHP647 on incidence of hospitalizations and total inpatient days
- To evaluate the impact of SHP647 on incidence of CD-related and other surgeries.

Rationale:
This study is designed to evaluate the efficacy and safety of SHP647 in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.

The CD clinical development program includes 3 completed studies: 1 Phase 1 study (A7281008) and 2 Phase 2 studies (A7281006 and A7281007). The SHP647 dose selection (25 mg and 75 mg) for this study is based on data from these 3 previous studies, which evaluated the activity of SHP647 in adult patients with moderately to severely active CD based on CDAI scores between 220 and 450. The Phase 1 study (A7281008, TOSCA) and Phase 2 studies (A7281006, OPERA; and A7281007, OPERA II [long-term safety study]) that investigated the safety, tolerance, pharmacokinetics, and pharmacodynamic properties of SHP647 support further clinical development of SHP647 using subcutaneous (SC) administration in subjects with moderate to severe CD.

Investigational product, dose, and mode of administration:
The test product is SHP647 (a fully human immunoglobulin G2 kappa antihuman mucosal addressin cell adhesion molecule [MAdCAM] monoclonal antibody), which will be provided as a sterile aqueous buffered solution for SC administration in a glass prefilled syringe (PFS) with a fixed needle. Each PFS contains 1 mL of SHP647 solution for injection at an appropriate concentration to provide the intended dose of drug (25 mg or 75 mg). Additional information is provided in the current SHP647 investigator's brochure (IB).

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain SHP647.

Methodology:
This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of SHP647 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 SHP647 treatment group, 387 subjects in the 75 mg SHP647 treatment group, and 258 subjects in the placebo group) are planned for enrollment into the study. 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 SHP647, 75 mg SHP647, or placebo) in a 3:3:2 ratio. Randomization will be stratified based upon the subject's status of prior antitumor necrosis factor (TNF) treatment (naïve or experienced), glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline), and Simple Endoscopic Score for CD (SES-CD) at baseline (SES-CD ≥17 or SES-CD <17). Subjects will receive SC injections of SHP647 or placebo, using a 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.

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). 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 treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

A planned interim analysis for the coprimary endpoints will take place 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 will be reassessed as part of this interim analysis.

Inclusion and exclusion criteria:
Inclusion criteria:

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and assent as applicable to participate in the study.

3. Subjects must be between ≥16 and ≤80 years of age at the time of the signing of the informed consent/assent form. Note: Subjects <18 years of age must weigh ≥40 kg and must have body mass index ≥16.5 kg/m^2.
4. Subjects must have active moderate to severe ileal (terminal ileum), ileocolic, or colonic CD at baseline (Visit 2) as defined by:
    a. CDAI score between 220 and 450 (inclusive) **AND**
    b. Presence of ulcerations that are characteristic to CD, as determined by a colonoscopy performed during screening, and as defined by the SES-CD >6 (SES-CD ≥4 for isolated ileitis) **AND**
    c. Meeting the following subscores in the 2-item PRO:
        i. Abdominal pain subscore ≥5 (average worst daily pain on the 11-point numerical rating scale [NRS]) **AND** abdominal pain subscore ≥2 (average daily pain on the 4-point abdominal pain variable of CDAI) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous) **AND/OR**
        ii. Average of the daily stool frequency subscore ≥4 of type 6/7 (very soft stools/liquid stools) as shown in the Bristol Stool Form Scale (BSFS) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous).
5. Subjects must have a documented diagnosis (endoscopic with histology) of CD for ≥3 months before screening. Documented diagnosis is defined as:
    - A biopsy report to confirm the histological diagnosis **AND**
    - A report documenting disease duration based upon prior colonoscopy.

    Note: If a biopsy report is not available in the source document at the time of screening, a biopsy must be performed during the screening colonoscopy and the histology report should be consistent with the CD diagnosis. If the histology diagnosis is not clear at this time point, the subject should not be randomized.
6. Subjects must be willing and able to undergo a colonoscopy during screening after all other inclusion criteria have been met.
7. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or mesalamine (5-aminosalicylic acid [5-ASA]), glucocorticoids, immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]), or anti-TNF (refer to Appendix 4 for guidance).. Subjects who have had an inadequate response to sulfasalazine or mesalamine should have also failed at least 1 other conventional treatment such as glucocorticoids.
8. Subjects receiving any treatment(s) for CD described in Section 5.2.1 of the protocol are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
9. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception for the duration of the study.

Exclusion criteria:

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

1. Subjects with indeterminate colitis, microscopic colitis, non-steroidal anti-inflammatory drug-induced colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of ulcerative colitis.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with presence of enterovesical (ie, between the bowel and urinary bladder) or enterovaginal fistulae.
5. Subjects with current symptomatic diverticulitis or diverticulosis.
6. Subjects with obstructive colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for CD during the treatment period.

7. Subjects with past medical history of multiple small bowel resections resulting in clinically significant short bowel syndrome.
8. Subjects requiring total parenteral nutrition.
9. Subjects with past medical history of bowel surgery resulting in an existing or current stoma. Subjects who had a j-pouch are excluded as a j-pouch could result in a stoma.
10. Subjects have had prior treatment with SHP647 (formerly PF-00547659).
11. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
12. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than AZA, 6-MP, or MTX) or continuous antibiotics (>2 weeks) for the treatment of CD within 30 days before baseline (Visit 2).
13. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
14. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).
15. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
16. Subjects have received lymphocytes apheresis or selective monocyte granulocytes apheresis within 60 days before baseline (Visit 2).
17. Subjects have received enteral nutrition treatment within 30 days before baseline (Visit 2).
18. Subjects have received parenteral or rectal glucocorticoids or rectal 5-ASA within 14 days before screening colonoscopy.
19. Subjects have taken >20 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 14 days before baseline (Visit 2) or have taken ≥40 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 6 weeks before baseline (Visit 2).
20. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before screening (Visit 1).
21. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).
22. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis [subjects with *C. difficile* infection at screening may be allowed retest after treatment], evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
23. Subjects with abnormal chest x-ray or other imaging findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray, computed tomography scan, etc., performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation.)
24. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) or subjects with this history who have not completed a generally accepted full course of treatment before baseline (Visit 2) are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon-gamma release assay (IGRA) performed.

    Subjects who have no history of previously diagnosed active or latent tuberculosis are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before baseline (Visit 2). If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

    - An IGRA is strongly recommended for subjects with a prior bacillus Calmette-Guérin vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON-TB Gold Plus In-Tube Test.

- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent tuberculosis, a positive test on repeat will exclude the subject. Subjects with a history of active or latent tuberculosis infection must follow instructions for "Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met" in this criterion.
- Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray, taken within the 3 months before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
- A chest x-ray performed within 3 months before screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.

25. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
26. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy based on the targeted neurological assessment during the screening period.
27. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
28. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
    - Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.
    - Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
    - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening (Visit 1).
    - History of significant cerebrovascular disease within 24 weeks before screening (Visit 1).
29. Subjects who have had significant trauma or major surgery within 4 weeks before screening (Visit 1), or with any major elective surgery scheduled to occur during the study.
30. Subjects with evidence of cirrhosis with or without decompensation (ie, esophageal varices, hepatic encephalopathy, portal hypertension, ascites).
31. Subjects with primary sclerosing cholangitis.

32. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Note: If a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if no presence of HBV DNA is confirmed by HBV DNA PCR reflex testing performed in the central laboratory.
33. Subjects with chronic hepatitis C (HCV) (positive HCVAb and hepatitis C ribonucleic acid [HCVRNA]). Note: Subjects who are HCVAb positive without evidence of HCVRNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCVRNA at least 12 weeks prior to baseline]).
34. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening (Visit 1). Note: Screening laboratory tests, if the results are 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 must be reviewed for eligibility prior to the screening colonoscopy procedure.
    - Alanine aminotransferase and aspartate aminotransferase levels ≥3 × the upper limit of normal (ULN)
    - Total bilirubin level ≥1.5 × ULN or >2.0 × ULN if the subject has a known documented history of Gilbert's syndrome
    - Hemoglobin level ≤80 g/L (8.0 g/dL)
    - Platelet count ≤100 × 10^9/L (100,000 cells/mm^3) or ≥1000 × 10^9/L (1,000,000 cells/mm^3)
    - White blood cell count ≤3.5 × 10^9/L (3500 cells/mm^3)
    - Absolute neutrophil count <2 × 10^9/L (2000 cells/mm^3)
    - Serum creatinine level >1.5 × ULN or estimated glomerular filtration rate <30 mL/min/1.73m^2 based on the abbreviated Modification of Diet in Renal Disease Study Equation.

      *Note: if platelet count is <150,000 cells/mm^3, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.
35. Subjects with known HIV infection based on documented history with positive serological test, or positive HIV serologic test at screening, tested at the site's local laboratory in accordance with country requirements, or tested at the central laboratory. Note: A documented negative HIV test within 6 months of screening is acceptable and does not need to be repeated.
36. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse of any kind including abuse of medicinal marijuana (cannabis).
37. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
38. Female subjects who are planning to become pregnant during the study period.
39. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
40. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: Up to 6 weeks
- Planned duration of treatment period: 16 weeks
- Planned duration of follow-up period: 16 weeks.

Endpoints and statistical analysis:

Analysis sets:

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

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

The per-protocol set will consist of all subjects in the FAS who do not have protocol deviations that may affect the coprimary efficacy endpoints.

The completer set will consist of all subjects in the FAS who have completed the Week 16 assessment for this study.

[redacted]

[redacted]

Coprimary efficacy endpoints:

The coprimary efficacy endpoints are:

- 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 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.
- Endoscopic response at Week 16 as measured by a decrease in SES-CD of at least 25% from baseline.

The coprimary efficacy endpoints, clinical remission at the Week 16 visit and endoscopic response at the Week 16 visit, will each be compared for each active treatment group (25 mg or 75 mg SHP647) to the placebo group using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use, and SES-CD at baseline for each of the stages of the study (stage 1 includes subjects whose primary efficacy data are used in the interim analysis and stage 2 includes all other subjects. Note: classification of stage 1 and stage 2 is based on the time of randomization rather than the time of study completion or termination). Subjects with missing data at the Week 16 visit will be considered failures and counted as nonresponders.

Weighted inverse normal p-value combination methods are used to combine the p-values from stage 1 and stage 2 through the following formula:

$$C(p_1, p_2) = 1 - \Phi[w_1 \Phi^{-1}(1-p_1) + w_2 \Phi^{-1}(1-p_2)]$$

Where p_1, p_2 are the p-values computed from the CMH chi-square test for each stage, $w_i^2 = n_i/(n_1 + n_2)$, n_1 and n_2 are the preplanned stage-wise sample sizes that are fixed at the time of the interim analysis based on an original total sample size, and Φ denotes the cumulative distribution function of the standard normal distribution (Bretz, et al., 2009a). Given that there is no possibility of stopping early for efficacy, that any potential stopping for futility of either or both doses of SHP647 is nonbinding, and that weights are prespecified, the test statistic $C(p_1, p_2)$ can be compared against the nominal alpha level to assess statistical significance (Chang, 2008).

The coprimary endpoints will each be tested by the following hypothesis:

$$H_0: \delta = 0$$
$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata. The common treatment difference is a weighted average of the stratum-specific treatment differences.

The global family-wise type I error rate (FWER) for the statistical tests of the coprimary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al. (2009b) will be utilized to propagate α from the coprimary endpoints to the key secondary endpoints and between the 2 SHP647 treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the coprimary endpoints (P) and alpha is propagated in a hierarchical manner to each of the 6 key secondary endpoints (K1–K6) within a pairwise treatment comparison. In order to pass alpha between the coprimary endpoints and the first key secondary endpoint, both coprimary endpoints must attain statistical significance.

Key secondary efficacy 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 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.

The key secondary endpoints will be analyzed using the same approach as described for the coprimary endpoints. Subjects with missing key secondary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.

Other secondary efficacy endpoints:

- 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 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.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods:

- Binary endpoints will be compared between each active treatment group and the placebo group using a CMH chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use at baseline, and SES-CD at baseline. The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% CI using the method of Yan and Su (2010) and the p-value computed from CHM test will be provided. Subjects with missing binary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.
- Continuous endpoints that are only measured at baseline and the Week 16 visit will be analyzed using an analysis of covariance model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (Visit 2) (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% confidence intervals (CIs) for least squares mean treatment differences will be provided.
- Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation. The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

Safety analyses:

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

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

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events and percentage of TEAEs will be calculated by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, serious AEs, and deaths will be similarly summarized or listed.

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

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

STUDY SCHEDULE

Table 1: Schedule of Assessments

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

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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
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				
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		

Table 1: 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
Treatment Procedures												
Randomization[x]			X									
Administration of SHP647 or placebo[x, y]			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[z]	X					X	X					

Ab=antibody; ADA=antidrug antibodies; β-hCG=beta-human chorionic gonadotropin; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; [redacted]; ECG=electrocardiogram; [redacted]; [redacted]; ET=early termination; FSH=follicle-stimulating hormone; GDH=glutamate dehydrogenase; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HCV RNA=hepatitis C virus ribonucleic acid; HRUA=Healthcare Resource Utilization Assessment; IBD=inflammatory bowel disease; IBDQ=Inflammatory Bowel Disease Questionnaire; JCV=John Cunningham virus; LTS=long-term safety extension; [redacted]; NAb=neutralizing antibody; PCR=polymerase chain reaction; PGA=physician's global assessment; [redacted]; [redacted]; [redacted]; PML=progressive multifocal leukoencephalopathy; PPD=purified protein derivative; PRO=patient-reported outcomes; SES-CD=Simple Endoscopic Score for CD; SF-36 v2=Short Form-36 Health Survey, version 2; TB=tuberculosis; [redacted]; [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 should be scheduled 1 to 3 day(s) before Part 2; this will allow for blood samples to be taken before starting the colonoscopy preparation and before the colonoscopy procedure at Part 2 of the visit (Section 7.2.2.4)
- Part 2 of Visit 7 should be scheduled preferably 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 (SHP647-304) study 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.

Table 1: 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

[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 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 for further details.

[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 *C. difficile* infection should be made using the central laboratory. If for any reason the central laboratory is not available, refer to Appendix 5 for guidance regarding alternate diagnostic algorithms.

[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 PPD test within 12 weeks before baseline (Visit 2) is acceptable provided that an interferon-gamma release assay official reading and method or test 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.

Table 1: 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

[s] Colonoscopy preparation will be according to local routine. Colonoscopy must be performed during the screening period within 5 to 7 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. 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. If the calculated CDAI scores is <220 or >450, 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 hematocrit results) should be available to calculate the CDAI scores. See Section 7.2.2.3 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 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 (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] 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 for the order in which assessments should be performed. Timing of visits is relative to baseline (Visit 2).

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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

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

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

1.2 Product Background and Clinical Information

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

SHP647 (previously known as PF-00547659) is a fully human immunoglobulin G2 kappa (IgG_{2k}) monoclonal antibody that binds to human MAdCAM to reduce lymphocyte homing to the gut and GI inflammation. SHP647 binds MAdCAM with high affinity and selectivity that prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM expressing sites in the high endothelial venules of the GI tract.

1.3 Benefit/Risk Assessment

SHP647 has been evaluated in Phase 1 and Phase 2 clinical studies in subjects with CD and UC. In Study A7281006 in subjects with CD, induction treatment with SHP647 did not meet the primary endpoint; no statistically significant differences were observed between the active treatment arms and the placebo arm in CD Activity Index (CDAI)-70 response rate at Week 8 or Week 12. Post hoc analyses did suggest evidence of drug effect in subjects with a higher inflammatory state at baseline (as indicated by higher serum CRP concentrations or higher endoscopic disease activity as measured by SES-CD). In Study A7281009 in subjects with UC, induction treatment with SHP647 at doses of 7.5 mg, 22.5 mg, or 75 mg every 4 weeks resulted in significantly higher proportions of subjects in remission at Week 12 based on total Mayo score (both local and central read) when compared with placebo treatment.

In the induction study A7281006 in subjects with CD, compared to placebo, nominally statistically significant decreases were observed in the 75 mg group at Week 8 and in the 22.5 mg and 75 mg groups at Week 12. Generally, decreases from baseline in hsCRP were observed in all 3 active treatment groups (7.5 mg, 22.5 mg, and 75 mg) over the 12-week induction period. Compared to placebo, nominally statistically significant decreased in hsCRP were observed in all 3 active treatment groups at Week 12. There was no evidence of a dose response for either of these parameters. A nominally statistically significant increase was observed in circulating β7 + central memory T lymphocytes at Week 8 and Week 12, consistent with the predicted mechanism of action. In the UC induction study, A7281009, decreases in fecal calprotectin were observed in all groups, including placebo; however, there were no nominally statistically significant differences in the decrease in fecal calprotectin between any dose level of SHP647 and placebo. Decreases in hsCRP were also observed in all 4 treatment groups; however, other than the 75 mg dose group at Week 12, no nominally significant differences were observed in active treatment vs placebo.

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

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

SHP647 appears to be generally well tolerated, with the majority of TEAEs distributed at similar frequencies among treatment arms with only peripheral edema, gastroenteritis, and arthralgia more frequently reported in SHP647- than placebo-treated subjects in the pooled induction studies. In the placebo-controlled induction studies, nasopharyngitis was not reported more frequently in SHP647- than placebo-treated subjects, but occurred at relatively high frequency during long-term safety studies. SHP647 does not appear to be associated with impaired central nervous system (CNS) immune surveillance. No case of progressive multifocal leukoencephalopathy (PML) or myocarditis has been reported. SHP647, in doses of 7.5 mg, 22.5 mg, and 75 mg, appears to increase the rate of remission in subjects with UC, and may have an effect in patients with CD who have greater evidence of inflammation based on biomarker or endoscopic data.

Always refer to the latest version of the SHP647 investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding the pharmacokinetics, efficacy, and safety of SHP647.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

SHP647, a fully human $IgG_{2\kappa}$ antihuman MAdCAM monoclonal antibody, is under development for the treatment of CD. SHP647 prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM-expressing sites with high affinity and selectivity. Principal sites of MAdCAM expression on normal tissue include intestine, pancreas, stomach, esophagus, spleen, and to a lesser extent lung, liver, and bladder but not the CNS (Steffen et al., 1996).

Although selective targeting of the MAdCAM receptors is a novel approach, the basic interference of lymphocyte homing by preventing the binding of these $\alpha_4\beta_7^+$ lymphocytes to the MAdCAM receptor and the resultant efficacy in CD is well established (Sandborn et al., 2013). SHP647 is differentiated from other molecules targeting the $\alpha_4\beta_7$-MAdCAM mediated lymphocyte trafficking used for the treatment of CD in that SHP647 blocks the interaction of $\alpha_4\beta_7^+$ lymphocytes with the MAdCAM receptor by selectively binding to MAdCAM on the endothelial cells surface in the gut (and related tissues) while the other molecules target the integrins on the infiltrating lymphocytes. Additionally, SHP647 does not bind to the vascular cell adhesion molecule (VCAM); therefore, SHP647 is not expected to affect lymphocyte homing or surveillance in the CNS or to be an effective treatment for multiple sclerosis.

This study is designed to evaluate the efficacy and safety of SHP647 in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.

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

Study A7281006 (OPERA) was a parallel, dose-ranging, randomized, double-blind, placebo-controlled study in which SHP647 was given as 3 subcutaneous (SC) dose levels (22.5 mg, 75 mg, and 225 mg) once every 4 weeks (Q4W) over an 8-week period. SHP647 was generally safe and well tolerated and there were no deaths. Three placebo-treated subjects and 9 subjects in the 22.5 mg, 75 mg, and 225 mg SHP647 groups discontinued treatment due to adverse events (AEs). Most TEAEs were mild or moderate in severity. Median serum concentrations of SHP647 increased with increasing dose. Positive antidrug antibodies (ADA) status did not appear to impact exposure to SHP647. The CDAI was the primary instrument to assess the efficacy of SHP647; no statistically significant differences were noted between the active treatment arms and the placebo arm. Therefore, the study did not meet its primary endpoint. However, post hoc analysis indicated increased remission rates in subjects in the 22.5 mg or 75 mg treatment arms who had higher serum concentrations of high-sensitivity C-reactive protein (hsCRP) or higher scores of Simple Endoscopic Score for CD (SES-CD) at baseline.

Study A7281008 (TOSCA) was an open-label multi-center, Phase 1 sequential cohort study that evaluated the effects of a maximum induction dose of SHP647 on CNS system immune surveillance.

Subjects with inflammatory bowel disease (IBD) (including CD), with or without stoma, who failed or were intolerant to both anti-TNF and immunosuppressant therapy and who had moderate to severe active disease underwent a lumbar puncture (LP), completed induction therapy with 3 doses of 225 mg SHP647 4 weeks apart, and then underwent a second LP 2 (±1) weeks later. The primary endpoint was the percent change from baseline (pretreatment) in absolute lymphocyte count in cerebrospinal fluid (CSF) in subjects with IBD after receiving 3 doses of 225 mg SHP647. The mean percentage change from baseline in absolute lymphocytes in CSF was 61.76% with a median change of 35.2% (range: -70.2% to 267.8%). The post-treatment LP/pretreatment LP geometric mean ratio for CSF lymphocytes was 1.33 with the lower bound of the 80% confidence interval (CI)=1.13, which was greater than 0.5, supporting rejection of the null hypothesis (ie, that the percent decrease in total lymphocytes counts after treatment would be ≥50% (equivalent to the geometric mean ratio in total lymphocyte counts being ≤0.5). This result supports the hypothesis that SHP647 does not impair trafficking of lymphocytes into the CNS and thus should not impair CNS immune surveillance.

Study A7281007 (OPERA II) was a Phase 2 open-label extension study to provide additional long-term safety data on subjects with moderate to severe CD who completed Study A7281006 or Study A7281008 and wished to continue to receive SHP647. SHP647 75 mg (with potential dose escalation to 225 mg) SC given every 4 weeks for 72 weeks was generally well tolerated in subjects with CD over the treatment period evaluated in this study. In subjects with positive ADA or neutralizing antibody (NAb) status, exposure to SHP647 was not affected. Serum concentrations of SHP647 in this study were consistent with what was predicted based on the Feeder Study A7281006. There were 2 deaths in the study: 1 subject died of multiple organ dysfunction syndromes in the treatment period and 1 subject died of metastatic neoplasm in the follow-up period. Neither death was reported as related to treatment with the study drug by the investigators. The most frequently reported SAE was CD in either the treatment period or the follow-up period. The system organ class with the most subjects experiencing TEAEs was GI disorders. Although Study A7281007 was not placebo controlled, the exploratory efficacy results (based on the modified Harvey Bradshaw Index) indicated that the effect of SHP647 on disease activity was maintained over the duration of treatment.

The SHP647 dose selection (25 mg and 75 mg) for this study is based on data from these 3 previous studies, which evaluated the activity of SHP647 in adult patients with moderately to severely active CD based on CDAI scores between 220 and 450. The results of a post hoc analysis of remission rate by baseline elevated serum concentration of hsCRP suggested that the greatest treatment effect was at a dose of 22.5 mg. Similarly, post hoc analysis of remission rates by endoscopic severity assessed using the SES-CD suggested best efficacy at a dose of 75 mg. Therefore, both dosage regimens 25 mg and 75 mg Q4W have been selected for the Phase 3 testing. The Phase 1 study (A7281008, TOSCA) and Phase 2 studies (A7281006, OPERA; and A7281007, OPERA II [long-term safety study]) that investigated the safety, tolerance, pharmacokinetics, and pharmacodynamic properties of SHP647 support further clinical development of SHP647 using SC administration in subjects with moderate to severe CD.

2.2 Study Objectives

2.2.1 Coprimary Objectives

The coprimary objectives of this study are to evaluate the efficacy of SHP647 in subjects with moderate to severe CD in:

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

2.2.2 Secondary Objectives

2.2.2.1 Key Secondary Objectives

The key secondary objectives are as follows:

- To evaluate the efficacy of SHP647 in inducing clinical remission as measured by CDAI
- To evaluate the efficacy of SHP647 in inducing enhanced endoscopic response based on centrally read colonoscopy
- To evaluate the efficacy of SHP647 in inducing clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)
- To evaluate the efficacy of SHP647 in inducing clinical response based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
- To evaluate the efficacy of SHP647 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 SHP647 in inducing endoscopic healing based on centrally read colonoscopy.

2.2.2.2 Other Secondary Objectives

The other secondary objectives are as follows:

- To evaluate the safety and tolerability of SHP647
- To evaluate the effect of SHP647 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 SHP647 induction treatment on other endoscopic outcomes
- To evaluate the effect of SHP647 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 SHP647 on incidence of hospitalizations and total inpatient days
- To evaluate the impact of SHP647 on incidence of CD-related and other surgeries.

2.2.3 Exploratory Objectives

The exploratory objectives are as follows:

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

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of SHP647 in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.

At study initiation, a total of 1032 subjects (387 subjects in the 25 mg SHP647 treatment group, 387 subjects in the 75 mg SHP647 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.

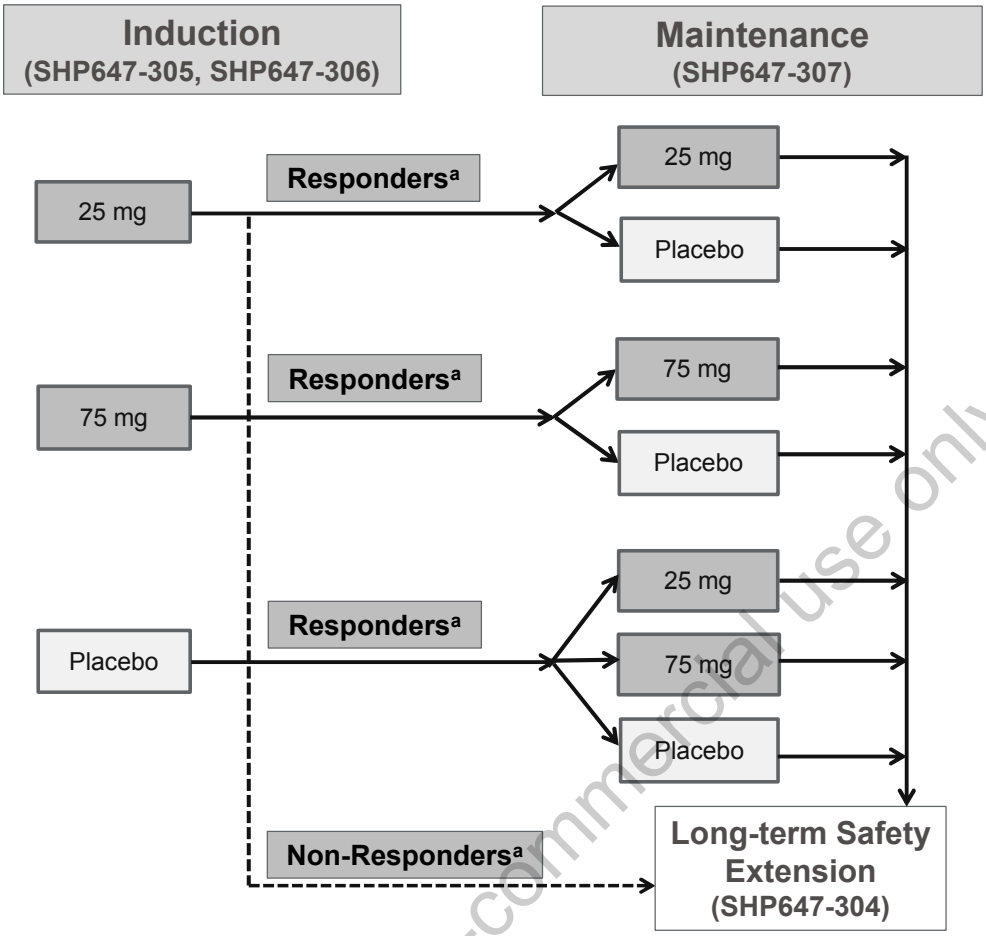
The study consists of a screening period up to 6 weeks and a 16-week treatment period. After the screening period, eligible subjects will be randomized to receive 1 of 3 treatments (25 mg SHP647, 75 mg SHP647, or placebo) in a 3:3:2 ratio. Randomization will be stratified based upon the subject's status of prior anti-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 SC injections of SHP647 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], [redacted], safety, and health outcome assessments at these visits and at the time points specified in Table 1.

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 treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

A planned interim analysis for the coprimary endpoints will take place 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 will be reassessed as part of this interim analysis. See Section 9.5 for further details of the planned interim analysis.

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; CD=Crohn's disease; CDAI= Crohn's Disease Activity Index; NRS=numerical rating scale; PRO=patient-reported outcomes; SES-CD=Simple Endoscopic Score for Crohn's Disease.

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

1. Subject is in clinical remission as determined by meeting the criteria for clinical remission using the 2-item PRO, ie, 2-item PRO subscore of average worst daily abdominal pain ≤3 (based on 11-point NRS) over the 7 most recent days and average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days.*

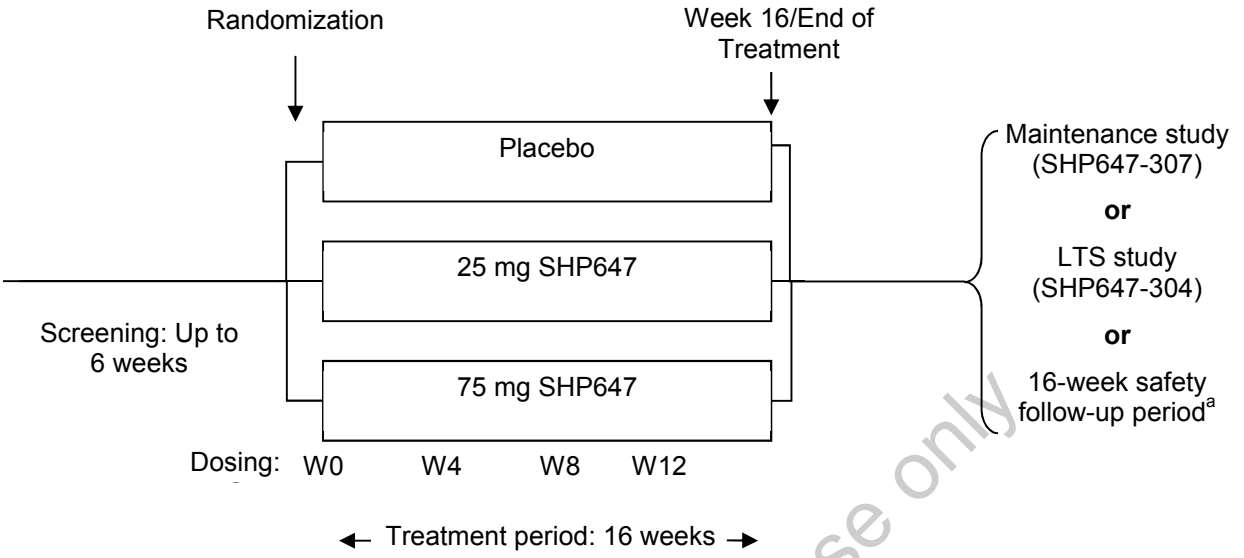
2. Subject has a decrease of at least 100 points in CDAI score (CDAI-70) from baseline.

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

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

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

Figure 2: Study Design Flow Chart



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.

Note: A planned interim analysis for the coprimary endpoints will take place 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.

3.1.1 Rationale for Coprimary Endpoints

In this study, clinical remission, as measured by a decrease below prespecified thresholds in the 2-item PRO (abdominal pain severity and very soft stool/liquid stool frequency [as shown in the Bristol Stool Form Scale, BSFS]), and enhanced endoscopic response, as measured by a decrease in SES-CD, will be the primary instruments to assess the efficacy of SHP647.

Rationale for Abdominal Pain Severity

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

This definition is further supported by a study conducted in a similar condition (irritable bowel syndrome) that examined the minimal clinically important difference on the 11-point NRS for abdominal pain (Spiegel et al., 2009) as well as post hoc analyses of the Phase 2 data from the SHP647 program (Study A7281006, OPERA).

Rationale for Very Soft Stool/Liquid Stool Frequency

Diarrhea is the most common sign in the presentation of CD, affecting approximately 85% of patients with a diagnosis of CD. In the CDAI, the number of liquid or soft stools (each day for 7 days) is used with a multiplier of 2. The coprimary endpoints for clinical remission in studies SHP647-305 and SHP647-306 requires the use of a definition without any such multiplying factor and will use the BSFS for defining the very soft or liquid stools according to types 6 and 7, respectively. A retrospective study of PROs in CD based on data from randomized controlled studies using rifaximin and methotrexate showed that a mean daily stool frequency score of ≤1.5 had an area under the receiving operating characteristic curve of 0.79 (Khanna et al., 2015) and provided a potential cutoff for defining remission as measured by CDAI. In a recent study to select the attributes determining overall disease severity and to rank the importance of and to score these individual attributes for both CD and UC based on specialist opinion, a sample of at least 10 loose stools per week was considered as an attribute contributing to overall disease severity in CD (Siegel et al., 2016). Based on post hoc analyses of the Phase 2 data in the SHP647 program (Study A7281006, OPERA) and by choosing the population of subjects satisfying the moderate to severe CD inclusion criteria, various cutoffs were explored and a stool frequency ≤2.0 was found to be optimal in terms of treatment separation while still allowing for a reasonable threshold for remission. Based on these and other recent data that support this cutoff, an average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) has been chosen as the stool frequency criterion for clinical remission.

Endoscopic Response

Endoscopic response is defined in 2 ways:

- 25% reduction in SES-CD score (“endoscopic response”)
- 50% reduction in SES-CD score (“enhanced endoscopic response”).

“Endoscopic response” will be used as a coprimary endpoint and “enhanced endoscopic response” will be used as a key secondary endpoint in this study as these magnitudes of changes are likely to be clinically relevant. In the recent trial with upadacitinib, the magnitude of difference between the different doses of the active drug and placebo at Week 16 was reported to be 9-36% for endoscopic response and 10-20% for enhanced endoscopic response (Sandborn et al., 2017). In the post hoc analysis of the Phase 2 OPERA study with SHP647 the magnitude of difference between the active treatment arms and placebo showed a similar pattern (higher for the endoscopic response than for enhanced endoscopic response) (D'Haens et al., 2018).

Mucosal healing or “endoscopic healing” is considered to be a pivotal long-term target in the treatment of CD; however, partial healing or endoscopic response may also provide benefits. Endoscopic response can be an important indicator that the mucosal inflammation has decreased as an effect of the investigational product.

Some treatments may result in a partial initial response, even though at a later stage a complete response may occur. Median duration of remission after 1 year treatment with infliximab was similar in subjects achieving complete absence of mucosal ulcer to subjects who achieved significant but incomplete mucosal healing (D'Haens et al., 2002).

The benefit of endoscopic response was also shown in the SONIC study; the presence of endoscopic response (defined in that study as at least a 50% decrease in endoscopic score at Week 26 of treatment) identified subjects most likely to be in corticosteroid-free clinical remission at Week 50 (Ferrante et al., 2013). The proportion of patients requiring major abdominal surgery in a single-center cohort study with infliximab was similar with complete healing or with partial healing. (Schnitzler et al., 2009; Panaccione et al., 2013). Subjects with such a treatment response should be identified by endoscopic assessment in order not to misclassify them as nonresponders and underestimate the response to the treatment.

3.1.2 Rationale for Key Secondary Endpoints

Clinical Remission Defined by CDAI Score

Conventionally, a CDAI score of <150 has been used to define clinical remission. While there has been widespread use of the CDAI over a long period of time, the items do not contribute equally to the score, and symptom items reported by subjects are not specific for CD and are not sensitive for inflammation seen at colonoscopy. There has been movement away from using the CDAI by regulatory authorities to the use of PROs and objective measures of disease such as endoscopy (Williet et al., 2014). However, for benchmarking or for comparative effectiveness purposes, CDAI endpoints are expected to be used.

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

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

The CDAI has been the traditionally used measure to assess clinical response and clinical remission in CD. In the CDAI, the degree of abdominal pain is one of 8 variables and is used with a multiplier of 5 in the overall score. Importantly, it is based on a 4-point scale, with scores ranging from 0 (none) to 3 (severe). With the shift to the new endpoint as evident from the coprimary endpoint of clinical remission in this study, it is still important to allow for a frame of reference to the existing standard for response, based on the CDAI components. A daily average abdominal pain threshold of ≤1 will help achieve this as 1 on the 4-point scale corresponds to mild abdominal pain. Although direct mapping between the scales has not been established, this will approximate to a score of 3 on the 11-point NRS scale, as this falls within the mild pain range on the NRS based on the literature.

Based on post hoc analyses of the Phase 2 data in the SHP647 program, regulatory requirements, and treatment separation assumptions, a threshold for the average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) was chosen for the coprimary endpoint of clinical remission.

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

Clinical Response

The goal of measuring clinical remission is to have a sensitive clinical measure to assess the complete absence of symptoms or the stabilization of noninflammatory symptoms. However, as response and remission are considered to be on a continuum of improvement or response to treatment, clinical remission is generally the chosen measurement over clinical response. Therefore, clinical remission is used as coprimary endpoint and clinical response is used as a key secondary endpoint in this study.

Clinical response is defined in Section 9.8.2.1. For both clinical response criteria, an additional requirement is that the symptom not being used to assess clinical response (ie, abdominal pain severity or very soft stool/liquid stool frequency) must remain unchanged/not worsen from the baseline score, or meet the criteria for clinical remission for that item of the 2-item PRO (either a 2-item PRO subscore of average daily stool frequency ≤2 of type 6/7 [very soft stools/liquid stools] as shown in the BSFS or average worst daily abdominal pain ≤3 [based on 11-point NRS] over the 7 most recent days).

The rationale for needing to meet at a minimum clinical response definition for either abdominal pain severity or very soft stool/liquid stool frequency (and not necessarily both) is based on the supposition that a lack of improvement in 1 of these symptoms is not necessarily an indicator of eventual lack of response (as assessed by the stricter clinical remission criterion). Based on Phase 2 data, it has been observed that the magnitude of placebo response rate can be higher for abdominal pain than for stool frequency. Therefore, the additional criterion of at least a 2-point decrease in abdominal pain severity from baseline is required for assessing clinical response for abdominal pain. Overall, the definition of clinical response used for this study has been chosen to allow for the maximal pool of subjects to be assessed for the effect of treatment and, if appropriate, the continuation of therapy in the maintenance study (SHP647-307).

Composite Score Endpoint of Both Clinical Remission by 2-item PRO and Endoscopic Response at Week 16

In theory, as the degree of inflammation decreases due to the effect of treatment, both clinical signs and symptoms of CD as well as endoscopic appearance can improve. However, in any given subject, the rates of clinical improvement and endoscopic improvement may not be the same. There are reasons for this discrepancy when evaluating clinical and endoscopic improvement in the same time period, including clinical symptoms not being well correlated to the mucosal inflammation. Due to the transmural feature of the disease, symptoms can correspond to the inflammation in some of the other gut layers as well. Previous clinical studies and clinical observations indicate that the improvement of clinical signs and symptoms and the improvement in endoscopic appearance may not go hand in hand.

Significant clinical improvement can precede significant endoscopic improvement. The healing process of the gut mucosa may take a long time and may depend on the baseline severity of the endoscopic appearance, which may not be in line with the actual baseline severity of the symptoms. Therefore, when evaluating clinical remission together with endoscopic endpoints, improvement in endoscopic scores could be more relevant than evaluating mucosal healing in the induction phase. For these reasons, the key secondary composite endpoint (which takes into account both clinical and endoscopic response to treatment in the same subject) consists of the evaluation of the clinical remission together with the endoscopic response.

Complete Endoscopic Healing

Endoscopic healing will be defined in 2 ways:

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

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

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

3.2 Duration and Study Completion Definition

Each subject's final visit in this study may be at the end of the treatment period (Week 16), if continuing to Study SHP647-307 or SHP647-304, or at the end of the safety follow-up period (Week 32), if not continuing to either of these studies. In either case, the final visit will be in person at the site. A subject's maximum duration of participation is expected to be approximately 38 weeks: a screening period of up to 6 weeks, a treatment period of 16 weeks, and a safety follow-up period of 16 weeks (if applicable). It is expected that the study will be completed in approximately 3 years.

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

3.3 Sites and Regions

It is anticipated that the study will be conducted in approximately 19 countries. Regions will include North America; Europe, the Middle East, and Africa; Latin America; and Asia Pacific. Approximately 210 sites will be utilized.

4. STUDY POPULATION

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

4.1 Inclusion Criteria

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and assent as applicable to participate in the study.
3. Subjects must be between ≥16 and ≤80 years of age at the time of the signing of the informed consent/assent form. Note: Subjects <18 years of age must weigh ≥40 kg and must have body mass index ≥16.5 kg/m^2.
4. Subjects must have active moderate to severe ileal (terminal ileum), ileocolic, or colonic CD at baseline (Visit 2) as defined by:
    a. CDAI score between 220 and 450 (inclusive) **AND**
    b. Presence of ulcerations that are characteristic to CD, as determined by a colonoscopy performed during screening, and as defined by the SES-CD >6 (SES-CD ≥4 for isolated ileitis) **AND**
    c. Meeting the following subscores in the 2-item PRO:
        i. Abdominal pain subscore ≥5 (average worst daily pain on the 11-point NRS) and abdominal pain subscore ≥2 (average daily pain on the 4-point abdominal pain variable of CDAI) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous) **AND/OR**
        ii. Average of the daily stool frequency subscore ≥4 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous).
5. Subjects must have a documented diagnosis (endoscopic with histology) of CD for ≥3 months before screening. Documented diagnosis is defined as:
    - A biopsy report to confirm the histological diagnosis **AND**
    - A report documenting disease duration based upon prior colonoscopy.

    Note: If a biopsy report is not available in the source document at the time of screening, a biopsy must be performed during the screening colonoscopy and the histology report should be consistent with the CD diagnosis. If the histology diagnosis is not clear at this time point, the subject should not be randomized.

6. Subjects must be willing and able to undergo a colonoscopy during screening after all other inclusion criteria have been met.
7. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or mesalamine (5-ASA), glucocorticoids, immunosuppressants (AZA, 6-MP, or MTX), or anti-TNF (refer to Appendix 4 for guidance). Subjects who have had an inadequate response to sulfasalazine or mesalamine should have also failed at least 1 other conventional treatment such as glucocorticoids.
8. Subjects receiving any treatment(s) for CD described in Section 5.2.1 of the protocol are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
9. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception (as described in Section 4.4) for the duration of the study.

4.2 Exclusion Criteria

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

1. Subjects with indeterminate colitis, microscopic colitis, non-steroidal anti-inflammatory drug-induced colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of ulcerative colitis.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with presence of enterovesical (ie, between the bowel and urinary bladder) or enterovaginal fistulae.
5. Subjects with current symptomatic diverticulitis or diverticulosis.
6. Subjects with obstructive colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for CD during the treatment period.
7. Subjects with past medical history of multiple small bowel resections resulting in clinically significant short bowel syndrome.
8. Subjects requiring total parenteral nutrition.
9. Subjects with past medical history of bowel surgery resulting in an existing or current stoma. Subjects who had a j-pouch are excluded as a j-pouch could result in a stoma.
10. Subjects have had prior treatment with SHP647 (formerly PF-00547659).

11. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
12. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than AZA, 6-MP, or MTX) or continuous antibiotics (>2 weeks) for the treatment of CD within 30 days before baseline (Visit 2).
13. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
14. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).
15. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
16. Subjects have received lymphocytes apheresis or selective monocyte granulocytes apheresis within 60 days before baseline (Visit 2).
17. Subjects have received enteral nutrition treatment within 30 days before baseline (Visit 2).
18. Subjects have received parenteral or rectal glucocorticoids or rectal 5-ASA within 14 days before screening colonoscopy.
19. Subjects have taken >20 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 14 days before baseline (Visit 2) or have taken ≥40 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 6 weeks before baseline (Visit 2).
20. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before screening (Visit 1).
21. Subjects have received a live (attenuated) vaccine within 30 days before baseline (Visit 2).
22. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis [subjects with *C. difficile* infection at screening may be allowed retest after treatment], evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before baseline (Visit 2).
23. Subjects with abnormal chest x-ray or other imaging findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray, computed tomography scan, etc., performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation).
24. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) or subjects with this history who have not completed a generally accepted full course of treatment before baseline (Visit 2) are excluded.

All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon-gamma release assay (IGRA) performed.

Subjects who have no history of previously diagnosed active or latent TB are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before baseline (Visit 2). If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

- An IGRA is strongly recommended for subjects with a prior bacillus Calmette-Guérin vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON-TB Gold Plus In-Tube Test.
- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent tuberculosis, a positive test on repeat will exclude the subject. Subjects with a history of active or latent tuberculosis infection must follow instructions for "Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met" in this criterion.
- Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray, taken within the 3 months before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.

- A chest x-ray performed within 3 months before screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.

25. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
26. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on the targeted neurological assessment during the screening period (Section 7.2.3.3).
27. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
28. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
    - Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.
    - Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
    - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening (Visit 1).
    - History of significant cerebrovascular disease within 24 weeks before screening (Visit 1).
29. Subjects who have had significant trauma or major surgery within 4 weeks before screening (Visit 1), or with any major elective surgery scheduled to occur during the study.
30. Subjects with evidence of cirrhosis with or without decompensation (ie, esophageal varices, hepatic encephalopathy, portal hypertension, ascites).
31. Subjects with primary sclerosing cholangitis.
32. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Note: If a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if no presence of HBV DNA is confirmed by HBV DNA PCR reflex testing performed in the central laboratory.

33. Subjects with chronic hepatitis C (HCV) (positive HCVAb and hepatitis C ribonucleic acid [HCVRNA]). Note: Subjects who are HCVAb positive without evidence of HCVRNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCVRNA at least 12 weeks prior to baseline]).

34. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening (Visit 1). Note: Screening laboratory tests, if the results are 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 must be reviewed for eligibility prior to the screening colonoscopy procedure.

    - Alanine aminotransferase and aspartate aminotransferase levels ≥3 × the upper limit of normal (ULN)
    - Total bilirubin level ≥1.5 × ULN or >2.0 × ULN if the subject has a known documented history of Gilbert's syndrome
    - Hemoglobin level ≤80 g/L (8.0 g/dL)
    - Platelet count ≤100 × 10^9/L (100,000 cells/mm^3) or ≥1000 × 10^9/L (1,000,000 cells/mm^3)
    - White blood cell count ≤3.5 × 10^9/L (3500 cells/mm^3)
    - Absolute neutrophil count <2 × 10^9/L (2000 cells/mm^3)
    - Serum creatinine level >1.5 × ULN or estimated glomerular filtration rate <30 mL/min/1.73m^2 based on the abbreviated Modification of Diet in Renal Disease Study Equation.

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

35. Subjects with known HIV infection based on documented history with positive serological test, or positive HIV serologic test at screening, tested at the site's local laboratory in accordance with country requirements, or tested at the central laboratory. Note: A documented negative HIV test within 6 months of screening is acceptable and does not need to be repeated.

36. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse of any kind including abuse of medicinal marijuana (cannabis).

37. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

38. Female subjects who are planning to become pregnant during the study period.

39. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm, or female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
40. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

4.3 Restrictions

- For the purposes of this protocol, dietary supplements (such as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties) are considered to be concomitant medications (Section 5.2).
- Smoking is considered to be a risk factor for CD. Reports have shown that smoking is not only related to the onset, relapse, and exacerbation of CD, but also that smoking cessation lowers the postoperative recurrence rate (Ueno et al., 2013). Subjects should inform the investigator of any changes to their smoking habits during the study (including starting or stopping smoking). Use of nicotine patches should be recorded as concomitant medication (Section 5.2.1).

4.4 Reproductive Potential

The potential effects of SHP647 on embryofetal or postnatal development have not yet been assessed in animals or humans; these will be assessed in future studies. To minimize the risk of unintentional exposure of the embryo or fetus in the clinical study, all sexually active male and female subjects who, in the opinion of the investigator, are biologically capable of having children and with their partners are at risk of pregnancy, must agree to use an appropriate form of contraception, in accordance with the package instructions/leaflet, for the duration of the active treatment period and for at least 16 weeks after the last dose of investigational product.

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

During the screening visit, the investigator or designee in consultation with the subject will confirm the subject's childbearing potential status. For subjects of childbearing potential, it must be confirmed and documented that the subject has selected the most appropriate method of contraception from the permitted list of contraception methods. Subjects must affirm the consistent and correct use of at least one of these selected methods. Regular contraception check discussions will take place at the time points specified in Table 1 (ie, at each site visit) and will be documented. In addition, the subject must be instructed to call the site immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

4.4.1 Contraceptive Methods for Female Study Subjects

Sexually active females of childbearing potential must already be using a highly effective form of contraception, and must be advised to use appropriate contraceptives throughout the study period and for 16 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert.

Female subjects should be in one of the following categories:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥51 years of age); postmenopausal status should be confirmed by follicle-stimulating hormone (FSH) testing.
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks poststerilization or has medically confirmed ovarian failure.
- Females of childbearing potential with a negative serum pregnancy test result at screening and a negative urine pregnancy test result at baseline (Visit 2). Females of childbearing potential must agree to practice true abstinence (refrain from sexual activity that could result in pregnancy) or agree to use appropriate methods of highly effective contraception.

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

- Combined (estrogen- and progestogen-containing) hormonal contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal) stabilized for at least 30 days before the screening visit (Visit 1)
- Progestogen-only hormonal contraception associated with inhibition of ovulation plus a barrier method
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization/vasectomized partner with documented absence of sperm in the postvasectomy ejaculate
- True abstinence (Section 4.4).

4.4.2 Contraceptive Methods for Male Study Subjects

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

Appropriate methods of contraception for male subjects are:

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

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

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

4.5 Withdrawal of Subjects

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

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 16/early termination (ET) (Visit 7) are to be performed. All subjects who discontinue treatment with investigational product should also undergo the protocol-specified 16-week safety follow-up period. In the event that subjects are unable to attend in person for the follow-up visits, all efforts should be made to collect information on AEs and concomitant medications. Comments (spontaneous or elicited) or complaints made by the subject must be recorded. The reason for termination and date of stopping investigational product must be recorded.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

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

- AEs
- SAEs
- Pregnancy

- Protocol violations
- Failure to return for visits.

A subject should be withdrawn from study treatment:

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

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

If a subject withdraws their consent, no further evaluation should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

4.5.2 Reasons for Withdrawal

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

Reasons for discontinuation include but are not limited to:

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

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

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

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal remedies and vitamins) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the first dose of investigational product. Use of biologics for indications other than CD during the 90 days before screening must also be recorded.

All prior and concomitant CD-specific treatments will be recorded. The subject's entire history of biologic CD-specific treatments will be recorded.

Subjects must have had an inadequate response to, or lost response to, or had intolerance to at least 1 conventional treatment such as sulfasalazine or 5-ASA, glucocorticoids, immunosuppressants (AZA, 6-MP, or MTX), or anti-TNF agents (Lichtenstein et al., 2018). Please refer to Appendix 4 for guidance on defining prior treatment failure and intolerance to prior treatment for CD.

5.2 Concomitant Treatment

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

5.2.1 Permitted Treatment

Subjects must remain on stable doses of permitted CD treatments until completion of the Week 16 visit, unless decreases are required because of AEs. Stable doses of the following treatments for CD are permitted as concomitant medication:

- Oral sulfasalazine or 5-ASA, providing that the dose is stable for at least 2 weeks before baseline (Visit 2)
- Immunosuppressants (AZA, 6-MP, or MTX), providing that the dose is stable for at least 8 weeks before baseline (Visit 2)
- Oral glucocorticoids (prednisone or equivalent [Appendix 3] up to a maximum of 20 mg/day or budesonide up to a maximum of 9 mg/day), providing that the dose is stable for at least 2 weeks before baseline (Visit 2). After baseline (Visit 2), a stable dose of 20 mg/day prednisone or equivalent oral systemic corticosteroid dose is allowed. Steroids may be decreased due to AEs.

Note: Rectal 5-ASA and parenteral or rectal glucocorticoids are prohibited from within 14 days before screening colonoscopy.

Antidiarrheal opiate drugs such as IMODIUM® (loperamide), LOMOTIL® (diphenoxylate hydrochloride and atropine sulfate), tincture of opium, and codeine will be recorded as concomitant medications. Subjects must be using such products in a stable regimen for at least 2 weeks before randomization at baseline (Visit 2). Reported use of any antidiarrheal opiate medicines will assist the investigator response to Question 5 of the CDAI.

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

Subjects using medicinal marijuana (cannabis) under a physician's prescription, and who obtain the product from a licensed pharmacy or provider, should continue to use it under the same regimen for the duration of the study, unless otherwise instructed by the investigator or treating physician. Such subjects must be using the product, in a stable regimen, for at least 3 months before screening.

Routine nonlive vaccinations are allowed during the study.

Dietary and herbal supplements and probiotics are allowed in the study, provided they are being taken at stable doses at the time of the baseline visit (Visit 2) and for the duration of the study. They should be recorded as concomitant medications.

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

Antibiotics are permitted, with the exception of antibiotics used to treat the underlying disease or any continuous antibiotic treatment exceeding 2 weeks within 30 days before starting PRO-CD daily e-diary data collection in the screening period or before Week 16 (Visit 7, Part 1).

5.2.2 Prohibited Treatment

Table 2 details the minimum required number of days before baseline (Visit 2) for common prior treatments that are excluded medications for this study.

Table 2: Common Excluded Treatments

	Excluded without any timeframe	Minimum Required Number of Days Before Baseline (Visit 2)			
Treatment		**14 days**	**30 days**	**60 days**	**90 days**
SHP647 (PF-00547659) in a previous study	X				
Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab)	X				
Parenteral and rectal glucocorticoids		X[a]			
Rectal 5-ASA		X[a]			
Investigational products			X[b]		
Live (attenuated) vaccine			X		
Nonbiologics with immunomodulatory properties[c]			X		
Anti-TNF treatment				X	

Table 2: Common Excluded Treatments

	Excluded without any timeframe	Minimum Required Number of Days Before Baseline (Visit 2)			
Treatment		**14 days**	**30 days**	**60 days**	**90 days**
Lymphocytes apheresis or selective monocyte granulocytes apheresis				X	
Biologics with immunomodulatory properties (other than anti-TNFs) including biosimilars					X

5-ASA=5-aminosalicylate; TNF=tumor necrosis factor.

[a] The minimum required number of days before baseline (Visit 2) for rectal 5-ASA and parenteral or rectal glucocorticoids is defined as 14 days before screening colonoscopy (Section 4.2, exclusion criterion 18).

[b] Or 5 half-lives if longer.

[c] Usage of immunosuppressants, eg used in transplantation or in autoimmune diseases that are not established therapies for CD (eg, mycophenolate mofetil, cyclosporine, rapamycin, thalidomide, tofacitinib, or tacrolimus).

Treatments not listed in Table 2 may be considered allowable; see Section 5.2.1 for further details.

In addition to the treatment listed in Table 2, the following common treatments are excluded medications for this study:

- Prednisone dose >20 mg/day, budesonide >9 mg/day, or other equivalent oral systemic corticosteroid dose
- Bismuth subsalicylate products
- Fecal microbiota transplantation.

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

Enteral nutrition is not permitted from within 30 days of baseline (Visit 2) or at any time during the study.

5.2.3 Rescue Therapy

Subjects must maintain their stable dose of background CD treatment, unless dose reduction or discontinuation is required due to associated AEs. If a subject requires initiation of a new therapy or increase in glucocorticoids for CD above the SHP647-305 or SHP647-306 baseline (Visit 2), the subject should be withdrawn from study treatment and enter the safety follow-up period, and appropriate treatment should be given at the discretion of the investigator.

Subjects who enter the safety follow-up period will no longer need to abstain from the medications that were prohibited during the baseline (Visit 2) and treatment periods. High-dose glucocorticoids and other CD treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated during the safety follow-up period without prior discussion with the sponsor study physician or designee due to the long half-life of SHP647.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is SHP647 (a fully human IgG_{2k} antihuman MAdCAM monoclonal antibody), which will be provided as a sterile aqueous buffered solution for SC administration in a glass PFS with a fixed needle. Each PFS contains 1 mL of SHP647 solution for injection at an appropriate concentration to provide the intended dose of drug (25 mg or 75 mg). Additional information is provided in the current SHP647 IB.

The reference product is placebo, which will be provided in a PFS with a fixed needle containing 1 mL of placebo solution for SC administration. The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain SHP647.

6.1.1 Blinding the Treatment Assignment

The placebo syringes and solution will match the SHP647 syringes in appearance. The fill volume for all syringes will be the same.

6.2 Administration of Investigational Products

6.2.1 Interactive Response Technology for Investigational Product Management

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

6.2.2 Allocation of Subjects to Treatment

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

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 SHP647, 75 mg SHP647, 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 $\geq$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 investigational product allocated to the subject, once eligibility has been determined. Individual subject treatment will be automatically assigned by the IRT system.

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

6.2.3 Dosing

Investigational product (SHP647 or placebo) will be administered subcutaneously by qualified site personnel Q4W (Weeks 0, 4, 8, and 12). See Section 7.2 for the timing of dosing relative to other procedures.

Investigational product should be administered in the anterolateral right or left thigh. If there are clinical reasons why the investigational product cannot be administered in the thigh, the investigational product may be administered in the deltoid area or abdomen with appropriate documentation. The location of the investigational product administration will be recorded.

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

Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is dispensed by qualified staff members.

6.2.4 Unblinding the Treatment Assignment

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

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

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

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

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

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

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

6.3.2 Packaging

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

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

6.3.3 Storage

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

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified minimum/maximum thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range.

Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

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

6.3.4 Special Handling

The investigational product should be protected from light and should not be frozen. Do not shake.

6.4 Drug Accountability

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

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

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented in the subject's source document and/or other investigational product record.

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

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

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

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

6.5 Subject Compliance

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

7. STUDY PROCEDURES

7.1 Study Schedule

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of assessments (Table 1), in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

7.1.1 Screening Period

7.1.1.1 Screening Visit (Visit 1)

Subjects will be screened within 6 weeks before the first dose of investigational product to determine eligibility to participate in the study and to perform the other assessments and procedures specified in Table 1. Each subject or subject's parent or legally authorized representative must participate in the informed consent process and provide written informed consent/assent before any assessments or procedures specified in the protocol are performed. Screening assessments will take place over more than 1 day (at least 2 visits will be necessary to complete the screening evaluations, including colonoscopy).

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

A subject may be rescreened if their condition has changed and they may potentially be eligible. Subjects may be rescreened 1 time only. Note: Screening laboratory tests, 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.

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.

Collection of the daily e-diary data must begin at least 10 days before colonoscopy preparation. Colonoscopy preparation will be according to local routine.

Colonoscopy must be performed on all subjects after the majority of other eligibility criteria (eg, laboratory values and 2-item PRO and CDAI scores) are met. It must be performed during the screening period within 5 to 7 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 (Section 7.2.2.4). If the calculated CDAI scores is <220 or >450, the subject will be considered a screen failure and should not proceed with the colonoscopy preparation and/or the colonoscopy. All colonoscopies will be evaluated using the SES-CD (Appendix 2).

If a subject has had the following procedures performed as a part of standard medical care within 12 weeks before screening (Visit 1), these procedures do not need to be repeated as a part of screening:

- Chest x-ray
- Documented negative PPD test or IGRA for TB.

7.1.1.2 Baseline Visit (Visit 2, Week 0)

The baseline visit (Visit 2) will take place on Day 1 (Week 0). The assessments and procedures specified in Table 1 will be performed.

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

Results of the baseline laboratory tests are not required for investigational product administration but must be reviewed as soon as possible thereafter.

7.1.2 Treatment Period

7.1.2.1 Visits 3, 4, 5, and 6 (Weeks 2, 4, 8, and 12)

Visits 3, 4, 5, and 6 are scheduled to take place on Day 14 ±3 days (Week 2), Day 28 ±3 days (Week 4), Day 56 ±3 days (Week 8), and Day 84 ±3 days (Week 12), respectively. The assessments and procedures specified in Table 1 will be performed.

7.1.2.2 Final On-treatment Visit: Visit 7, Parts 1, 2, and 3 (Week 16/Early Termination)

The Week 16/ET visit (Visit 7) consists of 3 parts.

Part 1 of Visit 7 should be scheduled 1 to 3 day(s) before Part 2; this will allow for blood samples to be taken before starting the colonoscopy preparation and before the colonoscopy procedure at Part 2 of the visit. The Week 16/ET assessments and procedures that will take place during Part 1 are specified in Table 1.

Part 2 of Visit 7 should be scheduled preferably within 5 to 7 days before Part 3; this will allow sufficient time to obtain the data from the centrally read colonoscopy. The Week 16/ET assessments and procedures that will take place during Part 2 are specified in Table 1.

Part 3 of Visit 7 will take place on Day 112 ±3 days. The Week 16/ET assessments and procedures that will take place during Part 3 are specified in Table 1.

At Part 3 of Visit 7, after review of CD assessments, health outcome assessments, and safety assessments, it will be determined whether the subject should enroll in the maintenance (SHP647-307) or LTS (SHP647-304) studies or enter the follow-up period of this study. Entry into the maintenance or LTS studies is dependent upon whether the subject fulfills the efficacy entry criteria of the maintenance study (SHP647-307), including achieving endoscopic and/or clinical response, and whether the subject agrees to participate.

The Week 16 assessments and procedures will also form the ET assessments for any subjects who are withdrawn early or discontinued from the study.

7.1.3 Follow-up Period

Subjects who are withdrawn early from the study, or who do not enter either the maintenance or LTS studies, should enter the 16-week safety follow-up period for safety monitoring.

During the safety follow-up period, the Week 24 visit (Visit 8) will take place on Day 168 ±7 days, or 8 weeks ±7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study. This visit will routinely be conducted by telephone; however, as an exception, the visit can be performed as a study site visit if preferred.

At the end of the safety follow-up period, there will be a visit at the site on Day 224 ±7 days, or 16 weeks ±7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study; this visit will form the Week 32 visit (Visit 9). The assessments and procedures specified in Table 1 will be performed, including querying for SAEs, AEs, and concomitant medications and treatments. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (Section 8.1).

Subjects who are proceeding to the maintenance or LTS studies will not enter the safety follow-up period.

7.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

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

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

- Health outcome and patient-reported questionnaires
- Vital signs and ECG
- Laboratory sample collection
- Investigational product administration
- Colonoscopy is performed at a separate visit (Section 7.2.2.4).

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

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics will be recorded at screening (Visit 1).

7.2.2 Efficacy

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

Patient-reported CD clinical signs and symptom 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 enter data on CD signs and symptoms items using the e-diary, which will be provided to subjects at the start of the study. Compliance will be assessed by site staff at each visit. The site staff will instruct the subject on the appropriate use of the e-diary when compliance is below 80% (eg, <23 out of 28 e-diary entries). If 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 (Section 4.1).

Subjects will be asked to record the following signs and symptom data, as experienced over the previous 24 hours, in the e-diary:

- Abdominal pain severity (NRS)
- Very soft stool/liquid stool frequency (as shown by BSFS type 6/7)
- Total stool frequency
- Rectal bleeding frequency
- Rectal urgency frequency
- Nausea severity
- Vomiting frequency
- Incontinence frequency
- Abdominal pain used in CDAI
- General wellbeing.

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.
- Visits 3, 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.
The PRO-CD daily e-diary is presented in Appendix 2.

7.2.2.2 Simple Endoscopic Score for Crohn's Disease

The SES-CD will be performed at the time points specified in Table 1. The SES-CD score at 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.

The SES-CD is a simple scoring system based on 4 endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of affected surface, and presence and severity of stenosis [narrowing]) measured in the same 5 ileocolonic segments as the CD index of severity. Overall, values on the SES-CD range from 0 to 56, with higher values indicating more severe disease. The 4 endoscopic variables are scored from 0 to 3 in each bowel segment (ileum, right/transverse/left colon, and rectum):

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

A complete colonoscopy is required (including visualization of the terminal ileum).
The maximum stenosis score in a segment distal to another evaluable segment cannot exceed 2, so that the stenosis scores cannot exceed a total of 11 (Reinisch et al., 2017).

Evidence of active inflammation and ulceration is required at screening (Visit 1), in the form of a centrally read score of at least 1 in one or more ileocolonic segments in the Presence of Ulcers component of the SES-CD, as well as a total score of >6.

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

For the evaluation of efficacy, in cases where 1 or 2 segments cannot be fully evaluated by central endoscopic readers, ileocolonic segments that are evaluable during screening (Visit 1) and Week 16/ET (matching segments approach) will be utilized.

The SES-CD is presented in Appendix 2.

7.2.2.3 Crohn's Disease Activity Index

The CDAI is a composite measure with 8 components; 3 components (abdominal pain severity, very soft stool/liquid stool frequency, and general wellbeing) will be self-reported by the subject and will be recorded as part of the daily e-diary, as described in Section 7.2.2.1 and 5 components will be recorded at the time points specified in Table 1.

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 (Section 7.2.2.1) and
- 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 (Section 7.2.2.1) and
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at the visit.

The CDAI score at 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 (Section 7.2.2.1) and
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at Part 1 and Part 3 of the Week 16/ET visit, where assessed.

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

The CDAI is presented in Appendix 2.

7.2.2.4 Colonoscopy and Histology

Colonoscopy will be performed at the time points specified in Table 1.

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

In general, a complete colonoscopy should be performed; this includes visualization of the rectum, sigmoid colon, left colon, transverse colon, right colon, ileocecal valve, and the terminal ileum. At screening, an incomplete colonoscopy will not be accepted; only a few exceptions will be evaluated on a case by case basis (eg. presence of impassable narrowing without any clinical signs of bowel obstruction and when the same time the investigated segments provide the SES-CD score required for inclusion). Similarly, a complete colonoscopy is the aim at Week 16/ET, with the exception of the presence of impassable stenosis or other CD-related complications as cause of failure to complete the colonoscopy procedure.

The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during colonoscopy. To achieve consistency in capturing and assessing endoscopic video recordings, each participating site will use an integrated hardware/software solution and associated tools for the capture and transmission of endoscopy video recordings for central reading. Nonreadable endoscopic images, as assessed by the investigator, should not be sent for central reading. The colonoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's medical record.

During 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. Colonoscopy and biopsy procedures will be defined in a colonoscopy instructions manual and/or reference card(s), on which all sites will be trained. Colonoscopy results will be reviewed by a central reader.

[redacted]
(Appendix 2). Biopsies for conventional histologic assessment will be collected in formalin and shipped to the central laboratory. The central laboratory will register all biopsies and create paraffin blocks. Blocks will be batched and shipped on an agreed schedule to specialty laboratory, where tissue processing (sectioning, hematoxylin and eosin staining, and affixation to glass slides), digitalization, and uploading of images will occur. All images for a subject will be scored by the same qualified central pathologists blinded to the subject and treatment sequence information, according to the scoring modality.

7.2.3 Safety

7.2.3.1 Medical and Medication History

Medical history will be documented at screening (Visit 1), including CD history, cardiac history, and smoking history. Prior and concomitant medications and procedures will also be documented at the time points specified in Table 1.

7.2.3.2 Physical Examination (Including Height and Weight)

Complete and targeted physical examinations will be performed at the time points specified in Table 1. Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; eyes; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; back; and lymph nodes. Targeted physical examination includes the review of the following body systems: skin and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

Weight will be measured at the time points specified in Table 1. Height will be measured at screening (Visit 1) only.

Changes after the screening visit that are deemed clinically significant in the opinion of the investigator will be recorded as an AE.

7.2.3.3 Targeted Neurological Assessment

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

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

Subjects with any unexplained positive neurological assessment item at screening that is suggestive of PML should be excluded from enrollment in the study (exclusion criterion 25, Section 4.2).

The neurological assessment plan is summarized in Table 3.

Table 3: Neurological Assessment Plan

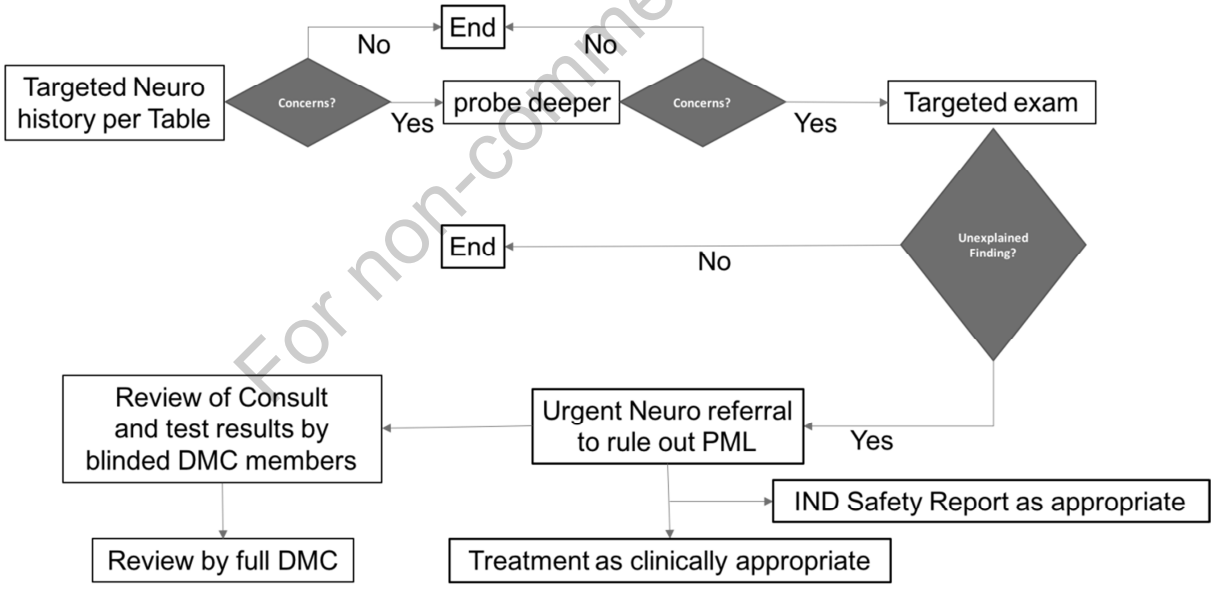
Domain	Step 1: Targeted Neurological History	Step 2: If Abnormal Response
Vision	Diplopia or visual/visual field loss	Perform visual field assessment
Motor	Major motor weakness (eg, legs, arms)	Test leg strength (hopping, foot tapping), finger tapping, pronator drift and bilateral muscle strength
Tactile sensation	Paresthesia, anesthesia in any domain (peripheral, central)	Pinprick test
Coordination/Cerebellar	Clumsiness, difficulty with walking, writing, or fine motor skills, etc.	Finger-nose, heel-shin, heel-toe walk, writing sample, draw a clock

Table 3: Neurological Assessment Plan

Domain	Step 1: Targeted Neurological History	Step 2: If Abnormal Response
Speech	Dysarthria, expressive aphasia	Naming objects, repeat multipart phrase, observe for dysarthria or aphasia
Verbal comprehension	Agnosia, receptive aphasia	Test to follow routine commands, eg, close eyes, touch finger to ear
Cognition/Behavior	New onset of difficulties with memory or thinking, important changes in behavior	Recall 3 objects over 1 minute, serial 7s, proverbs. Changes in activities of daily living over prior 6 months

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

Figure 3: Flow Diagram for Quarterly Neurological Assessments



DMC=Data Monitoring Committee; IND=investigational new drug; Neuro=neurological; PML=progressive multifocal leukoencephalopathy.

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

7.2.3.4 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent and/or assent is signed until the end of the study or the defined follow-up period stated in Section 7.1.3 (Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.3.5 Vital Signs

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

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

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

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

Any deviations from baseline (Visit 2) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE, unless documented in the subject's medical history as a pre-existing medical condition.

7.2.3.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant.

Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

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

Serum chemistry

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

Hematology

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

Virology

- hepatitis B surface antigen (HBsAg)
- hepatitis B core antibody (HBcAb)
- hepatitis B DNA reflex testing if HBsAg is negative and HBcAb is positive
- hepatitis C virus antibody (HCVAb)
- HCV ribonucleic acid polymerase chain reaction if HCVAb is positive
- HIV

Urinalysis

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

Virology test results must be confirmed as negative before enrollment in the study; if a virology test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor but will not be collected in the electronic case report form (eCRF) database.

Stool microbiology will be performed at the screening visit (Visit 1). Diagnosis of *C.difficile* infection should be made using the central laboratory. If, for any reason, the central laboratory is not available, please refer to Appendix 5 for guidance regarding the diagnostic algorithms.

A TB test (PPD or QuantiFERON-TB Gold Plus) will be performed at the screening visit (Visit 1). A documented negative PPD test within 12 weeks before baseline (Visit 2) is acceptable provided that an IGRA official reading and method or test is located in the source documentation.

A serum sample will be collected and banked for John Cunningham virus antibody testing at baseline (Visit 2). It may be analyzed if a subject shows neurological symptoms suggestive of PML.

All laboratory assessments should be performed at central laboratories, with the exception of the following assessments: stool microbiology (local or central laboratory) and TB test (PPD or QuantiFERON-TB Gold Plus) (refer to laboratory manual for details).

7.2.3.7 Pregnancy Test and Follicle-stimulating Hormone Test

A beta-human chorionic gonadotropin (β-hCG) pregnancy test will be performed on all females of childbearing potential at the time points specified in Table 1; if pregnancy is suspected; or on withdrawal of the subject from the study. A serum pregnancy test will be performed at the screening visit (Visit 1); all other pregnancy tests will be urine tests.

Pregnancy tests are not required for females of nonchildbearing potential who have undergone hysterectomy or bilateral oophorectomy, have medically confirmed ovarian failure, or are medically confirmed postmenopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; postmenopausal status should be confirmed by FSH testing in females who have had 12 consecutive months of spontaneous amenorrhea and are 51 years of age or older).

7.2.3.8 Electrocardiogram

A 12-lead ECG will be recorded at the time points specified in Table 1.

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

7.2.3.9 Chest X-ray

A chest x-ray will be performed during screening (Visit 1). If a subject has had a chest x-ray performed as a part of standard medical care within 12 weeks before screening (Visit 1), it does not need to be repeated as a part of screening. The official reading must be located in the subject's source documentation.

7.2.3.10 Antidrug Antibodies and Neutralizing Antibodies

A blood sample for measurement of ADA and NAb will be collected at the time points specified in Table 1. Blood samples must be collected before administration of investigational product.

7.2.4 Others

7.2.4.1 [redacted]

[redacted]

7.2.4.2 [redacted]

[redacted]

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

[redacted]

[redacted]

7.2.4.3 Health-related Quality of Life Assessments

Each subject will complete the HRQL assessments at the site during the visits specified in Table 1, using an electronic device. All health outcome and patient-reported questionnaires should be completed before any other assessments. The study site staff should check for completion of all PRO questionnaires.

It is important to note that PRO assessments are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and PRO data collected from subjects. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded by the investigator.

Inflammatory Bowel Disease Questionnaire

The IBDQ is a psychometrically validated PRO instrument for measuring the disease-specific HRQL in subjects with inflammatory bowel disease, including CD. The IBDQ consists of 32 items, which are grouped into 4 domains: bowel, systemic, emotional, and social function (Irvine et al., 1994). The 4 domains are scored as follows:

- Bowel function: 10 to 70
- Systemic function: 5 to 35
- Emotional function: 12 to 84
- Social function: 5 to 35.

The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better HRQL. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement.

The IBDQ is presented in Appendix 2.

[redacted]

The [redacted] is presented in Appendix 2.

[redacted]

The [redacted] and [redacted] are presented in Appendix 2.

[redacted]

Short Form-36 Health Survey (Version 2, Acute Form)

The SF-36 is a generic quality-of-life instrument that has been widely used to assess HRQL of subjects. Generic instruments are used in general populations to assess a wide range of domains applicable to a variety of health states, conditions, and diseases. The SF-36 consists of 36 items that are aggregated into 8 multi-item scales (physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional, and mental health), with scores ranging from 0 to 100 (Ware and Sherbourne, 1992). Higher scores indicate better HRQL.

[redacted]

7.2.4.4 Healthcare Resource Utilization Assessments

Hospitalizations, inpatient days, and ED visits will be recorded at the time points specified in Table 1. Information regarding Crohn's disease-related and other surgeries will be collected from subjects during the treatment period.

7.2.5 Volume of Blood to Be Drawn From Each Subject

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

Table 4: Volume of Blood to Be Drawn From Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Hematology	2	7	14
Serum chemistry	6	7	42
HBsAg	2	1	2
HBcAb	2	1	2
HCV Ab	2	1	2
HBV DNA	6	1	6
HIV	2	1	2
FSH	2	1	2
Serum β-hCG[a]	2	1	2
TB test (QuantiFERON-TB Gold Plus or PPD)	4	1	4

Table 4: Volume of Blood to Be Drawn From Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
JCV antibody banked sample	3.5	1	3.5
[redacted]			
[redacted]	2	3	6
[redacted]	5	3	15
[redacted]	4	3	12
[redacted]	3	6	18
ADA and NAb sampling	3	7	21
Total (mL)			**153.5**

Ab=antibody; ADA=antidrug antibodies; β-hCG=beta-human chorionic gonadotropin; [redacted]; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HCV=hepatitis C virus; JCV=John Cunningham virus; [redacted]; NAb=neutralizing antibody; PPD=purified protein derivative; TB=tuberculosis.

[a] β-hCG testing for female subjects only.

[b] If a catheter is used, the first mL is to be discarded; then take 4 mL into appropriate tube for [redacted]. A total of 5 mL of blood drawn has been used in determination of sample volume.

The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 153.5 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

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

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

All AEs are collected from the time the informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured in the subject's source document. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the subject's source document.

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

8.1.1 Severity Categorization

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

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

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

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Outcome Categorization

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

- Fatal
- Not recovered/Not resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown.

8.1.4 Symptoms of the Disease Under Study

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

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value.

When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

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

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

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

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

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

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

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

8.1.7 Abuse, Misuse, Overdose, and Medication Error

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

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

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

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

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

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

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

There is no specific antidote for overdose with SHP647. Treatment should be symptomatic and supportive.

8.1.8 Unexpected Adverse Event

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

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

8.1.9 Suspected Unexpected Serious Adverse Reaction

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

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

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

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is Section 6.8 of the SHP647 IB, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (Section 8.1.7) unless they result in an SAE.

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

8.2.3 Serious Adverse Event Definition

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

- Results in death
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).

- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an ED or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

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

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

In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs (ie, SUSARs) occurring during all interventional studies across the SHP647 program.

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

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

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

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

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities per Table 5 should be evaluated further to definitively determine the etiology of the abnormal laboratory values. The measurement(s) should be reconfirmed with another blood draw preferably within 48-72 hours of the initial finding of potential concern. Please refer to lab manual for further instructions.

Guidance for Dosing Interruption: Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

Table 5: Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action
Normal baseline ALT ≥5× ULN **Elevated baseline[a]:** ALT ≥3× baseline *or* ≥300 U/L (whichever occurs first)	Normal Patients with Gilbert's syndrome or hemolysis: No change in baseline TBL	None	Repeat ALT, AST, ALP, TBL, in 2-5 days. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation.[c]
Normal baseline ALT ≥8× ULN **Elevated baseline[a]:** ALT ≥5× baseline or ≥500 U/L (whichever occurs first	Normal Patients with Gilbert's syndrome or hemolysis: No change in baseline TBL	None	Interrupt study drug.[b] Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation.[c]
Normal baseline ALT ≥3 × ULN **Elevated baseline[a]:** ALT ≥2 × baseline or ≥300 U/L (whichever occurs first)	TBL≥2mg/dL increased over baseline *or* Patients with Gilbert's syndrome of hemolysis: Doubling of baseline direct bilirubin	None	Interrupt study drug.[b] Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation.[c]
Normal baseline ALT ≥5 × ULN **Elevated baseline[a]:** ALT ≥2 × baseline or ≥300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain or Immunologic symptoms Rash Eosinophilia >5%	Interrupt study drug.[b] Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline. Testing for hepatitis A, B, and/or C infection may be warranted. Subjects who entered the study with HBcAb with or without HBsAb would need evaluation with HBV DNA to rule out HBV reactivation.[c]

Table 5: Safety Monitoring Rules for Treatment-emergent Elevated ALT and/or Bilirubin

Treatment emergent ALT	Treatment-emergent total bilirubin	Treatment-emergent symptoms	Action

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; TBL=total bilirubin; ULN=upper limit of normal

[a] Elevated baseline ALT defined as ALT ≥1.5× ULN

[b] Confirmatory repeat liver-related blood tests should be performed within 2-3 days before the investigational product (IP) is interrupted.

[c] If HBV DNA positive antivirals would need to be started ASAP.

Source: Adapted from Chalasani and Regev, 2016.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

9.3 Data Handling Considerations

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

9.4 Statistical Analysis Process

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

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

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

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

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

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

A planned interim analysis for the coprimary endpoints will take place 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. Recruitment will not pause for this interim analysis. The purpose of the unblinded interim analysis is to reassess the appropriateness of the premises used for the coprimary endpoints when the study was designed. There is no possibility to stop early for overwhelming efficacy as the studies must continue in order to enroll an appropriate number of subjects in the SHP647-307 study. The reassessment of sample size will be performed using conditional power methods. Results at the interim analysis may be futile for one or both of the SHP647 doses and lead to the discontinuation of that dose for CD or the SHP647 CD program. Full details of the interim analysis, the guidelines for increasing the sample size, and futility rules to stop a dose will be included in a prespecified interim analysis SAP. The interim analysis SAP will be finalized before the interim analysis is conducted.

The planned interim analysis will be conducted by an external independent statistical group and given to the independent Interim Analysis Review Committee; the individuals involved in the day-to-day conduct of the study will not be involved in the interim analysis nor have access to the results of the interim analysis. The sponsor will only be notified by the Interim Analysis Review Committee of recommendations to modify the SHP647 CD program according to the guidelines specified in the interim analysis SAP.

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

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

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

9.6 Sample Size Calculation and Power Considerations

Graphical methods are used to control the global family-wise type I error rate (FWER) at the .05 level (2-sided) for the comparisons of the 2 SHP647 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 was calculated based on the chi-square test of proportions using nQuery Advisor® Version 7.0 (Statistical Solutions Ltd, Cork, Ireland) for an individual SHP647 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 SHP647 treatment group, 387 subjects in the 75 mg SHP647 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% SHP647 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% SHP647 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 6 provides the power for detecting a treatment difference between a SHP647 treatment group and the placebo group for the key secondary endpoints.

Table 6: Power to Detect the Corresponding Treatment Effect for Key Secondary Endpoints

Key Secondary Endpoint at Week 16	SHP647 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.

9.7 Study Population

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

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

The per-protocol set will consist of all subjects in the FAS who do not have protocol deviations that may affect the coprimary efficacy endpoints.

The completer set will consist of all subjects in the FAS who have completed the Week 16 assessment for this study.

[redacted]

9.8 Efficacy Analyses

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

9.8.1 Coprimary Efficacy Endpoints

The coprimary efficacy endpoints are:

- Clinical remission at the Week 16 visit as defined by the following: 2-item PRO subscores of average worst daily abdominal pain ≤3 (based on 11-point NRS) over the 7 most recent days and average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days. The 7 most recent days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the endpoint will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the endpoint will be treated as missing.
- Endoscopic response at Week 16 as measured by a decrease in SES-CD of at least 25% from baseline.

The coprimary efficacy endpoints, clinical remission at the Week 16 visit and endoscopic response at the Week 16 visit, will each be compared for each active treatment group (25 mg or 75 mg SHP647) to the placebo group using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use, and SES-CD at baseline for each of the stages of the study (stage 1 includes subjects whose primary efficacy data are used in the interim analysis and stage 2 includes all other subjects. Note: classification of stage 1 and stage 2 is based on the time of randomization rather than the time of study completion or termination). Subjects with missing data at the Week 16 visit will be considered failures and counted as nonresponders.

Weighted inverse normal p-value combination methods are used to combine the p-values from stage 1 and stage 2 through the following formula:

$$C(p_1, p_2) = 1 - \Phi[w_1 \Phi^{-1}(1-p_1) + w_2 \Phi^{-1}(1-p_2)]$$

Where p_1, p_2 are the p-values computed from the CMH chi-square test for each stage, $w_i^2 = n_i/(n_1 + n_2)$, n_1 and n_2 are the preplanned stage-wise sample sizes that are fixed at the time of the interim analysis based on an original total sample size, and Φ denotes the cumulative distribution function of the standard normal distribution (Bretz et al., 2009a). Given that there is no possibility of stopping early for efficacy, that any potential stopping for futility of either or both doses of SHP647 is nonbinding, and that weights are prespecified, the test statistic $C(p_1, p_2)$ can be compared against the nominal alpha level to assess statistical significance (Chang and Chow, 2008).

The coprimary endpoints will each be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata. The common treatment difference is a weighted average of the stratum-specific treatment differences.

The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% CI using the method of Yan and Su (2010) and the p-value computed from the p-value combination method will be presented for each active treatment group to placebo comparison for each endpoint.

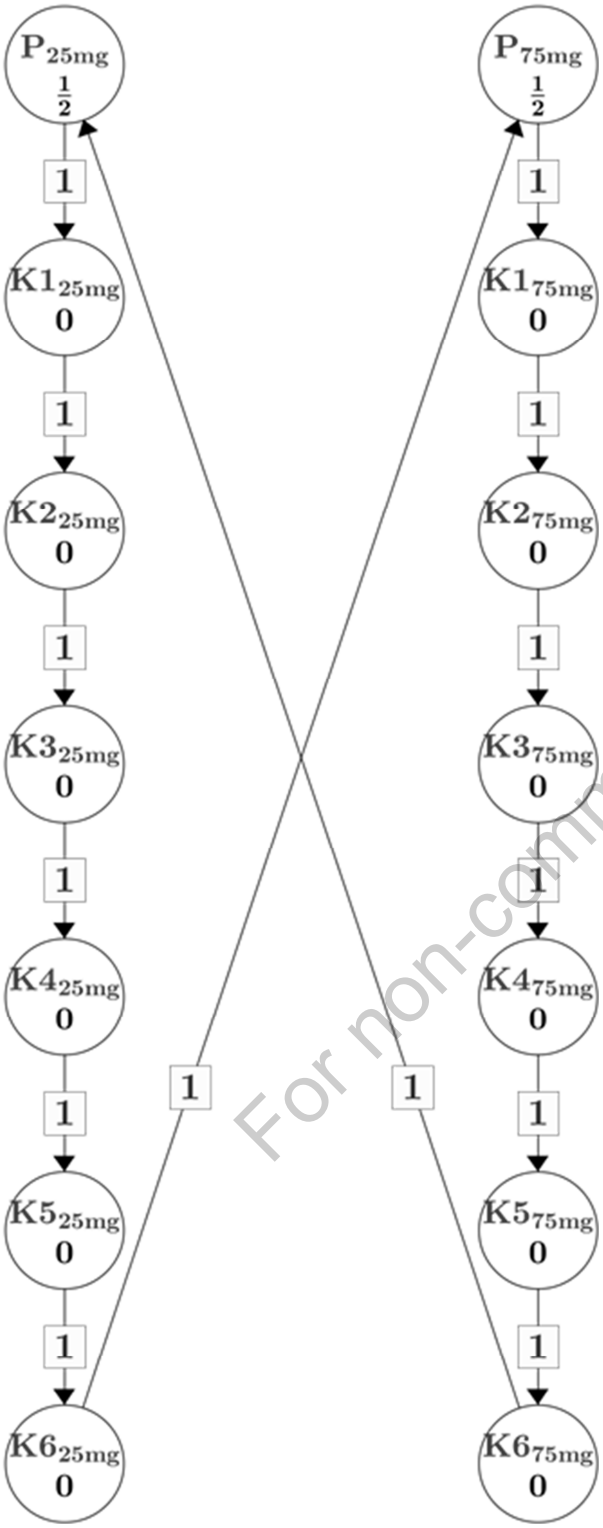
Sensitivity analyses to explore the impact of missing data on the coprimary efficacy endpoints and key secondary endpoints will be conducted. These analyses may compare imputations of the missing values which favor placebo (eg, worst case) and/or imputations which favor active treatment (eg, best case). In addition, imputation methods based on informative missingness and other missing data mechanisms may be performed. Additional sensitivity analyses will also be conducted using the per-protocol set and the completer set. Additional analyses may be developed in the SAP. All sensitivity analyses will be described in the SAP.

Prespecified subgroup analyses are planned for the coprimary endpoints including, but not limited to gender, prior anti-TNF treatment, glucocorticoid use at baseline, SES-CD at baseline, region, age group, randomization stratum, and other important subgroups. A full list of important subgroups will be described in the SAP. Within subgroups, efficacy endpoints will be compared for each active treatment group (25 mg SHP647 and 75 mg SHP647) with the placebo group using a chi-square test. The estimate of the treatment difference, along with the corresponding Newcombe (hybrid-score) 95% CI and chi-square test p-value, will be presented.

Statistical Testing and Protection of the Type I Error

The global FWER for the statistical tests of the coprimary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al. (2009b) will be utilized to propagate α from the coprimary endpoints to the key secondary endpoints and between the 2 SHP647 treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the coprimary endpoints (P) and alpha is propagated in a hierarchical manner to each of the 6 key secondary endpoints (K1–K6) within a pairwise treatment comparison. In order to pass alpha between the coprimary endpoints and the first key secondary endpoint, both coprimary endpoints must attain statistical significance. A graphical visualization of the α propagation is presented in Figure 4.

Figure 4: Visualization of Multiple Testing Strategy



K=key secondary endpoint; P=coprimary endpoints.

Only p-values that are significant according to this graphical approach are inferential and statistically significant. All other p-values are descriptive.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- Clinical remission at the Week 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 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.

Similar to the coprimary endpoints, the 6 key secondary endpoints will all be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

The key secondary endpoints will be analyzed using the same approach as described for the coprimary endpoints. Subjects with missing key secondary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.

9.8.2.2 Other Secondary Efficacy Endpoints

The 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 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.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods:

- Binary endpoints will be compared between each active treatment group and the placebo group using a CMH chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use at baseline, and SES-CD at baseline.

The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% CI using the method of Yan and Su (2010) and the p-value computed from CHM test will be provided. Subjects with missing binary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.

- Continuous endpoints that are only measured at baseline and the Week 16 visit will be analyzed using an analysis of covariance model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences will be provided.
- Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation. The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

9.8.3 Exploratory Efficacy Endpoints

The exploratory endpoints are as follows:

[redacted]

Exploratory efficacy endpoints will be summarized with descriptive statistics and presented by treatment group using the same approach described as for the other secondary endpoints. See Section 9.8.2.2 for an overview of the planned analyses. Full details for the analysis of exploratory efficacy endpoints will be included in the SAP.

9.9 Safety Analyses

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

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

Treatment-emergent AEs are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events and percentage of TEAEs will be calculated by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, serious AEs, and deaths will be similarly summarized or listed.

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

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

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

9.10 Other Analyses

9.10.1 [redacted]

[redacted]

9.10.2 [redacted]

[redacted]

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

[redacted]

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

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

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

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

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

10.1.2 Indemnity/Liability and Insurance

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

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

10.1.3 Public Posting of Study Information

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

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

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

10.1.5 Study Suspension, Termination, and Completion

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

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

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

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

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

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

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

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

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

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

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

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

10.2.3.3 Audit/Inspection

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

10.2.3.4 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and/or assent from all study subjects before any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP.

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

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

10.3.2 Institutional Review Board or Ethics Committee

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

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

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

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

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

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

10.4 Privacy and Confidentiality

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

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

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP647; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

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

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

10.5 Study Results/Publication Policy

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

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish before release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications.

To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

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

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

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

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

11. REFERENCES

[redacted]

Atreya, R.and Neurath, M. F. 2017. Current and Future Targets for Mucosal Healing in Inflammatory Bowel Disease. *Visceral Medicine,* 33, 82-88.

Azulfidine® 2016. US Prescribing Information.

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

Bretz, F., Koenig, F., Brannath, W., Glimm, E.and Posch, M. 2009a. Adaptive designs for confirmatory clinical trials. *Statistics in Medicine,* 28, 1181-1217.

Bretz, F., Maurer, W., Brannath, W.and Posch, M. 2009b. A graphical approach to sequentially rejective multiple test procedures. *Stat Med,* 28, 586-604.

Briskin, M., Winsor-Hines, D., Shyjan, A., Cochran, N., Bloom, S., Wilson, J., McEvoy, L. M., Butcher, E. C., Kassam, N., Mackay, C. R., Newman, W.and Ringler, D. J. 1997. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol,* 151, 97-110.

[redacted]

Chalasani, N.and Regev, A. 2016. Drug-Induced Liver Injury in Patients With Preexisting Chronic Liver Disease in Drug Development: How to Identify and Manage? *Gastroenterology,* 151, 1046-1051.

Chang, M.and Chow, S. C. 2008. Adaptive design methods in clinical trials - a review. *Orphanet journal of rare diseases,* 3, 11.

D'Haens, Gorelick, Wang, Cataldiand Sandborn 2018. Su2010 - The Anti-Madcam Antibody Shp647 in Crohn's Disease: Endoscopic Effects of Induction Therapy. *Gastroenterology,* 154, S-665.

D'Haens, G., Noman, M., Baert, F.and et al. 2002. Endoscopic healing after infliximab treatment for Crohn's disease provides a longer time to relapse [abstract]. *Gastroenterology,* 122, Abstract 104936.

D'Haens, G. R., Geboes, K., Peeters, M., Baert, F., Penninckx, F.and Rutgeerts, P. 1998. Early Lesions of Recurrent Crohn's Disease Caused by Infusion of Intestinal Contents in Excluded Ileum. *Gastroenterol,* 114, 262-7.

Ferrante, M., Colombel, J., Sandborn, W., Reinisch, W., Mantzaris, G., Kornbluth, A., Rachmilewitz, D., Lichtiger, S., D'Haens, G., Van der Woude, C., Danese, S., Diamond, R., Oortwijn, A., Tang, K., Miller, M., Cornillie, F.and Rutgeerts, P. 2013. Validation of Endoscopic Activity Scores in Patients With Crohn's Disease Based on a Post Hoc Analysis of Data From SONIC. *Gastroenterology,* 145, 978-0131.

Humira® 2017. US Prescribing Information.
Imuran® 2014. US Prescribing Information.
Irvine, E., Feagan, B. G., Rochon, J., Archambault, A., Fedorak, R. N.and Groll, A. 1994. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of IBD. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology,* 106, 287-296.
Khanna, R., Zou, G., D'Haens, G., Feagan, B. G., Sandborn, W. J., Vandervoort, M. K., Rolleri, R. L., Bortey, E., Paterson, C., Forbes, W. P.and Levesque, B. G. 2015. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. *Alimentary Pharmacology & Therapeutics,* 41, 77-86.
Khanna, S., Shin, A.and Kelly, C. 2017. Management of Clostridium difficile Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol,* 15, 166-74.
[redacted]
Lacy, C., Armstrong, L., Goldman, M.and Lance, L. 2001-2002. *Drug Information Handbook,* Cleveland, OH, LexiComp, Inc.
Lialda® 2018. US Prescribing Information.
Liaskou, E., Karikoski, M., Reynolds, G. M., Lalor, P. F., Weston, C. J., Pullen, N., Salmi, M., Jalkanen, S.and Adams, D. H. 2011. Regulation of mucosal addressin cell adhesion molecule 1 expression in human and mice by vascular adhesion protein 1 amine oxidase activity. *Hepatology,* 53, 661-72.
Lichtenstein, G. R., Loftus, E., Isaacs, K., Regueiro, M., Gerson, L.and Sands, B. 2018. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol,* 113, 481-517.
McDonald, L. C., Gerding, D. N., Johnson, S., Bakken, J. S., Carroll, K. C., Coffin, S. E., Dubberke, E. R., Garey, K. W., Gould, C. V., Kelly, C., Loo, V., Shaklee Sammons, J., Sandora, T. J.and Wilcox, M. H. 2018. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clinical Infectious Diseases,* 66, e1-e48.
Medrol® 2018. US Prescribing Information.
Methotrexate® 2018. US Prescribing Information.
Molodecky, N. A., Soon, I. S., Rabi, D. M., Ghali, W. A., Ferris, M., Chernoff, G., Benchimol, E. I., Panaccione, R., Ghosh, S., Barkema, H. W.and Kaplan, G. G. 2012. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology,* 142, 46-54.e42; quiz e30.
Panaccione, R., Colombel, J.-F., Louis, E., Peyrin-Biroulet, L.and Sandborn, W. J. 2013. Evolving Definitions of Remission in Crohn's Disease. *Inflammatory Bowel Diseases,* 19, 1645-1653.
Peyrin-Biroulet, L., Ferrante, M., Magro, F., Campbell, S., Franchimont, D., Fidder, H., Strid, H., Ardizzone, S., Veereman-Wauters, G., Chevaux, J.-B., Allez, M.and Dane 2011. Results from the 2nd Scientific Workshop of the ECCO (I): Impact of mucosal healing on the course of inflammatory bowel disease. *Journal of Crohn's and Colitis,* 5, 477-483.
Purinethol® 2011. US Prescribing Information.

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

Sandborn, Feagan, Panes, D'Haens, Colombel, Zhou, Huang, Enejosa, Panganand 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.

Sandborn, W. J., Feagan, B. G., Rutgeerts, P., Hanauer, S., Colombel, J. F., Sands, B. E., Lukas, M., Fedorak, R. N., Lee, S., Bressler, B., Fox, I., Rosario, M., Sankoh, S., Xu, J., Stephens, K., Milch, C.and Parikh, A. 2013. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med,* 369, 711-21.

Schnitzler, F., Fidder, H., Ferrante, M., Noman, M., Arijs, I., Van Assche, G., Hoffman, I., Van Steen, K., Vermeire, S. v.and Rutgeerts, P. 2009. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease Supported by an unrestricted scientific grant from Centocor. Fabian Schnitzler received a research grant by ECCO (European Crohn's and Colitis Organisation). *Inflammatory Bowel Diseases,* 15, 1295-1301.

Shane, A. L., Mody, R. K., Crump, J. A., Tarr, P. I., Steiner, T. S., Kotloff, K., Langley, J. M., Wanke, C., Warren, C. A., Cheng, A. C., Cantey, J.and Pickering, L. K. 2017. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. *Clinical Infectious Diseases,* 65, 1963-1973.

Shyjan, A. M., Bertagnolli, M., Kenney, C. J.and Briskin, M. J. 1996. Human mucosal addressin cell adhesion molecule-1 (MAdCAM-1) demonstrates structural and functional similarities to the alpha 4 beta 7-integrin binding domains of murine MAdCAM-1, but extreme divergence of mucin-like sequences. *J Immunol,* 156, 2851-7.

Siegel, C. A., Whitman, C. B., Spiegel, B. M. R., Feagan, B., Sands, B., Loftus, E. V., Panaccione, R., D'Haens, G., Bernstein, C. N., Gearry, R., Ng, S. C., Mantzaris, G. J., Sartor, B., Silverberg, M. S., Riddell, R., Koutroubakis, I. E., O'Morain, C., Lakatos, P. L., McGovern, D. P. B., Halfvarson, J., Reinisch, W., Rogler, G., Kruis, W., Tysk, C., Schreiber, S., Danese, S., Sandborn, W., Griffiths, A., Moum, B.and Gasche, C. 2016. Development of an index to define overall disease severity in IBD. *Gut*, gutjnl-2016-312648.

Spiegel, B., Bolus, R., Harris, L. A., Lucak, S., Naliboff, B., Esrailian, E., Chey, W. D., Lembo, A., Karsan, H., Tillisch, K., Talley, J., Mayer, E.and Chang, L. 2009. Measuring irritable bowel syndrome patient-reported outcomes with an abdominal pain numeric rating scale. *Aliment Pharmacol Ther,* 30, 1159-70.

Steffen, B. J., Breier, G., Butcher, E. C., Schulz, M.and Engelhardt, B. 1996. ICAM-1, VCAM-1, and MAdCAM-1 are expressed on choroid plexus epithelium but not endothelium and mediate binding of lymphocytes in vitro. *Am J Pathol,* 148, 1819-38.

Ueno, F., Matsui, T., Matsumoto, T., Matsuoka, K., Watanabe, M.and Hibi, T. 2013. Evidence-based clinical practice guidelines for Crohn's disease, integrated with formal consensus of experts in Japan. *Journal of Gastroenterology,* 48, 31-72.

Vuitton, L., Marteau, P., Sandborn, W. J., Levesque, B. G., Feagan, B., Vermeire, S., Danese, S., D'Haens, G., Lowenberg, M., Khanna, R., Fiorino, G., Travis, S., Mary, J. Y.and Peyrin-Biroulet, L. 2016. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut,* 65, 1447-1455.

Ware, J. E., Jr.and Sherbourne, C. D. 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care,* 30, 473-83.

Williet, N., Sandborn, W.and Peyrin–Biroulet, L. 2014. Patient-Reported Outcomes as Primary End Points in Clinical Trials of Inflammatory Bowel Disease. *Clinical Gastroenterology and Hepatology,* 12, 1246-1256.e6.

Yan, X.and Su, X. 2010. Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions. *Stat Biopharm Res,* 2, 329-35.

12. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Protocol Amendment 1	21 Aug 2018	Global
Original Protocol	15 Dec 2017	Global

APPENDIX 2 SCALES AND ASSESSMENTS

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

- Simple Endoscopic Score for Crohn's Disease
- Crohn's Disease Activity Index
- Colonic Global Histologic Disease Score and Ileal Global Histologic Disease Score
- Patient-reported Outcome Crohn's Disease daily e-diary
- Inflammatory Bowel Disease Questionnaire
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Short Form-36 Health Survey
- [redacted]

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

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

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

Definitions of Simple Endoscopic Score for Crohn's Disease

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

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

Crohn's Disease Activity Index (CDAI)

Crohn's Disease Activity Index (CDAI)

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

CDAI=Crohn's Disease Activity Index; ePRO=electronic patient-reported outcome; Hct=hematocrit.
Note: Variable 5: 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 CD
- 221-450 points: Moderate to severe active CD
- >451 points: Severely active to fulminant disease.

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

Reference: D'Haens et al., 1998

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

1. Please rate your worst abdominal pain over the past 24 hours.

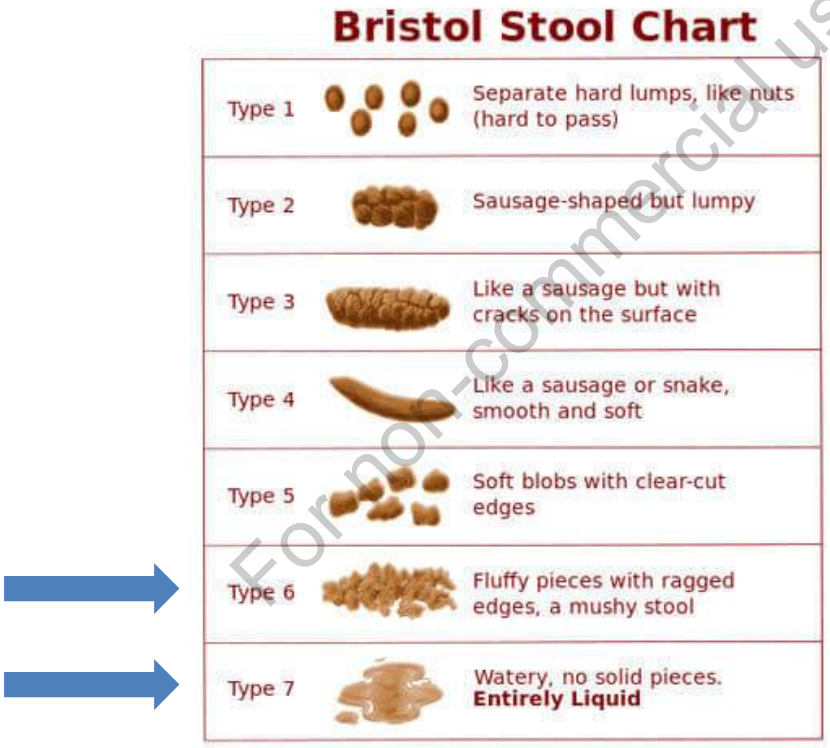
   0 1 2 3 4 5 6 7 8 9 10

   No pain Worst imaginable pain

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

   Enter number of bowel movements passed: _____

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



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

   Enter number of liquid or very soft bowel movements: _____

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

   Enter number of bowel movements with blood: _____

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

   Enter number of bowel movements with urgency: _____

6. Please rate your worst feeling of nausea (feeling sick to your stomach or like you might throw up) over the past 24 hours.

   None

   Mild

   Moderate

   Severe

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

   Enter number of vomiting episodes: _____

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

   Enter number of bowel incontinence episodes: _____

9. Please rate your abdominal pain over the past 24 hours.

   None

   Mild

   Moderate

   Severe

10. How would you rate your general wellbeing over the past 24 hours?

    Generally well

    Slightly below par

    Poor

    Very poor

    Terrible

Inflammatory Bowel Disease Questionnaire (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks.

You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last 2 weeks? Please indicate how frequent your bowel movements have been during the last 2 weeks by picking one of the options from:

    1. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
    2. EXTREMELY FREQUENT
    3. VERY FREQUENT
    4. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    5. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    6. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    7. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from:

    1. NO ENERGY AT ALL
    2. VERY LITTLE ENERGY
    3. A LITTLE ENERGY
    4. SOME ENERGY
    5. A MODERATE AMOUNT OF ENERGY
    6. A LOT OF ENERGY
    7. FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:

    1. A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
    2. A LOT OF DIFFICULTY
    3. A FAIR BIT OF DIFFICULTY
    4. SOME DIFFICULTY
    5. A LITTLE DIFFICULTY
    6. HARDLY ANY DIFFICULTY
    7. NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from:

    1. A MAJOR PROBLEM
    2. A BIG PROBLEM
    3. A SIGNIFICANT PROBLEM
    4. SOME TROUBLE
    5. A LITTLE TROUBLE
    6. HARDLY ANY TROUBLE
    7. NO TROUBLE

18. Overall, in the last 2 weeks, how much a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from:

    1. A MAJOR PROBLEM
    2. A BIG PROBLEM
    3. A SIGNIFICANT PROBLEM
    4. SOME TROUBLE
    5. A LITTLE TROUBLE
    6. HARDLY ANY TROUBLE
    7. NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from:

    1. NONE OF THE TIME
    2. A LITTLE OF THE TIME
    3. SOME OF THE TIME
    4. A GOOD BIT OF THE TIME
    5. MOST OF THE TIME
    6. ALMOST ALL OF THE TIME
    7. ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from:

    1. NO SEX AS A RESULT OF BOWEL DISEASE
    2. MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
    3. MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
    4. SOME LIMITATION AS A RESULT OF BOWEL DISEASE
    5. A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
    6. HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
    7. NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from:

    1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
    2. GENERALLY DISSATISFIED, UNHAPPY
    3. SOMEWHAT DISSATISFIED, UNHAPPY
    4. GENERALLY SATISFIED, PLEASED
    5. SATISFIED MOST OF THE TIME, HAPPY
    6. VERY SATISFIED MOST OF THE TIME, HAPPY
    7. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

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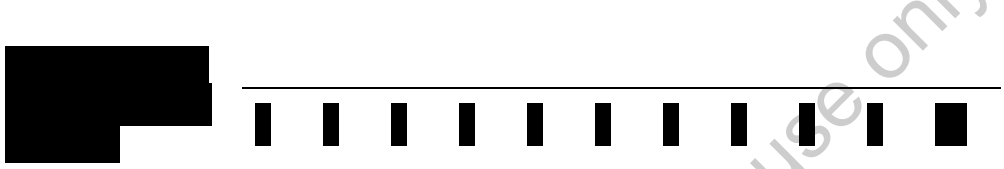

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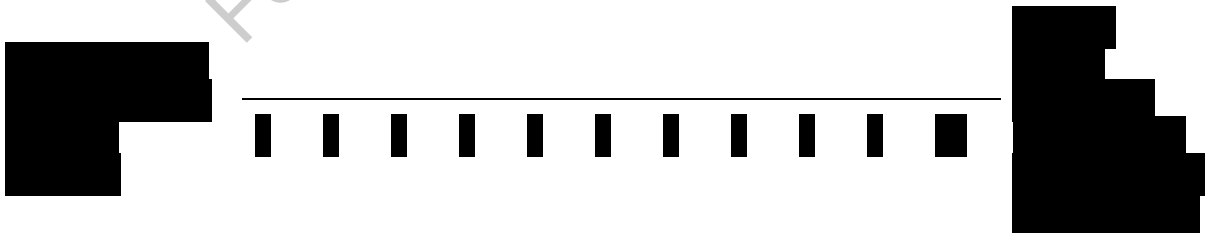

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Short Form-36 Health Survey (Version 2), Acute Form

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past week</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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APPENDIX 3 GLUCOCORTICOID EQUIVALENT DOSES

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

Reference: Lacy et al., 2001-2002.

APPENDIX 4 DETERMINATION OF INADEQUATE RESPONSE/LOSS OF RESPONSE OR INTOLERANCE TO PRIOR TREATMENT FOR CROHN'S DISEASE

The information below should serve as guidance. Local therapeutic standards and investigator judgment should be used.

AMINOSALICYLATES

Mesalamine (5-ASA)

Inadequate response or loss of response: Although the use of mesalamine in UC is well established (eg, induction treatment up to 4.8 g/day up to 8 weeks) and based upon evidence-based criteria, its use in CD is not well established. Oral mesalamine has not consistently been demonstrated to be effective compared with placebo for induction of remission and achieving mucosal healing in patients with active CD. Similarly, topical mesalamine is of limited benefit in CD (Lichtenstein et al., 2018). For the purpose of this study, inadequate response or loss of response is defined as signs and symptoms of persistently active disease despite a history of mesalamine use for at least 8 weeks at daily doses of 4.8 g/day.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related mesalamine treatment. As guidance, the US package insert of mesalamine lists the following AEs. Please check the respective latest label of your country as well (Lialda®, 2018):

> ***Renal Impairment*** *including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure.*
>
> ***Acute intolerance syndrome*** *includes cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash.*
>
> ***Hypersensitivity Reactions*** *including cardiac hypersensitivity reactions (myocarditis and pericarditis)*
>
> ***Hepatic Impairment:*** *hepatic failure in patients with pre-existing liver disease*
>
> ***Photosensitivity*** *in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema*
>
> ***Other*** *treatment related adverse events: headache, flatulence, abnormal liver function test, alopecia, pruritus, tachycardia, hypertension, hypotension, acne, prurigo, rash, urticaria, abdominal distention, colitis, diarrhea, pancreatitis, rectal polyp, vomiting, decreased platelet count, arthralgia, back pain, somnolence, tremor, pharyngolaryngeal pain, asthenia, face edema, fatigue, pyrexia, ear pain. Based on postmarketing experience when it is not always possible to reliably establish a causal relationship to drug exposure: lupus-like syndrome, drug fever, pericarditis, pericardial effusion, myocarditis, pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer, jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, Kawasaki-like syndrome including changes in liver enzymes,*

agranulocytosis, aplastic anemia, anaphylactic reaction, angioedema, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), myalgia, lupus-like syndrome, peripheral neuropathy, Guillain-Barre syndrome, transverse myelitis, intracranial hypertension, interstitial nephritis, nephrogenic diabetes insipidus, interstitial lung disease, hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis), psoriasis, pyoderma gangrenosum, erythema nodosum, photosensitivity, oligospermia.

Sulfasalazine (SSZ):

Inadequate response or loss of response: Although the use of sulfasalazine in UC is accepted (eg, induction treatment up to 4 g/day up to 8 weeks) its use in CD is not well established.

For the purpose of this study, inadequate response or loss of response is defined as signs and symptoms of persistently active disease despite a history of sulfasalazine use for at least 8 weeks at daily doses of 4 g/day.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related sulfasalazine treatment.

As guidance, the US package insert of sulfasalazine lists the following AEs. Please check the respective latest label of your country as well (Azulfidine®, 2016):

Hypersensitivity reactions: *erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell´s syndrome) with corneal damage, drug rash with eosinophilia and systemic symptoms (DRESS), anaphylaxis, serum sickness syndrome, interstitial lung disease, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, lupus erythematosus-like syndrome, hepatitis and hepatic necrosis with or without immune complexes, fulminant hepatitis, sometimes leading to liver transplantation, parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection, and alopecia.*

Blood dyscrasias: *agranulocytosis, leukopenia, myelodysplastic syndrome, aplastic anemia, megaloblastic (macrocytic) anemia, hemolytic anemia, cyanosis, methemoglobinemia, Heinz body anemia, hypoprothrombinemia, and thrombocytopenia.*

Gastrointestinal reactions: *hepatitis, hepatic failure, pancreatitis, bloody diarrhea, impaired folic acid absorption, impaired digoxin absorption, stomatitis, diarrhea, abdominal pains, and neutropenic enterocolitis.*

Central nervous system reactions: *transverse myelitis, convulsions, meningitis, transient lesions of the posterior spinal column, cauda equina syndrome, Guillian-Barre syndrome, peripheral neuropathy, mental depression, vertigo, hearing loss, insomnia, ataxia, hallucinations, tinnitus, and drowsiness.*

Renal reactions: *toxic nephrosis with oliguria and anuria, nephritis, nephrotic syndrome, urinary tract infections, hematuria, crystalluria, proteinuria, and hemolytic-uremic syndrome.*

Other reactions: *urine discoloration and skin discoloration, Goiter production, diuresis and hypoglycemia, oligospermia. Based on postmarketing experience when it is not always possible to reliably establish a causal relationship to drug exposure: elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure, folate deficiency, nephrolithiasis, oropharyngeal pain, angioedema.*

In addition anorexia, headache, nausea, vomiting, gastric distress, pruritus, urticaria, rash, fever, sore throat, fever, pallor, purpura.

GLUCOCORTICOIDS

Inadequate response or loss of response: Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or intravenously for 1 week OR two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related glucocorticoid treatment.

As guidance, the US package insert of Medrol® lists the following AEs. Please check the respective latest label of your country as well (Medrol®, 2018):

Fluid and Electrolyte Disturbances: *sodium retention, congestive heart failure, hypertension, fluid retention, potassium loss, and hypokalemic alkalosis*

Musculoskeletal: *muscle weakness, loss of muscle mass, steroid myopathy, osteoporosis, tendon rupture, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, and pathologic fracture of long bones.*

Gastrointestinal: *peptic ulcer with or without perforation and hemorrhage, pancreatitis, abdominal distention, and ulcerative esophagitis,*

Dermatologic: *impaired wound healing, petechiae and ecchymoses, thin fragile skin, facial erythema, and increased sweating*

Neurological: *increased intracranial pressure with papilledema (pseudo-tumor cerebri), convulsions, vertigo, and headache*

Psychic derangements*: euphoria, insomnia, mood swings, personality changes, severe depression, psychotic manifestations, aggravated existing emotional instability or psychotic tendencies.*

Endocrine: *Cushingoid state, secondary adrenocortical and pituitary unresponsiveness, menstrual irregularities, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements of insulin or oral hypoglycemic agents in diabetics*

Ophthalmic: *Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, and secondary ocular infections.*

Metabolic: *negative nitrogen balance due to protein catabolism*

Other: *urticaria and other allergic, anaphylactic or hypersensitivity reactions.*

IMMUNOSUPPRESSANTS

Azathioprine (AZA)

Inadequate response or loss of response: Signs and symptoms of persistently active disease despite a history of AZA use for at least 12 weeks at daily doses ≥1.5 mg/kg, including its use as adjunctive therapy or steroid-sparing therapy.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related AZA treatment.

As guidance, the US package insert of an AZA product lists the following AEs. Please check the respective latest label of your country as well (Imuran®, 2014):

Gastrointestinal hypersensitivity reaction *characterized by severe nausea, vomiting and potentially with diarrhea, rash, fever, malaise, myalgias, elevations in liver enzymes, and occasionally, hypotension.*

Hypersensitivity pancreatitis.

Hepatotoxicity *that may be associated with anorexia, diarrhea, jaundice and ascites.*

Cytopenias: *leukopenia, thrombocytopenia, anemias including macrocytic anemia, and/or pancytopenia, bone marrow suppression, and myelotoxicity.*

Serious infections *(bacterial, viral, fungal, protozoal, and opportunistic infections, including reactivation of latent infections) secondary to treatment*

Other: *skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea, negative nitrogen balance, reversible interstitial pneumonitis, hepatosplenic T-cell lymphoma and Sweet's Syndrome (acute febrile neutrophilic dermatosis).*

Mercaptopurine (6-MP)

Inadequate response or loss of response: Signs and symptoms of persistently active disease despite a history of 6-MP use for at least 12 weeks at daily doses ≥0.75 mg/kg, including its use as adjunctive therapy or steroid-sparing therapy.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related 6-MP treatment.

As guidance, the US package insert of a 6-MP product lists the following AEs. Please check the respective latest label of your country as well (Purinethol®, 2011):

> ***Myelosuppression:*** *anemia, leukopenia, and thrombocytopenia*
>
> ***Embryo-Fetal Toxicity***
>
> ***Treatment Related Malignancies***
>
> ***Renal:*** *hyperuricemia and/or hyperuricosuria*
>
> ***Gastrointestinal****: including hepatotoxicity: elevated transaminases, elevated bilirubin, ascites potentially intestinal ulceration, oral lesions, nausea, vomiting, anorexia, diarrhea and sprue-like symptoms, pancreatitis*
>
> ***Miscellaneous****: skin rashes, hyperpigmentation, alopecia, drug fever, oligospermia*

Methotrexate (MTX)

Inadequate response or loss of response: Failure to respond to at least one 8-week regimen of or maintain remission at doses of at least 15 mg/week, given by the intramuscular or subcutaneous route.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related MTX treatment.

As guidance, the US package insert of a MTX product lists the following AEs. Please check the respective latest label of your country as well (Methotrexate®, 2018):

> ***Alimentary System:*** *gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.*
>
> ***Blood and Lymphatic System Disorders:*** *anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia, lymphadenopathy and lymphoproliferative disorders, hypogammaglobulinemia*

Cardiovascular: *pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus)*

Central Nervous System: *headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions, cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy*

Hepatobiliary: *acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity decrease in serum albumin, and liver enzyme elevations*

Infection: *opportunistic infections e.g. Pneumocystis carinii pneumonia, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, H. simplex hepatitis, and disseminated H. simplex*

Musculoskeletal System: *stress fracture*

Ophthalmic: *conjunctivitis, serious visual changes of unknown etiology*

Pulmonary System: *respiratory fibrosis, respiratory failure, interstitial pneumonitis, chronic interstitial obstructive pulmonary disease*

Skin: *erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.*

Urogenital System: *severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects*

Other: *nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis, anaphylactoid reactions*

ANTI-TNF AGENTS

Inadequate response or loss of response: Anti-TNF agents are rapid in onset of effect, with benefit often noted within 2 weeks of initiating therapy. As a result, assessment of inadequate response may be done sooner than with immunosuppressants. These include signs and symptoms of persistently active disease despite at least one 4 week induction regimen with the following minimum doses of:

- infliximab (5 mg/kg IV, 2 doses at least 2 weeks apart) or
- adalimumab (one 80 mg SC dose followed by one 40 mg dose at least 2 weeks apart) or

- certolizumab pegol (400 mg SC, 2 doses at least 2 weeks apart) or recurrence of symptoms during maintenance therapy. (approved for CD in US)

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related Anti-TNF agents.

As guidance, the US package insert of a Humira lists the following AEs. Please check the respective latest labels for the other Anti-TNF agents and the labels of your country as well (Humira®, 2017):

Anaphylaxis or serious allergic reactions: *generalized rash and flushing, hypersensitivity reactions including angioneurotic edema*

Development of neutralizing autoantibodies

Body As A Whole: *Pain in extremity, pelvic pain, surgery, thorax pain*

Cardiovascular System: *Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, heart failure*

Gastrointestinal: *Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, vomiting, nausea, abdominal pain, hepatic reactions including acute liver failure, hepatic necrosis*

Lupus-like syndrome

Endocrine System: *Parathyroid disorder*

Hemic and Lymphatic System: *Cytopenias, pancytopenia, Agranulocytosis, polycythemia*

Infections: *tuberculosis (new and reactivation of latent tuberculosis) and opportunistic infections pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis*

Metabolic And Nutritional Disorders: *Dehydration, healing abnormal, ketosis, paraproteinemia,peripheral edema*

Musculo-Skeletal System: *Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder*

Neoplasia: *Adenoma*

Nervous System: *Confusion, paresthesia, subdural hematoma, tremor*

Respiratory System: *upper respiratory infection, sinusitis, flu syndrome, asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion*

Special Senses: *Cataract*

Thrombosis: *Thrombosis leg*

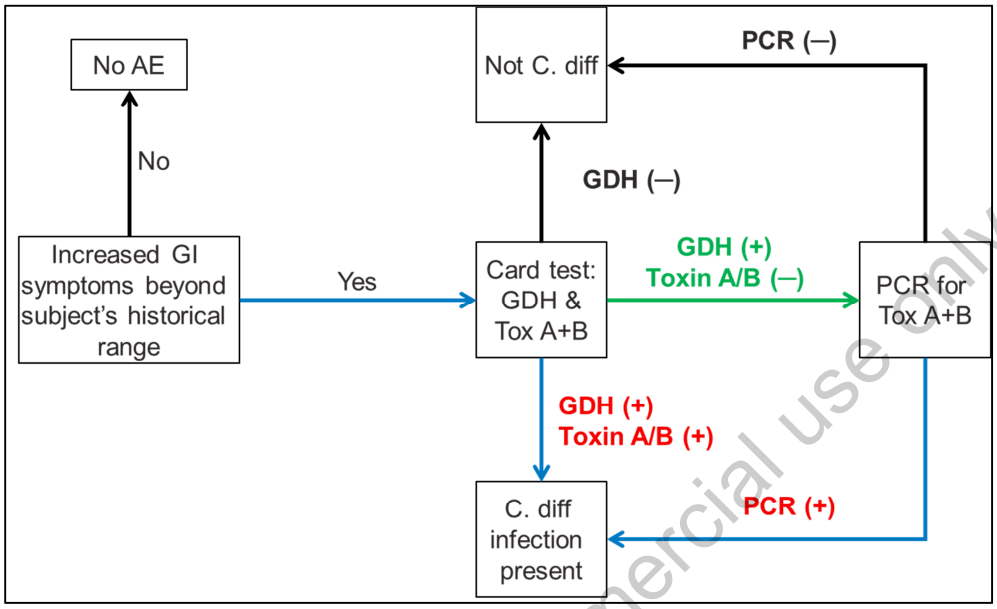
Urogenital System: *Cystitis, kidney calculus, menstrual disorder*

Other: *headache, rash, injection site reaction, infusion-related reactions such as fever or chills, cardiopulmonary reactions such as chest pain, hypotension, hypertension, or dyspnea and/or pruritus or urticaria, back pain, urinary tract infection, hypertension*

APPENDIX 5 GUIDANCE FOR DIAGNOSIS AND TREATMENT OF INCREASED GASTROINTESTINAL SYMPTOMS

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

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



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

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

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

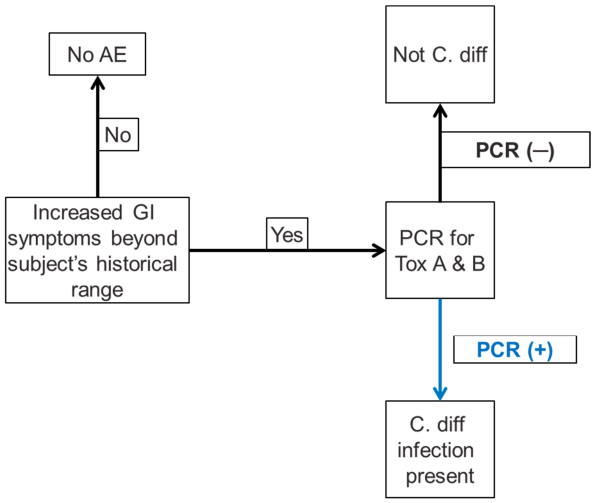


Figure A3 Alternative 2 for *C difficile* Testing Using Local Laboratory When No Card Test is Available

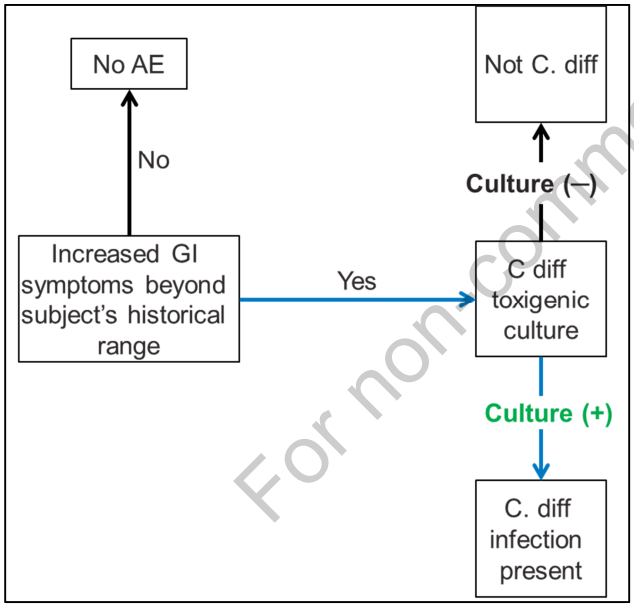
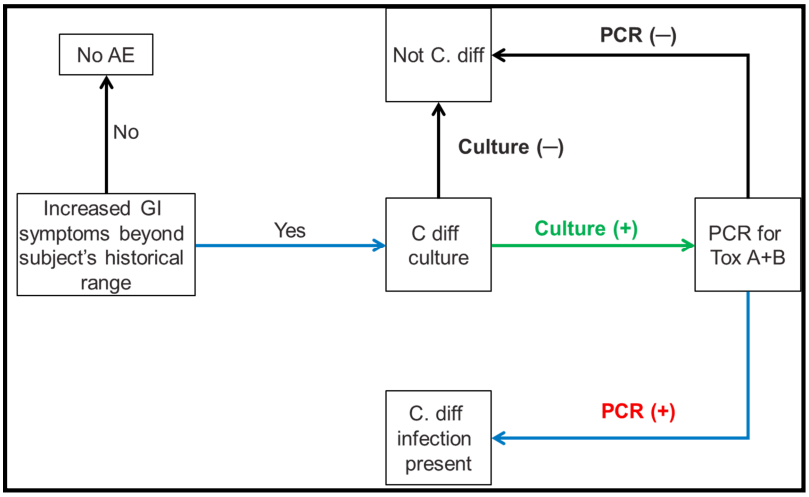


Figure A4 Alternative 3 for *C difficile* Testing Using Local Laboratory When No Alere Quick Chek Card Test is Available



Treatment

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

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

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

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

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

PROTOCOL: SHP647-305

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)
DRUG:	Ontamalimab (SHP647)
IND:	100,222
EUDRACT NO.:	2017-000575-88
SPONSOR:	Shire Human Genetic Therapies, Inc. ("Shire") 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted], MD
PROTOCOL HISTORY:	Protocol Amendment 2: 22 Nov 2019 Protocol Amendment 1: 21 Aug 2018 Original Protocol: 15 Dec 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted] **Date:** [redacted]

[redacted] MD, [redacted]

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP647-305.

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).

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

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

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

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

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

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

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2**	**Amendment Date** **22 Nov 2019**	**Global/Region/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Product Quality Complaints	Updated language regarding reporting of product quality complaints.	To align product quality complaints language with current Shire template.
Study Synopsis, Inclusion Criteria Section 4.1, Inclusion Criteria Section 7.1.1.1, Screening Visit (Visit 1) Section 7.2.2, Efficacy	Reordered inclusion criteria #4a, 4b and 4c so that the colonoscopy is last. Clarified that the subject must meet inclusion criteria #4a and 4b (CDAI score and PRO subscores) prior to the colonoscopy (criterion #4c) being performed.	To clarify the order of assessments to prevent unnecessary colonoscopies being performed.
Study Synopsis, Inclusion Criteria Section 4.1, Inclusion Criteria Section 4.4, Reproductive Potential	Revised inclusion criterion #9 to add "highly effective methods for female and medically appropriate methods for male study subjects" in parentheses after "appropriate contraception". Also added this language after the terms 'appropriate form of contraception' and 'appropriate method of contraception' in Section 4.4.	To clarify what is meant by appropriate contraception methods.
Study Synopsis, Exclusion Criteria Section 4.2, Exclusion Criteria	Revised exclusion criterion #6 to clarify that subjects with obstructive colonic stricture are excluded if it is clinically significant. Updated exclusion criterion #6 to state that subjects who have undergone previous colonic resection or ileocolectomy are excluded unless it was at least 6 months before screening and they have at least 25 cm of colon remaining (previously all subjects who had undergone previous colonic resection were excluded.)	To provide clarity regarding the exclusion around prior bowel surgeries. As ileocolectomy or partial colectomy is common in Crohn's disease, the population previously defined in the protocol has been too restrictive and thus could not reflect the broader Crohn's disease population. There is no reason to believe that ontamalimab would work differently after ileocolectomy or partial colectomy. The length of the remaining colon is required to be at least 25 cm in order to be able to evaluate and score the mucosal inflammation appropriately.

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Section(s) Affected by Change	**Description of Change**	**Rationale**
Study Synopsis, Exclusion Criteria Section 4.2, Exclusion Criteria	Revised exclusion criterion #19 to state that subjects who have taken >9 mg/day of budesonide within 14 days before baseline (Visit 2) are excluded.	To clarify the allowed doses of steroids.
Study Synopsis, Exclusion Criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #36 to include 'dependency' along with substance/drug abuse for any kind of abuse including medicinal marijuana (cannabis).	For clarity.
Study Synopsis, Safety Analyses Section 9.9, Safety Analyses	Added that adverse events of special interest will be summarized by treatment group.	To include analysis of adverse events of special interest.
Table 1, Schedule of Assessments, footnote "b" Section 7.1.2.2, Final On-treatment Visit: Visit 7, Parts 1, 2, and 3 (Week 16/Early Termination)	Revised to clarify that, for the colonoscopies required at ET/Week 16, the specified blood sampling should be taken before colonoscopy preparation.	To clarify the order of procedures.
Table 1, Schedule of Assessments, footnote "l" Section 7.2.3.6, Clinical Laboratory Evaluations Section 7.2.3.12, Evaluation of Increased Gastrointestinal Symptoms	Added new subsection (7.2.3.12) to Section 7.2.3 to describe evaluation of increased gastrointestinal symptoms.	To clarify that infectious etiology must be evaluated when a subject experiences an increase in gastrointestinal symptoms.
Table 1, Schedule of Assessments, footnote "s" Section 7.1.1.1, Screening Visit (Visit 1) Section 7.2.2.4, Colonoscopy	Revised to clarify that, for the colonoscopies required at screening and ET/Week 16, the preparation may be done on the same day as the colonoscopy procedure.	To reduce logistical burden around the colonoscopy requirements.
Table 1, Schedule of Assessments, footnote "s" Section 7.1.1.1, Screening Visit (Visit 1)	Revised to extend the window between the screening colonoscopy procedure and baseline (Visit 2) from 5-7 days to 10 days; however, within 5 to 7 days is stated as being preferable. Updated to indicate that colonoscopy preparation may be done on the same day as the colonoscopy procedure. Updated screen failure criteria to include PRO scores.	To allow sites to receive SES-CD results in time to schedule randomization within the eligibility window. To provide additional flexibility on timing of colonoscopy preparation. For consistency with inclusion criterion #4.

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Section(s) Affected by Change	**Description of Change**	**Rationale**
Table 1, Schedule of Assessments, footnote "z" Section 7.2.3.11, Monitoring for Type I and Type III Immune Reactions	Added new row and footnote to Table 1, new subsection to Section 7.2.3, and language to describe the monitoring for hypersensitivity.	To address Food and Drug Administration (FDA) recommendation to evaluate the risk of hypersensitivity reactions in the Phase 3 studies and aid in the collection of relevant safety data.
Section 4.4, Reproductive Potential	Updated text to reflect results of an enhanced pre-and postnatal development (ePPND) toxicity study in nonhuman primates.	To reflect preliminary results from an ePPND toxicity study of ontamalimab in nonhuman primates, which indicated that, at the dose levels tested (30 mg/kg and 60 mg/kg), infant losses were increased in ontamalimab-exposed animals when compared both to control animals in the study and to the historical control animal data from the testing facility. The relevance of this finding to humans is unknown but cannot be excluded. Results of the ePPND study are reported in the ontamalimab Investigator's Brochure Edition 8.0.
Section 4.4.1, Contraceptive Methods for Female Study Subjects	Added text to specify that contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the clinical study.	To align with guidance document "Recommendations related to contraception and pregnancy testing in clinical trials" of Clinical Trial Facilitation Group.
Section 4.5.1, Subject Withdrawal Criteria	Changed the term 'protocol violations' to 'protocol deviations'.	For consistency with Section 4.5.2 (Reasons for Withdrawal).
Section 5.1, Prior Treatment	Updated to specify that prior and concomitant Crohn's disease-specific treatments from the previous 10 years will be recorded rather than all prior and concomitant Crohn's disease-specific treatments.	For consistency with Study SHP647-301.
Section 5.2.1, Permitted Treatment	Updated text on permitted use of antibiotics to align with exclusion criterion #12.	For consistency.

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Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 7.1.1.1, Screening Visit (Visit 1)	Changed the term 'first dose of investigational product' to 'baseline visit (Visit 2)'.	For consistency with other sections.
Section 7.2.2.2, Simple Endoscopic Score for Crohn's Disease	Added reference citation to Daperno et al., 2004.	To provide additional information regarding the Simple Endoscopic Score for Crohn's Disease (SES-CD).
Section 7.2.2.2, Simple Endoscopic Score for Crohn's Disease Section 7.2.2.4, Colonoscopy and Histology	Updated text to clarify that a complete colonoscopy (including visualization of the terminal ileum) and collection of biopsies from all bowel segments may not be possible due to impassable stenosis or previous partial colectomy/ileocolectomy. If a complete colonoscopy is not possible, the aim is to visualize the remaining colon and, if it exists, the terminal ileum.	To clarify the colonoscopy procedure if the subject has undergone partial colectomy/ileocolectomy.
Section 7.2.3.3, Targeted Neurological Assessment	Updated column heading in Table 3 from Targeted Neurological History' to 'Interim Neurologic History and Targeted Neurologic Examination.'	To align with language of newly proposed electronic case report form.
Section 7.2.5, Volume of Blood to be Drawn From Each Subject	Decreased serum chemistry sample volume from 6 mL to 4 mL. Increased pharmacokinetic sample volume from 3 mL to 5 mL.	To correct the sample volume needed for the serum chemistry test and for the pharmacokinetic assessment.
Section 8.1.3, Adverse Events of Special Interest	Added new subsection to describe classification of hypersensitivity as an adverse event of special interest.	To address FDA recommendation to evaluate the risk of hypersensitivity reactions in the Phase 3 studies and aid in the collection of relevant safety data.
Section 8.1.7, Pregnancy	Added text to specify that in cases of pregnancy, where the outcome is a live birth, the vital status and clinical condition of the infant should be obtained and documented at 1 year postpartum.	To extend the time frame for follow-up of pregnancy outcomes for female study participants or partners of male study participants in response to preliminary findings of the ePPND study.

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Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 9.5, Planned Interim Analysis, Adaptive Design, Data Monitoring Committee, and Hypersensitivity Adjudication Committee	Added text to specify that an external hypersensitivity adjudication committee will be established to review data from subjects who experience a suspected Type I or Type III hypersensitivity reaction.	To address FDA recommendation to evaluate the risk of hypersensitivity reactions in the Phase 3 studies and aid in the collection of relevant safety data.
Section 9.8.3, Exploratory Efficacy Endpoints	[redacted]	For consistency with other Phase 3 ontamalimab studies. To correctly describe scoring for the Treatment Satisfaction Questionnaire for Medication (TSQM).
Section 10.1.5, Study Suspension, Termination, and Completion	Clarified that the end-of study declaration may be made by the sponsor or alternatively its representatives.	To improve clarity.
Appendix 2, Scales and Assessments	Updated the example SES-CD worksheet.	To provide the scoring values for the SES-CD endoscopic variables and clarify how the scores are recorded for each ileocolonic segment.
Throughout protocol	Updated 'SHP647' to 'ontamalimab" throughout the protocol. Updated with minor changes to wording.	To reflect that ontamalimab is the international nonproprietary name for SHP647. To improve clarity, consistency, and remove redundancy of text.

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

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

Fax
[redacted] (Global)

Email
[redacted]

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

North America:

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

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

Latin America:

PPD 24 Hour Safety Hotline: [redacted]

PPD 24 Hour Safety Hotline Fax: [redacted]

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

PPD 24 Hour Safety Hotline: [redacted]

PPD 24 Hour Safety Hotline Fax: [redacted]

PRODUCT QUALITY COMPLAINTS

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

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

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

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

[redacted]

Telephone number (provided for reference if needed):

Shire, Lexington, MA (USA)

[redacted]

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

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
β-hCG	beta-human chorionic gonadotropin
BSFS	Bristol Stool Form Scale
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
[redacted]	[redacted]
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
[redacted]	[redacted]
CRO	contract research organization
CSF	cerebrospinal fluid
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
[redacted]	[redacted]
[redacted]	[redacted]
EMA	European Medicines Agency
[redacted]	[redacted]
[redacted]	[redacted]
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration

FSH	follicle-stimulating hormone
FWER	family-wise Type I error rate
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
$IgG_{2\kappa}$	immunoglobulin G2 kappa
[redacted]	[redacted]
IGRA	interferon-gamma release assay
IRB	institutional review board
IRT	interactive response technology
LP	lumbar puncture
LTS	long-term safety extension
MAdCAM	mucosal addressin cell adhesion molecule
MTX	methotrexate
NAb	neutralizing antibody
NRS	numerical rating scale
PCR	polymerase chain reaction
[redacted]	[redacted]
PFS	prefilled syringe
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PML	progressive multifocal leukoencephalopathy

PP	per protocol
PPD	purified protein derivative
PRO	patient-reported outcome
Q4W	once every 4 weeks
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's disease
SF-36	Short Form-36 Health Survey
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
[redacted]	[redacted]
UC	ulcerative colitis
ULN	upper limit of normal
[redacted]	[redacted]

STUDY SYNOPSIS

Protocol number: SHP647-305	**Drug:** Ontamalimab (SHP647)
Title of the study: 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)	
Number of subjects (total and for each treatment arm): 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.	
Investigator(s): Multicenter study.	
Site(s) and region(s): It is anticipated that the study will be conducted in approximately 19 countries. Regions will include North America; Europe, the Middle East, and Africa; Latin America; and Asia Pacific. Approximately 210 sites will be utilized.	
Study period (planned): 2018 to 2021	**Clinical phase:** 3

Objectives:

Coprimary: 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 patient-reported outcome (PRO) (abdominal pain severity and very soft stool/liquid stool frequency)
- Inducing endoscopic response based on centrally read colonoscopy.

Key secondary:

- To evaluate the efficacy of ontamalimab in inducing clinical remission as measured by CD 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.

Other secondary:

- 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 (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.

Rationale:
This study is designed to evaluate the efficacy and safety of ontamalimab in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.

The CD clinical development program includes 3 completed studies: 1 Phase 1 study (A7281008) and 2 Phase 2 studies (A7281006 and A7281007). The ontamalimab dose selection (25 mg and 75 mg) for this study is based on data from these 3 previous studies, which evaluated the activity of ontamalimab in adult patients with moderately to severely active CD based on CDAI scores between 220 and 450. The Phase 1 study (A7281008, TOSCA) and Phase 2 studies (A7281006, OPERA; and A7281007, OPERA II [long-term safety study]) that investigated the safety, tolerance, pharmacokinetics (PK), and pharmacodynamic (PD) properties of ontamalimab support further clinical development of ontamalimab using subcutaneous (SC) administration in subjects with moderate to severe CD.

Investigational product, dose, and mode of administration:
The test product is ontamalimab (SHP647), which will be provided as a sterile aqueous buffered solution for SC administration in a glass prefilled syringe (PFS) with a fixed needle. Each PFS contains 1 mL of ontamalimab solution for injection at an appropriate concentration to provide the intended dose of drug (25 mg or 75 mg). Additional information is provided in the current ontamalimab investigator's brochure.

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

Methodology:
This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study 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. 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 antitumor necrosis factor (TNF) treatment (naïve or experienced), glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline), and Simple Endoscopic Score for CD (SES-CD) at baseline (SES-CD ≥17 or SES-CD <17). Subjects will receive SC injections of ontamalimab or placebo, using a 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], [redacted], safety, and health outcome assessments at these visits.

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). 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 treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

A planned interim analysis for the coprimary endpoints will take place 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 will be reassessed as part of this interim analysis.

Inclusion and exclusion criteria:
Inclusion criteria:

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.

2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must be between ≥16 and ≤80 years of age at the time of the signing of the informed consent/assent form.

   Note: Subjects <18 years of age must weigh ≥40 kg and must have body mass index ≥16.5 kg/m^2.
4. Subjects must have active moderate to severe ileal (terminal ileum), ileocolic, or colonic CD at baseline (Visit 2) as defined by:
   a. CDAI score between 220 and 450 (inclusive) **AND**
   b. Meeting the following subscores in the 2-item PRO:
      i. Abdominal pain subscore ≥5 (average worst daily pain on the 11-point numerical rating scale [NRS]) **AND** abdominal pain subscore ≥2 (average daily pain on the 4-point abdominal pain variable of CDAI) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous) **AND/OR**
      ii. Average of the daily stool frequency subscore ≥4 of type 6/7 (very soft stools/liquid stools) as shown in the Bristol Stool Form Scale (BSFS) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous).

   AND
   c. Presence of ulcerations that are characteristic to CD, as determined by a colonoscopy performed during screening, and as defined by the SES-CD >6 (SES-CD ≥4 for isolated ileitis)

   Note that the subject must be confirmed as meeting the CDAI score and PRO subscore requirements **before** a colonoscopy is done.
5. Subjects must have a documented diagnosis (endoscopic with histology) of CD for ≥3 months before screening. Documented diagnosis is defined as:
   - A biopsy report in which the description of the histological findings is consistent with the CD diagnosis **AND**
   - A report documenting disease duration based upon prior colonoscopy.

   Note: If a biopsy report is not available in the source document at the time of screening, a biopsy must be performed during the screening colonoscopy and the histology report should be consistent with the CD diagnosis. If the histology description does not support the CD diagnosis at this time point, the subject should not be randomized.
6. Subjects must be willing and able to undergo a colonoscopy during screening after all other inclusion criteria have been met.
7. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or mesalamine (5-aminosalicylic acid [5-ASA]), glucocorticoids, immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]), or anti-TNF (see Appendix 4 of the protocol for guidance). Subjects who have had an inadequate response to sulfasalazine or mesalamine should have also failed at least 1 other conventional treatment such as glucocorticoids.
8. Subjects receiving any treatment(s) for CD described in Section 5.2.1 of the protocol are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
9. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception (ie, highly effective methods for female and medically appropriate methods for male study subjects) (as described in Section 4.4 of the protocol) for the duration of the study.

Exclusion criteria:

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

1. Subjects with indeterminate colitis, microscopic colitis, nonsteroidal anti-inflammatory drug-induced colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of ulcerative colitis.

2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with presence of enterovesical (ie, between the bowel and urinary bladder) or enterovaginal fistulae.
5. Subjects with current symptomatic diverticulitis or diverticulosis.
6. Subjects with clinically significant obstructive colonic stricture, or who have a history of bowel surgery within 6 months before screening, or who are likely to require surgery for CD during the treatment period. Subjects who have undergone previous colonic resection or ileocolectomy more than 6 months before screening must have at least 25 cm of colon remaining.
7. Subjects with past medical history of multiple small bowel resections resulting in clinically significant short bowel syndrome.
8. Subjects requiring total parenteral nutrition.
9. Subjects with past medical history of bowel surgery resulting in an existing or current stoma. Subjects who had a j-pouch are excluded as a j-pouch could result in a stoma.
10. Subjects have had prior treatment with ontamalimab (formerly PF-00547659; SHP647).
11. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
12. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than AZA, 6-MP, or MTX) or continuous antibiotics (>2 weeks) for the treatment of CD within 30 days before baseline (Visit 2).
13. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
14. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).
15. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
16. Subjects have received lymphocytes apheresis or selective monocyte granulocytes apheresis within 60 days before baseline (Visit 2).
17. Subjects have received enteral nutrition treatment within 30 days before baseline (Visit 2).
18. Subjects have received parenteral or rectal glucocorticoids or rectal 5-ASA within 14 days before screening colonoscopy.
19. Subjects have taken >20 mg/day of prednisone, >9 mg/day of budesonide, or equivalent oral systemic corticosteroid dose within 14 days before baseline (Visit 2) or have taken ≥40 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 6 weeks before baseline (Visit 2).
20. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before screening (Visit 1).
21. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).
22. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis [subjects with *C. difficile* infection at screening may be allowed retest after treatment], evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
23. Subjects with abnormal chest x-ray or other imaging findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray, computed tomography scan, etc., performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation.)

24. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) or subjects with this history who have not completed a generally accepted full course of treatment before baseline (Visit 2) are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon-gamma release assay (IGRA) performed.

    Subjects who have no history of previously diagnosed active or latent TB are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before screening. If the IGRA cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

    - An IGRA is strongly recommended for subjects with a prior Bacillus Calmette-Guérin vaccination but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON-TB Gold Plus In-Tube Test.
    - If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent TB, a positive test on repeat will exclude the subject. Subjects with a history of active or latent TB infection must follow instructions for "Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met" in this criterion.
    - Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

    Results from a chest x-ray, taken within the 12 weeks before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

    Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met:

    - The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
    - A chest x-ray performed within 12 weeks before screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.

25. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
26. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy based on the targeted neurological assessment during the screening period (see Section 7.2.3.3 of the protocol).
27. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
28. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:

    - Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study

- Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence)
- Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening (Visit 1)
- History of significant cerebrovascular disease within 24 weeks before screening (Visit 1).

29. Subjects who have had significant trauma or major surgery within 4 weeks before screening (Visit 1), or with any major elective surgery scheduled to occur during the study.
30. Subjects with evidence of cirrhosis with or without decompensation (ie, esophageal varices, hepatic encephalopathy, portal hypertension, ascites).
31. Subjects with primary sclerosing cholangitis.
32. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Note: if a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if no presence of hepatitis B virus (HBV) DNA is confirmed by HBV DNA polymerase chain reaction reflex testing performed in the central laboratory.
33. Subjects with chronic hepatitis C virus (HCV) (positive HCV antibody [HCVAb] and HCV RNA). Note: Subjects who are HCVAb positive without evidence of HCV RNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCV RNA at least 12 weeks prior to baseline]).
34. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening (Visit 1). Note: Screening laboratory tests, if the results are 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 must be reviewed for eligibility prior to the screening colonoscopy procedure.
    - Alanine aminotransferase and aspartate aminotransferase levels ≥3.0 × the upper limit of normal (ULN)
    - Total bilirubin level ≥1.5 × ULN or >2.0 × ULN if the subject has a known documented history of Gilbert's syndrome
    - Hemoglobin level ≤80 g/L (8.0 g/dL)
    - Platelet count ≤100 × 10^9/L (100,000 cells/mm^3) or ≥1000 × 10^9/L (1,000,000 cells/mm^3)*
    - White blood cell count ≤3.5 × 10^9/L (3500 cells/mm^3)
    - Absolute neutrophil count <2 × 10^9/L (2000 cells/mm^3)
    - Serum creatinine level >1.5 × ULN or estimated glomerular filtration rate <30 mL/min/1.73 m^2 based on the abbreviated Modification of Diet in Renal Disease Study Equation.

      *Note: if platelet count is <150,000 cells/mm^3, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.
35. Subjects with known human immunodeficiency virus (HIV) infection based on documented history with positive serological test, or positive HIV serologic test at screening, tested at the site's local laboratory in accordance with country requirements or tested at the central laboratory. Note: A documented negative HIV test within 6 months of screening is acceptable and does not need to be repeated.
36. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse or dependency of any kind including abuse of medicinal marijuana (cannabis).
37. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
38. Female subjects who are planning to become pregnant during the study period.
39. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm, and female subjects who are planning to harvest or donate eggs, for the

duration of the study and through 16 weeks after last dose of investigational product.

40. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: Up to 6 weeks
- Planned duration of treatment period: 16 weeks
- Planned duration of follow-up period: 16 weeks.

Endpoints and statistical analysis:

Analysis sets:

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

The full analysis set (FAS) will consist of all subjects in the randomized set who have received at least 1 dose of investigational product.

The per-protocol set will consist of all subjects in the FAS who do not have predefined protocol deviations that may affect the coprimary efficacy endpoints.

The completer set will consist of all subjects in the FAS who have completed the Week 16 assessment for this study.

[redacted]

[redacted]

Coprimary efficacy endpoints:

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

The coprimary efficacy endpoints are:

- 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 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.
- Endoscopic response at Week 16 as measured by a decrease in SES-CD of at least 25% from baseline.

The coprimary efficacy endpoints, clinical remission at the Week 16 visit and endoscopic response at the Week 16 visit, will each be compared for each active treatment group (25 mg or 75 mg ontamalimab) to the placebo group using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use, and SES-CD at baseline for each of the stages of the study (stage 1 includes subjects whose primary efficacy data are used in the interim analysis and stage 2 includes all other subjects. Note: classification of stage 1 and stage 2 is based on the time of randomization rather than the time of study completion or termination). Subjects with missing data at the Week 16 visit will be considered failures and counted as nonresponders.

Weighted inverse normal p-value combination methods are used to combine the p-values from stage 1 and stage 2 through the following formula:

$$C(p_1, p_2) = 1 - \Phi[w_1 \Phi^{-1}(1-p_1) + w_2 \Phi^{-1}(1-p_2)]$$

Where p_1, p_2 are the p-values computed from the CMH chi-square test for each stage, $w_i^2 = n_i/(n_1 + n_2)$, n_1 and n_2 are the preplanned stage-wise sample sizes that are fixed at the time of the interim analysis based on an original total sample size, and Φ denotes the cumulative distribution function of the standard normal distribution (Bretz, et al., 2009a). Given that there is no possibility of stopping early for efficacy, that any potential stopping for futility of either or both doses of ontamalimab is nonbinding, and that weights are prespecified, the test statistic $C(p_1, p_2)$ can be compared against the nominal alpha level to assess statistical significance (Chang and Chow, 2008).

The coprimary endpoints will each be tested by the following hypothesis:

$$H_0: \delta = 0$$
$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata. The common treatment difference is a weighted average of the stratum-specific treatment differences.

The global family-wise Type I error rate (FWER) for the statistical tests of the coprimary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al. (2009b) will be utilized to propagate α from the coprimary endpoints to the key secondary endpoints and between the 2 ontamalimab treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the coprimary endpoints (P) and alpha is propagated in a hierarchical manner to each of the 6 key secondary endpoints (K1–K6) within a pairwise treatment comparison. In order to pass alpha between the coprimary endpoints and the first key secondary endpoint, both coprimary endpoints must attain statistical significance.

Key secondary efficacy 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 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.

The key secondary endpoints will be analyzed using the same approach as described for the coprimary endpoints. Subjects with missing key secondary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.

Other secondary efficacy endpoints:

- 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 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.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods:

- Binary endpoints will be compared between each active treatment group and the placebo group using a CMH chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use at baseline, and SES-CD at baseline. The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% confidence interval (CI) using the method of Yan and Su (2010) and the p-value computed from CHM test will be provided. Subjects with missing binary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.
- Continuous endpoints that are only measured at baseline and the Week 16 visit will be analyzed using an analysis of covariance model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (Visit 2) (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences will be provided.
- Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation. The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

Safety analyses:

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

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

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, serious AEs, and deaths will be similarly summarized or listed. Adverse events of special interest will be summarized by treatment group.

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

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

STUDY SCHEDULE

Table 1 Schedule of Assessments

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

Table 1 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
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				
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		

Table 1 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
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; ß-hCG=beta-human chorionic gonadotropin; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; [redacted]; ECG=electrocardiogram; [redacted]; e-diary=electronic diary; [redacted]; ET=early termination; FSH=follicle-stimulating hormone; 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 day(s) 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 (SHP647-304) study 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.

Table 1 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

[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 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 for further details.

[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 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.

[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.

Table 1 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

[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 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 hematocrit results) should be available to calculate the CDAI scores. See Section 7.2.2.3 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 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.

Table 1 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

[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 for the order in which assessments should be performed. Timing of visits is relative to baseline (Visit 2).

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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

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

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

1.2 Product Background and Clinical Information

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

Ontamalimab (previously known as PF-00547659 and SHP647) is a fully human immunoglobulin G2 kappa ($IgG_{2\kappa}$) monoclonal antibody that binds to human MAdCAM to reduce lymphocyte homing to the gut and GI inflammation. Ontamalimab binds MAdCAM-1 with high affinity and selectivity that prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM-expressing sites in the high endothelial venules of the GI tract.

1.3 Benefit/Risk Assessment

Ontamalimab has been evaluated in Phase 1 and Phase 2 clinical studies in subjects with CD and ulcerative colitis (UC). In CD Study A7281006, induction with ontamalimab did not meet the primary endpoint; no statistically significant differences were observed between the active treatment arms and the placebo arm in CD Activity Index (CDAI)-70 response rate at Week 8 or Week 12. Post hoc analyses suggested evidence of drug effect in subjects with more inflammation at baseline, as indicated by higher serum concentrations of C-reactive protein (CRP) or Simple Endoscopic Score for CD (SES-CD). In UC Study A7281009, induction with ontamalimab at doses of 7.5 mg, 22.5 mg, or 75 mg once every 4 weeks (Q4W) resulted in statistically significantly higher proportions of subjects in remission at Week 12 based on total Mayo score (both local and central read) when compared with placebo treatment.

In the induction study A7281006 in subjects with CD, compared to placebo, nominally statistically significant decreases in fecal calprotectin were observed in the 75 mg group at Week 8 and in the 22.5 mg and 75 mg groups at Week 12. Generally, decreases from baseline in high-sensitivity (hs)CRP were observed in all 4 treatment groups over the 12-week induction period. Compared to placebo, nominally statistically significant decreases in hsCRP were observed in all 3 active treatment groups (22.5 mg, 75 mg, and 225 mg) at Week 12. There was no evidence of a dose response for either of these parameters. A nominally statistically significant increase was observed in circulating β_7^+ central memory T lymphocytes at Weeks 8 and 12, consistent with the predicted mechanism of action. In the UC induction study, A7281009, decreases in fecal calprotectin were observed in all groups, including placebo; however, there were no nominally statistically significant differences in the decrease in fecal calprotectin between any dose level of ontamalimab and placebo. Decreases in hsCRP were also observed in all 4 treatment groups; however, other than the 75 mg dose group at Week 12, no nominally significant differences were observed in active treatment vs placebo.

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

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

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

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

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

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

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

This study is designed to evaluate the efficacy and safety of ontamalimab in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.

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

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

Study A7281008 (TOSCA) was an open-label multi-center, Phase 1 sequential cohort study that evaluated the effects of a maximum induction dose of ontamalimab on CNS system immune surveillance.

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

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

The ontamalimab dose selection (25 mg and 75 mg) for this study is based on data from these 3 previous studies, which evaluated the activity of ontamalimab in adult patients with moderately to severely active CD based on CDAI scores between 220 and 450. The results of a post hoc analysis of remission rate by baseline elevated serum concentration of hsCRP suggested that the greatest treatment effect was at a dose of 22.5 mg. Similarly, post hoc analysis of remission rates by endoscopic severity assessed using the SES-CD suggested best efficacy at a dose of 75 mg. Therefore, both dosage regimens 25 mg and 75 mg Q4W have been selected for the Phase 3 testing. The Phase 1 study (A7281008, TOSCA) and Phase 2 studies (A7281006, OPERA; and A7281007, OPERA II [long-term safety study]) that investigated the safety, tolerance, PK, and pharmacodynamic (PD) properties of ontamalimab support further clinical development of ontamalimab using SC administration in subjects with moderate to severe CD.

2.2 Study Objectives

2.2.1 Coprimary Objectives

The coprimary objectives of this study are to evaluate the efficacy of ontamalimab in subjects with moderate to severe CD in:

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

2.2.2 Secondary Objectives

2.2.2.1 Key Secondary Objectives

The key secondary objectives are as follows:

- To evaluate the efficacy of ontamalimab in inducing clinical remission as measured by 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.

2.2.2.2 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.

2.2.3 Exploratory Objectives

The exploratory objectives are as follows:

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

3. STUDY DESIGN

3.1 Study Design and Flow Chart

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.

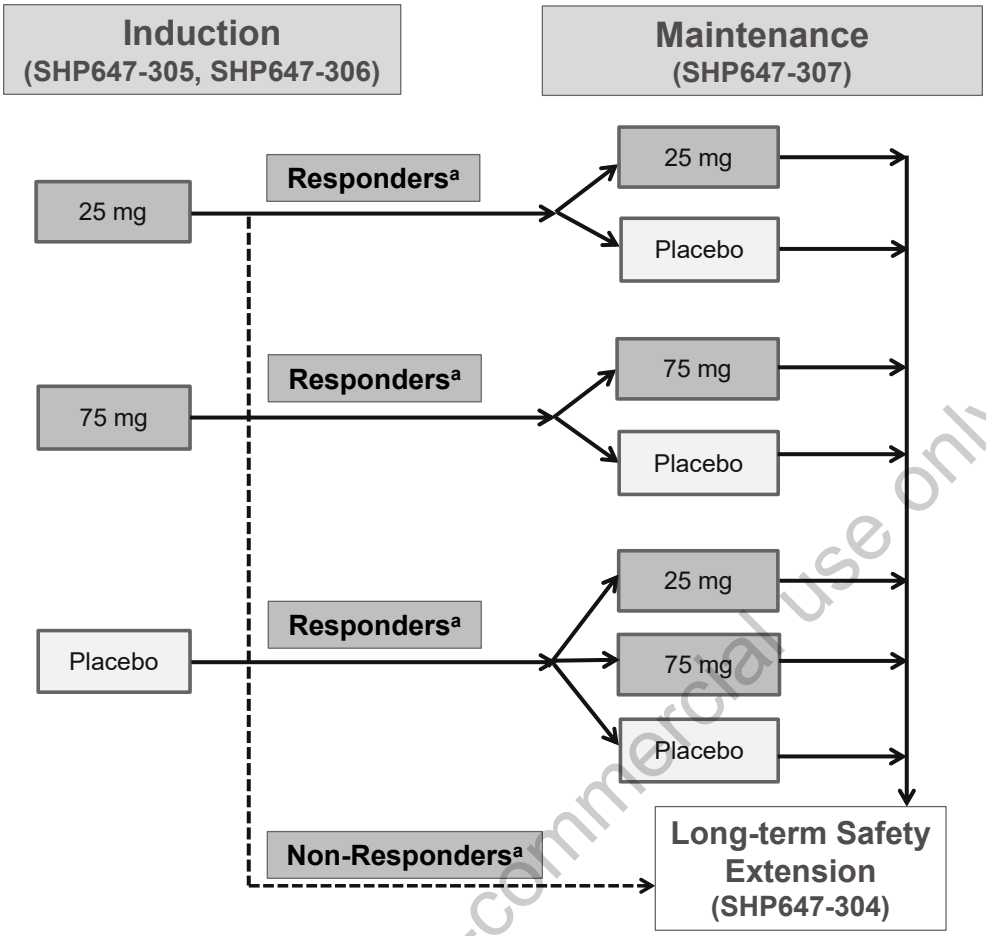
The study consists of a screening period up to 6 weeks and a 16-week treatment period. After the screening period, eligible subjects will be randomized to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo) in a 3:3:2 ratio. Randomization will be stratified based upon the subject's status of prior anti-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 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], [redacted], safety, and health outcome assessments at these visits as detailed in Table 1.

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 treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

A planned interim analysis for the coprimary endpoints will take place 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 will be reassessed as part of this interim analysis. See Section 9.5 for further details of the planned interim analysis.

The overall study design is shown in Figure 2.

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



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

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

1. Subject is in clinical remission as determined by meeting the criteria for clinical remission using the 2-item PRO, ie, 2-item PRO subscore of average worst daily abdominal pain ≤3 (based on 11-point NRS) over the 7 most recent days and average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days.*

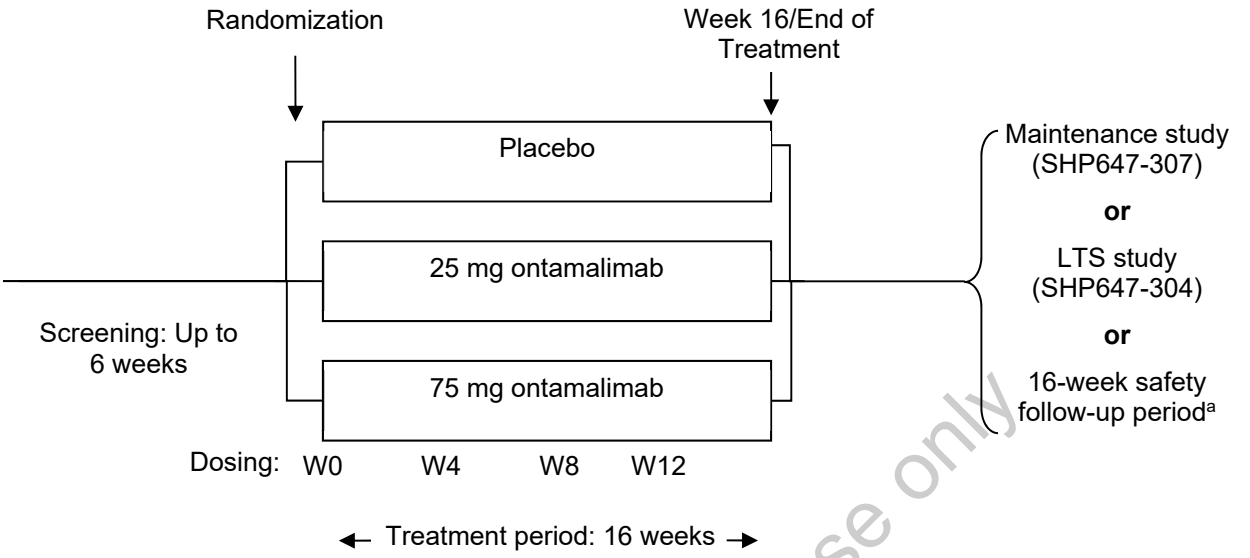
2. Subject has a decrease of at least 100 points in CDAI score (CDAI-70) from baseline.

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

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

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

Figure 2 Study Design Flow Chart



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.

Note: A planned interim analysis for the coprimary endpoints will take place 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.

3.1.1 Rationale for Coprimary Endpoints

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

Rationale for Abdominal Pain Severity

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

condition (irritable bowel syndrome) that examined the minimal clinically important difference on the 11-point NRS for abdominal pain (Spiegel et al., 2009) as well as post hoc analyses of the Phase 2 data from the ontamalimab program (Study A7281006, OPERA).

Rationale for Very Soft Stool/Liquid Stool Frequency

Diarrhea is the most common sign in the presentation of CD, affecting approximately 85% of patients with a diagnosis of CD. In the CDAI, the number of liquid or soft stools (each day for 7 days) is used with a multiplier of 2. The coprimary endpoints for clinical remission in studies SHP647-305 and SHP647-306 requires the use of a definition without any such multiplying factor and will use the BSFS for defining the very soft or liquid stools according to types 6 and 7, respectively. A retrospective study of PROs in CD based on data from randomized controlled studies using rifaximin and MTX showed that a mean daily stool frequency score of ≤1.5 had an area under the receiving operating characteristic curve of 0.79 (Khanna et al., 2015) and provided a potential cutoff for defining remission as measured by CDAI. In a recent study to select the attributes determining overall disease severity and to rank the importance of and to score these individual attributes for both CD and UC based on specialist opinion, a sample of at least 10 loose stools per week was considered as an attribute contributing to overall disease severity in CD (Siegel et al., 2016). Based on post hoc analyses of the Phase 2 data in the ontamalimab program (Study A7281006, OPERA) and by choosing the population of subjects satisfying the moderate to severe CD inclusion criteria, various cutoffs were explored and a stool frequency ≤2.0 was found to be optimal in terms of treatment separation while still allowing for a reasonable threshold for remission. Based on these and other recent data that support this cutoff, an average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) has been chosen as the stool frequency criterion for clinical remission.

Endoscopic Response

Endoscopic response is defined in 2 ways:

- 25% reduction in SES-CD score (“endoscopic response”)
- 50% reduction in SES-CD score (“enhanced endoscopic response”).

“Endoscopic response” will be used as a coprimary endpoint and “enhanced endoscopic response” will be used as a key secondary endpoint in this study as these magnitudes of changes are likely to be clinically relevant. In the recent trial with upadacitinib, the magnitude of difference between the different doses of the active drug and placebo at Week 16 was reported to be 9% to 36% for endoscopic response and 10% to 20% for enhanced endoscopic response (Sandborn et al., 2017). In the post hoc analysis of the Phase 2 OPERA study with ontamalimab the magnitude of difference between the active treatment arms and placebo showed a similar pattern (higher for the endoscopic response than for enhanced endoscopic response) (D'Haens et al., 2018).

Mucosal healing or “endoscopic healing” is considered to be a pivotal long-term target in the treatment of CD; however, partial healing or endoscopic response may also provide benefits. Endoscopic response can be an important indicator that the mucosal inflammation has decreased as an effect of the investigational product. Some treatments may result in a partial initial

response, even though at a later stage a complete response may occur. Median duration of remission after 1 year treatment with infliximab was similar in subjects achieving complete absence of mucosal ulcer to subjects who achieved significant but incomplete mucosal healing (D'Haens et al., 2002).

The benefit of endoscopic response was also shown in the SONIC study; the presence of endoscopic response (defined in that study as at least a 50% decrease in endoscopic score at Week 26 of treatment) identified subjects most likely to be in corticosteroid-free clinical remission at Week 50 (Ferrante et al., 2013). The proportion of patients requiring major abdominal surgery in a single-center cohort study with infliximab was similar with complete healing or with partial healing. (Schnitzler et al., 2009; Panaccione et al., 2013). Subjects with such a treatment response should be identified by endoscopic assessment in order not to misclassify them as nonresponders and underestimate the response to the treatment.

3.1.2 Rationale for Key Secondary Endpoints

Clinical Remission Defined by CDAI Score

Conventionally, a CDAI score of <150 has been used to define clinical remission. While there has been widespread use of the CDAI over a long period of time, the items do not contribute equally to the score, and symptom items reported by subjects are not specific for CD and are not sensitive for inflammation seen at colonoscopy. There has been movement away from using the CDAI by regulatory authorities to the use of PROs and objective measures of disease such as endoscopy (Williet et al., 2014). However, for benchmarking or for comparative effectiveness purposes, CDAI endpoints are expected to be used.

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

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

The CDAI has been the traditionally used measure to assess clinical response and clinical remission in CD. In the CDAI, the degree of abdominal pain is one of 8 variables and is used with a multiplier of 5 in the overall score. Importantly, it is based on a 4-point scale, with scores ranging from 0 (none) to 3 (severe). With the shift to the new endpoint as evident from the coprimary endpoint of clinical remission in this study, it is still important to allow for a frame of reference to the existing standard for response, based on the CDAI components. A daily average abdominal pain threshold of ≤1 will help achieve this as 1 on the 4-point scale corresponds to mild abdominal pain. Although direct mapping between the scales has not been established, this will approximate to a score of 3 on the 11-point NRS scale, as this falls within the mild pain range on the NRS based on the literature.

Based on post hoc analyses of the Phase 2 data in the ontamalimab program, regulatory requirements, and treatment separation assumptions, a threshold for the average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) was chosen for the coprimary endpoint of clinical remission. However, given the limited data available for this endpoint, recent evidence

from literature suggesting that thresholds ≤3 are likely to be quite stringent (Sandborn et al., 2017), and the refractory nature of the disease in those with moderate to severe CD, it is also important to assess the effects of treatment using a more realistic measure. Hence, for this key secondary endpoint of clinical remission, average daily stool frequency ≤3 of type 6/7 (very soft stools/liquid stools) has been chosen as the appropriate threshold.

Clinical Response

The goal of measuring clinical remission is to have a sensitive clinical measure to assess the complete absence of symptoms or the stabilization of noninflammatory symptoms. However, as response and remission are considered to be on a continuum of improvement or response to treatment, clinical remission is generally the chosen measurement over clinical response. Therefore, clinical remission is used as coprimary endpoint and clinical response is used as a key secondary endpoint in this study.

Clinical response is defined in Section 9.8.2.1. For both clinical response criteria, an additional requirement is that the symptom not being used to assess clinical response (ie, abdominal pain severity or very soft stool/liquid stool frequency) must remain unchanged/not worsen from the baseline score, or meet the criteria for clinical remission for that item of the 2-item PRO (either a 2-item PRO subscore of average daily stool frequency ≤2 of type 6/7 [very soft stools/liquid stools] as shown in the BSFS or average worst daily abdominal pain ≤3 [based on 11-point NRS] over the 7 most recent days).

The rationale for needing to meet at a minimum clinical response definition for either abdominal pain severity or very soft stool/liquid stool frequency (and not necessarily both) is based on the supposition that a lack of improvement in 1 of these symptoms is not necessarily an indicator of eventual lack of response (as assessed by the stricter clinical remission criterion). Based on Phase 2 data, it has been observed that the magnitude of placebo response rate can be higher for abdominal pain than for stool frequency. Therefore, the additional criterion of at least a 2-point decrease in abdominal pain severity from baseline is required for assessing clinical response for abdominal pain. Overall, the definition of clinical response used for this study has been chosen to allow for the maximal pool of subjects to be assessed for the effect of treatment and, if appropriate, the continuation of therapy in the maintenance study (SHP647-307).

Composite Score Endpoint of Both Clinical Remission by 2-item PRO and Endoscopic Response at Week 16

In theory, as the degree of inflammation decreases due to the effect of treatment, both clinical signs and symptoms of CD as well as endoscopic appearance can improve. However, in any given subject, the rates of clinical improvement and endoscopic improvement may not be the same. There are reasons for this discrepancy when evaluating clinical and endoscopic improvement in the same time period, including clinical symptoms not being well correlated to the mucosal inflammation. Due to the transmural feature of the disease, symptoms can correspond to the inflammation in some of the other gut layers as well. Previous clinical studies and clinical observations indicate that the improvement of clinical signs and symptoms and the improvement in endoscopic appearance may not go hand in hand. Significant clinical improvement can precede significant endoscopic improvement. The healing process of the gut

mucosa may take a long time and may depend on the baseline severity of the endoscopic appearance, which may not be in line with the actual baseline severity of the symptoms. Therefore, when evaluating clinical remission together with endoscopic endpoints, improvement in endoscopic scores could be more relevant than evaluating mucosal healing in the induction phase. For these reasons, the key secondary composite endpoint (which takes into account both clinical and endoscopic response to treatment in the same subject) consists of the evaluation of the clinical remission together with the endoscopic response.

Complete Endoscopic Healing

Endoscopic healing will be defined in 2 ways:

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

- Complete endoscopic healing defined by SES-CD=0-2.

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

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

3.2 Duration and Study Completion Definition

Each subject's final visit in this study may be at the end of the treatment period (Week 16), if continuing to Study SHP647-307 or SHP647-304, or at the end of the safety follow-up period (Week 32), if not continuing to either of these studies. In either case, the final visit will be in person at the site. A subject's maximum duration of participation is expected to be approximately 38 weeks: a screening period of up to 6 weeks, a treatment period of 16 weeks, and a safety follow-up period of 16 weeks (if applicable). It is expected that the study will be completed in approximately 3 years.

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

3.3 Sites and Regions

It is anticipated that the study will be conducted in approximately 19 countries. Regions will include North America; Europe, the Middle East, and Africa; Latin America; and Asia-Pacific. Approximately 210 sites will be utilized.

4. STUDY POPULATION

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

4.1 Inclusion Criteria

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

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must be between ≥16 and ≤80 years of age at the time of the signing of the informed consent/assent form.

   Note: Subjects <18 years of age must weigh ≥40 kg and must have body mass index ≥16.5 kg/m^2.
4. Subjects must have active moderate to severe ileal (terminal ileum), ileocolic, or colonic CD at baseline (Visit 2) as defined by:
   a. CDAI score between 220 and 450 (inclusive) **AND**
   b. Meeting the following subscores in the 2-item PRO:
      i. Abdominal pain subscore ≥5 (average worst daily pain on the 11-point NRS) and abdominal pain subscore ≥2 (average daily pain on the 4-point abdominal pain variable of CDAI) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous) **AND/OR**
      ii. Average of the daily stool frequency subscore ≥4 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous)

   AND

   c. Presence of ulcerations that are characteristic to CD, as determined by a colonoscopy performed during screening, and as defined by the SES-CD >6 (SES-CD ≥4 for isolated ileitis)

   Note that the subject must be confirmed as meeting the CDAI score and PRO subscore requirements **before** a colonoscopy is done.

5. Subjects must have a documented diagnosis (endoscopic with histology) of CD for ≥3 months before screening. Documented diagnosis is defined as:
    - A biopsy report in which the description of the histological findings is consistent with the CD diagnosis **AND**
    - A report documenting disease duration based upon prior colonoscopy.

    Note: If a biopsy report is not available in the source document at the time of screening, a biopsy must be performed during the screening colonoscopy and the histology report should be consistent with the CD diagnosis. If the histology description does not support the CD diagnosis at this time point, the subject should not be randomized.
6. Subjects must be willing and able to undergo a colonoscopy during screening after all other inclusion criteria have been met.
7. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or mesalamine (5-ASA), glucocorticoids, immunosuppressants (AZA, 6-MP, or MTX), or anti-TNF (see Appendix 4 for guidance). Subjects who have had an inadequate response to sulfasalazine or mesalamine should have also failed at least 1 other conventional treatment such as glucocorticoids.
8. Subjects receiving any treatment(s) for CD described in Section 5.2.1 are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
9. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception (ie, highly effective methods for female and medically appropriate methods for male study subjects, as described in Section 4.4) for the duration of the study.

4.2 Exclusion Criteria

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

1. Subjects with indeterminate colitis, microscopic colitis, nonsteroidal anti-inflammatory drug-induced colitis, ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of UC.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with presence of enterovesical (ie, between the bowel and urinary bladder) or enterovaginal fistulae.
5. Subjects with current symptomatic diverticulitis or diverticulosis.

6. Subjects with clinically significant obstructive colonic stricture, or who have a history of bowel surgery within 6 months before screening, or who are likely to require surgery for CD during the treatment period. Subjects who have undergone previous colonic resection or ileocolectomy more than 6 months before screening must have at least 25 cm of colon remaining.
7. Subjects with past medical history of multiple small bowel resections resulting in clinically significant short bowel syndrome.
8. Subjects requiring total parenteral nutrition.
9. Subjects with past medical history of bowel surgery resulting in an existing or current stoma. Subjects who had a j-pouch are excluded as a j-pouch could result in a stoma.
10. Subjects have had prior treatment with ontamalimab (formerly PF-00547659; SHP647).
11. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
12. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than AZA, 6-MP, or MTX) or continuous antibiotics (>2 weeks) for the treatment of CD within 30 days before baseline (Visit 2).
13. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
14. Subjects have received any biologic with immunomodulatory properties (other than anti-TNFs) within 90 days before baseline (Visit 2).
15. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
16. Subjects have received lymphocytes apheresis or selective monocyte granulocytes apheresis within 60 days before baseline (Visit 2).
17. Subjects have received enteral nutrition treatment within 30 days before baseline (Visit 2).
18. Subjects have received parenteral or rectal glucocorticoids or rectal 5-ASA within 14 days before screening colonoscopy.
19. Subjects have taken >20 mg/day of prednisone, >9 mg/day of budesonide, or equivalent oral systemic corticosteroid dose (see Appendix 3) within 14 days before baseline (Visit 2) or have taken ≥40 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 6 weeks before baseline (Visit 2).
20. Subjects have participated in other investigational studies within either 30 days or 5 half-lives of investigational product used in the study (whichever is longer) before screening (Visit 1).
21. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).

22. Subjects with active enteric infections (positive stool culture and sensitivity), *Clostridium difficile* infection or pseudomembranous colitis (subjects with *C. difficile* infection at screening may be allowed retest after treatment), evidence of active cytomegalovirus infection or *Listeria monocytogenes*, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
23. Subjects with abnormal chest x-ray or other imaging findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x-ray, computed tomography scan, etc., performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation).
24. Subjects with evidence of active or latent infection with *Mycobacterium tuberculosis* (TB) or subjects with this history who have not completed a generally accepted full course of treatment before baseline (Visit 2) are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon-gamma release assay (IGRA) performed.

    Subjects who have no history of previously diagnosed active or latent TB are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie ≥5 mm induration) or a positive IGRA (the latter to be tested at the site's local laboratory) during screening or within 12 weeks before screening. If the IGRA cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.

    - An IGRA is strongly recommended for subjects with a prior Bacillus Calmette-Guérin vaccination but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON®-TB Gold Plus In-Tube Test.
    - If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent TB, a positive test on repeat will exclude the subject. Subjects with a history of active or latent TB infection must follow instructions for "Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met" in this criterion.
    - Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.

    Results from a chest x-ray, taken within the 12 weeks before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Subjects with a prior diagnosis of active or latent TB are excluded unless both of the following criteria are met:

- The subject has previously received an adequate course of treatment for either **latent** (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or **active** (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
- A chest x-ray performed within 12 weeks before or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.

25. Subjects with a pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
26. Subjects with any unexplained symptoms suggestive of PML based on the targeted neurological assessment during the screening period (see Section 7.2.3.3).
27. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
28. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
    - Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study
    - Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence)
    - Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening (Visit 1)
    - History of significant cerebrovascular disease within 24 weeks before screening (Visit 1).
29. Subjects who have had significant trauma or major surgery within 4 weeks before the screening (Visit 1), or with any major elective surgery scheduled to occur during the study.

30. Subjects with evidence of cirrhosis with or without decompensation (ie, esophageal varices, hepatic encephalopathy, portal hypertension, ascites).
31. Subjects with primary sclerosing cholangitis.
32. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Note: if a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if no presence of hepatitis B virus (HBV) DNA is confirmed by HBV DNA polymerase chain reaction (PCR) reflex testing performed in the central laboratory.
33. Subjects with chronic hepatitis C virus (HCV) (positive HCV antibody [HCVAb] and HCV RNA). Note: Subjects who are HCVAb positive without evidence of HCV RNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCV RNA at least 12 weeks prior to baseline]).
34. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening (Visit 1). Note: Screening laboratory tests, if the results are 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 must be reviewed for eligibility prior to the screening colonoscopy procedure.
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥3.0 × the upper limit of normal (ULN)
    - Total bilirubin level ≥1.5 × ULN or >2.0 × ULN if the subject has a known documented history of Gilbert's syndrome
    - Hemoglobin level ≤80 g/L (8.0 g/dL)
    - Platelet count ≤100 × 10^9/L (100,000 cells/mm^3) or ≥1000 × 10^9/L (1,000,000 cells/mm^3)*
    - White blood cell count ≤3.5 × 10^9/L (3500 cells/mm^3)
    - Absolute neutrophil count <2 × 10^9/L (2000 cells/mm^3)
    - Serum creatinine level >1.5 × ULN or estimated glomerular filtration rate <30 mL/min/1.73 m^2 based on the abbreviated Modification of Diet in Renal Disease Study Equation.

    *Note: if platelet count is <150,000 cells/mm^3, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.
35. Subjects with known human immunodeficiency virus (HIV) infection based on documented history with positive serological test, or positive HIV serologic test at screening, tested at the site's local laboratory in accordance with country requirements or tested at the central laboratory. Note: A documented negative HIV test within 6 months of screening is acceptable and does not need to be repeated.

36. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse or dependency of any kind including abuse of medicinal marijuana (cannabis).
37. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
38. Female subjects who are planning to become pregnant during the study period.
39. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
40. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

4.3 Restrictions

For the purposes of this protocol, dietary supplements (such as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties) are considered to be concomitant medications (see Section 5.2).

Smoking is considered to be a risk factor for CD. Reports have shown that smoking is not only related to the onset, relapse, and exacerbation of CD, but also that smoking cessation lowers the postoperative recurrence rate (Ueno et al., 2013). Subjects should inform the investigator of any changes to their smoking habits during the study (including starting or stopping smoking). Use of nicotine patches should be recorded as concomitant medication (see Section 5.2.1).

4.4 Reproductive Potential

The potential effects of ontamalimab on embryofetal or postnatal development have not been assessed in humans. Preliminary results from an enhanced pre- and postnatal development toxicity study of ontamalimab in nonhuman primates indicated that, at the dose levels tested (30 and 60 mg/kg), infant losses were increased in ontamalimab-exposed animals when compared both to control animals in the study and to the historical control animal data from the testing facility. The relevance of this finding to humans is unknown but cannot be excluded. Based on the exposure in the Phase 2 clinical study A7281009 (area under the concentration-time curve [AUC] from 0 to 672 hours [$AUC_{0\text{-}672h}$] at 6140 µg·h/mL following repeated SC administration of 75 mg SHP647 Q4W), maternal exposure (AUC) in cynomolgus monkeys within a similar duration at 30 and 60 mg/kg once every 10 days is approximately 77 times and 172 times the clinical exposure, respectively.

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

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

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

4.4.1 Contraceptive Methods for Female Study Subjects

Sexually active females of childbearing potential must already be using an established highly effective form of contraception and must be advised to use appropriate contraceptives throughout the study period and for 16 weeks following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert.

Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the clinical study. The following highly effective contraceptive methods are considered to be methods with low user dependency:

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization/vasectomized partner
- Implantable progesterone-only hormonal contraception associated with inhibition of ovulation.

Female subjects should be in one of the following categories:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥51 years of age); postmenopausal status should be confirmed by follicle-stimulating hormone (FSH) testing.
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks poststerilization or has medically confirmed ovarian failure.
- Females of childbearing potential with a negative serum pregnancy test result at screening and a negative urine pregnancy test result at baseline (Visit 2). Females of childbearing potential must agree to practice true abstinence (refrain from sexual activity that could result in pregnancy) or agree to use appropriate methods of highly effective contraception.

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

- Combined (estrogen- and progestogen-containing) hormonal contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal) stabilized for at least 30 days before screening (Visit 1)
- Progestogen-only hormonal contraception associated with inhibition of ovulation plus a barrier method
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization/vasectomized partner with documented absence of sperm in the postvasectomy ejaculate
- True abstinence (see Section 4.4).

4.4.2 Contraceptive Methods for Male Study Subjects

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

Appropriate methods of contraception for male subjects are:

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

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

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

4.5 Withdrawal of Subjects

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

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 16/early termination (ET; Visit 7) are to be performed. All subjects who discontinue treatment with investigational product should also undergo the protocol-specified 16-week safety follow-up period. In the event that subjects are unable to attend in person for the follow-up visits, all efforts should be made to collect information on AEs and concomitant medications. Comments (spontaneous or elicited) or complaints made by the subject must be recorded. The reason for termination and date of stopping investigational product must be recorded.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

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

- Adverse events
- Serious AEs
- Pregnancy
- Protocol deviations
- Failure to return for visits.

A subject should be withdrawn from study treatment:

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

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

If a subject withdraws their consent, no further evaluation should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

4.5.2 Reasons for Withdrawal

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

Reasons for discontinuation include but are not limited to:

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

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

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

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal remedies and vitamins) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the first dose of investigational product. Use of biologics for indications other than CD during the 90 days before screening must also be recorded.

Prior and concomitant CD-specific treatments from the previous 10 years will be recorded. The subject's entire history of biologic CD-specific treatments will be recorded.

Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or 5-ASA, glucocorticoids, immunosuppressants (AZA, 6-MP, or MTX), or anti-TNF agents (Lichtenstein et al., 2018). Please see Appendix 4 for guidance on defining prior treatment failure and intolerance to prior treatment for CD.

5.2 Concomitant Treatment

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

5.2.1 Permitted Treatment

Subjects must remain on stable doses of permitted CD treatments until completion of the Week 16 visit, unless decreases are required because of AEs. Stable doses of the following treatments for CD are permitted as concomitant medication:

- Oral sulfasalazine or 5-ASA, providing that the dose is stable for at least 2 weeks before baseline (Visit 2)
- Immunosuppressants (AZA, 6-MP, or MTX), providing that the dose is stable for at least 8 weeks before baseline (Visit 2)
- Oral glucocorticoids (prednisone or equivalent [see Appendix 3] up to a maximum of 20 mg/day or budesonide up to a maximum of 9 mg/day), providing that the dose is stable for at least 2 weeks before baseline (Visit 2). After baseline (Visit 2), a stable dose of 20 mg/day prednisone or equivalent oral systemic corticosteroid dose is allowed. Steroids may be decreased due to AEs.

Note: Rectal 5-ASA and parenteral or rectal glucocorticoids are prohibited from within 14 days before screening colonoscopy.

Antidiarrheal opiate drugs such as IMODIUM® (loperamide), LOMOTIL® (diphenoxylate hydrochloride and atropine sulfate), tincture of opium, and codeine will be recorded as concomitant medications. Subjects must be using such products in a stable regimen for at least 2 weeks before randomization at baseline (Visit 2). Reported use of any antidiarrheal opiate medicines will assist the investigator response to Question 5 of the CDAI. Antidiarrheal opiate drugs must be taken at stable doses for the duration of the study unless dose reduction or discontinuation is required due to clinical improvement of AE. However, escalations of the dose after dose reduction or re-initiation after drug discontinuation are not allowed (see Section 5.2.3).

Subjects using medicinal marijuana (cannabis) under a physician's prescription, and who obtain the product from a licensed pharmacy or provider, should continue to use it under the same regimen for the duration of the study, unless otherwise instructed by the investigator or treating physician. Such subjects must be using the product, in a stable regimen, for at least 3 months before screening.

Routine nonlive vaccinations are allowed during the study.

Dietary and herbal supplements and probiotics are allowed in the study, provided they are being taken at stable doses at the time of the baseline visit (Visit 2) and for the duration of the study. They should be recorded as concomitant medications.

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

Antibiotics are permitted, with the exception of antibiotics used to treat the underlying disease exceeding 2 weeks within 30 days before baseline (Visit 2) or before Week 16 (Visit 7, Part 1).

5.2.2 Prohibited Treatment

Table 2 details the minimum required number of days before baseline (Visit 2) for common prior treatments that are excluded medications for this study.

Table 2 Common Excluded Treatments

	Permanently Excluded	Minimum Required Number of Days Before Baseline (Visit 2)			
Treatment		**14**	**30**	**60**	**90**
Ontamalimab (PF-00547659, SHP647) in a previous study	X				
Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab)	X				
Parenteral and rectal glucocorticoids		X[a]			
Rectal 5-ASA		X[a]			
Investigational products			X[b]		
Live (attenuated) vaccine			X		
Nonbiologics with immunomodulatory properties[c]			X		
Anti-TNF treatment				X	
Lymphocytes apheresis or selective monocyte granulocytes apheresis				X	
Biologics with immunomodulatory properties (other than anti-TNFs) including biosimilars					X

5-ASA=5-aminosalicylic acid; TNF=tumor necrosis factor

[a] The minimum required number of days before baseline (Visit 2) for rectal 5-ASA and parenteral or rectal glucocorticoids is defined as 14 days before screening colonoscopy (see Section 4.2, exclusion criterion 18).

[b] Or 5 half-lives if longer.

[c] Usage of immunosuppressants, eg used in transplantation or in autoimmune diseases that are not established therapies for CD (eg, mycophenolate mofetil, cyclosporine, rapamycin, thalidomide, tofacitinib, or tacrolimus).

Treatments not listed in Table 2 may be considered allowable; see Section 5.2.1 for further details.

In addition to the treatments listed in Table 2, the following common treatments are excluded medications for this study:

- Prednisone dose >20 mg/day, budesonide >9 mg/day, or other equivalent oral systemic corticosteroid dose
- Bismuth subsalicylate products
- Fecal microbiota transplantation.

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

Enteral nutrition is not permitted from within 30 days of baseline (Visit 2) or at any time during the study.

5.2.3 Rescue Therapy

Subjects must maintain their stable dose of background CD treatment, unless dose reduction or discontinuation is required due to associated AEs. If a subject requires initiation of a new therapy or increase in glucocorticoids for CD above the SHP647-305 or SHP647-306 baseline (Visit 2), the subject should be withdrawn from study treatment and enter the safety follow-up period, and appropriate treatment should be given at the discretion of the investigator.

Subjects who enter the safety follow-up period will no longer need to abstain from the medications that were prohibited during the baseline (Visit 2) and treatment periods. High-dose glucocorticoids and other CD treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated during the safety follow-up period without prior discussion with the sponsor study physician or designee due to the long half-life of ontamalimab.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

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

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

6.1.1 Blinding the Treatment Assignment

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

6.2 Administration of Investigational Products

6.2.1 Interactive Response Technology for Investigational Product Management

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

6.2.2 Allocation of Subjects to Treatment

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

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 investigational product allocated to the subject, once eligibility has been determined. Individual subject treatment will be automatically assigned by the IRT system.

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

6.2.3 Dosing

Investigational product (ontamalimab or placebo) will be administered subcutaneously by qualified site personnel Q4W (Weeks 0, 4, 8, and 12). See Section 7.2 for the timing of dosing relative to other procedures.

Investigational product should be administered in the anterolateral right or left thigh. If there are clinical reasons why the investigational product cannot be administered in the thigh, the investigational product may be administered in the deltoid area or abdomen with appropriate documentation. The location of the investigational product administration will be recorded.

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

Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is dispensed by qualified staff members.

6.2.4 Unblinding the Treatment Assignment

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

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

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

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

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

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

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

6.3.2 Packaging

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

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

6.3.3 Storage

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

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified minimum/maximum thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range.

Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

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

6.3.4 Special Handling

The investigational product should be protected from light and should not be frozen. Do not shake.

6.4 Drug Accountability

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

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

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented in the subject's source document and/or other investigational product record.

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

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

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

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

6.5 Subject Compliance

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

7. STUDY PROCEDURES

7.1 Study Schedule

The investigator may schedule visits (unscheduled visits) in addition to those listed on the schedule of assessments (Table 1), in order to conduct evaluations or assessments required to protect the well-being of the subject.

7.1.1 Screening Period

7.1.1.1 Screening Visit (Visit 1)

Subjects will be screened within 6 weeks before the baseline visit (Visit 2) to determine eligibility to participate in the study and to perform the other assessments and procedures specified in Table 1. Each subject or subject's parent or legally authorized representative must participate in the informed consent process and provide written informed consent/assent before any assessments or procedures specified in the protocol are performed. Screening assessments will take place over more than 1 day (at least 2 visits will be necessary to complete the screening procedures, including colonoscopy).

A screen failure is a subject who has given informed consent or assent, as applicable (and whose parents or legally authorized representatives have given informed consent, as applicable), failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria, and has not been randomized or administered investigational product.

A subject may be rescreened if their condition has changed and they may potentially be eligible. Subjects may be rescreened 1 time. Note: Screening laboratory tests, if considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results of repeated tests must be reviewed for eligibility prior to the screening colonoscopy procedure.

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.

Collection of the daily e-diary data must begin at least 10 days before colonoscopy preparation. Note that the subject must be confirmed as meeting the CDAI and PRO subscore requirements per inclusion criteria 4a and 4b **before** a colonoscopy is done. Colonoscopy preparation will be according to local routine.

Colonoscopy during the screening period must be performed 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 (see Section 7.2.2.4). Colonoscopy preparation may be done on the same day as the colonoscopy procedure. 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. All colonoscopies will be evaluated using the SES-CD (see Appendix 2).

If a subject has had the following procedures performed as a part of standard medical care within 12 weeks before screening (Visit 1), these procedures do not need to be repeated as a part of screening:

- Chest x-ray
- Documented negative PPD test or IGRA for TB.

7.1.1.2 Baseline Visit (Visit 2; Week 0)

The baseline visit (Visit 2) will take place on Day 1 (Week 0). The assessments and procedures specified in Table 1 will be performed.

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

Results of the baseline laboratory tests are not required for investigational product administration but must be reviewed as soon as possible thereafter.

7.1.2 Treatment Period

7.1.2.1 Visits 3, 4, 5, and 6 (Weeks 2, 4, 8, and 12)

Visits 3, 4, 5, and 6 are scheduled to take place on Day 14 ±3 days (Week 2), Day 28 ±3 days (Week 4), Day 56 ±3 days (Week 8), and Day 84 ±3 days (Week 12), respectively. The assessments and procedures specified in Table 1 will be performed.

7.1.2.2 Final On-treatment Visit: Visit 7, Parts 1, 2, and 3 (Week 16/Early Termination)

The Week 16/ET visit (Visit 7) consists 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 day(s) before Part 2. If Parts 1 and 2 are done on the same day, blood samples must be taken before starting the colonoscopy preparation. The Week 16/ET assessments and procedures that will take place during Part 1 are specified in Table 1.

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. The Week 16/ET assessments and procedures that will take place during Part 2 are specified in Table 1.

Part 3 of Visit 7 will take place on Day 112 ±3 days. The Week 16/ET assessments and procedures that will take place during Part 3 are specified in Table 1.

At Part 3 of Visit 7, after review of CD assessments, health outcome assessments, and safety assessments, it will be determined whether the subject should enroll in the maintenance (SHP647-307) or LTS (SHP647-304) studies or enter the follow-up period of this study. Entry into the maintenance or LTS studies is dependent upon whether the subject fulfills the efficacy entry criteria of the maintenance study (SHP647-307), including achieving endoscopic and/or clinical response, and whether the subject agrees to participate.

The Week 16 assessments and procedures will also form the ET assessments for any subjects who are withdrawn early or discontinued from the study.

7.1.3 Follow-up Period

Subjects who are withdrawn early from the study, or who do not enter either the maintenance or LTS studies, should enter the 16-week safety follow-up period for safety monitoring.

During the safety follow-up period, the Week 24 visit (Visit 8) will take place on Day 168 ±7 days, or 8 weeks ±7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study. This visit will routinely be conducted by telephone; however, as an exception, the visit can be performed as a study site visit if preferred.

At the end of the safety follow-up period, there will be a visit at the site on Day 224 ±7 days, or 16 weeks ±7 days after the subject's last visit in the treatment period for subjects who are withdrawn early from the study; this visit will form the Week 32 visit (Visit 9). The assessments and procedures specified in Table 1 will be performed, including querying for SAEs, AEs, and concomitant medications and procedures. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

Subjects who are proceeding to the maintenance or LTS studies will not enter the safety follow-up period.

7.1.4 Additional Care of Subjects After the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

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

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

- Health outcome and patient-reported questionnaires
- Vital signs and ECG
- Laboratory sample collection
- Investigational product administration
- Colonoscopy is performed at a separate visit (see Section 7.2.2.4).

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

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics will be recorded at screening (Visit 1).

7.2.2 Efficacy

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

Patient-reported CD clinical signs and symptom 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 enter data on CD signs and symptoms items using the e-diary, which will be provided to subjects at the start of the study. Compliance will be assessed by site staff at each visit. The site staff will instruct the subject on the appropriate use of the e-diary 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 Section 4.1).

Subjects will be asked to record the following signs and symptom data, as experienced over the previous 24 hours, in the e-diary:

- Abdominal pain severity (numeric rating scale [NRS])
- Very soft stool/liquid stool frequency (as shown by BSFS type 6/7)
- Total stool frequency
- Rectal bleeding frequency
- Rectal urgency frequency
- Nausea severity
- Vomiting frequency
- Incontinence frequency
- Abdominal pain used in CDAI
- General well-being.

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 done.
- Visits 3, 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.
The PRO-CD daily e-diary is presented in Appendix 2.

7.2.2.2 Simple Endoscopic Score for Crohn's Disease

The SES-CD will be performed at the time points specified in Table 1. The SES-CD score at 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.

The SES-CD is a simple scoring system based on 4 endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of affected surface, and presence and severity of stenosis [narrowing]) measured in the same 5 ileocolonic segments as the CD index of severity (Daperno et al., 2004). Overall, values on the SES-CD range from 0 to 56, with higher values indicating more severe disease. The 4 endoscopic variables are scored from 0 to 3 in each bowel segment (ileum, right/transverse/left colon, and rectum):

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

A complete colonoscopy is required (including visualization of the terminal ileum except when it is not possible due to impassable stenosis or previous partial colectomy/ileocolectomy). The maximum stenosis score in a segment distal to another evaluable segment cannot exceed 2, so that the stenosis scores cannot exceed a total of 11 (Reinisch et al., 2017).

Evidence of active inflammation and ulceration is required at screening (Visit 1), in the form of a centrally read score of at least 1 in one or more ileocolonic segments in the Presence of Ulcers component of the SES-CD, as well as a total score of >6.

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

For the evaluation of efficacy, in cases where 1 or 2 segments cannot be fully evaluated by central endoscopic readers, ileocolonic segments that are evaluable during screening (Visit 1) and Week 16/ET (matching segments approach) will be utilized.

The SES-CD is presented in Appendix 2.

7.2.2.3 Crohn's Disease Activity Index

The CDAI is a composite measure with 8 components; 3 components (abdominal pain severity, very soft stool/liquid stool frequency, and general well-being) will be self-reported by the subject and will be recorded as part of the daily e-diary, as described in Section 7.2.2.1 and 5 components will be recorded at the time points specified in Table 1.

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 (see Section 7.2.2.1) and
- 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.

Note that the subject must be confirmed as meeting the CDAI score requirements at screening **before** a colonoscopy is done.

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 (see Section 7.2.2.1) and
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at the visit.

The CDAI score at 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 (see Section 7.2.2.1) and
- Components 4 to 8 (weight, medical and physical examination, use of diarrhea treatment, and hematocrit value) collected at Part 1 and Part 3 of the Week 16/ET visit, where assessed.

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

The CDAI is presented in Appendix 2.

7.2.2.4 Colonoscopy and Histology

Colonoscopy will be performed at the time points specified in Table 1.

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

In general, a complete colonoscopy should be performed; this includes visualization of the rectum, sigmoid colon, left colon, transverse colon, right colon, ileocecal valve, and the terminal ileum (except after partial colectomy/ileocolectomy when the aim is to visualize the remaining colon and, if it exists, the terminal ileum). At screening, incomplete colonoscopy will be accepted only on a case by case basis (eg, presence of impassable narrowing without any clinical signs of bowel obstruction and when the same time the investigated segments provide the SES-CD score required for inclusion). Similarly, a complete colonoscopy is the aim at Week 16/ET, with the exception of the presence of impassable stenosis or other CD-related complications as cause of failure to complete the colonoscopy procedure.

The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during colonoscopy. To achieve consistency in capturing and assessing endoscopic video recordings, each participating site will use an integrated hardware/software solution and associated tools for the capture and transmission of endoscopy video recordings for central reading. Nonreadable endoscopic images, as assessed by the investigator, should not be sent for central reading. The colonoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's medical record.

During 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. Colonoscopy and biopsy procedures will be defined in a colonoscopy instructions manual and/or reference card(s), on which all sites will be trained. Colonoscopy results will be reviewed by a central reader.

[redacted]
(see Appendix 2). Biopsies for conventional histologic assessment will be collected in formalin and shipped to the central laboratory. The central laboratory will register all biopsies and create paraffin blocks. Blocks will be batched and shipped on an agreed schedule to specialty laboratory, where tissue processing (sectioning, hematoxylin and eosin staining, and affixation to glass slides), digitalization, and uploading of images will occur. All images for a subject will be scored by the same qualified central pathologists blinded to the subject and treatment sequence information, according to the scoring modality.

7.2.3 Safety

7.2.3.1 Medical and Medication History

Medical history will be documented at screening (Visit 1), including CD history, cardiac history, and smoking history. Prior and concomitant medications and procedures will also be documented at the time points specified in Table 1.

7.2.3.2 Physical Examination (Including Height and Weight)

Complete and targeted physical examinations will be performed at the time points specified in Table 1. Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; eyes; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; back; and lymph nodes. Targeted physical examination includes the review of the following body systems: skin and mucosa (specifically including perianal for fistula and oral cavity for stomatitis), heart, lungs, eyes, abdomen, and examination of body systems where there are symptom complaints by the subject.

Weight will be measured at the time points specified in Table 1. Height will be measured at screening (Visit 1) only.

Changes after screening that are deemed clinically significant in the opinion of the investigator will be recorded as an AE.

7.2.3.3 Targeted Neurological Assessment

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

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

Subjects with any unexplained positive neurological assessment item at screening should be excluded from enrollment in the study (exclusion criterion 25, Section 4.2).

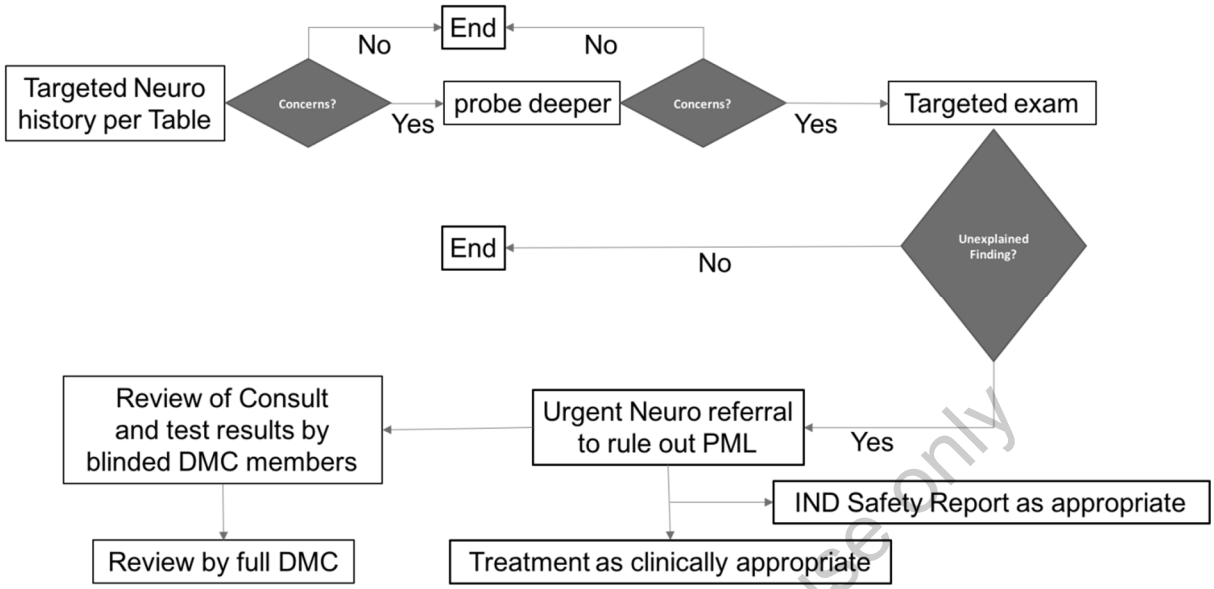
A step-wise approach for the proposed neurological assessment plan is provided in Table 3.

Table 3 Quarterly Neurological Assessment

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

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

Figure 3 Flow Diagram for Quarterly Neurological Assessments



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

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

7.2.3.4 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, “Have you had any health problems since your last visit?”). Adverse events are collected from the time informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3 (See Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.3.5 Vital Signs

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

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

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

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

Any deviations from baseline (Visit 2) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE, unless documented in the subject's medical history as a pre-existing medical condition.

7.2.3.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant.

Abnormal clinical laboratory values that are unexpected or not explained by the subject's clinical condition may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

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

Serum chemistry

alkaline phosphatase
AST
ALT
total bilirubin
total protein
albumin
glucose
blood urea nitrogen
creatinine
sodium
potassium
chloride
calcium
carbon dioxide

Hematology

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

Virology

HBsAg
HBcAb
hepatitis B DNA if HBsAg is negative and HBcAb is positive
HCVAb
HCV RNA PCR if HCVAb is positive
HIV

Urinalysis

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

Virology test results must be confirmed as negative before enrollment in the study; if a virology test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor but will not be collected in the electronic case report form (eCRF) database.

Stool microbiology will be performed at screening (Visit 1) or at any time a subject experiences an increase in GI symptoms (see Section 7.2.3.12). Diagnosis of *C. difficile* infection should be made using the central laboratory. If, for any reason, the central laboratory is not available, please see Appendix 5 for guidance regarding diagnostic algorithms.

A TB test (PPD or QuantiFERON-TB Gold Plus) will be performed at screening (Visit 1). A documented negative PPD test within 12 weeks before screening (Visit 1) is acceptable. The IGRA official reading and method or test must be located in the source documentation.

A serum sample will be collected and banked for John Cunningham virus antibody testing. It may be analyzed if a subject shows neurological symptoms suggestive of PML.

All laboratory assessments should be performed at central laboratories, with the exception of the following assessments: stool microbiology (local or central laboratory) and TB test (PPD or QuantiFERON-TB Gold Plus) (refer to laboratory manual for details).

7.2.3.7 Pregnancy Test and Follicle-stimulating Hormone Test

A beta-human chorionic gonadotropin (β-hCG) pregnancy test will be performed on all females of childbearing potential at the time points specified in Table 1; if pregnancy is suspected; or on withdrawal of the subject from the study. A serum pregnancy test will be performed at screening (Visit 1); all other pregnancy tests will be urine tests.

Pregnancy tests are not required for females of nonchildbearing potential who have undergone hysterectomy or bilateral oophorectomy, have medically confirmed ovarian failure, or are medically confirmed postmenopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; postmenopausal status should be confirmed by FSH testing in females who have had 12 consecutive months of spontaneous amenorrhea and are 51 years of age or older).

7.2.3.8 Electrocardiogram

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

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

7.2.3.9 Chest X-ray

A chest x-ray will be performed during screening (Visit 1). If a subject has had a chest x-ray performed as a part of standard medical care within 12 weeks before screening (Visit 1), it does not need to be repeated as a part of screening. The official reading must be located in the subject's source documentation.

7.2.3.10 Antidrug Antibodies

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

7.2.3.11 Monitoring for Type I and Type III Immune Reactions

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

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

Subjects who experience a hypersensitivity reaction or severe or serious injection-related reaction (eg, shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs) should discontinue investigational product until the adjudication committee assesses the case and finalizes recommendation of permanent discontinuation or rechallenge with investigational product.

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

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

7.2.3.12 Evaluation of Increased Gastrointestinal Symptoms

When a subject experiences an increase in GI symptoms, which could be an exacerbation of disease, an infectious etiology must be evaluated including testing for *C. difficile* as described in Appendix 5.

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

7.2.4 Others

7.2.4.1 [redacted]

[redacted]

7.2.4.2 [redacted]

[redacted]

[redacted]

7.2.4.3 Health-related Quality-of-life Assessments

Each subject will complete the HRQL assessments at the site during the visits specified in Table 1, using an electronic device. All health outcome and patient-reported questionnaires should be completed before any other assessments. The study site staff should check for completion of all PRO questionnaires.

It is important to note that PRO assessments are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and PRO data collected from subjects. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded by the investigator.

Inflammatory Bowel Disease Questionnaire

The IBDQ is a psychometrically validated PRO instrument for measuring the disease-specific HRQL in subjects with IBD, including CD. The IBDQ consists of 32 items, which are grouped into 4 domains: bowel function, systemic symptoms, emotional status, and social function (Irvine et al., 1994). The 4 domains are scored as follows:

- Bowel symptoms: 10 to 70
- Systemic symptoms: 5 to 35
- Emotional function: 12 to 84
- Social function: 5 to 35.

The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better HRQL. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement.

The IBDQ is presented in Appendix 2.

[redacted]

The [redacted] is presented in Appendix 2.

[redacted]

The [redacted] and [redacted] are presented in Appendix 2.

[redacted]

Short Form-36 Health Survey (Version 2, Acute Form)

The SF-36 is a generic quality-of-life instrument that has been widely used to assess HRQL of subjects. Generic instruments are used in general populations to assess a wide range of domains applicable to a variety of health states, conditions, and diseases. The SF-36 consists of 36 items that are aggregated into 8 multi-item scales (physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional, and mental health), with scores ranging from 0 to 100 (Ware and Sherbourne, 1992). Higher scores indicate better HRQL.

The SF-36 is presented in Appendix 2.

[redacted]

7.2.4.4 Healthcare Resource Utilization Assessments

Hospitalizations, inpatient days, and [redacted] will be recorded at the time points specified in Table 1. Information regarding CD-related and other surgeries will be collected from subjects during the treatment period.

7.2.5 Volume of Blood to Be Drawn From Each Subject

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

Table 4 Volume of Blood to Be Drawn From Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Hematology	2	7	14
Serum chemistry	4	7	28
HBsAg	2	1	2
HBcAb	2	1	2
HCVAb	2	1	2
HBV DNA	6	1	6
HIV	2	1	2
FSH	2	1	2
Serum β-hCG[a]	2	1	2
TB test (QuantiFERON-TB Gold Plus or PPD)	4	1	4
JCV antibody banked sample	3.5	1	3.5
[redacted]			
[redacted]	2	3	6
[redacted]	5	3	15
[redacted]	4	3	12
[redacted]	5	6	30
ADA and NAb sampling	3	7	21
Total mL			**151.5**

ADA=antidrug antibody; β-hCG=beta-human chorionic gonadotropin; [redacted]; 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; JCV=John Cunningham virus; [redacted]; NAb=neutralizing antibody; PPD=purified protein derivative; TB=tuberculosis

[a] β-hCG testing for female subjects only.

[b] If a catheter is used, the first mL is to be discarded; then take 4 mL into appropriate tube for [redacted]. A total of 5 mL of blood drawn has been used in determination of sample volume.

The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 151.5 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

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

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

All AEs are collected from the time the informed consent and/or assent is signed until the end of the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured in the subject's source document. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the subject's source document.

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

8.1.1 Severity Categorization

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

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

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

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Adverse Events of Special Interest

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

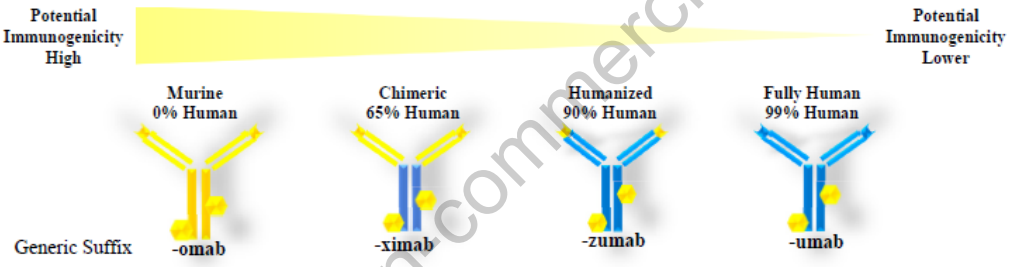
8.1.3.1 Hypersensitivity

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

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

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

Figure 4 Potential Immunogenicity of Therapeutic Monoclonal Antibodies



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

Nonetheless, the possibility of a hypersensitivity reaction occurring after drug exposure cannot be fully ruled out. The reactions of concern are Type I (anaphylaxis) and Type III (immune complex) reactions. The clinical presentation of anaphylactic reactions is described in Table 5.

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

Anaphylaxis is highly likely when the first criterion below and at least one of the following criteria a and b are fulfilled:

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b) Reduced BP[a] or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

BP=blood pressure; PEF=peak expiratory flow

[a] Low systolic BP for children is defined as less than 90 mmHg from 11 to 17 years.
Source: Adapted from Sampson et al., 2006.

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

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

8.1.4 Outcome Categorization

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

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

8.1.5 Symptoms of the Disease Under Study

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

8.1.6 Clinical Laboratory and Other Safety Evaluations

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

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

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

8.1.7 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up

reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

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

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

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

8.1.8 Abuse, Misuse, Overdose, and Medication Error

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

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

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

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

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

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

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

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

8.1.9 Unexpected Adverse Event

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

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

8.1.10 Suspected Unexpected Serious Adverse Reaction

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

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

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

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

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

8.2.2 Reporting Procedures

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

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

8.2.3 Serious Adverse Event Definition

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

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

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

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

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

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

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

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

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

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

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

Guidance for Dosing Interruption: Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the subject should continue with the treatment. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-305 or SHP647-306) will be eligible to continue in the maintenance study or LTS study.

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

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

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

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

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBV=hepatitis B virus; TBL=total bilirubin; ULN=upper limit of normal

[a] Elevated baseline ALT defined as ALT ≥1.5× ULN

[b] Confirmatory repeat liver-related blood tests should be performed within 2 to 3 days before the investigational product is interrupted.

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

Source: Adapted from Chalasani and Regev, 2016.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

9.3 Data Handling Considerations

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

9.4 Statistical Analysis Process

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

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

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

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

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

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

A planned interim analysis for the coprimary endpoints will take place 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. Recruitment will not pause for this interim analysis. The purpose of the unblinded interim analysis is to reassess the appropriateness of the premises used for the coprimary endpoints when the study was designed. There is no possibility to stop early for overwhelming efficacy as the studies must continue in order to enroll an appropriate number of subjects in the SHP647-307 study. The reassessment of sample size will be performed using conditional power methods. Results at the interim analysis may be futile for one or both of the ontamalimab doses and lead to the discontinuation of that dose for CD or the ontamalimab CD program. Full details of the interim analysis, the guidelines for increasing the sample size, and futility rules to stop a dose will be included in a prespecified interim analysis SAP. The interim analysis SAP will be finalized before the interim analysis is conducted.

The planned interim analysis will be conducted by an external independent statistical group and given to the independent Interim Analysis Review Committee; the individuals involved in the day-to-day conduct of the study will not be involved in the interim analysis nor have access to the results of the interim analysis. The sponsor will only be notified by the Interim Analysis Review Committee of recommendations to modify the ontamalimab CD program according to the guidelines specified in the interim analysis SAP.

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

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

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

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

9.6 Sample Size Calculation and Power Considerations

Graphical methods are used to control the global family-wise Type I error rate (FWER) 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 7 provides the power for detecting a treatment difference between a ontamalimab treatment group and the placebo group for the key secondary endpoints.

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

Key Secondary Endpoint at Week 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

9.7 Study Population

The screened set will consist of all subjects who have signed an informed consent document.

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

The safety set will consist of all subjects who have received at least 1 dose of investigational product.

The full analysis set (FAS) will consist of all subjects in the randomized set who have received at least 1 dose of investigational product.

The per-protocol (PP) set will consist of all subjects in the FAS who do not have predefined protocol deviations that may affect the coprimary efficacy endpoints.

The completer set will consist of all subjects in the FAS who have completed the Week 16 assessment for this study.

The PK set will consist of all subjects who have received at least 1 dose of investigational product and who have at least 1 evaluable postdose PK concentration value.

The PD set will consist of all subjects who have received at least 1 dose of investigational product and who have at least 1 evaluable postdose PD value.

9.8 Efficacy Analyses

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

9.8.1 Coprimary Efficacy Endpoints

The coprimary efficacy endpoints are:

- Clinical remission at the Week 16 visit as defined by the following: 2-item PRO subscores of average worst daily abdominal pain ≤3 (based on 11-point NRS) over the 7 most recent days and average daily stool frequency ≤2 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days. The 7 most recent days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the endpoint will be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the endpoint will be treated as missing.
- Endoscopic response at Week 16 as measured by a decrease in SES-CD of at least 25% from baseline.

The coprimary efficacy endpoints, clinical remission at the Week 16 visit and endoscopic response at the Week 16 visit, will each be compared for each active treatment group (25 mg or 75 mg ontamalimab) to the placebo group using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use, and SES-CD at baseline for each of the stages of the study (stage 1 includes subjects whose primary efficacy data are used in the interim analysis and stage 2 includes all other subjects. Note: classification of stage 1 and stage 2 is based on the time of randomization rather than the time of study completion or termination). Subjects with missing data at the Week 16 visit will be considered failures and counted as nonresponders.

Weighted inverse normal p-value combination methods are used to combine the p-values from stage 1 and stage 2 through the following formula:

$$C(p_1, p_2) = 1 - \Phi[w_1 \Phi^{-1}(1-p_1) + w_2 \Phi^{-1}(1-p_2)]$$

Where p_1, p_2 are the p-values computed from the CMH chi-square test for each stage, $w_i^2 = n_i/(n_1 + n_2)$, n_1 and n_2 are the preplanned stage-wise sample sizes that are fixed at the time of the interim analysis based on an original total sample size, and Φ denotes the cumulative distribution function of the standard normal distribution (Bretz et al., 2009a). Given that there is no possibility of stopping early for efficacy, that any potential stopping for futility of either or both doses of ontamalimab is nonbinding, and that weights are prespecified, the test statistic $C(p_1, p_2)$ can be compared against the nominal alpha level to assess statistical significance (Chang and Chow, 2008).

The coprimary endpoints will each be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata. The common treatment difference is a weighted average of the stratum-specific treatment differences.

The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% CI using the method of Yan and Su (2010) and the p-value computed from the p-value combination method will be presented for each active treatment group to placebo comparison for each endpoint.

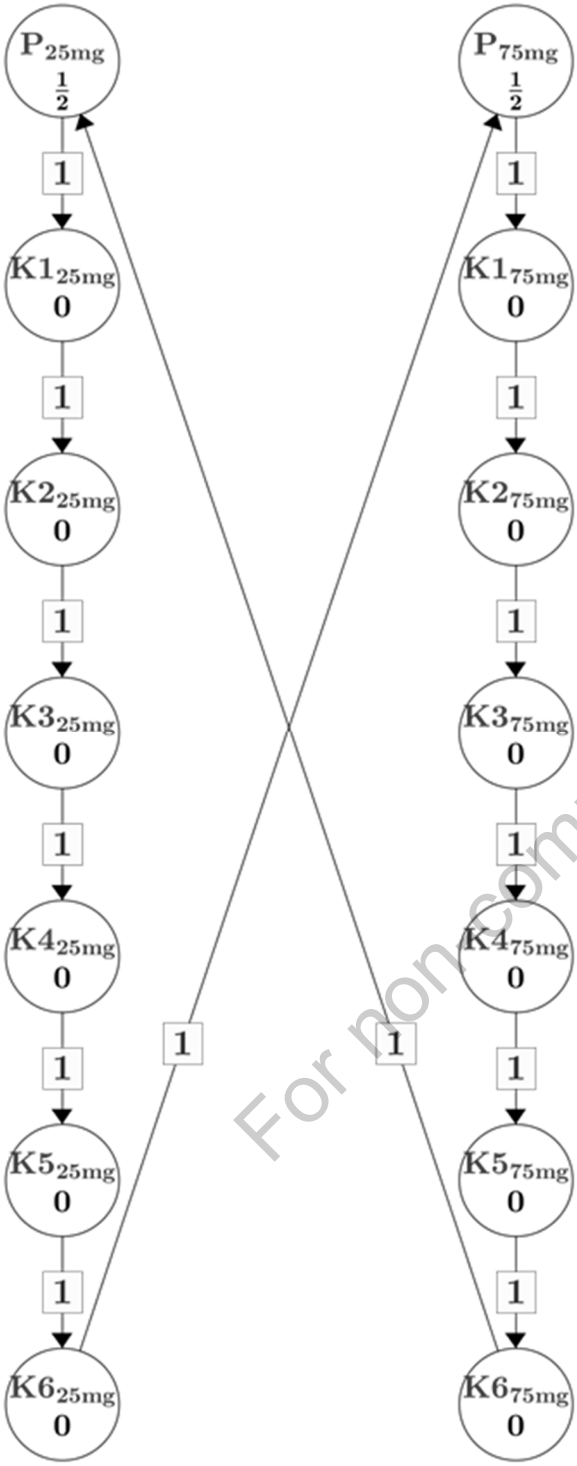
Sensitivity/supplementary analyses to explore the impact of missing data on the coprimary efficacy endpoints and key secondary endpoints will be conducted. These analyses may compare imputations of the missing values which favor placebo (eg, worst case) and/or imputations which favor active treatment (eg, best case). In addition, imputation methods based on informative missingness and other missing data mechanisms may be performed. Additional sensitivity/supplementary analyses will also be conducted using the PP set and the completer set. Additional analyses may be developed in the SAP. All sensitivity/supplementary analyses will be described in the SAP.

Prespecified subgroup analyses are planned for the coprimary endpoints including, but not limited to gender, prior anti-TNF treatment, glucocorticoid use at baseline, SES-CD at baseline, region, age group, randomization stratum, and other important subgroups. A full list of important subgroups will be described in the SAP. Within subgroups, efficacy endpoints will be compared for each active treatment group (25 mg ontamalimab and 75 mg ontamalimab) with the placebo group using a chi-square test. The estimate of the treatment difference, along with the corresponding Newcombe (hybrid-score) 95% CI and chi-square test p-value, will be presented.

Statistical Testing and Protection of the Type I Error

The global FWER for the statistical tests of the coprimary and key secondary endpoints will be strongly controlled at .05 (2-sided). To control the FWER, graphical methods discussed in Bretz et al. (2009b) will be utilized to propagate α from the coprimary endpoints to the key secondary endpoints and between the 2 ontamalimab treatment group and placebo comparisons. Alpha is initially split equally at the .025 level (2-sided) for each of the pairwise treatment comparisons for the coprimary endpoints (P) and alpha is propagated in a hierarchical manner to each of the 6 key secondary endpoints (K1–K6) within a pairwise treatment comparison. In order to pass alpha between the coprimary endpoints and the first key secondary endpoint, both coprimary endpoints must attain statistical significance. A graphical visualization of the α propagation is presented in Figure 5.

Figure 5 Visualization of Multiple Testing Strategy



K=key secondary endpoint; P=coprimary endpoints

Only p-values that are significant according to this graphical approach are inferential and statistically significant. All other p-values are descriptive.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- Clinical remission at the Week 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 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.

Similar to the coprimary endpoints, the 6 key secondary endpoints will all be tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

The key secondary endpoints will be analyzed using the same approach as described for the coprimary endpoints. Subjects with missing key secondary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.

9.8.2.2 Other Secondary Efficacy Endpoints

The 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 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.

Other secondary endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, other secondary efficacy endpoints will be analyzed with the following analysis methods:

- Binary endpoints will be compared between each active treatment group and the placebo group using a CMH chi-square test stratified by status of prior anti-TNF treatment, glucocorticoid use at baseline, and SES-CD at baseline. The estimate of the common treatment difference along with the corresponding stratified Newcombe 95% CI using the method of Yan and Su (2010) and the p-value computed from CHM test will be provided. Subjects with missing binary endpoint data at the Week 16 visit will be considered failures and counted as nonresponders.
- Continuous endpoints that are only measured at baseline and the Week 16 visit will be analyzed using an analysis of covariance model with fixed effects for treatment group (categorical), status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (categorical), and the baseline value as a continuous covariate. From this model, estimates of the least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences will be provided.
- Continuous endpoints that are measured repeatedly over time will be analyzed using a linear repeated measures mixed model with restricted maximum likelihood estimation. The model will include fixed effects for treatment group (categorical), visit (categorical), treatment group by visit interaction, status of prior anti-TNF treatment (categorical), glucocorticoid use at baseline (categorical), and SES-CD at baseline (categorical); baseline value as a continuous covariate; and repeated measures across visit for subject. From this model, estimates of least squares means, treatment differences, standard errors, p-values, and 95% CIs for least squares mean treatment differences for each visit will be provided.

9.8.3 Exploratory Efficacy Endpoints

The exploratory endpoints are as follows:

[redacted]

Exploratory efficacy endpoints will be summarized with descriptive statistics and presented by treatment group using the same approach described as for the other secondary endpoints. See Section 9.8.2.2 for an overview of the planned analyses. Full details for the analysis of exploratory efficacy endpoints will be included in the SAP.

9.9 Safety Analyses

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

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

Treatment-emergent AEs are defined as AEs with start dates at the time of or following the first exposure to investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by SOC, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events leading to withdrawal, SAEs, and deaths will be similarly summarized or listed. Adverse events of special interest will be summarized by treatment group.

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

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

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

9.10 Other Analyses

9.10.1 [redacted]

[redacted]

9.10.2 [redacted]

[redacted]

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

[redacted]

[redacted]

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

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

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

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

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

10.1.2 Indemnity/Liability and Insurance

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

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

10.1.3 Public Posting of Study Information

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

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

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

10.1.5 Study Suspension, Termination, and Completion

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

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

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

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

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

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

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

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

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

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

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

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

10.2.3.3 Audit/Inspection

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

10.2.3.4 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

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

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

10.3.2 Institutional Review Board or Ethics Committee

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

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

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

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

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

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

10.4 Privacy and Confidentiality

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

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

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

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

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

10.5 Study Results/Publication Policy

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

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

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

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

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

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

11. REFERENCES

[redacted]

Atreya, R. and Neurath, M. F. 2017. Current and Future Targets for Mucosal Healing in Inflammatory Bowel Disease. *Visceral Medicine,* 33, 82-88.

Azulfidine® 2016. US Prescribing Information.

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

Bretz, F., Koenig, F., Brannath, W., Glimm, E. and Posch, M. 2009a. Adaptive designs for confirmatory clinical trials. *Statistics in Medicine,* 28, 1181-1217.

Bretz, F., Maurer, W., Brannath, W. and Posch, M. 2009b. A graphical approach to sequentially rejective multiple test procedures. *Stat Med,* 28, 586-604.

Briskin, M., Winsor-Hines, D., Shyjan, A., Cochran, N., Bloom, S., Wilson, J., McEvoy, L. M., Butcher, E. C., Kassam, N., Mackay, C. R., Newman, W. and Ringler, D. J. 1997. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol,* 151, 97-110.

[redacted]

Chalasani, N. and Regev, A. 2016. Drug-Induced Liver Injury in Patients With Preexisting Chronic Liver Disease in Drug Development: How to Identify and Manage? *Gastroenterology,* 151, 1046-1051.

Chang, M. and Chow, S. C. 2008. Adaptive design methods in clinical trials - a review. *Orphanet journal of rare diseases,* 3, 11.

D'Haens, Gorelick, Wang, Cataldi and Sandborn 2018. Su2010 - The Anti-Madcam Antibody Shp647 in Crohn's Disease: Endoscopic Effects of Induction Therapy. *Gastroenterology,* 154, S-665.

D'Haens, G., Noman, M., Baert, F. and et al. 2002. Endoscopic healing after infliximab treatment for Crohn's disease provides a longer time to relapse [abstract]. *Gastroenterology,* 122, Abstract 104936.

D'Haens, G. R., Geboes, K., Peeters, M., Baert, F., Penninckx, F. and Rutgeerts, P. 1998. Early Lesions of Recurrent Crohn's Disease Caused by Infusion of Intestinal Contents in Excluded Ileum. *Gastroenterol,* 114, 262-7.

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. and 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.

Ferrante, M., Colombel, J., Sandborn, W., Reinisch, W., Mantzaris, G., Kornbluth, A., Rachmilewitz, D., Lichtiger, S., D'Haens, G., Van der Woude, C., Danese, S., Diamond, R., Oortwijn, A., Tang, K., Miller, M., Cornillie, F. and Rutgeerts, P. 2013. Validation of Endoscopic Activity Scores in Patients With Crohn's Disease Based on a Post Hoc Analysis of Data From SONIC. *Gastroenterology,* 145, 978-0131.

Humira® 2017. US Prescribing Information.

Imuran® 2014. US Prescribing Information.

Irvine, E., Feagan, B. G., Rochon, J., Archambault, A., Fedorak, R. N. and Groll, A. 1994. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of IBD. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology,* 106, 287-296.

Isabwe, G. A. C., Garcia Neuer, M., de Las Vecillas Sanchez, L., Lynch, D. M., Marquis, K. and Castells, M. 2018. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. *J Allergy Clin Immunol,* 142, 159-170 e2.

Khanna, R., Zou, G., D'Haens, G., Feagan, B. G., Sandborn, W. J., Vandervoort, M. K., Rolleri, R. L., Bortey, E., Paterson, C., Forbes, W. P. and Levesque, B. G. 2015. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. *Alimentary Pharmacology & Therapeutics,* 41, 77-86.

Khanna, S., Shin, A. and Kelly, C. 2017. Management of Clostridium difficile Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol,* 15, 166-74.

[redacted]

Lacy, C., Armstrong, L., Goldman, M. and Lance, L. 2001-2002. *Drug Information Handbook,* Cleveland, OH, LexiComp, Inc.

Lialda® 2018. US Prescribing Information.

Liaskou, E., Karikoski, M., Reynolds, G. M., Lalor, P. F., Weston, C. J., Pullen, N., Salmi, M., Jalkanen, S. and Adams, D. H. 2011. Regulation of mucosal addressin cell adhesion molecule 1 expression in human and mice by vascular adhesion protein 1 amine oxidase activity. *Hepatology,* 53, 661-72.

Lichtenstein, G. R., Loftus, E., Isaacs, K., Regueiro, M., Gerson, L. and Sands, B. 2018. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol,* 113, 481-517.

McDonald, L. C., Gerding, D. N., Johnson, S., Bakken, J. S., Carroll, K. C., Coffin, S. E., Dubberke, E. R., Garey, K. W., Gould, C. V., Kelly, C., Loo, V., Shaklee Sammons, J., Sandora, T. J. and Wilcox, M. H. 2018. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clinical Infectious Diseases,* 66, e1-e48.

Medrol® 2018. US Prescribing Information.

Methotrexate® 2018. US Prescribing Information.

Molodecky, N. A., Soon, I. S., Rabi, D. M., Ghali, W. A., Ferris, M., Chernoff, G., Benchimol, E. I., Panaccione, R., Ghosh, S., Barkema, H. W. and Kaplan, G. G. 2012. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology,* 142, 46-54.e42; quiz e30.

Panaccione, R., Colombel, J.-F., Louis, E., Peyrin-Biroulet, L. and Sandborn, W. J. 2013. Evolving Definitions of Remission in Crohn's Disease. *Inflammatory Bowel Diseases,* 19, 1645-1653.

Peyrin-Biroulet, L., Ferrante, M., Magro, F., Campbell, S., Franchimont, D., Fidder, H., Strid, H., Ardizzone, S., Veereman-Wauters, G., Chevaux, J.-B., Allez, M. and Dane 2011. Results from the 2nd Scientific Workshop of the ECCO (I): Impact of mucosal healing on the course of inflammatory bowel disease. *Journal of Crohn's and Colitis,* 5, 477-483.

Purinethol® 2011. US Prescribing Information.

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

Sampson, H. A., Munoz-Furlong, A., Campbell, R. L., Adkinson, N. F., Jr., Bock, S. A., Branum, A., Brown, S. G., Camargo, C. A., Jr., Cydulka, R., Galli, S. J., Gidudu, J., Gruchalla, R. S., Harlor, A. D., Jr., Hepner, D. L., Lewis, L. M., Lieberman, P. L., Metcalfe, D. D., O'Connor, R., Muraro, A., Rudman, A., Schmitt, C., Scherrer, D., Simons, F. E., Thomas, S., Wood, J. P. and Decker, W. W. 2006. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *The Journal of allergy and clinical immunology,* 117, 391-7.

Sandborn, Feagan, Panes, D'Haens, Colombel, Zhou, Huang, Enejosa, Pangan and 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.

Sandborn, W. J., Feagan, B. G., Rutgeerts, P., Hanauer, S., Colombel, J. F., Sands, B. E., Lukas, M., Fedorak, R. N., Lee, S., Bressler, B., Fox, I., Rosario, M., Sankoh, S., Xu, J., Stephens, K., Milch, C. and Parikh, A. 2013. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med,* 369, 711-21.

Schnitzler, F., Fidder, H., Ferrante, M., Noman, M., Arijs, I., Van Assche, G., Hoffman, I., Van Steen, K., Vermeire, S. v. and Rutgeerts, P. 2009. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease Supported by an unrestricted scientific grant from Centocor. Fabian Schnitzler received a research grant by ECCO (European Crohn's and Colitis Organisation). *Inflammatory Bowel Diseases,* 15, 1295-1301.

Shane, A. L., Mody, R. K., Crump, J. A., Tarr, P. I., Steiner, T. S., Kotloff, K., Langley, J. M., Wanke, C., Warren, C. A., Cheng, A. C., Cantey, J. and Pickering, L. K. 2017. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. *Clinical Infectious Diseases,* 65, 1963-1973.

Shyjan, A. M., Bertagnolli, M., Kenney, C. J. and Briskin, M. J. 1996. Human mucosal addressin cell adhesion molecule-1 (MAdCAM-1) demonstrates structural and functional similarities to the alpha 4 beta 7-integrin binding domains of murine MAdCAM-1, but extreme divergence of mucin-like sequences. *J Immunol,* 156, 2851-7.

Siegel, C. A., Whitman, C. B., Spiegel, B. M. R., Feagan, B., Sands, B., Loftus, E. V., Panaccione, R., D'Haens, G., Bernstein, C. N., Gearry, R., Ng, S. C., Mantzaris, G. J., Sartor, B., Silverberg, M. S., Riddell, R., Koutroubakis, I. E., O'Morain, C., Lakatos, P.

L., McGovern, D. P. B., Halfvarson, J., Reinisch, W., Rogler, G., Kruis, W., Tysk, C., Schreiber, S., Danese, S., Sandborn, W., Griffiths, A., Moum, B. and Gasche, C. 2016. Development of an index to define overall disease severity in IBD. *Gut*, gutjnl-2016-312648.

Spiegel, B., Bolus, R., Harris, L. A., Lucak, S., Naliboff, B., Esrailian, E., Chey, W. D., Lembo, A., Karsan, H., Tillisch, K., Talley, J., Mayer, E. and Chang, L. 2009. Measuring irritable bowel syndrome patient-reported outcomes with an abdominal pain numeric rating scale. *Aliment Pharmacol Ther,* 30, 1159-70.

Steffen, B. J., Breier, G., Butcher, E. C., Schulz, M. and Engelhardt, B. 1996. ICAM-1, VCAM-1, and MAdCAM-1 are expressed on choroid plexus epithelium but not endothelium and mediate binding of lymphocytes in vitro. *Am J Pathol,* 148, 1819-38.

Ueno, F., Matsui, T., Matsumoto, T., Matsuoka, K., Watanabe, M. and Hibi, T. 2013. Evidence-based clinical practice guidelines for Crohn's disease, integrated with formal consensus of experts in Japan. *Journal of Gastroenterology,* 48, 31-72.

Vuitton, L., Marteau, P., Sandborn, W. J., Levesque, B. G., Feagan, B., Vermeire, S., Danese, S., D'Haens, G., Lowenberg, M., Khanna, R., Fiorino, G., Travis, S., Mary, J. Y. and Peyrin-Biroulet, L. 2016. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut,* 65, 1447-1455.

Ware, J. E., Jr. and Sherbourne, C. D. 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care,* 30, 473-83.

Warrington, R., Silviu-Dan, F. and Wong, T. 2018. Drug allergy. *Allergy, Asthma & Clinical Immunology,* 14, 1-11.

Williet, N., Sandborn, W. and Peyrin–Biroulet, L. 2014. Patient-Reported Outcomes as Primary End Points in Clinical Trials of Inflammatory Bowel Disease. *Clinical Gastroenterology and Hepatology,* 12, 1246-1256.e6.

Yan, X. and Su, X. 2010. Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions. *Stat Biopharm Res,* 2, 329-35.

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Protocol Amendment 2	22 Nov 2019	Global
Protocol Amendment 1	21 Aug 2018	Global
Original Protocol	15 Dec 2017	Global

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number 1	**Amendment Date 21 Aug 2018**	**Global/Country/Site Specific Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Emergency contact information	Updated global fax number for Shire Global Drug Safety	To provide updated emergency contact information
Study Synopsis, Inclusion and exclusion criteria Section 4.1, Inclusion Criteria	Updated inclusion criterion #4c to indicate that subjects must have abdominal pain subscores ≥2 on the 4-point severity scale (used in the CDAI), in addition to abdominal pain subscores ≥5 on the 11-point numerical rating scale.	To collect additional data for abdominal pain at study entry using the 0-3 CDAI severity scale.
Study Synopsis, Inclusion and exclusion criteria Section 4.1, Inclusion Criteria Section 5.1, Prior Treatment	Updated inclusion criterion #7 to add hyperlink to Section 5.1 in which "inadequate response to, lost response to, or intolerance to at least 1 conventional treatment" (eg, sulfasalazine, mesalamine, glucocorticoids, immunosuppressants, or anti-TNF) is defined.	To cross-reference section where prior treatments are defined.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #1 to indicate that subjects with nonsteroidal anti-inflammatory drug-induced colitis will be excluded.	To further define the exclusion of subjects with colitis.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #24 to clarify that subjects with a history of *Mycobacterium tuberculosis* (TB) infection who have not completed a generally accepted full course of treatment before baseline will also be excluded.	To further define the exclusion of subjects with any history of positive TB.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #30 to indicate that subjects with cirrhosis with or without decompensation will be excluded.	To further define the exclusion of subjects with compromised liver function.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Moved exclusion of subjects with primary sclerosing cholangitis from exclusion criterion #30 to new criterion #31.	To further define the exclusion of subjects with compromised liver function.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #32 to indicate that subjects with negative HBsAg but positive HBcAb may be eligible if no presence of HBV DNA is confirmed.	To clarify that subjects with positive HBcAb, without HBV DBA, may be eligible for the study.

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1**	**Amendment Date** **21 Aug 2018**	**Global/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #33 to indicate that subjects with chronic hepatitis C without evidence of HCV RNA within 12 weeks of baseline may be considered eligible.	To clarify that subjects with chronic hepatitis C, without HCV RNA, may be eligible for the study (in case of spontaneous viral clearance or previously treated and cured).
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #34 to indicate that subjects meeting the following lab criteria would be excluded: • ALT or AST ≥3×ULN • Total bilirubin ≥1.5×ULN or >2×ULN if the subject has a known documented history of Gilbert's syndrome Added note to exclusion criterion #34 to specify that, if platelet count is <150,000 cells/mm^3, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.	To align criteria with FDA guidelines.
Study Synopsis, Inclusion and exclusion criteria Table 1, Schedule of Assessments, footnote 'n' Section 4.2, Exclusion Criteria	Added new exclusion criterion #35 to clarify that documentation of HIV status should be performed within 6 months of screening.	To clarify the timing of acceptable documentation of HIV status.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #36 to include exclusion of subjects with abuse of medicinal marijuana. Deleted former exclusion criterion #36 related to medicinal marijuana dependency.	To indicate that subjects with medicinal marijuana abuse would be excluded.
Study Synopsis, Inclusion and exclusion criteria Section 4.2, Exclusion Criteria	Updated exclusion criterion #39 to indicate the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm and female subjects who are planning to harvest or donate eggs, for the duration of the study and for 16 weeks after last dose of investigational product.	To specify the exclusion of subjects who do not agree to postpone donation of any organ or tissue, including sperm banking or donation for male subjects and egg donation or harvest for female subjects, are excluded.
Section 1.3, Benefit/Risk Assessment	Added new section describing risk and benefits of SHP647 treatment.	To provide updated risk and benefit information for SHP647.
Section 3.1.1, Rationale for Coprimary Endpoints	Added text describing results from recent trial with upadacitinib and from Phase 2 OPERA study with SHP647 as supporting rationale for the coprimary endpoint of endoscopic response.	To provide additional supporting rationale for the coprimary endpoint of endoscopic response.

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number 1	**Amendment Date 21 Aug 2018**	**Global/Country/Site Specific Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Table 1, Schedule of Assessments, footnote 'l' Section 7.2.3.6, Clinical Laboratory Evaluations Appendix 5	Updated SOA footnote 'l' and added Appendix 5 to clarify that diagnosis of *C. difficile* infection should be made using the central laboratory. Added diagnostic algorithms and relevant information related to *C. difficile* testing and diagnosis.	To provide appropriate guidance regarding laboratory testing for *C. difficile* infection.
Table 1, Schedule of Assessments, footnote 'n'	Added new row to SOA and footnote 'n' to indicate HIV tests may be performed at local laboratories (per local requirements), or centrally, if documentation of a negative HIV test within 6 months of screening is unavailable.	To clarify the timing of acceptable documentation of HIV status.
Section 4.5.1, Subject Withdrawal Criteria	Added pregnancy to the list of reasons a subject may be withdrawn from study treatment.	For clarity and consistency with language in Section 8.1.6.
Section 5.2.1, Permitted Treatment	Added language to specify that any antidiarrheal opiate drugs must be taken at stable doses for the duration of the study unless dose reduction or discontinuation is required due to clinical improvement or adverse event, and that escalation of the dose after dose reduction, or re-initiation after drug discontinuation, is not allowed.	To clarify that concomitant antidiarrheal opiate drugs are permitted if taken at stable doses for the duration of the study, with dose reduction or discontinuation allowed only if required due to clinical improvement or adverse event.
Section 7.2, Study Procedures	Added language to specify that the duration of blood and tissue sample storage is dependent on local regulations.	To clarify that local regulations should be considered for duration of blood and tissue sample storage.
Section 7.2.3.6, Clinical Laboratory Evaluations	Added HIV and HBV DNA samples to virology table.	To reflect new eligibility criteria regarding HIV testing and HBV DNA reflex testing.
Section 7.2.5, Volume of Blood to be Drawn from Each Subject	Added 2 new rows to Table 4 for collection of HBV DNA and HIV samples. Increased TB test sample volume by 1 mL.	To reflect changes in eligibility criteria regarding HIV testing and HBV DNA reflex testing and to correct the sample volume needed for the TB test.

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number 1	**Amendment Date 21 Aug 2018**	**Global/Country/Site Specific Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 8.2.8, Safety Monitoring Table 5	Added new section and table describing safety monitoring and stopping criteria for elevated hepatic blood tests.	To provide appropriate guidance on subjects who have been enrolled with elevated liver function test or who have elevated liver function test(s) during the study.
Section 10, Sponsor's and Investigator's Responsibilities	Added a statement that compliance with the noted regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.	To clarify that the study is conducted in accordance with the ethical principles in the Declaration of Helsinki.
Appendix 4, Determination of Failure or Intolerance to Prior Treatment for Crohn's Disease	Added new appendix section, "Determination of Inadequate Response/Loss of Response or Intolerance to Prior Treatment for Crohn's Disease" to provide guidance as related to inclusion criterion #7 in which subjects meeting these criteria on prior conventional treatments (eg, sulfasalazine, mesalamine, glucocorticoids, immunosuppressants, or anti-TNF) may be eligible for this study.	To provide additional granularity regarding the eligibility of subjects who demonstrated inadequate response, loss of response, or intolerance on conventional treatment.
Appendix 5, Guidance for Diagnosis and Treatment of Increased Gastrointestinal Symptoms	Added new Appendix 5, "Guidance for Diagnosis and Treatment of Increased Gastrointestinal Symptoms related to diagnosis and treatment of *C. difficile* infection.	To provide updated treatment guidance for subjects diagnosed with *C. difficile* infection.
Throughout protocol	Minor changes to wording.	To improve clarity, consistency, and remove redundancy of text.

APPENDIX 2 SCALES AND ASSESSMENTS

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

- Simple Endoscopic Score for Crohn's Disease
- Crohn's Disease Activity Index
- Colonic Global Histologic Disease Score and Ileal Global Histologic Disease Score
- Patient-reported Outcome – Crohn's Disease Daily E-diary
- Inflammatory Bowel Disease Questionnaire
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Short Form-36 Health Survey
- [redacted]

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

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

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

Definitions of Simple Endoscopic Score for Crohn's Disease

Score / Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (∅ 0.1 to 0.5 cm)	Large ulcers (∅ 0.5 to 2 cm)	Very large ulcers (∅ >2 cm)
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected segment	<50%	50–75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

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

Crohn's Disease Activity Index (CDAI)

Crohn's Disease Activity Index (CDAI)

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

CDAI=Crohn's Disease Activity Index; ePRO=electronic patient-reported outcome; Hct=hematocrit
Note: Variable 5: This variable covers taking medication for symptomatic relief from diarrhea, eg, bulking agents, opiates etc.
Variable 7: Absolute deviation of hematocrit is the difference in hematocrit from standard. A male subject with a hematocrit of 40% has an absolute deviation of 7. Each percentage deviation has a value of 6 points. If hematocrit subtotal is <0, enter 0.
Variable 8: This variable is based on Metropolitan Life Tables (these are programmed into the ePRO device).
Percent deviation from standard weight is (1 - weight/standard weight) × 100; therefore, positive percent deviation represents weight loss, which adds points to the CDAI. Percentage deviation from standard weight = 1 point for each percent deviation. If body weight subtotal is less than -10, enter -10.

CDAI Interpretation:

- 0-149 points: Asymptomatic remission (Note: subjects requiring steroids to remain asymptomatic are not considered to be in remission but are 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.

Reference: D'Haens et al., 1998.

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

1. Please rate your worst abdominal pain over the past 24 hours.

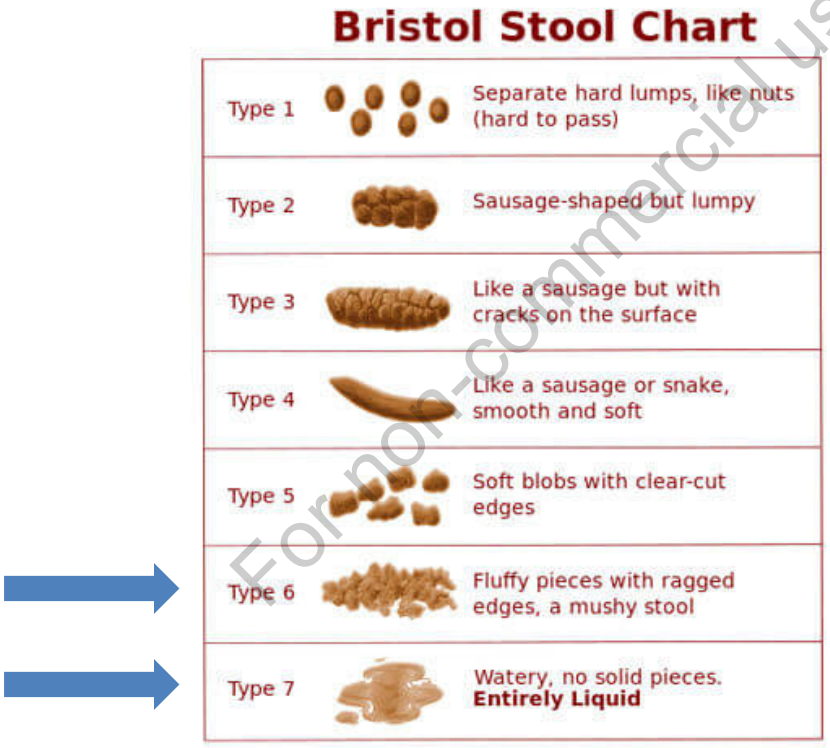
   0 1 2 3 4 5 6 7 8 9 10

   No pain Worst imaginable pain

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

   Enter number of bowel movements passed: _____

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



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

   Enter number of liquid or very soft bowel movements: _____

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

   Enter number of bowel movements with blood: _____

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

   Enter number of bowel movements with urgency: _____

6. Please rate your worst feeling of nausea (feeling sick to your stomach or like you might throw up) over the past 24 hours.

   None

   Mild

   Moderate

   Severe

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

   Enter number of vomiting episodes: _____

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

   Enter number of bowel incontinence episodes: _____

9. Please rate your abdominal pain over the past 24 hours.

   None

   Mild

   Moderate

   Severe

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

    Generally well

    Slightly below par

    Poor

    Very poor

    Terrible

Inflammatory Bowel Disease Questionnaire (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks.

You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from:

    1. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
    2. EXTREMELY FREQUENT
    3. VERY FREQUENT
    4. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    5. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    6. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    7. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from:

    1. NO ENERGY AT ALL
    2. VERY LITTLE ENERGY
    3. A LITTLE ENERGY
    4. SOME ENERGY
    5. A MODERATE AMOUNT OF ENERGY
    6. A LOT OF ENERGY
    7. FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:

    1. A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
    2. A LOT OF DIFFICULTY
    3. A FAIR BIT OF DIFFICULTY
    4. SOME DIFFICULTY
    5. A LITTLE DIFFICULTY
    6. HARDLY ANY DIFFICULTY
    7. NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from:

    1. A MAJOR PROBLEM
    2. A BIG PROBLEM
    3. A SIGNIFICANT PROBLEM
    4. SOME TROUBLE
    5. A LITTLE TROUBLE
    6. HARDLY ANY TROUBLE
    7. NO TROUBLE

18. Overall, in the last 2 weeks, how much a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from:

    1. A MAJOR PROBLEM
    2. A BIG PROBLEM
    3. A SIGNIFICANT PROBLEM
    4. SOME TROUBLE
    5. A LITTLE TROUBLE
    6. HARDLY ANY TROUBLE
    7. NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from:

    1. NONE OF THE TIME
    2. A LITTLE OF THE TIME
    3. SOME OF THE TIME
    4. A GOOD BIT OF THE TIME
    5. MOST OF THE TIME
    6. ALMOST ALL OF THE TIME
    7. ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from:

    1. NO SEX AS A RESULT OF BOWEL DISEASE
    2. MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
    3. MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
    4. SOME LIMITATION AS A RESULT OF BOWEL DISEASE
    5. A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
    6. HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
    7. NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from:

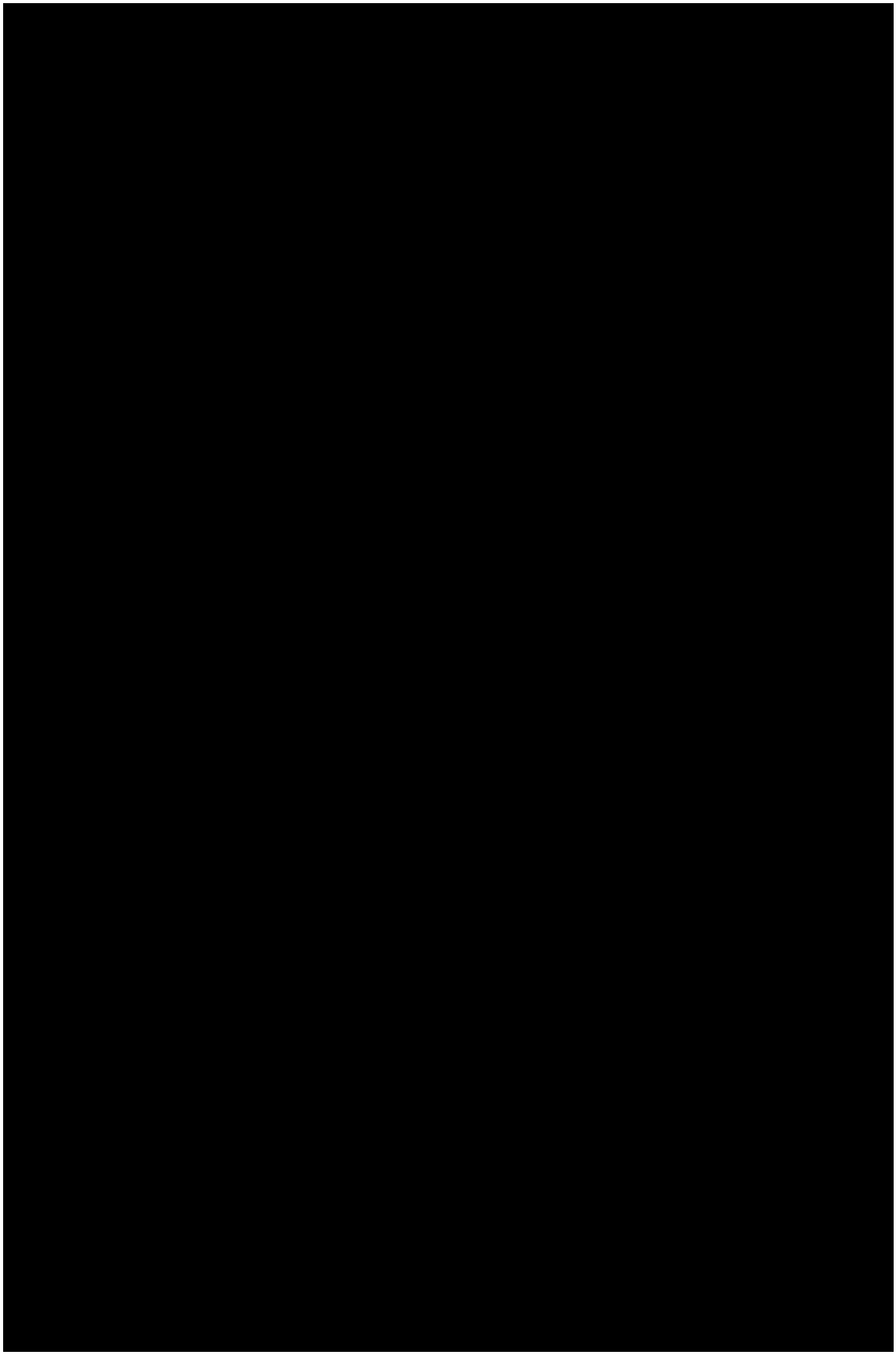
    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

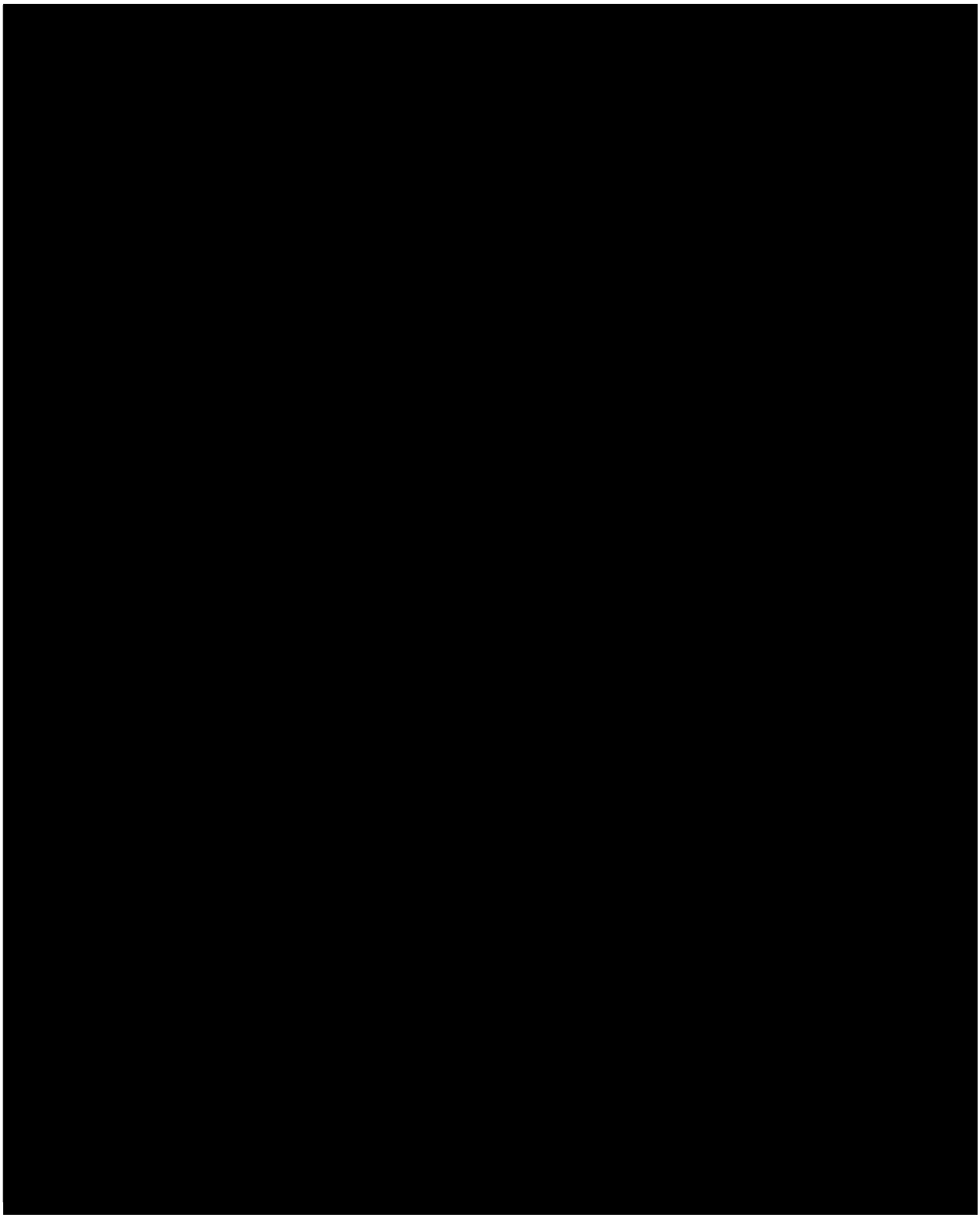
31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from:

    1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
    2. GENERALLY DISSATISFIED, UNHAPPY
    3. SOMEWHAT DISSATISFIED, UNHAPPY
    4. GENERALLY SATISFIED, PLEASED
    5. SATISFIED MOST OF THE TIME, HAPPY
    6. VERY SATISFIED MOST OF THE TIME, HAPPY
    7. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED





[redacted]

Short Form-36 Health Survey (Version 2), Acute Form

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much bodily pain have you had during the past week?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 3 GLUCOCORTICOID EQUIVALENT DOSES

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

Reference: Lacy et al., 2001-2002.

APPENDIX 4 DETERMINATION OF INADEQUATE RESPONSE/LOSS OF RESPONSE OR INTOLERANCE TO PRIOR TREATMENT FOR CROHN'S DISEASE

The information below should serve as guidance. Local therapeutic standards and investigator judgment should be considered.

AMINOSALICYLATES

Mesalamine (5-ASA)

Inadequate response or loss of response: Although the use of mesalamine in UC is well established (eg, induction treatment up to 4.8 g/day up to 8 weeks) and based upon evidence-based criteria, its use in CD is not well established. Oral mesalamine has not consistently been demonstrated to be effective compared with placebo for induction of remission and achieving mucosal healing in patients with active CD. Similarly, topical mesalamine is of limited benefit in CD (Lichtenstein et al., 2018). For the purpose of this study, inadequate response or loss of response is defined as persistent signs and symptoms of active disease despite treatment with mesalamine for at least 8 weeks at daily doses of 4.8 g/day.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to mesalamine treatment.

As guidance, the US package insert of mesalamine lists the following AEs. Please check the respective latest label of your country as well (Lialda®, 2018):

> ***Renal impairment*** *including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure.*
>
> ***Acute intolerance syndrome*** *includes cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash.*
>
> ***Hypersensitivity reactions*** *including cardiac hypersensitivity reactions (myocarditis and pericarditis)*
>
> ***Hepatic impairment:*** *hepatic failure in patients with pre-existing liver disease*
>
> ***Photosensitivity*** *in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema*
>
> ***Other*** *treatment-related AEs: headache, flatulence, abnormal liver function test, alopecia, pruritus, tachycardia, hypertension, hypotension, acne, prurigo, rash, urticaria, abdominal distention, colitis, diarrhea, pancreatitis, rectal polyp, vomiting, decreased platelet count, arthralgia, back pain, somnolence, tremor, pharyngolaryngeal pain, asthenia, face edema, fatigue, pyrexia, ear pain. Based on postmarketing experience when it is not always possible to reliably establish a causal relationship to drug exposure: lupus-like syndrome, drug fever, pericarditis, pericardial effusion, myocarditis,*

pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer, jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, Kawasaki-like syndrome including changes in liver enzymes, agranulocytosis, aplastic anemia, anaphylactic reaction, angioedema, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), myalgia, lupus-like syndrome, peripheral neuropathy, Guillain-Barre syndrome, transverse myelitis, intracranial hypertension, interstitial nephritis, nephrogenic diabetes insipidus, interstitial lung disease, hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis), psoriasis, pyoderma gangrenosum, erythema nodosum, photosensitivity, oligospermia

Sulfasalazine (SSZ)

Inadequate response or loss of response: Although the use of sulfasalazine in UC is accepted (eg, induction treatment up to 4 g/day up to 8 weeks), its use in CD is not well established.

For the purpose of this study, inadequate response or loss of response is defined as persistent signs and symptoms of active disease despite treatment with at least one 8-week induction regimen at a daily dose of 4 g/day.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to sulfasalazine treatment.

As guidance, the US package insert of sulfasalazine lists the following AEs. Please check the respective latest label of your country as well (Azulfidine®, 2016):

Hypersensitivity reactions: *erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell´s syndrome) with corneal damage, drug rash with eosinophilia and systemic symptoms (DRESS), anaphylaxis, serum sickness syndrome, interstitial lung disease, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, lupus erythematosus-like syndrome, hepatitis and hepatic necrosis with or without immune complexes, fulminant hepatitis, sometimes leading to liver transplantation, parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection, and alopecia*

Blood dyscrasias: *agranulocytosis, leukopenia, myelodysplastic syndrome, aplastic anemia, megaloblastic (macrocytic) anemia, hemolytic anemia, cyanosis, methemoglobinemia, Heinz body anemia, hypoprothrombinemia, and thrombocytopenia*

Gastrointestinal reactions: *hepatitis, hepatic failure, pancreatitis, bloody diarrhea, impaired folic acid absorption, impaired digoxin absorption, stomatitis, diarrhea, abdominal pains, and neutropenic enterocolitis*

Central nervous system reactions: *transverse myelitis, convulsions, meningitis, transient lesions of the posterior spinal column, cauda equina syndrome, Guillain-Barre syndrome, peripheral neuropathy, mental depression, vertigo, hearing loss, insomnia, ataxia, hallucinations, tinnitus, and drowsiness*

Renal reactions: *toxic nephrosis with oliguria and anuria, nephritis, nephrotic syndrome, urinary tract infections, hematuria, crystalluria, proteinuria, and hemolytic-uremic syndrome*

Other reactions: *urine discoloration and skin discoloration, Goiter production, diuresis and hypoglycemia, oligospermia. Based on postmarketing experience when it is not always possible to reliably establish a causal relationship to drug exposure: elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure, folate deficiency, nephrolithiasis, oropharyngeal pain, angioedema*

In addition, anorexia, headache, nausea, vomiting, gastric distress, pruritus, urticaria, rash, fever, sore throat, fever, pallor, purpura.

GLUCOCORTICOIDS

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or intravenously for 1 week OR 2 failed attempts to taper corticosteroids to below a dose equivalent to 10 mg prednisone (oral) daily.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to glucocorticoid treatment.

As guidance, the US package insert of Medrol® lists the following AEs. Please check the respective latest label of your country as well (Medrol®, 2018):

Fluid and electrolyte disturbances: *sodium retention, congestive heart failure, hypertension, fluid retention, potassium loss, and hypokalemic alkalosis*

Musculoskeletal: *muscle weakness, loss of muscle mass, steroid myopathy, osteoporosis, tendon rupture, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, and pathologic fracture of long bones*

Gastrointestinal: *peptic ulcer with or without perforation and hemorrhage, pancreatitis, abdominal distention, and ulcerative esophagitis*

Dermatologic: *impaired wound healing, petechiae and ecchymoses, thin fragile skin, facial erythema, and increased sweating*

Neurological: *increased intracranial pressure with papilledema (pseudo-tumor cerebri), convulsions, vertigo, and headache*

Psychic derangements*: euphoria, insomnia, mood swings, personality changes, severe depression, psychotic manifestations, aggravated existing emotional instability or psychotic tendencies*

Endocrine: *Cushingoid state, secondary adrenocortical and pituitary unresponsiveness, menstrual irregularities, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements of insulin or oral hypoglycemic agents in diabetics*

Ophthalmic: *posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, and secondary ocular infections.*

Metabolic: *negative nitrogen balance due to protein catabolism*

Other: *urticaria and other allergic, anaphylactic or hypersensitivity reactions.*

IMMUNOSUPPRESSANTS

Azathioprine (AZA)

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite a history of AZA use for at least 12 weeks at daily doses ≥1.5 mg/kg, including its use as adjunctive therapy or steroid-sparing therapy.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related AZA treatment.

As guidance, the US package insert of an AZA product lists the following AEs. Please check the respective latest label of your country as well (Imuran®, 2014):

Gastrointestinal hypersensitivity reaction *characterized by severe nausea, vomiting and potentially with diarrhea, rash, fever, malaise, myalgia, elevations in liver enzymes, and occasionally, hypotension.*

Hypersensitivity pancreatitis

Hepatotoxicity *that may be associated with anorexia, diarrhea, jaundice and ascites.*

Cytopenias: *leukopenia, thrombocytopenia, anemias including macrocytic anemia, and/or pancytopenia, bone marrow suppression, and myelotoxicity.*

Serious infections *(bacterial, viral, fungal, protozoal, and opportunistic infections, including reactivation of latent infections) secondary to treatment*

Other: *skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea, negative nitrogen balance, reversible interstitial pneumonitis, hepatosplenic T-cell lymphoma and Sweet's syndrome (acute febrile neutrophilic dermatosis).*

Mercaptopurine (6-MP)

Inadequate response or loss of response: defined as persistent signs and symptoms of active disease despite a history of 6-MP use for at least 12 weeks at daily doses ≥0.75 mg/kg, including its use as adjunctive therapy or steroid-sparing therapy.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to 6-MP treatment.

As guidance, the US package insert of a 6-MP product lists the following AEs. Please check the respective latest label of your country as well (Purinethol®, 2011):

Myelosuppression: *anemia, leukopenia, and thrombocytopenia*

Embryo-fetal toxicity

Treatment-related malignancies

Renal: *hyperuricemia and/or hyperuricosuria*

Gastrointestinal: *including hepatotoxicity: elevated transaminases, elevated bilirubin, ascites potentially intestinal ulceration, oral lesions, nausea, vomiting, anorexia, diarrhea and sprue-like symptoms, pancreatitis*

Miscellaneous: *skin rashes, hyperpigmentation, alopecia, drug fever, oligospermia*

Methotrexate (MTX)

Inadequate response or loss of response: defined as failure to respond to at least one 8-week regimen of or maintain remission at doses of at least 15 mg/week, given by the intramuscular or subcutaneous route.

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to MTX treatment.

As guidance, the US package insert of an MTX product lists the following AEs. Please check the respective latest label of your country as well (Methotrexate®, 2018):

Alimentary system: *gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.*

Blood and lymphatic system disorders: *anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia, lymphadenopathy and lymphoproliferative disorders, hypogammaglobulinemia*

Cardiovascular: *pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus)*

Central nervous system: *headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions, cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy*

Hepatobiliary: *acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity decrease in serum albumin, and liver enzyme elevations*

Infection: *opportunistic infections, eg Pneumocystis carinii pneumonia, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, H. simplex hepatitis, and disseminated H. simplex*

Musculoskeletal system: *stress fracture*

Ophthalmic: *conjunctivitis, serious visual changes of unknown etiology*

Pulmonary system: *respiratory fibrosis, respiratory failure, interstitial pneumonitis, chronic interstitial obstructive pulmonary disease*

Skin: *erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiformе, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.*

Urogenital system: *severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects*

Other: *nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis, anaphylactoid reactions*

ANTI-TNF AGENTS

Inadequate response or loss of response: Anti-TNF agents are rapid in onset of effect, with benefit often noted within 2 weeks of initiating therapy. As a result, assessment of inadequate response may be done sooner than with immunosuppressants. These include persistent signs and symptoms of active disease despite at least one 4-week induction regimen with the following minimum doses of:

- infliximab (5 mg/kg IV, 2 doses at least 2 weeks apart) or
- adalimumab (one 80 mg SC dose followed by one 40 mg dose at least 2 weeks apart) or
- certolizumab pegol (400 mg SC, 2 doses at least 2 weeks apart) or recurrence of symptoms during maintenance therapy (approved for CD in the United States).

Intolerance: defined as documented treatment discontinuation for AEs suspected to be related to anti-TNF agents.

As guidance, the US package insert of Humira lists the following AEs. Please check the respective latest labels for the other anti-TNF agents and the labels of your country as well (Humira®, 2017):

> ***Anaphylaxis or serious allergic reactions:*** *generalized rash and flushing, hypersensitivity reactions including angioneurotic edema*
>
> ***Development of neutralizing autoantibodies***
>
> ***Body as a whole:*** *pain in extremity, pelvic pain, surgery, thorax pain*
>
> ***Cardiovascular system:*** *arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, heart failure*
>
> ***Gastrointestinal:*** *cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, vomiting, nausea, abdominal pain, hepatic reactions including acute liver failure, hepatic necrosis*
>
> ***Lupus-like syndrome***
>
> ***Endocrine system:*** *parathyroid disorder*
>
> ***Hemic and lymphatic system:*** *cytopenias, pancytopenia, agranulocytosis, polycythemia*
>
> ***Infections:*** *tuberculosis (new and reactivation of latent tuberculosis) and opportunistic infections pneumonia, septic arthritis, prosthetic and postsurgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis*

Metabolic and nutritional disorders: *dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema*

Musculoskeletal system: *arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder*

Neoplasia: *adenoma*

Nervous system: *confusion, paresthesia, subdural hematoma, tremor*

Respiratory system: *upper respiratory infection, sinusitis, flu syndrome, asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion*

Special senses: *cataract*

Thrombosis: *thrombosis leg*

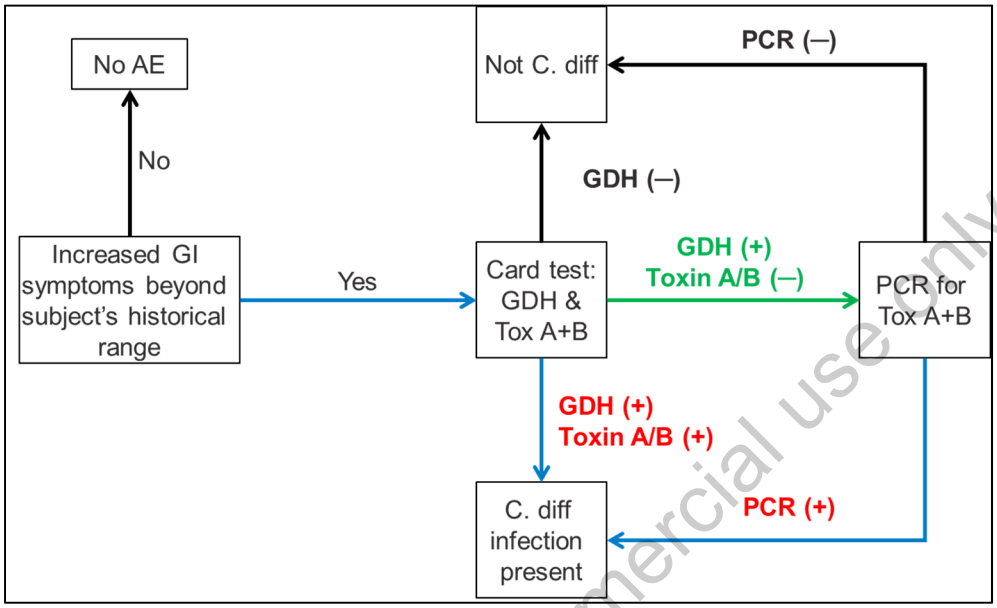
Urogenital system: *cystitis, kidney calculus, menstrual disorder*

Other: *headache, rash, injection site reaction, infusion-related reactions such as fever or chills, cardiopulmonary reactions such as chest pain, hypotension, hypertension, or dyspnea and/or pruritus or urticaria, back pain, urinary tract infection, hypertension*

APPENDIX 5 GUIDANCE FOR DIAGNOSIS AND TREATMENT OF INCREASED GASTROINTESTINAL SYMPTOMS

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

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



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

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

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

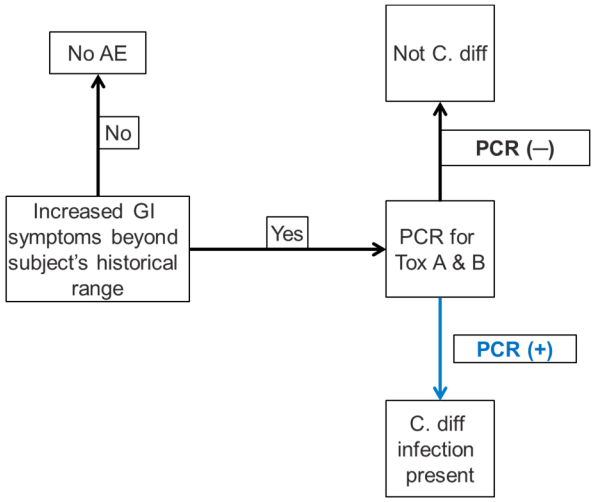


Figure A3 Alternative 2 for *C. difficile* Testing Using Local Laboratory When No Card Test is Available

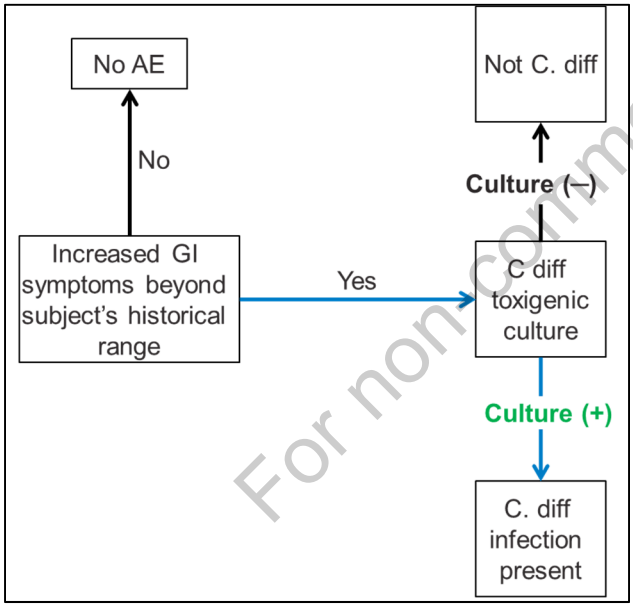
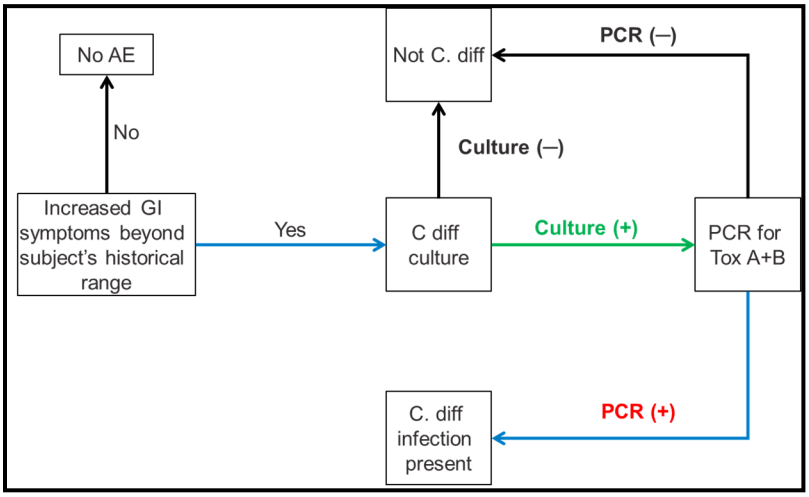


Figure A4 Alternative 3 for *C. difficile* Testing Using Local Laboratory When No Alere Quick Chek Card Test is Available



Treatment

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

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

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

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

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