Title: Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy

NCT Number: NCT02611817

SAP Approve Date: 24 June 2019

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: MLN0002SC-3031

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy

PHASE 3

Version: Amendment 01

Date: 24 June 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 06

Protocol Date: 24 August 2017

Original SAP Date: 20 July 2018

1.1 APPROVAL SIGNATURES

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AESI	adverse event of special interest
CCI	[redacted]
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
C_{trough}	trough serum concentration
ECG	Electrocardiogram
EQ-5D	Euro Quality of Life-5D
FAS	full analysis set
HLT	high level term
IBDQ	Inflammatory Bowel Disease Questionnaire
IV	intravenous(ly)
KM	Kaplan-Meier
LTFU	long-term follow-up
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
OLE	open-label extension
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PP	per-protocol
PRO	patient-reported outcome
PT	preferred term
Q2W	once every 2 weeks
Q8W	once every 8 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
CCI	[redacted]
SI	Systeme International
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
VAS	visual analog scale
WHODRUG	World Health Organization Drug Dictionary
CCI	[redacted]

4.0 OBJECTIVES

4.1 Primary Objectives

- To assess the effect of vedolizumab subcutaneous (SC) maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active Crohn's disease (CD) who achieved clinical response at Week 6 following administration of vedolizumab intravenous (IV) at Weeks 0 and 2.

4.2 Secondary Objectives

- To determine the effect of vedolizumab SC maintenance treatment on enhanced clinical response at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To determine the effect of vedolizumab SC maintenance treatment on corticosteroid-free remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects who are naïve to TNF-α antagonist exposure, and achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.

4.3 Exploratory Objectives

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4.4 Study Design

This is a pivotal, phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC in adult subjects with moderately to severely active CD who achieved a clinical response at Week 6 with open-label therapy with 300 mg vedolizumab IV at Weeks 0 and 2.

Moderately to severely active CD is defined as described in Inclusion Criteria in protocol Section 7.1. Subjects who are either tumor necrosis factor-alpha (TNF-α) antagonist naïve or with TNF-α antagonist failure will be included ensuring approximately 50% of subjects with TNF-α antagonist failure are enrolled. Subjects with previous use of TNF-α antagonist but not failed will be included ensuring that no more than 10% of such subjects are enrolled.

The study includes a 4-week (28-day) Screening Period, a 6-week open-label vedolizumab IV Induction Phase, and a 46-week randomized, double-blind, placebo-controlled Maintenance Phase with vedolizumab SC with final visit at Week 52.

Eligible subjects, will be enrolled into the Induction Phase at Week 0, will receive open-label infusions of vedolizumab IV 300 mg at Weeks 0 and 2, and will be assessed for clinical response by CDAI (defined as a ≥70 point decrease in CDAI score from Baseline [Week 0]) at Week 6:

- Subjects who achieve a clinical response at Week 6 will be randomized into the Maintenance Phase. Upon completion of the Week 52 assessment or upon early discontinuation due to treatment failure (ie, disease worsening after Week 6 or need for rescue medications after Week 14) these subjects will be eligible to enter the MLN0002SC-3030 open-label extension (OLE) study with vedolizumab SC.
- Subjects who do not achieve a clinical response at Week 6 will not be randomized in to the Maintenance Phase, and instead will receive a third infusion of vedolizumab IV 300 mg at Week 6. Subjects who achieve a clinical response at Week 14 (by CDAI) will be eligible to enroll in the OLE study. Subjects who respond but choose not to enroll in the OLE study and subjects who do not achieve clinical response at Week 14 will be discontinued.

Subjects who achieve a clinical response at Week 6 will be randomized at a 2:1 ratio to receive blinded injections of vedolizumab SC 108 mg or placebo SC once every 2 weeks (Q2W), beginning at Week 6 through Week 50.

Randomization will be stratified by:

- Concomitant use of oral corticosteroids.
- Clinical remission status at Week 6.
- Previous TNF-α antagonist failure/exposed or concomitant immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate) use.

At Week 6, subjects receiving oral corticosteroids who achieved a clinical response and are randomized into the Maintenance Phase will begin a corticosteroid tapering regimen.

Subjects who do not participate in the OLE study or are discontinued from the study before Week 6, will enter the Follow-Up Period and complete a final on-site safety assessment at 18 weeks (ie, 5 vedolizumab half-lives) from the last study drug dose.

Additionally, subjects who do not participate in the OLE study or a discontinued before Week 6 will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 6 months after the last dose of study drug.

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5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

- Proportion of subjects with clinical remission, defined as CDAI score ≤150, at Week 52.

5.2 Secondary Endpoints

- Proportion of subjects with enhanced clinical response, defined as a ≥100 point decrease in CDAI score from Baseline (Week 0), at Week 52.
- Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.
- Proportion of TNF-α antagonist naïve subjects who achieved clinical remission, defined as CDAI score ≤150, at Week 52.

5.3 Patient Reported Outcome (PRO) Endpoints

- Changes in inflammatory bowel disease questionnaire (IBDQ) total score and subscores, from Baseline (Week 0) to Week 52 and from Week 6 to Week 52.
- Changes in Euro Quality of Life-5D (EQ-5D) utility scores and EQ-5D visual analog scale (VAS) score from Baseline (Week 0) to Week 52 and from Week 6 to Week 52.

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5.4 Exploratory Endpoints

Other Efficacy Endpoints:

CCI [redacted]

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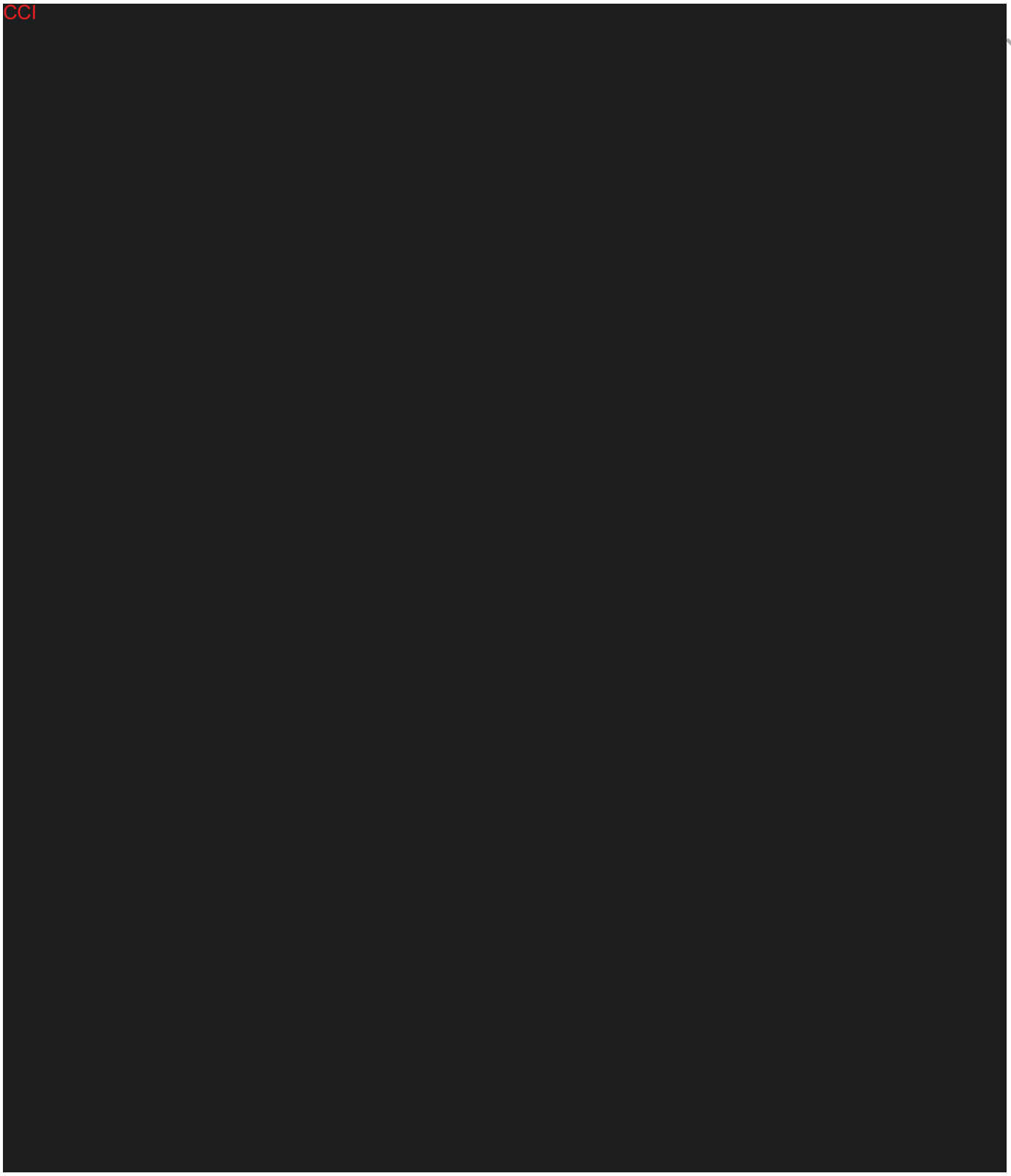

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5.5 Safety Assessments

Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs) (including serious infections including opportunistic infection such as progressive multifocal leukoencephalopathy (PML), liver injury, malignancies, infusion-related or injection site reactions or systemic reactions and hypersensitivity), serious adverse events (SAEs), vital signs, results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis), and results of 12-lead electrocardiograms (ECGs).

6.0 DETERMINATION OF SAMPLE SIZE

Assuming a clinical remission rate of 38% for vedolizumab SC and 22% for placebo at Week 52, a sample size of 258 subjects in the vedolizumab SC group and 129 subjects in the placebo group will provide 90% power at 2-sided 0.05 level of significance. To ensure a randomized sample size of 387 subjects, assuming 47% of the subjects entering induction will achieve clinical response at Week 6, approximately 824 subjects will need to be enrolled into the study.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Considerations

Statistical analysis will be performed using the SAS System, Version 9.2 or higher.

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. Continuous data will be summarized using number of subjects with non-missing values, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated.

7.1.1 Study Terms and Definitions

Term	Definition
Clinical remission by CDAI	A CDAI score ≤150.
CCI	[redacted]
Clinical response	A ≥70 point decrease in CDAI score from Baseline (Week 0).
Corticosteroid-free remission	Subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.
Disease worsening	A ≥100 point increase in CDAI score from the Week 6 value on 2 consecutive visits and a minimum CDAI score of 220 points.
Durable clinical remission	Clinical remission at Week 6 and Week 52.
Enhanced clinical response	A ≥100 point decrease in CDAI score from Baseline (Week 0).
Treatment failure	Defined as disease worsening, need for rescue medications (as defined in Section 7.3.1 of the protocol), or need for surgical intervention for treatment of Crohn's Disease.

7.1.2 Definition of Study Days and Visit Window

Study day will be calculated relative to the date of the first dose of study drug (IV infusion) in the study. The study day prior to the first dose of study drug will be calculated as:

Date of assessment/event – date of first dose of study drug.

The study day on or after the first dose of study drug will be calculated as:

Date of assessment/event – date of first dose of study drug +1.

Baseline is defined as the last non-missing measurement prior to or on the date of the first dose of study drug (Study Day 1). The visit windows for the postbaseline visits are defined in Table 7.a and Table 7.b. If a subject has more than 1 non-missing measurement in the same visit window, the measurement closest to the target day will be used. If 2 measurements in the same window are of equal distance to the target day, the measurement that occurs later will be used. If 2 or more measurements occur on the same day, the average value will be used, unless specified otherwise.

Table 7.a Visit Windows (Induction Phase for Non-responders at Week 6)

Visit	Scheduled Day	Safety Labs	Vital Signs	Urinalysis	IBDQ, EQ-5D, CCI CRP	CCI	CDAI
Baseline	Day 1	≤1	≤1	≤1	≤1	≤1	≤1
Week 2	Day 14	2-28	2-28	NA	NA	NA	2-28
Week 6	Day 42	29-70	29-70	2-70	2-70	NA	29-70
Week 14[a]	Day 98	71-133	71-133	71-133	71-133	NA	71-133[b]
Week 24[c]	Day 168	≥134	≥134	NA	NA	NA	NA

[a] Week 14 will end on Day 133 or the day prior to the first dosing of the extension study (for patients entering the extension study), whichever comes first.
[b] Week 14 for CDAI score will end on Day 133 or the day of the first dosing of the extension study (for patients entering the extension study), whichever comes first.
[c] Safety follow up visit. Only for subjects who do not enter the Extension Study MLN0002SC-3030 (including early terminators and Week 14 non-responders).

For the purpose of diary compliance calculation and derivation of diary-based endpoints, the last visit day of study will not be included since the subject is not expected to have completed the diary entries for that day by the Final Visit.

AEs that start more than 126 days after the last dose of study drug will be listed, but excluded from the summaries and analyses.

Table 7.b Visit Windows (Randomized Subjects)

Visit	Scheduled Day	Safety Labs	Vital Signs	Urinalysis	ECG	IBDQ, EQ-5D, CCI [redacted] CRP	Endoscopy, Histology	CDAI
Baseline	Day 1	≤1	≤1	≤1	≤1	≤1	≤1	≤1
Week 2	Day 14	2-28	2-28	NA	NA	NA	NA	2-28
Week 6	Day 42	29-70	29-70	2-70	NA	2-70	NA	29-70
Week 14	Day 98	71-126	71-126	NA	NA	NA	NA	71-126
Week 22	Day 154	127-182	127-182	NA	NA	NA	NA	127-182
Week 30	Day 210	183-238	183-238	NA	NA	71-238	NA	183-238
Week 38	Day 266	239-294	239-294	NA	NA	NA	NA	239-294
Week 46	Day 322	295-336	295-336	NA	NA	NA	NA	295-336
Week 50	Day 350	337-357	337-357	NA	NA	NA	NA	337-357
Week 52	Day 364	358-420	358-420	≥71	≥2	≥239	≥2	≥358
Week 68[a]	Day 476	≥ 421	≥ 421	NA	NA	NA	NA	NA

[a] Safety follow up visit. Only for subjects who do not enter the Extension Study MLN0002SC-3030.

7.1.3 Convention for Calculations of CDAI Scores

The CDAI score is a weighted sum of 8 components. Subscores should be integers. The scoring details including multiplication factors are in Appendix C.

CDAI scores will be derived at each scheduled visit utilizing the most recent available patient reported eDiary components, physician reported outcomes components and body weight (collected via SitePRO device), and Lab (hematocrit) in following steps:

1. Identify the completion date of the physician reported CDAI components, and set it as the CDAI calculation date.
2. Calculate the 3 eDiary subscores (liquid/soft stool frequency, abdominal pain and general wellbeing) as follows:
   a) Select the diary data from 10 days prior to the CDAI calculation date identified in (1).
   b) Merge in endoscopy dates and set diary data one day prior, on the day and one day after the endoscopy to missing.
   c) Take 7 most recent days of diary data. If there are multiple entries on the same day for the eDiary items, use the worst result of the day for calculation.
   d) If less than 4 days of diary data is non-missing, then a subscore cannot be calculated. Otherwise:
      i. If 4, 5 or 6 days of diary is non-missing, the subscore is calculated as the (average of non-missing diary×7), multiplying by the factor appropriate for the given subscore and rounding to the nearest integer.

ii. If 7 or more days of diary is non-missing, the subscore is calculated as the sum of the most recent 7 days of non-missing diary, and multiplying by the factor appropriate for the given subscore.

3. Calculate Extra-intestinal manifestations of Crohn's Disease Subscore, usage of Lomotil/Imodium/opiates for diarrhea and abdominal mass according to Appendix C.
4. Calculate Hematocrit subscore as follows:
   a) Identify the Hematocrit (%) results using the visit window defined in Section 7.1.2. Select the value closest to the CDAI calculation date in (1). If two hematocrits are of equal distance to, but on either side of, the CDAI calculation date, select the later measurement. If two hematocrits occur on the same date, take the average.
   b) If week 52 hematocrit is missing, week 50 value will be used if available.
   c) Subtract from 47 for males and from 42 for females, multiply by a factor of 6 and round to the nearest integer. If the hematocrit subscore is <0, set it to 0.
5. Calculate Body Weight subscore as follows:
   a) Identify the body weight result reported on the CDAI calculation date.
   b) Identify the standard weight based on subject's gender and baseline height (cm) as follows:
      i. Standard weight for men in kilogram = (height in cm/100)^2×22.1.
      ii. Standard weight for women in kilogram = (height in cm/100)^2×20.8.
   c) Calculate the subscore as maximum of [(1 – (Body weight/Standard Weight)) ×100, -10] and round to the nearest integer.
6. Calculate total score as the weighted sum of the 8 subscores only if none of the subscores are missing. Otherwise, the total score is set to be missing for the visit.

7.1.4 Convention for Missing Efficacy Data

- Missing data for dichotomous (ie, proportion-based) endpoints will be handled using the non-responder imputation method, ie, any subject with missing information for determination of endpoint status will be considered as a non-responder in the analysis. Sensitivity analysis will be conducted to assess the impact of dropouts for different missing mechanisms using a hybrid approach where discontinuation due to AE or lack of efficacy will be imputed as non-responder (under MNAR) and other discontinuation/missing will be imputed using multiple imputation (under MAR) for primary and all secondary efficacy endpoints.
- Missing data for continuous endpoints will be imputed using last available post-baseline observation carried forward (LOCF) method. For subjects without any non-missing post-baseline measurement, the missing data will be imputed using baseline observation carried forward method. Other missing data imputation method may be explored.

7.2 Analysis Sets

7.2.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will include all randomized subjects who receive at least 1 dose of study drug. Subjects who only receive induction IV therapy and not randomized into the maintenance phase will not be included in the FAS. Subjects in this set will be analyzed according to the treatment they were randomized to receive. The FAS will be used for all the efficacy analysis with the following exceptions:

- corticosteroid-free remission, will be based on a subset of the FAS subjects with baseline concomitant oral corticosteroid use.
- proportion of TNF-α antagonist naïve subjects who achieved clinical remission, will be based on a subset of the FAS subjects who are TNF-α antagonist naïve.
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

7.2.2 Intent-To-Treat Set (ITT)

The intent-to-treat (ITT) population will include all randomized subjects. Subjects in this set will be analyzed according to the treatment they were randomized to receive. Analyses of primary and secondary efficacy endpoints will be performed in the ITT population as an additional analysis.

7.2.3 Per-Protocol Set (PPS)

The per-protocol (PP) population is a subset of the FAS. The PP population consists of all subjects who do not violate the terms of the protocol in a way that would impact the study output significantly. All decisions to exclude subjects for the PP population dataset will be made prior to the unblinding of the study. Analyses of primary and secondary efficacy endpoints will be performed using the PP population as a sensitivity analysis, if more than 5% of the total subjects in the FAS are excluded from the PPS.

7.2.4 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will include all subjects who receive at least 1 dose of study SC (placebo or vedolizumab) drug. Subjects in this set will be analyzed according to the treatment they actually received. SAF-I will include all subjects who receive at least 1 induction dose, and

were not dosed in the maintenance phase. SAF-C will include all subjects who receive at least 1 dose of vedolizumab IV.

7.2.5 Pharmacokinetic Set

The PK evaluable population is defined as all subjects who receive at least 1 dose of study drug (placebo or vedolizumab) and have sufficient blood sampling to allow for PK evaluation.

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7.3 Disposition of Subjects

A subject disposition summary will be provided. Subjects' study completion data, including reasons for premature termination, will be provided in listings and also summarized.

Significant protocol deviations captured on the electronic case report form will be summarized.

A summary of screening failures will also be provided.

7.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics variables will be summarized for the SAF-C. If the actual treatment of any patient is different from the randomized treatment, the demographic variables will also be summarized for the FAS.

For continuous variables (age, weight, height, and body mass index [BMI]), summary statistics will be generated. BMI (in kg/m^2) will be calculated using the subject's baseline height and weight measurements and summarized.

For categorical variables, the number and percentage of subjects in each category will be presented.

The following CD-related disease characteristics will be summarized for subjects:

- Duration of CD (<1 year, ≥1 to <3 years, ≥3 to <7 years, ≥7 years).
- Subjects without prior corticosteroids or immunomodulators.
- Subjects with only prior corticosteroids.
- Subjects with only prior immunomodulators.
- Subjects with prior corticosteroids and immunomodulators.
- Subjects without baseline concomitant corticosteroids or immunomodulators.
- Subjects with only baseline concomitant corticosteroids.
- Subjects with only baseline concomitant immunomodulators.
- Subjects with baseline concomitant corticosteroids and immunomodulators.

- Subjects with prior TNF-α antagonist use (Naïve, exposed but not failure, failure).
- Subjects with prior immunomodulator and prior TNF-α antagonist failure.
- Worst prior treatment failure (subjects with prior TNF-α anatomist failure, subjects with prior immunomodulator failure, subjects with prior corticosteroid failure).
- Baseline disease activity (moderate [CDAI≤330], severe [CDAI>330]).
- Baseline CRP (≤2.87 mg/L, >2.87 mg/L to ≤5 mg/L, >5 mg/L to ≤10 mg/L, >10 mg/L).
- Baseline fecal calprotectin (≤250 µg/g, >250 to ≤500 µg/g, >500 µg/g).
- History of prior surgery for CD.
- Disease localization (ileum only, colon only, ilocolonic, other).
- History of fistulizing disease.
- Fistula status at Baseline (draining, all closed, none).
- Extraintestinal manifestations.

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be presented in a data listing and will be summarized for the SAF.

7.6 Medication History and Concomitant Medications and Procedures

All medication history and concomitant medications will be coded by therapeutic classification, subclassification, and preferred medication name using the World Health Organization Drug Dictionary (WHODrug). A concomitant medication is defined as a medication that is ongoing as of Study Day 1, ends on or after Study Day 1, or starts on or after Study Day 1 and no more than 126 days after the last dose of study drug.

The number and percentage of subjects taking each concomitant medication during the induction phase and maintenance phase will be summarized for the SAF. Additional summaries for SAF-I during the induction phase will be provided. A subject with 1 or more concomitant medications within the same level of the WHODrug classification will be counted only once in that level. WHODrug preferred term and therapeutic classification will be used for summary:

- Medication history that the study subjects stopped taking within 30 days prior to the Screening Visit.
- Concomitant medications that started and stopped prior to Baseline.
- Concomitant medications that started prior to and were ongoing at Baseline.
- Concomitant medications that started after Baseline.
- Concomitant medications that were ongoing at baseline and those that started after Baseline.

In addition, concomitant IBD medication during maintenance phase will be summarized by preferred term.

Concomitant procedures will not be coded, but will be presented in listings for each subject.

7.7 Study Drug Exposure and Compliance

Overall study drug compliance (%) will be determined as (total count of complete injections taken / total number of injections expected during study treatment) × 100%.

For IV infusion during induction period, a subject must receive at least 75% of the infusion in order for it to be considered complete for each dose.

The total number of days on study drug (exposure) will be calculated as date of last dose of study drug - date of first dose of study drug + 127 days. Any gaps in dosing will be ignored when calculating the total. If last dose date is missing, then 127 days will be imputed as treatment period. Summary statistics for the total number of days on study drug and overall compliance will be generated for the SAF.

The number and percentage of subjects with overall study drug compliance of <80%, 80 to <90%, and ≥90% will also be summarized for the SAF. Subjects with unreturned study drug will be assumed to have injected Q2W of study drug for each 2 weeks of exposure for the calculation of overall compliance. Subjects with overall compliance ≥100% will be set to 100% in the analysis.

In addition, diary compliance will be determined as the percentage of days during treatment with a diary entry and will be summarized based on FAS:

> Diary Compliance =
> (Number of days with diary entries collected during treatment period)/(Number of days with diary entries expected during treatment period) × 100%

7.8 Efficacy Analysis

Unless otherwise stated, the FAS will be used for the summary of the efficacy endpoints. All statistical testing will be performed at 2-sided significance level of 0.05.

7.8.1 Primary Efficacy Endpoint

The primary endpoint is proportion of subjects with clinical remission, defined as CDAI score ≤150, at Week 52.

The null and alternative hypotheses for the primary efficacy endpoint, clinical remission at Week 52, are:

H_0: Clinical Remission $_{\text{Vedolizumab SC}}$ at Week 52 = Clinical Remission $_{\text{Placebo}}$ at Week 52

versus

H_A: Clinical Remission $_{\text{Vedolizumab SC}}$ at Week 52 ≠ Clinical Remission $_{\text{Placebo}}$ at Week 52

Clinical remission at Week 52 will be analyzed in the FAS using Cochran-Mantel-Haenszel (CMH) tests stratified by randomization stratification factors according to:

- Concomitant use of oral corticosteroids.
- Clinical remission status at Week 6.
- Previous TNF-α antagonists failure/exposure or concomitant immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate) use.

Descriptive statistics will be presented by treatment group. Count, percentage and associated 95% CI using the Clopper-Pearson method will be provided for each treatment group. The p-value and point estimate of treatment difference based on the CMH method adjusted for stratification factors along with 95% confidence interval will be presented. If the number of remitters or non-remitters in either of treatment arm is too small (i.e., ≤5), the exact method (ie, Fisher's Exact test and exact unconditional confidence limits) will be performed instead. All subjects with missing data for determination of clinical remission status at Week 52 will be considered as non-remitters in the analysis.

7.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Proportion of subjects with enhanced clinical response, defined as a ≥100 point decrease in CDAI score from Baseline (Week 0), at Week 52.
- Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.
- Proportion of TNF-α antagonist naïve subjects who achieved clinical remission, defined as CDAI score ≤150, at Week 52.

Enhanced clinical response at Week 52 will be analyzed for the FAS subjects. Corticosteroid-free remission at Week 52 will be analyzed in a subset of the FAS subjects with baseline concomitant oral corticosteroid use (consider both prednisone equivalent and budesonide equivalent). Proportion of TNF-α antagonist naïve subjects who achieved clinical remission will be analyzed in a subset of the FAS subjects who are TNF-α antagonist naïve.

All secondary endpoints will be analyzed using CMH tests for treatment differences, stratified by randomization stratification factors (except for corticosteroid-free remission where concomitant use of oral corticosteroid stratification factor will not be considered). The descriptive statistics will be presented for each of the secondary endpoints in a similar way to the primary endpoint. All subjects with missing data for determination of status of secondary efficacy endpoints at Week 52 will be considered as non-responders/non-remitters in the analysis.

The null and alternative hypotheses for the first secondary efficacy endpoint, enhanced clinical response at Week 52, are:

H_0: Enhanced Clinical Response $_{\text{Vedolizumab SC}}$ at Week 52 = Enhanced Clinical Response $_{\text{Placebo}}$ at Week 52

versus

H_A: Enhanced Clinical Response $_{\text{Vedolizumab SC}}$ at Week 52 ≠ Enhanced Clinical Response $_{\text{Placebo}}$ at Week 52

The null and alternative hypotheses for the second secondary efficacy endpoint, corticosteroid-free remission at Week 52, are:

H_0: Corticosteroid-free Remission $_{\text{Vedolizumab SC}}$ at Week 52 = Corticosteroid-free Remission $_{\text{Placebo}}$ at Week 52

versus

H_A: Corticosteroid-free Remission $_{\text{Vedolizumab SC}}$ at Week 52 ≠ Corticosteroid-free Remission $_{\text{Placebo}}$ at Week 52

The null and alternative hypotheses for the third secondary efficacy endpoint, Clinical Remission at Week 52 among TNF-α antagonist naïve subjects, are:

H_0: Clinical Remission $_{\text{Vedolizumab SC}}$ at Week 52 among TNF-α antagonist naïve subjects = Clinical Remission $_{\text{Placebo}}$ at Week 52 among TNF-α antagonist naïve subjects

versus

H_A: Clinical Remission $_{\text{Vedolizumab SC}}$ at Week 52 among TNF-α antagonist naïve subjects ≠ Clinical Remission $_{\text{Placebo}}$ at Week 52 among TNF-α antagonist naïve subjects

7.8.3 Multiplicity Adjustment

To control the overall Type I error rate for the comparison between vedolizumab SC and placebo groups for the primary and secondary endpoints, a hierarchical approach will be applied to the statistical testing of the primary and secondary endpoints. The statistical inference for the first secondary endpoint of enhanced clinical response at Week 52 will only be performed if the primary endpoint, proportion of subjects with clinical remission at Week 52, is statistically significant ($p < 0.05$). The second secondary endpoint of corticosteroid-free clinical remission at Week 52 will only be tested if the first secondary endpoint is statistically significant ($p < 0.05$). The third secondary endpoint of clinical remission at Week 52 among TNF-α antagonist naïve subjects will only be tested if the second secondary endpoint is statistically significant ($p < 0.05$). Multiplicity will not be adjusted across additional endpoints.

7.8.4 Patient Reported Outcomes (PROs) Endpoints

Changes from Baseline to Week 52 in IBDQ, EQ-5D scores, CCI [redacted] components will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline score as a covariate. Changes from Week 6 to Week 52 will be analyzed in a similar

fashion. Missing data will be handled as described in Section 7.1.4. No multiplicity adjustments will be performed for PRO endpoints. Nominal p-value will be presented.

The scoring details of these PROs are included in Appendix G.

7.8.5 Exploratory Efficacy Endpoints

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[redacted]

7.8.6 Subgroup Analysis

Exploratory analyses will be performed on the primary and all secondary endpoints to summarize the treatment effects across subpopulations. The treatment effect in proportions in Vedolizumab SC and placebo and associated 95% confidence interval using Clopper-Pearson method will be provided for each subgroup. Point estimate of the absolute treatment difference between Vedolizumab SC and placebo based on crude estimate and associated 95% confidence interval (using normal approximation method) will be presented. If the number of events is too small (ie, ≤5), the exact method will be performed instead. The results will be tabulated and the corresponding forest plots for the subgroup analyses will be presented as well.

For subgroup analysis by prior use of TNF-α antagonist only, nominal p-value will be obtained by the CMH test stratifying by randomization stratification factors, or Fisher's exact test in the event of small number of responders/remitters or non-responders/non-remitters (ie, ≤5).

If the value of the baseline grouping variable cannot be determined, the subject will be excluded from the corresponding subgroup analysis. If the number of subjects in any subgroup is less than 10, that subgroup will not be presented.

Subpopulations will be defined by the following baseline characteristics.

- Age (<35, ≥35 to <65, ≥65 years).
- Gender.
- Race (Asian, Black or African American, White, Other).
- Duration of CD (<1 year, ≥1 to <3 years, ≥3 to <7 years, ≥7 years).
- Geographic region (Appendix D).
- Baseline disease activity (moderate [CDAI≤330], severe [CDAI>330]).
- Baseline fecal calprotectin (≤250 µg/g, >250 to ≤500 µg/g, >500 µg/g).
- Baseline CRP (≤5 mg/L, >5 mg/L to ≤10 mg/L, >10 mg/L).
- Baseline fistula status (draining, all closed, none).
- Disease localization (ileum only, colon only, ilocolonic, other).
- Clinical remission status at Week 6.

- Prior TNF-α antagonist therapy (naïve, exposed but not failure, failure. Failure will be further categorized by type of failure – Inadequate response, Loss of response, Intolerance).
- Prior immunomodulator and TNF-α antagonist failure (Y/N).
- Prior corticosteroids failure (Y/N).
- Prior immunomodulator failure (Y/N).
- Baseline concomitant therapies: corticosteroids and immunomodulators (Concomitant corticosteroids only, concomitant immunomodulators only, concomitant corticosteroids and immunomodulators, no concomitant corticosteroids or immunomodulators).
- Worst prior treatment failure (subjects with prior TNF-α antagonist failure, subjects with prior immunomodulator failure but not TNF-α antagonist failure, subjects with prior corticosteroid failure but not TNF-α antagonist or immunomodulator failure).

7.8.7 Additional Analysis and Sensitivity Analysis

Analyses using the ITT population will be provided as an additional analysis for primary endpoint and all secondary endpoints.

Analyses using the PPS population may be provided as a sensitivity analysis for primary endpoint and all secondary endpoints.

CCI

[redacted]

In addition, if any clinical site has detected or reported significant noncompliance with regulatory requirements during the course of study, additional sensitivity analysis will be conducted for the primary efficacy endpoint in the FAS excluding all subjects from that particular site.

CCI

[redacted]

Additional Analysis for Induction Phase Data

The proportion of subjects with clinical response at Week 6 or Week 14 in subjects who completed Week 6 or Week 14 of the induction phase will be tabulated based on SAF-C.

7.9 Pharmacokinetic Analysis

CCI [redacted]

7.10 Other Outcomes

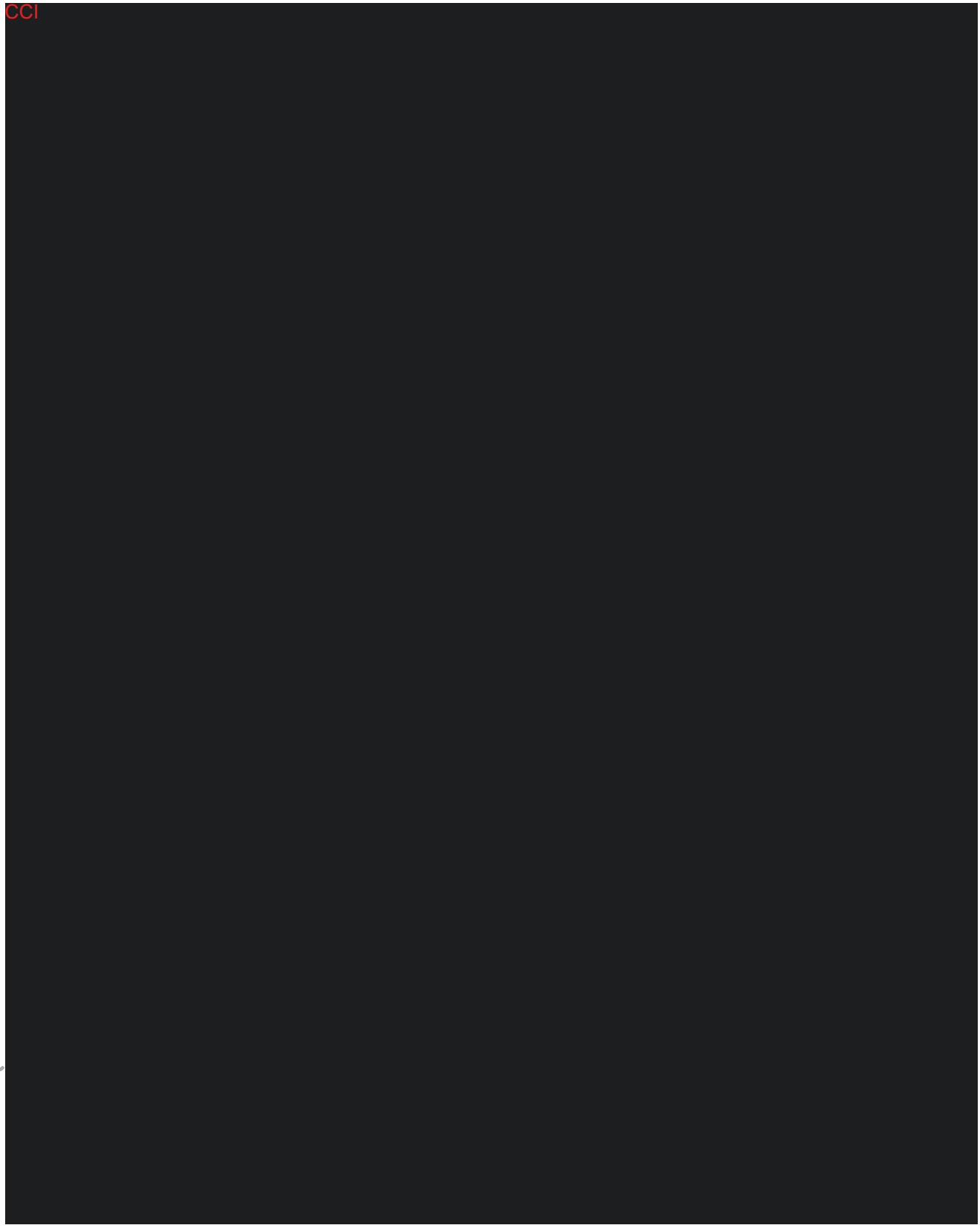
7.10.1 Immunogenicity Endpoints

CCI [redacted]

7.10.2 CCI [redacted]

CCI [redacted]

CCI



CCI

[redacted]

7.10.3 CCI

CCI

[redacted]

7.11 Safety Analysis

All safety analyses will be performed using the SAF unless otherwise specified. Data will be summarized by treatment group. No statistical inference will be made for safety analyses.

7.11.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Agencies (MedDRA).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts or worsens on or after Study Day 1 (defined as day first dosed), and no more than 18 weeks/126 days after the last dose of study drug and the day prior to the first dose of the extension study (for patients entering the OLE study). All TEAEs will be listed by subject number and MedDRA coding. A listing of all unique coded terms will also be provided.

The number and percentage of subjects with TEAEs will be summarized in several different tables; in addition, exposure-adjusted AE rates will be summarized.

- An overview TEAE table in SAF-C.
- All TEAEs by system organ class (SOC), high level term (HLT), and preferred term (PT).

- Adverse events of special interested (AESIs) (ie, serious infections including opportunistic infection such as PML, malignancies, liver injury, infusion reactions, injection site reactions and hypersensitivity).
- Treatment-related TEAEs by SOC, HLT, and PT.
- Serious TEAEs by SOC, HLT, and PT in SAF-C (subject and event level).
- Most frequent TEAEs by SOC, HLT and PT (sorted by frequency of HLT occurring in ≥5% of subjects).
- Most frequent treatment-related TEAEs by SOC, HLT and PT (sorted by frequency of HLT occurring in ≥2% of subjects).
- Severity of all TEAEs by SOC and PT (mild, moderate, or severe).
- Severity of treatment-related TEAEs by SOC and PT (mild, moderate, or severe).
- Relationship to study drug for all TEAEs by SOC and PT (not related, related).
- Exposure-adjusted TEAEs and serious TEAEs by SOC, HLT, and PT.
- Exposure-adjusted treatment-emergent infections and serious treatment-emergent infections by SOC, HLT and PT.
- Subject mapping of TEAEs by SOC, HLT, and PT.

A subject with 2 or more AEs within the same level of the MedDRA term will be counted only once in that level using the most extreme incident (most severe for the severity tables and related for the relationship to study drug tables).

The exposure-adjusted incidence rate is defined as the number of subjects with AEs divided by the total exposure-time of the subjects in the respective treatment group. The exposure-time is defined as follows:

- For subjects do not enroll in the OLE study: (date of last dose – date of first dose + 1) + 126.
- For subjects enroll in the OLE study: (date of first dose in the OLE study – date of first dose in MLN0002SC-3031).

Additional summaries of TEAEs will be provided that only include TEAEs that occur in the Maintenance Phase between the Week 6 dose and 18 weeks/126 days after the last dose date of the study drug, or up to the first dose of the open-label extension study, whichever comes first.

Additionally, treatment-emergent SAEs, deaths, and TEAEs resulting in premature discontinuation from study drug will be listed and summarized by SOC, HLT, and PT. The most frequent treatment-emergent non-serious AEs will also be summarized by SOC, HLT, and PT in SAF-C (subject and event level).

A pretreatment event (PTE) will be defined as an AE that starts before Study Day 1. A list of pretreatment AEs by subject number and MedDRA coding will be presented separately. Pretreatment AEs will be summarized by SOC and PT.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory variables will be summarized by treatment groups using descriptive statistics for baseline, postbaseline, and change from baseline to postbaseline values.

Individual results for clinical hematology and chemistry laboratory tests that are within the predefined "markedly abnormal laboratory value (MAV) criteria" (Appendix A) will be summarized in tables. All clinical laboratory data will be presented in data listings.

Elevated hepatic parameters will be summarized.

Summaries and listings of laboratory data will be presented in System International (SI) and conventional units. MAV tables and listings will be presented in the unit specified in the MAV criteria in Appendix A.

7.11.3 Vital Signs

Vital signs will be summarized by treatment using descriptive statistics for Baseline, postbaseline, and change from Baseline to postbaseline values.

Individual vital signs which meet predefined criteria for abnormal changes from Baseline of vital signs (Appendix B) will be summarized in tables. All vital sign data will be presented in data listings.

7.11.4 12-Lead ECGs

ECG results will be interpreted using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The shift in ECG interpretation from Baseline will be summarized by treatment group.

All ECG data will be presented in a data listing.

7.11.5 Other Observations Related to Safety

Physical examination results will be presented in a data listing and will not be summarized. PML checklist data will be presented in data listings.

Data from the long-term follow-up (LTFU) survey will be summarized descriptively.

7.12 Interim Analysis

No interim analysis is planned.

As pre-specified in the original SAP and prior to this SAP amendment, blinded safety update was conducted to support the BLA/MAA filing for Ulcerative Colitis. The blinded safety update included subject disposition, demographic summary, AEs, AESIs, SAEs, markedly abnormal values for lab, markedly abnormal values for vital signs, and markedly abnormal values for ECG. The blinded safety data were summarized and presented in "Total" column only to maintain the blinding of the study.

7.13 Changes in the Statistical Analysis Plan

Changes from Protocol:

- No multiplicity adjustments will be performed for PRO endpoints. Nominal p-value will be presented.

  Rationale for Change: PRO endpoints are exploratory.
- CCI [redacted]
- For time-to-event endpoints, the KM estimates of Week 46 event-free rates will be presented, instead of Week 48.

  Rationale for Change: Week 46 from randomization is equivalent to Week 52 from Week 0, a primary time point for efficacy assessment.

Summary of changes from the previous version of the SAP

Changes made in this amendment (Amendment 01) to the previous SAP version dated 20JUL2018 are summarized in this section. Substantive changes are described in the table below. In addition, several editorial changes were made in sections where improvement to clarity, transparency, completeness, flow or corrections to typographical errors was considered necessary. Not all of these editorial changes are described below.

Section	Description of Change	Rationale for Change
4.4 Study Design	Clarification to the Final Visit/Early Termination procedures for subjects who complete (OLE Enroller/Non-enroller) at Week 14 (Induction Phase), and subjects who complete (Week 52) or discontinue from the Maintenance Phase. CCI [redacted]	To be consistent with Protocol Amendment 06 dated 24AUG2017.
5.4 Exploratory Endpoints	• CCI [redacted] • Add "**enhanced**" to clinical response-related exploratory endpoints.	• Correct typographical error. • Clarity on the definitions of several exploratory endpoints.
7.1.2 Definition of Study Days and Visit Window	• If 2 or more measurements occur on the same day, use the **average** value instead of the last value (original SAP), unless specified otherwise. • CCI [redacted]	• To account for scenarios when multiple measurements occur on the same day and a tie on the time/date of measurement cannot be broken. • Correct typographical error. • Visit window convention updated to

Section	Description of Change	Rationale for Change
	CCI [redacted]	add endpoints previously not included. • Clarity on week 14 window for CDAI score for week 6 non-responders.
7.1.3 Convention for Calculations of CDAI Scores	New section added with details on the CDAI score calculation.	For clarity and completeness on the CDAI score.
7.1.4 Convention for Missing Efficacy Data	Clarified that sensitivity analysis by hybrid model approach will be conducted for primary and all secondary efficacy endpoints, NOT in subgroup analysis by prior anti-TNF status.	Sensitivity analysis is not needed for a subgroup analyses.
7.2 Analysis Set	• 7.2.1 FAS: Clarified exploratory endpoints that will be analyzed based on a subset of FAS. • 7.2.2 ITT: ITT population added. • 7.2.3 PPS: Clarified analysis of primary and secondary endpoints will be performed based on PPS if more than 5% of the total subjects in the FAS are excluded. • 7.2.4 SAF: For SAF-I, the definition changed from "subjects who receive at least 1 induction dose, and were not randomized to maintenance phase" to "were not **dosed** in the maintenance phase". • CCI [redacted]	• For completeness and clarity on exploratory analyses and subset definitions. • CCI [redacted] • SAF-I definition updated to account for subjects randomized but not dosed in the maintenance phase.
7.4 Demographic and Baseline Characteristics	• Added prior corticosteroids and/or immunomodulators use categories for the summary of CD-related disease characteristics. • Added categories for Fistula status at Baseline: draining, all closed, none.	Added new categories and specified fistula status levels for better presentation of CD-related disease characteristics data.
7.6 Medication History and Concomitant Medications and Procedures	The following sentence added: *In addition, concomitant IBD medication during maintenance phase will be summarized by preferred term*	Summary of concomitant IBD medication added for clarity on concomitant medication data.
7.7 Study Drug Exposure and Compliance	Specified diary compliance will be summarized based on FAS.	Diary data include patient reported outcome CDAI components which are efficacy-related; therefore, it is more appropriate to summarize based on FAS.
7.8.1 Primary Efficacy Endpoint	Removed the following sentence from SAP: *The absolute treatment difference based on crude estimates with 95% CI using the normal approximation method will be displayed as well.*	Point estimate of treatment difference and its 95% CI based on CMH method will be presented as described in original SAP, which will be consistent with the p-value reported from CMH test. Crude estimate and its 95% CI are not informative and

Section	Description of Change	Rationale for Change
		hence removed.
7.8.2 Secondary Efficacy Endpoints	• For corticosteroid-free remission, added detail that both prednisone equivalent and budesonide equivalent will be considered. • Specified that the stratification factor related to the concomitant use of oral corticosteroids will not be used in the analysis of corticosteroid-free remission. • Added null and alternative hypotheses for the third secondary efficacy endpoint.	• Clarity on the analysis of the second secondary efficacy endpoint. • For completeness. Hypotheses for the third secondary efficacy endpoint was not specified in original SAP.
7.8.3 Multiplicity Adjustment	New section.	For clarity on multiplicity adjustments for the primary and secondary efficacy endpoints.
7.8.4 Patient Reported Outcomes (PROs) Endpoints	Added the following sentences: *No multiplicity adjustments will be performed for PRO endpoints. Nominal p-value will be presented.* *The scoring details of these PROs are included in Appendix G.*	To clarify that the PRO endpoints are not part of the multiplicity adjustment and add cross-reference to Appendix G for completeness.
7.8.5 Exploratory Efficacy Endpoints	Added details on endpoint derivation and analysis methods details for exploratory endpoints	For completeness and clarity.
7.8.6 Subgroup Analysis	New section.	For clarity and completeness on the subpopulations to be studied for the primary and secondary efficacy endpoints and associated statistical methods.
7.8.7 Additional Analysis and Sensitivity Analysis	• Added ITT analysis. • CCI [redacted] • Added sensitivity analysis excluding sites with major compliance issue. • CCI [redacted] • Added additional analysis for induction phase data.	For completeness. The additional ITT analysis and sensitivity analysis were considered necessary to evaluate robustness of the results to the assumptions made in the related primary analyses.
7.10 Other Outcomes	• CCI [redacted] • CCI [redacted] •	
7.11 Safety	• Clarified the definition of TEAE as an AE	• Updated TEAE definition to prevent

Section	Description of Change	Rationale for Change
Analysis	that starts or worsens on or after Study Day 1 (defined as day first dosed), and no more than 18 weeks/126 days after the last dose of study drug **and the day prior to the first dose of the extension study (for patients entering the OLE study).** • Added derivation details for exposure-adjusted event rate. • Specified both subject and event level summary are required for the tabulation of serious TEAEs and most frequent non-serious TEAEs.	double counting. For subjects who enrolled in the SC-3030 study, AEs onset post OLE dosing are considered treatment-emergent in SC-3030, not in SC-3031. • For clarity on the exposure-time calculation for exposure-adjusted AE summaries. • Updates to certain AE summary for result disclosure requirement.
8.0 References	References added.	For completeness.
Appendix D Geographic Regions	• Separated East Asia and Africa/Australia as two regions. • Added Ukraine and included under Eastern Europe region.	For better categorization of geographic regions.

8.0 REFERENCES

1. Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, et al. (2015). A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Aliment Pharmacol Ther 2015;41(1):77-86.
2. Ratitch, B.R., Lipkovich, I. and O'Kelly, M. (2013). Combining Analysis Results from Multiply Imputed Categorical Data. PharmaSUG Proceedings 2013 - Paper SP03. https://www.pharmasug.org/proceedings/2013/SP/PharmaSUG-2013-SP03.pdf.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
Hemoglobin	<0.8 × LLN	>1.2 × ULN
Hematocrit	<0.8 × LLN	>1.2 × ULN
RBC count	<0.8 × LLN	>1.2 × ULN
WBC count	$<2.0 \times 10^3/\mu L$	>1.5 × ULN
Platelet count	$<70 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$

RBC=red blood cell, WBC=white blood cell. LLN=lower limit of normal, ULN=upper limit of normal.

Chemistry—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
ALT	--	>3 ×ULN
AST	--	>3 × ULN
GGT	--	>3 × ULN
Alkaline phosphatase	--	>3 × ULN
Total bilirubin	--	>2.0 mg/dL
Albumin	<2.5 g/dL	--
Total protein	<0.8 × LLN	>1.2 × ULN
Creatinine	--	>2.0 mg/dL
Sodium	<130 mEq/L	>150 mEq/L
Potassium	<3.0 mEq/L	>6.0 mEq/L
Bicarbonate	<8.0 mmol/L	--
Chloride	<75 mmol/L	>126 mmol/L
Calcium	<1.50 mmol/L	>3.25 mmol/L
Glucose	≤2.8 mmol/L	≥20 mmol/L
Phosphorous	<0.52 mmol/L	>2.10 mmol/L
CPK	--	>5 × ULN

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, CPK=creatine phosphokinase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Criterion Value	Change Relative to Baseline
Pulse	≥120 beats/min	
	≤50 beats/min	
Systolic blood pressure	≥180 mm Hg	
	≤85 mm Hg	
Diastolic blood pressure	≥110 mm Hg	
	≤50 mm Hg	
Body temperature	<35.6°C	
	>37.7°C	

Appendix C CDAI Scoring System for the Assessment of Crohn's Disease Activity

Category	Count	Initial Total	Multiplication Factor	Total
Number of liquid or very soft stools	7-day total number of liquid or very soft stools (reported on the 7 days immediately prior to the study visit)		× 2	
Abdominal pain	7-day total of daily abdominal pain scores on a 3-point scale: 0=none, 1=mild, 2=moderate, 3=severe (reported on the 7 days immediately prior to the study visit)		× 5	
General well being	7-day total of daily general well-being scores on a 4-point scale: 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible (reported on the 7 days immediately prior to the study visit)		× 7	
Extra-intestinal manifestations of Crohn's Disease	Total number of checked boxes (check **all** that apply): ☐ Arthritis/arthralgia ☐ Iritis/uveitis ☐ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis ☐ Anal fissure, fistula, or abscess ☐ Other fistula ☐ Fever over 37.8°C during past week		× 20	
Lomotil/Imodium/opiates for diarrhea	Yes = 1 No = 0		× 30	
Abdominal mass	None = 0 Questionable = 2 Definite = 5		× 10	
Hematocrit (%)[a]	Males: subtract value from 47 Females: subtract value from 42		× 6	
Body Weight[b]	(1 – (Body weight/ Standard Weight)) × 100		× 1	
Final Score			Add totals:	

a If hematocrit subtotal <0, enter 0.
b If body weight subtotal <-10, enter -10.

Adapted from: Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70(3):439-44.

Appendix D Geographic Regions

Region		Countries	
North America	Canada	United States	
South America	Argentina	Brazil	Mexico
Western/ Northern Europe	Belgium	Denmark	Germany
	Italy	Lithuania	Netherlands
	Sweden	Spain	United Kingdom
Central Europe	Czech Republic	Hungary	Poland
	Romania	Serbia	Slovak Republic
Eastern Europe	Bosnia and Herzegovina	Bulgaria	Croatia
	Estonia	Israel	Russia
	Turkey	Ukraine	
East Asia	Japan	Republic of Korea	Taiwan
Africa / Australia	Australia	South Africa	

Appendix E AEs of Special Interest

Events	MedDRA Terms or definitions
Malignancies	SOC: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)
Infections	SOC: INFECTIONS AND INFESTATIONS
Infusion Related Reactions	Analysis for these AEs will occur on two levels: • Investigator defined Infusion Related Reactions (as indicated on the AE CRF). • All AEs that occur on or one calendar day after the infusion date.
Injection site reaction	Injection Site Reaction (HLT)
Hypersensitivity Reactions	Anaphylactic/anaphylactoid shock conditions SMQ (broad). Angioedema SMQ (broad). Hypersensitivity SMQ (broad).
PML	Human polyomavirus infection PT JC virus infection PT Leukoencephalopathy PT Progressive multifocal leukoencephalopathy PT JC virus CSF test positive PT Polyomavirus test positive PT JC polyomavirus test positive PT
Liver injury	Cholestasis and jaundice of hepatic origin SMQ (broad) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (broad) Hepatitis, non-infectious SMQ (broad) Liver related investigations, signs and symptoms SMQ (narrow) Liver infections SMQ (broad)

Appendix F Prior Therapies

	Systemic Corticosteroids	Immunomodulators	TNF Antagonist
CRF label	Systemic Corticosteroids	Azathioprine	Infliximab
	Budesonide	6-Merrcaptopurine	Adalimumab
		Methotrexate	Certolizumab

Appendix G Patient Reported Outcomes

IBDQ, EQ-5D CCI [redacted]

Variable	Sub-score	Calculation
IBDQ	IBDQ Bowel symptoms score	Sum of (Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, Q29), Ranging from 10 to 70, 10 questions
	IBDQ Emotional function score	Sum of (Q3, Q7, Q11, Q15, Q19, Q21, Q23, Q25, Q27, Q30, Q31, Q32), Ranging from 12 to 84, 12 questions
	IBDQ Social function score	Sum of (Q4, Q8, Q12, Q16, Q28), Ranging from 5 to 35, 5 questions
	IBDQ Systemic symptoms score	Sum of (Q2, Q6, Q10, Q14, Q18), Ranging from 5 to 35, 5 questions
Note	For each component score above, if 50% or less of the component score is missing at a visit, the MEAN of the remaining component score will be imputed as the value for the missing component score. If more than 50% of the component score is missing for the item, the imputed value will be set to missing.	
	IBDQ score	Sum of (bowel, emotion, social, system)
Note	If any of the component score is missing at a visit, the imputed value will be set to missing.	
EQ-5D	EQ5D Mobility component score	Ranging from 1 to 3
	EQ5D self-care component score	Ranging from 1 to 3
	EQ5D usual activities component score	Ranging from 1 to 3
	EQ5D Pain/discomfort component score	Ranging from 1 to 3
	EQ5D anxiety/depression component score	Ranging from 1 to 3
Note	If 2 or less out of 5 of the components are missing at a visit, the MEAN of the remaining component score will be imputed as the value for the missing component score. If 3 or more components are missing, the imputed value will be set to missing.	

CCI [redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	25-Jun-2019 06:41 UTC