Title: An Open-Label Phase 3b Study to Assess Mucosal Healing in Subjects with Moderately to Severely Active Crohn's Disease Treated With Vedolizumab IV
Effect of Vedolizumab IV on Mucosal Healing in Crohn's Disease

NCT Number: NCT02425111

SAP Approve Date: 21 March 2018

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TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: MLN0002-3028

An Open-Label Phase 3b Study to Assess Mucosal Healing in Subjects with Moderately to Severely Active Crohn's Disease Treated With Vedolizumab IV

Effect of Vedolizumab IV on Mucosal Healing in Crohn's Disease

PHASE 3B

Version**:** Final

Date**:** 21 March 2018

Prepared by:

PPD

1.1 APPROVAL SIGNATURES

Study Title: An Open-Label Phase 3b Study to Assess Mucosal Healing in Subjects With Moderately to Severely Active Crohn's Disease Treated With Vedolizumab IV

TDC Approvals:

PPD _____ Date

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TDC Approvals:

PPD

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate transaminase
AVA	anti-vedolizumab antibody; also called HAHA
BMI	body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CRP	C-reactive protein
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EQ-5D	Euro Quality of Life-5D
ET	early termination
FAS	full analysis set
FSH	follicle-stimulating hormone
GGT	γ-glutamyl transferase
GHAS	Global Histological Disease Activity Score
GI	gastrointestinal
HAHA	human antihuman antibody
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLT	high level term
HRQOL	health-related quality of life
IBDQ	inflammatory bowel disease questionnaire
INR	international normalized ratio
IRR	infusion-related reactions
IV	intravenous
LOCF	Last available post-baseline Observation Carried Forward
MaRIA	Magnetic Resonance Index of Activity
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MR	magnetic resonance
MREn	magnetic resonance enterography
PML	progressive multifocal leukoencephalopathy
PPS	per protocol set
PRO	patient reported outcome
PT	preferred term
PT	prothrombin time
PTE	pretreatment event
QOL	quality of life
RAMP	Risk Assessment and Minimization for PML
RBC	red blood cell
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SES-CD	simple endoscopic score for Crohn's Disease
SI	International System of Units
SMQ	standard MedDRA query

SOC	system organ class
TEAE	treatment emergent adverse event
TNF-α	tumor necrosis factor-alpha
URTI	upper respiratory tract infection
VAS	visual analog scale
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment
WPAI-CD	Work Productivity and Activity Impairment for Crohn's Disease

4.0 OBJECTIVES

4.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate endoscopic remission of Crohn's Disease (CD) at Week 26 as assessed by ileocolonoscopy.

4.2 SECONDARY OBJECTIVES

The secondary objectives for Study Part A are:

- To examine the relationship among endoscopic, imaging, histological, and clinical assessments of CD.
- To evaluate endoscopic remission at Week 14.
- To evaluate endoscopic response at Weeks 14 and 26.
- To evaluate clinical response assessed by Crohn's Disease Activity Index (CDAI) at Weeks 10 and 26.
- To evaluate clinical remission assessed by CDAI at Weeks 10 and 26.

The secondary objectives for Study Part B are:

- To examine the relationship among endoscopic, imaging, histological, and clinical assessments of CD.
- To evaluate endoscopic remission at Week 52.
- To evaluate endoscopic response at Week 52.
- To evaluate clinical response assessed by CDAI at Week 52.
- To evaluate clinical remission assessed by CDAI at Week 52.
- To evaluate durable endoscopic remission at Week 52 in patients with endoscopic remission at Week 26.

4.3 ADDITIONAL OBJECTIVES

The additional objectives for Study Part A are:

- To evaluate changes in transmural bowel wall activity and other measures of bowel wall inflammation using magnetic resonance enterography (MREn) at Week 26.
- To assess histological response at Week 26.
- To evaluate C-reactive protein (CRP) at Weeks 10 and 26.
- To evaluate fecal calprotectin at Weeks 14 and 26.
- To evaluate immunogenicity of vedolizumab.
- To evaluate health-related quality of life (as assessed by inflammatory bowel disease questionnaire [IBDQ] and Euro Quality of Life-5D [EQ-5D]) at Weeks 14 and 26.

- To explore the relationship between endoscopic remission and health-related quality of life (QOL).
- To evaluate impact on loss of work productivity and activity impairment assessed by Work Productivity and Activity Impairment (WPAI):CD at Weeks 14 and 26.

The additional objectives for Study Part B are:

- To evaluate changes in transmural bowel wall activity and other measures of bowel wall inflammation using MREn at Week 52.
- To assess histological response at Week 52.
- To evaluate CRP at Weeks 38 and 52.
- To evaluate fecal calprotectin at Weeks 38 and 52.
- To evaluate immunogenicity of vedolizumab.
- To evaluate clinical response assessed by CDAI at Weeks 38 and 46.
- To evaluate clinical remission assessed by CDAI at Weeks 38 and 46.
- To evaluate health-related quality of life (IBDQ and EQ-5D) at Weeks 38 and 52.
- To explore the relationship between endoscopic remission and health-related QOL.
- To evaluate impact on loss of work productivity and activity impairment assessed by WPAI:CD at Week 52.

4.4 STUDY DESIGN

This is a phase 3b single-arm, open-label multicenter study to evaluate the efficacy and safety of vedolizumab 300 mg intravenous (IV) infusion over a 26-week treatment period using ileocolonoscopy for the assessment in subjects with moderately to severely active CD (Study Part A) followed by a 26-week treatment extension period (Part B). Biopsies will be collected for histological assessments per the schedule of events for all subjects. The study will be conducted at sites in North America and Europe. The 26-week treatment extension (Study Part B) is included as part of Protocol Amendment No. 04 (dated 27 April 2016), ongoing subjects at the time of the amendment will have the option to either stop treatment at Week 26 (Study Part A) or continue treatment into Part B. Subjects who enroll into the study after Protocol Amendment No. 04 will be treated directly for 52 weeks (Study Parts A and B).

Approximately 100 subjects with moderately to severely active CD who have failed treatment with corticosteroids, immunosuppressants, and/or biologics will be enrolled. Subjects who are tumor necrosis factor-alpha (TNF-α) antagonist naïve as well as those who are TNF-α antagonist failures will be included, such that approximately 50% of enrolled subjects are TNF-α antagonist naïve.

The study consists of a 4-week screening period, a 26-week treatment period (Study Part A), followed by a 26-week extension treatment period (Part B from 7 days after Week 26 to 52 with last dose at Week 46), and an 18-week follow-up period following the last dose. The duration of the study will be approximately 44 weeks for subjects completing Study Part A and 70 weeks for subjects completing Study Part B. All subjects included in the study will also have a 6 month

safety follow-up telephone call following last dose. End of trial will be the date of the last visit of the last subject at the Postdose 18 Week Safety Follow-up visit.

Subjects that meet all the inclusion criteria and none of the exclusion criteria will be dosed on site with vedolizumab 300 mg IV. Subjects will visit the site for dosing at Day 1, Weeks 2, 6, 14, and 22 for Study Part A and at Weeks 30, 38, and 46 for Study Part B. Ileocolonoscopy will be performed at the Screening, Week 14, Week 26 (Study Part A), and Week 52 (Study Part B) or early termination (ET) visits. Biopsies will be taken during the Screening, Week 26 (Study Part A), and Week 52 (Study Part B) or ET visit. All ileocolonoscopies will be evaluated by a blinded central reader.

An MREn substudy will be conducted at selected qualified centers using a standardized magnetic resonance (MR) acquisition and procedure to assess bowel wall activity. Only subjects from the pre-selected sites will be included in this study; these subjects will undergo an MREn assessment at the Screening, Week 26 (Study Part A), and Week 52 (Study Part B) or ET visit, unless they have contraindications to the procedure. All MREn results will be evaluated by a blinded independent central reader.

Additional procedures will be performed according to the Schedule of Study Procedures (Appendix A).

Figure 4.a Schematic of Study Design - For Subjects on 26 Weeks of Treatment

Days -28 to -1	**Day 1**	**Part A Weeks 2, 6, 10, 14, 22, 26**	**Week 26**	Postdose 18-week Safety Follow-Up Visit	6 month Telephone Follow-Up
Screening	1st dose 300 mg IV	300 mg IV (all visits except Week 10 and 26)	Final Visit / Early Termination Visit		

Figure 4.b Schematic of Study Design - For Subjects on 52 Weeks of Treatment

Days -28 to -1	**Day 1**	**Part A Weeks 2, 6, 10, 14, 22, 26**	**Part B Weeks 30, 38, 46**	**Week 52**	Postdose 18-week Safety Follow-Up Visit	6 month Telephone Follow-Up
Screening	1st dose 300 mg IV	300 mg IV (all visits except Week 10 and 26)	300 mg IV	Final Visit / Early Termination Visit		

5.0 ANALYSIS ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of subjects achieving endoscopic remission at Week 26. Endoscopic Remission is assessed by ileocolonoscopy and defined as simple endoscopic score for Crohn's Disease (SES-CD) score of ≤ 4.

5.2 SECONDARY ENDPOINTS

The secondary endpoints for Study Part A are:

- Proportion of subjects achieving complete mucosal healing at Week 26. Complete mucosal healing is defined as absence of ulceration.
- Proportion of subjects achieving endoscopic remission at Week 14.
- Proportion of subjects with endoscopic response at Week 14. Endoscopic response is defined as SES-CD reduction by ≥ 50%.
- Proportion of subjects with endoscopic response at Week 26.
- Proportion of subjects achieving clinical response at Week 10. Clinical response is defined as CDAI decrease from Baseline of ≥ 100 points.
- Proportion of subjects achieving clinical response at Week 26.
- Proportion of subjects achieving clinical remission at Week 10. Clinical remission is defined as CDAI ≤ 150.
- Proportion of subjects achieving clinical remission at Week 26.

The secondary endpoints for Study Part B are:

- Proportion of subjects achieving complete mucosal healing at Week 52. Complete mucosal healing is defined as absence of ulceration.
- Proportion of subjects achieving endoscopic remission at Week 52.
- Proportion of subjects with endoscopic response at Week 52. Endoscopic response is defined as SES-CD reduction by ≥ 50%.
- Proportion of subjects achieving clinical response at Week 52. Clinical response is defined as CDAI decrease from Baseline of ≥ 100 points.
- Proportion of subjects achieving clinical remission at Week 52. Clinical remission is defined as CDAI ≤ 150.
- Proportion of subjects with durable clinical remission. Durable clinical remission is defined as clinical remission at Week 26 and Week 52.

5.3 ADDITIONAL ENDPOINTS

The additional endpoints for Study Part A are:

- Change from Baseline to Week 26 in individual MREn parameters (including wall thickening, relative contrast enhancement, presence of ulcerations, presence of edema) for each ileocolonic segment and for more proximal bowel segments, if evaluable.
- Proportion of subjects achieving Magnetic Resonance Index of Activity (MaRIA) score <7 at Week 26 globally and on a per segment basis.
- Proportion of subjects with 25% and 75% reduction of SES-CD at Weeks 14 and 26.
- Proportion of subjects with no granulocytes present in bowel biopsy at Week 26.
- Proportion of subjects with a change in histology at Week 26.
- Proportion of subjects with elevated CRP at Baseline who achieve normalization of CRP at Weeks 10 and 26.
- Change from Baseline to Weeks 14 and 26 in fecal calprotectin.
- Proportion of subjects positive for anti-vedolizumab antibody (AVA; also called human antihuman antibody [HAHA]) at Baseline, Week 26, and at the Postdose 18 Week Safety Follow-up Visit.
- Proportion of subjects with positive neutralizing AVA at Baseline, Week 26, and at the Postdose 18 Week Safety Follow-up Visit.
- Change from Baseline to Weeks 14 and 26 in the IBDQ total and subscale scores.
- Change from Baseline to Weeks 14 and 26 in the EQ-5D utility score and visual analog scale (VAS) score.
- Change from Baseline to Weeks 14 and 26 in percent work time missed due to CD.
- Change from Baseline to Weeks 14 and 26 in percent impairment while working due to CD.
- Change from Baseline to Weeks 14 and 26 in percent overall work impairment due to CD.
- Change from Baseline to Weeks 14 and 26 in percent activity impairment due to CD.
- Adverse events (AEs), serious AEs (SAEs), vital signs, and laboratory tests.

The additional endpoints for Study Part B are:

- Change from Baseline to Week 52 in individual MREn parameters (including wall thickening, relative contrast enhancement, presence of ulcerations, presence of edema) for each ileocolonic segment and for more proximal bowel segments, if evaluable.
- Proportion of subjects achieving MaRIA score < 7 at Week 52 globally and on a per segment basis.
- Proportion of subjects with 25% and 75% reduction of SES-CD at Week 52.
- Proportion of subjects with no granulocytes present in bowel biopsy at Week 52.

- Proportion of subjects with a change in histology at Week 52.
- Proportion of subjects with elevated CRP at Baseline who achieve normalization of CRP at Weeks 38 and 52.
- Change from Baseline to Weeks 38 and 52 in fecal calprotectin.
- Proportion of subjects positive for AVA at Week 52 and at the Postdose 18 Week Safety Follow-up Visit.
- Proportion of subjects with positive neutralizing AVA at Week 52 and at the Postdose 18 Week Safety Follow-up Visit.
- Proportion of subjects achieving clinical response at Weeks 38 and 46. Clinical response is defined as CDAI decrease from Baseline of $\geq$ 100 points.
- Proportion of subjects achieving clinical remission at Weeks 38 and 46. Clinical remission is defined as CDAI $\leq$ 150.
- Change from Baseline to Weeks 38 and 52 in the IBDQ total and subscale scores.
- Change from Baseline to Weeks 38 and 52 in the EQ-5D utility score and VAS score.
- Change from Baseline to Week 52 in percent work time missed due to CD.
- Change from Baseline to Week 52 in percent impairment while working due to CD.
- Change from Baseline to Week 52 in percent overall work impairment due to CD.
- Change from Baseline to Week 52 in percent activity impairment due to CD.
- AEs, SAEs, vital signs, and laboratory tests.

6.0 DETERMINATION OF SAMPLE SIZE

A sample size of 100 subjects will be sufficient to provide a 95% confidence interval based on normal approximation for the primary endpoint (endoscopic remission rate at Week 26) that extends no more than 10% in each direction from the estimated rate.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 GENERAL PRINCIPLES

Where appropriate, variables will be summarized descriptively by study visit and subgroups. For categorical variables, counts and proportions will be tabulated. Percentages will be calculated out of the total number of patients in the analysis set and by subgroups, when applicable. Percentages will be presented to 1 decimal place. Every effort will be made to limit the amount of missing data; however, if any missing data is present in the clinical database, a Missing category will be added in the tabulation, unless otherwise stated.

For continuous variables, the number of subjects with non-missing values, mean, median, standard deviation (SD), minimum, and maximum values will be tabulated. Means and medians will be presented to 1 more decimal place than the recorded data. The SDs will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

All confidence intervals will be reported as 2-sided and will be assessed at the α=0.05 significance level. No inferential statistics are planned for this study.

The data summaries will be accompanied by individual subject data listings.

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses. Details are provided in section 7.1.5.

All statistical analyses will be conducted using SAS System® Version 9.2, or higher.

7.1.1 Study Terms and Definitions

Study terms and definitions are provided below.

Term	Definition
Endoscopic Remission	SES-CD score ≤ 4
Complete Mucosal Healing	Absence of ulcerations
Endoscopic Response	SES-CD reduction by ≥ 50%
Clinical Response	CDAI decrease from baseline of ≥ 100 points
Clinical Remission	CDAI ≤ 150 points

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication, as recorded on the electronic case report form (eCRF) dosing page. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

All protocol-specified study visit dates are defined relative to Study Day 1 (for example, the date for the scheduled Week 2 Visit should be Study Day 15).

7.1.3 Definition of Baseline Values

Unless otherwise specified, baseline values are defined as the last observed value before the first dose of study medication. Values measured on Day 1 must be prior to administration of study medication to be classified as Baseline.

7.1.4 Definition of Screen Failure

Screen failure subjects are subjects who signed the informed consent and were not enrolled in the study. The primary reason for screen failure is collected in the eCRF using the following categories:

- Pretreatment Event (PTE)/AE
- Did Not Meet Entrance Criteria
- Significant Protocol Deviation
- Lost to Follow-Up
- Voluntary Withdrawal
- Study Termination
- Other

7.1.5 Definitions of Study Visit Windows

Day 1 will be analyzed as Day 1, provided that the date of the assessment matches the date of the first dose of study drug. Assessments recorded as Day 1 on the eCRF but occurring prior to the date of first dose will be windowed to Baseline.

Unless otherwise specified the rules provided below in Table 7.a, Table 7.b, Table 7.c, and Table 7.d will be used for all variables. The lower and upper bounds of each window are the approximate midpoints between the scheduled days for the current visit and its adjacent scheduled visits. The value used in analysis for by-visit summaries is the value within the specified window. If a patient has more than one measurement within an analysis window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the later assessment will be used in analyses. In case of ties located on the same side of the target day (i.e., more than one value for the same day), the mean of the values will be used for continuous parameters and the worst result will be chosen over a more positive one for categorical parameters (i.e., an abnormal electrocardiogram [ECG] value will be chosen over a normal ECG value).

For safety measurements (laboratory tests and vital signs), descriptive statistics are presented for each scheduled visit including the Final Visit. Final Visit during the Treatment Period will be defined as the last visit (inclusive of both scheduled and unscheduled) which falls between Baseline and Week 26 or date of early termination, whichever comes first, using the visit analysis windows defined above. Final Visit during the Treatment Extension Period will be defined as the last visit (inclusive of both scheduled and unscheduled) which falls just after Week 26 and up to Week 52 or date of early termination, whichever comes first, using the visit analysis windows defined above.

Data identified on the eCRF as coming from an “unscheduled” visit will be eligible for windowing and Final Visit summaries. There will not be a separate “unscheduled” categorization for the reporting of these observations.

The visit windows and applicable study day ranges are presented below for study.

Table 7.a Visit Analysis Windows for Efficacy Variables Evaluated by Visit (Subjects on 26 Weeks of Treatment)

Visit	Target Day	CDAI Scheduled at Baseline and Weeks 6, 10, 14, and 26	AVA, Biopsies, and MREn Scheduled at Baseline and Week 26	C-reactive protein Scheduled at Baseline and Weeks 10 and 26	Ileocolonoscopy Scheduled at Baseline and Weeks 14 and 26	Fecal calprotectin and PRO related QOLs Scheduled at Baseline and Weeks 14 and 26
Baseline	1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Week 2	15					
Week 6	43	2 – 56				
Week 10	71	57 – 84		2 – 126		
Week 14	99	85 – 140			2 – 140	2 – 140
Week 22	155					
Final / Week 26	183	141 – 224	2 – 232	127 – 224	141 – 232	141 – 224

Table 7.b Visit Analysis Windows for Safety Variables Evaluated by Visit (Subjects on 26 Weeks of Treatment)

Visit	Target Day	Weight and Hematology laboratory tests Scheduled at Baseline and Weeks 6, 10, 14, and 26	Chemistry laboratory tests and Urinalysis laboratory tests Scheduled at Baseline and Week 26	Serum Creatinine and eGFR for MREn subjects Scheduled at Baseline and Weeks 22 and 26	Dosing and variables Scheduled at Baseline and Weeks 2, 6, 14, and 22	Vital Signs Scheduled at Baseline and Weeks 2, 6, 14, 22, and 26	Safety Variables by Visit
Visit days are relative to the first dose of open-label medication.							
Baseline	1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Week 2	15				2 – 28	2 – 28	2 – 28
Week 6	43	2 – 56			29 – 70	29 – 70	29 – 56
Week 10	71	57 – 84					57 – 84
Week 14	99	85 – 140			71 – 126	71 – 126	85 – 126
Week 22	155			2 – 168	127 – 196	127 – 168	127 – 168
Final / Week 26	183	141 – 196	2 – 196	169 – 196		169 – 196	169 – 196

Table 7.c Visit Analysis Windows for Efficacy Variables Evaluated by Visit (Subjects on 52 Weeks of Treatment)

Visit	Target Day	CDAI Scheduled at Baseline and Weeks 6, 10, 14, 26, 38, 46 and 52	AVA, Biopsies, and MREn Scheduled at Baseline and Weeks 26, and 52	C-reactive protein Scheduled at Baseline and Weeks 10, 26, 38, and 52	Ileocolonoscopy Scheduled at Baseline and Weeks 14, 26, and 52	Fecal calprotectin and PRO related QOLs Scheduled at Baseline and Weeks 14, 26, 38, and 52
Baseline	1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Week 2	15					
Week 6	43	2 – 56				
Week 10	71	57 – 84		2 – 126		
Week 14	99	85 – 140			2 – 140	2 – 140
Week 22	155					
Week 26	183	141 – 224	2 – 232	127 – 224	141 – 232	141 – 224
Week 30	211					
Week 38	267	225 – 294		225 – 315		225 – 315
Week 46	323	295 – 343				
Final / Week 52	365	344 – 406	233 – 406	316 – 406	233 – 406	316 – 406

Table 7.d Visit Analysis Windows for Safety Variables Evaluated by Visit (Subjects on 52 Weeks of Treatment)

Visit	Target Day	Weight Scheduled at Baseline and Weeks 6, 10, 14, 26, 30, 38, 46 and 52	Urinalysis laboratory tests Scheduled at Baseline and Weeks 26, and 52	Hematology laboratory tests Scheduled at Baseline and Weeks 6, 10, 14, 26, 38, and 52	Chemistry laboratory tests Scheduled at Baseline and Weeks 26, 38, and 52	Serum Creatinine and eGFR for MREn subjects Scheduled at Baseline and Weeks 22, 26, 38, 46, and 52	Dosing Scheduled at Baseline and Weeks 2, 6, 14, 22, 30, 38, and 46	Vital signs Scheduled at Baseline and Weeks 2, 6, 14, 22, 26, 30, 38, 46, and 52	Safety Variables by Visit
Visit days are relative to the first dose of open-label medication.									
Baseline	1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Week 2	15						2 – 28	2 – 28	2 – 28
Week 6	43	2 – 56		2 – 56			29 – 70	29 – 70	29 – 56
Week 10	71	57 – 84		57 – 84					57 – 84
Week 14	99	85 – 140		85 – 140			71 – 126	71 – 126	85 – 126
Week 22	155					2 – 168	127 – 196	127 – 168	127 – 168
Week 26	183	141 – 196	2 – 196	141 – 196	2 – 196	169 – 196		169 – 196	169 – 196
Week 30	211	197 – 238					197 – 238	197 – 238	197 – 231
Week 38	267	239 – 294		197 – 315	197 – 315	197 – 294	239 – 294	239 – 294	239 – 294
Week 46	323	295 – 343				295 – 343	295 – 392	295 – 343	295 – 343
Final / Week 52	365	344 – 392	197 – 392	316 – 392	316 – 392	344 – 392		344 – 392	344 – 392

Data identified on the eCRF as coming from the "follow-up" visit (i.e., Postdose 18 Week Safety Follow-up) will be summarized as collected and entered. These study visits will not be windowed.

The study window convention will not be applied to data listings; the data listings will display the visits as collected and entered in the eCRF.

7.1.6 Convention for Calculation of SES-CD Scores

The SES-CD has been shown to be comparable to the Crohn's Disease Endoscopic Index of Severity and a straightforward scoring system for Crohn's disease [2]. The overall SES-CD score ranges from 0 to 56 and is the sum of 4 variables (i.e., size of ulcers [cm], ulcerated surface [%], affected surface [%], and presence of narrowing) across 5 bowel segments (i.e., rectum, descending and sigmoid colon, transverse colon, ascending colon, and ileum). Each variable is coded from 0 to 3 based on severity, where 0 is none or not severe and 3 is the most severe case, with the sum of the scores for each variable ranging from 0 to 15, except for presence of narrowing. Presence of narrowing ranges from 0 to 11 since a severity of 3 represents a narrowing which a colonscope cannot be passed and, thus, can only be observed once among the bowel segments. The segmental SES-CD score is the sum of the 4 variables for each bowel segment and can range from 0 to 12, where each individual variable score ranges from 0 to 3 (see Appendix B).

7.1.7 Convention for Calculation of CDAI Scores

The CDAI score is the summation of 8 components, including number of liquid or very soft stools, abdominal pain, general well-being, extra-intestinal manifestations of Crohn's Disease, Lomotil/Imodium/opiates for diarrhea usage, abdominal mass, hematocrit level, and body weight (see Appendix C).

Number of liquid or very soft stools, abdominal pain, and general well-being are self-reported via subject electronic diary entries. To calculate subscores at each visit, the diary data from the 10 days prior to the date of CDAI calculation were used and the following rules were applied:

1. Take the 7 most recent days of diary data prior to the date of CDAI calculation. If the CDAI analysis visit is Screening and less than 7 days of data are present, a subscore cannot be calculated.
2. For number of liquid or very soft stools only, if any of the 7 most recent days of diary data have stool frequency values greater than 24, set the value for the stool record for that day to missing.
3. If less than 4 non-missing results remain, the subscore cannot be calculated, and the subject will be categorized as a non-responder. Otherwise, calculate the subscore by summing the values, dividing by the number of non-missing records included in the summation, and multiplying by the factor appropriate for the given subscore.
    a. For stool, the factor is 2.
    b. For abdominal pain, the factor is 5.

c. For general well-being, the factor is 7.

Table 7.e provides examples of calculated CDAI scores using various eDiary scenarios (excluding eligibility). Table 7.f provides examples of calculated CDAI scores using various eDiary scenarios for eligibility. Patient diaries can be completed 14 days prior to the eligibility visit. Any on-study colonoscopies and/or MREn are taken into account such that the diary data from the day prior, day of, and day after are excluded from the visit's CDAI calculation.

Table 7.e Examples of eDiary Subscore Entries and Corresponding Subscore Derivation (Excluding Eligibility)

Day -14	Day -13	Day -12	Day -11	Day -10	Day -9	Day - 8	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Raw Sum	Final Subtotal (factor = x 2)
1	2	M	2	2	2	2	1	1	1	1	1	1	1	7	14
1	X	MRE	X	3	X	C	X	1	1	1	1	1	1	9	18
1	2	M	2	M	3	M	3	M	3	M	3	3	3	21	42
1	2	M	2	M	2	M	M	M	1	3	2	2	M	14	28
1	M	M	2	3	X	MRE	X	X	C	X	3	3	3	21	42
1	M	X	MRE	X	C	X	M	2	M	M	M	2	0	N/A	N/A

M = Missing data.
C = Colonoscopy.
N/A = Not Available.
Used days are highlighted.

Table 7.f Examples of eDiary Subscore Entries for Eligibility and Corresponding Subscore Derivation (for Eligibility, only rule #1 applies)

Day -14	Day -13	Day -12	Day -11	Day -10	Day -9	Day - 8	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Raw Sum	Final Subtotal (factor = x 2)
1	2	M	2	2	2	2	1	1	1	1	1	1	1	7	14
X	MRE	X	3	3	3	X	C	X	3	3	3	3	M	21	42
1	2	M	2	3	3	3	M	1	2	2	3	R	1	17	34
1	2	M	2	3	3	3	3	2	2	2	R	2	3	18	36
1	X	MRE	X	3	X	C	X	2	2	3	R	3	1	N/A	N/A
2	3	2	2	3	X	C	X	3	2	2	2	3	3	18	36
1	3	M	M	2	1	2	3	X	C	X	3	R	2	N/A	N/A

M = Missing data.
C = Colonoscopy.
R = Subscore requested.
N/A = Not Available.
Used days are highlighted.

In addition to the subscores originating from the subject electronic diary entries, subscores for extra-intestinal manifestations of Crohn's Disease, usage of Lomotil/Imodium/opiates for diarrhea, abdominal mass, hematocrit level, and body weight are calculated.

Extra-intestinal manifestations of Crohn's Disease include arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum/aphthous stomatitis, anal fissure fistula, or abscess,

other fistula, and fever over 37.8°C during the past week. The total number of extra-intestinal manifestations is summed and multiplied by a factor of 20.

If a subject used Lomotil/Imodium/opiates for diarrhea, they have a subscore of 30. Otherwise, their usage of Lomotil/Imodium/opiates for diarrhea subscore is 0.

For a definite, questionable, or no abdominal mass, a subject receives a subscore of 50, 20, or 0, respectively.

Hematocrit results are subtracted from 47 for males and from 42 for females to obtain the hematocrit subtotal. The hematocrit subtotal is then multiplied by a factor of 6 to determine the hematocrit subscore. If the hematocrit subtotal is 0, the hematocrit subscore is also 0.

Lastly, the body weight subscore is obtained with the following formula:

$$\left[1 - \left(\frac{\text{Body Weight}}{\text{Standard Weight}}\right)\right] \times 100$$

where standard weight is calculated as $(\text{height in m})^2 \times 22.1$ for males and $(\text{height in m})^2 \times 20.8$ for females. If the body weight subscore is < -10, the body weight subscore is set to -10.

To calculate the total CDAI score for a study visit, sum all 8 component subscores at that particular study visit. If any of the 8 subscores are missing, the total CDAI score cannot be calculated for that study visit.

7.1.8 Conventions for Missing Adverse Events Dates

Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

For AEs or SAEs, a missing or incomplete onset date will be imputed according to the following conventions:

1. If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):
   - First study medication date
   - Informed consent date (for SAEs only)
2. If an onset date is incomplete, the derived onset date will be calculated following:
   - Missing day, but month and year present: the day will be imputed as the 15th of the month. If the month and year are equal to the month and year of the first study medication dose and the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.
   - Missing day and month, but year present: the day and month will be imputed as the 30th June of the year. If the year is equal to the year of the first study medication dose and the first study medication dose occurs after the imputed date, the derived onset

date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.

- If the imputed AE onset date occurs after the database lock date, the imputed AE onset date will be imputed as the database lock date.

For AEs or SAEs, a missing or incomplete end date will be imputed according to the following conventions:

1. If an end date is missing, the derived end date will be imputed as the last assessment date, assuming that the last assessment occurs after the AE start. If the last assessment occurs prior to the AE start date, the derived end date will be imputed as the AE start date.
2. If an end date is incomplete, the derived end date will be calculated following:
    - Missing day, but month and year present: the day will be imputed as the last date (for example February 2009 will be imputed as 28 February 2009) of the month.
    - Missing day and month, but year present: the day and month will be imputed as the 31st December of the year.
    - If the imputed AE end date occurs after the database lock date, the imputed AE end date will be imputed as the database lock date.

7.1.9 Conventions for Missing Concomitant Medications Dates

Start and stop dates for all concomitant medications are collected on the eCRF. However, in case of missing or partial information in these dates, the following rules will be used:

If the start date is missing or partial:

- If the day is missing, the start day will be the first day of the month.
- If the month is missing, the start month will be the month corresponding to 90 days prior to the first study medication date.
- If the year is missing, the start year will be the minimum of the year of the first clinic visit or the year of the informed consent date.
- If the entire date is missing, the start date will be the date of first study drug administration.

If the stop date is missing, partial or “continuing”:

- If the day is missing, the stop day will be the last day of the month reported.
- If the month is missing, the stop month will be the month during which the last dose of treatment was administered.
- If the year or the entire date is missing or if the medication is “continuing”, the stop year will be the year in which the last dose of treatment was administered.

7.1.10 Conventions for Missing Previous Medications Dates

No dates will be imputed for previous medications.

7.1.11 Conventions for Calculation of Duration of CD

Duration of CD is calculated as the number of years from CD diagnosis date to first dose date:

$$\frac{1 + \text{date}_{\text{first dose}} - \text{date}_{\text{diagnosis}}}{365.25}$$

The duration of CD will be included in the baseline CD characteristics listing. If the date CD was diagnosed is partially missing, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30th June of the year.

7.1.12 Calculation of Body Mass Index

BMI will be calculated as the ratio of patient's weight (in kilograms) to the square of the patient's height (in meters):

$$\text{BMI}\left(\frac{\text{kg}}{\text{m}^2}\right) = \frac{\text{weight(kg)}}{[\text{height(m)}]^2}$$

7.1.13 Methods for Handling of Missing Efficacy Data

Through the end of the treatment period, the missing efficacy data will be handled as follows:

- Missing data for dichotomous (i.e., proportion-based) endpoints will be handled using the non-responder imputation method, i.e. any subject with missing information for determination of endpoint status will be considered as a non-responder in the analysis.
- Missing data for continuous endpoints will be imputed using last available post-baseline observation carried forward (LOCF) method.

7.2 ANALYSIS SETS

The Study Part A analyses will be performed on the following analysis sets:

- The Full Analysis Set (FAS) will include all enrolled subjects who receive at least 1 dose of study drug.
- The FAS-MREn is the FAS within the MREn substudy.
- The Per Protocol Analysis Set (PPS) is a subset of the FAS and consists of all subjects who do not violate the terms of the protocol in a way that would impact the study outcome significantly. Major protocol violations that exclude a subject from the PPS are listed in Section 7.4. Efficacy analyses for the primary and secondary endpoints using the PPS population may be provided as part of a sensitivity analysis.
- The PPS-MREn is a subset of the FAS-MREn and consists of all subjects who do not violate the terms of the protocol in a way that would impact the study outcome significantly. Major protocol violations that exclude a subject from the PPS-MREn are

listed in Section 7.4. Efficacy analyses for the MREn endpoints using the PPS-MREn population may be provided as part of a sensitivity analysis.

The Study Part B analyses will performed on the following analysis sets:

- The FAS-Extension is the subset of subjects in the FAS who consented to Part B.
- The FAS-MREn-Extension is the subset of subjects in the FAS-MREn who consented to Part B.
- The PPS-Extension is the subset of subjects in the FAS-Extension and consists of all subjects who do not violate the terms of the protocol in a way that would impact the study outcome significantly. Major protocol violations that exclude a subject from the PPS-Extension are listed in Section 7.4. Efficacy analysis for the primary and secondary endpoints using the PPS-Extension population may be provided as part of a sensitivity analysis.
- The PPS-MREn-Extension is the subset of subjects in the FAS-MREn-Extension and consists of all subjects who do not violate the terms of the protocol in a way that would impact the study outcome significantly. Major protocol violations that exclude a subject from the PPS-MREn-Extension are listed in Section 7.4. Efficacy analysis for the MREn endpoints using the PPS-MREn-Extension population may be provided as part of a sensitivity analysis.

The FAS and FAS-Extension will be used in both efficacy and safety analyses. The FAS-MREn and FAS-MREn-Extension will be used in the MREn analyses. Analyses using PPS, PPS-Extension, PPS-MREn, and PPS-MREn-Extension populations may be provided as sensitivity analyses.

Sensitivity analyses for the primary and secondary efficacy endpoints using PPS/PPS-Extension will be conducted only if more than 15% of the subjects in the FAS/FAS-Extension have at least 1 significant protocol deviation.

7.3 DISPOSITION OF SUBJECTS

Disposition will be evaluated for the following study periods: screening and treatment period.

Disposition of all screened subjects (denominator) will be tabulated (count and percent).

Disposition of screen failures (denominator) will be tabulated according to primary screen failure reason (e.g., pretreatment event, major protocol deviation, lost to follow-up, etc.) as entered on the eCRF.

Disposition of all enrolled subjects will be tabulated as:

- All enrolled subjects (denominator)
- Subjects who were enrolled but not treated, if applicable
- All subjects who completed the study drug/visits
- All subjects who prematurely discontinued (permanently) study drug/visits

Primary reasons for discontinuation of study drug/visits, as entered on the eCRF, will be tabulated; the reasons include adverse event, significant protocol deviation, lost to follow-up, voluntary withdrawal, study termination, pregnancy, lack of efficacy and other.

Disposition of enrolled subjects by analysis set will be also tabulated.

The date of first dose, date of last dose, duration of treatment and the reason for premature discontinuation of study drug/study visit will be listed for each enrolled subject. A listing of inclusion/exclusion criteria responses by subject will also be provided. A separate listing of screen failures and criteria will be presented.

Study information, including date first subject signed ICF, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, Medical Dictionary for Regulatory Activities (MedDRA) version, World Health Organization Drug Dictionary (WHODrug) version, and SAS Version will be presented.

Summary of eligibility from entrance into the treatment phase will be tabulated and listed.

The enrolled subjects who did not meet at least one inclusion criteria or who did meet at least one exclusion criteria will be listed.

The number of subjects enrolled by site will be tabulated and listed.

7.4 MAJOR PROTOCOL VIOLATIONS

Major protocol violations used to exclude subjects from the PPS population include:

1. A missing Week 26 ileocolonoscopy.
2. An Entry Criteria significant protocol deviation.

Additional major protocol violations for exclusion from the PPS population may be finalized as part of a final data review and documented prior to database lock.

Major protocol violations used to exclude subjects from the PPS-Extension population include:

1. A missing Week 52 ileocolonoscopy.
2. An Entry Criteria significant protocol deviation.

Additional major protocol violations for exclusion from the PPS-Extension population may be finalized as part of a final data review and documented prior to database lock.

Major protocol violations used to exclude subjects from the PPS-MREn population include:

1. Missing numeric scores in more than 3 ileocolonic bowel segments at both Baseline and Week 26.

Major protocol violations used to exclude subjects from the PPS-MREn-Extension population include:

1. Missing numeric scores in more than 3 ileocolonic bowel segments at both Baseline and Week 52.

All major protocol violations will be tabulated and listed.

7.5 SIGNIFICANT PROTOCOL DEVIATIONS

Significant protocol deviations will be collected onto the eCRF throughout the conduct of the study. Significant deviations will be tabulated using the following categories:

- Entry Criteria
- Concomitant Medication
- Procedures Not Performed Per Protocol (Primary Endpoint or Safety Related)
- Study Medication
- Withdrawal Criteria

Significant protocol deviations will be also listed by subject.

7.6 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Table 7.g lists the variables which will be tabulated in the demographic and baseline characteristics table for enrolled subjects.

Table 7.g Summaries of Demographic and Baseline Characteristics

Demography (unit)	Summarized as	Categories
Age (years)	Continuous and Categorical	<35, ≥ 35 <65, ≥ 65 <75, ≥ 75
Gender	Categorical	Male Female
Race[a]	Categorical	American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White
Ethnicity	Categorical	Hispanic or Latino Non-Hispanic and Latino
Height (cm)	Continuous	
Weight (kg)	Continuous	
Body Mass Index (BMI) (kg/m^2)	Continuous	
Smoking Classification	Categorical	Subject has never smoked Subject is a current smoker Subject is an ex-smoker
Female Reproductive Status	Categorical	Postmenopausal Surgically Sterile Female of Childbearing Potential N/A (Subject is a Male)

[a] recorded on the eCRF. Subjects who identify themselves as more than one race on the eCRF will be classified as Multiracial for tabulation, and will be included only in the Multiracial category.

Screen failures will be tabulated and listed for age, age group, gender, ethnicity and race. All other demographic and baseline characteristic summaries will be tabulated and listed using the FAS, the FAS-Extension, the FAS-MREn, and the FAS-MREn-Extension. In addition, original read MREn parameters (i.e., image adequacy, adequacy reason, relative contrast enhancement,

wall thickness, ulceration, edema, global MaRIA score, segmental MaRIA score, presence of fistulas, fistulas description, presence of obstructive lesions, fluid collections, fluid collection change, inflammatory mass, and inflammatory mass change) at the Screening visit for screen failures at the selected MREn substudy centers will be summarized for each ileocolonic segment and more proximal bowel segments, if evaluable, using the FAS-MREn and the FAS-MREn-Extension. Ileocolonic bowel segments include the ascending colon, descending colon, transverse colon, sigmoid colon, rectum, and terminal ileum. Proximal bowel segments include the jejunum J-1, jejunum J-2, proximal ileum PI-1, and proximal ileum PI-2.

Table 7.h lists the CD-related baseline characteristics which will be tabulated and listed.

Table 7.h Summaries of CD-Related Baseline Characteristics

Characteristics (unit)	Summarized as	Categories
Duration of Crohn's Disease (years)	Continuous and Categorical	< 1 year ≥ 1 to < 3 years ≥ 3 to < 7 years ≥ 7 years
Baseline CRP (mg/L)	Continuous and Categorical	≤ 2.87 mg/L > 2.87 mg/L ≤ 5 mg/L > 5 mg/L ≤ 10 mg/L > 10 mg/L
Elevated baseline CRP (mg/L)	Continuous and Categorical	Yes (CRP > 2.87 mg/L) No (CRP ≤ 2.87 mg/L)
Concomitant use of oral corticosteroids	Categorical	Yes No
Prior TNF-alpha status	Categorical	Naïve Failure
Baseline Fecal Calprotectin (µg/g)	Continuous and Categorical	≤ 250 µg/g > 250 µg/g ≤ 500 µg/g > 500 µg/g
Baseline CDAI Activity	Continuous and Categorical	≤ 330 > 330
Baseline SES-CD Score	Continuous and Categorical	<7 7-15 (moderate) >15 (severe)

In addition, Baseline MREn parameters for enrolled subjects at the selected MREn substudy centers will be summarized for each ileocolonic segment and more proximal bowel segments, if evaluable, using the FAS-MREn and the FAS-MREn-Extension.

All individual demographic and baseline characteristics will be listed by region, site, and subject number.

7.7 Medical History and Concurrent Medical Conditions

Summaries of medical history, defined as significant conditions or diseases that stopped at or prior to the time of informed consent, and concurrent medical conditions, defined as significant ongoing conditions or diseases present at signing of informed consent, will be summarized based on the FAS.

Medical history and concurrent medical conditions will be coded using the MedDRA (Version 19 or higher) coding system. Medical history and concurrent medical conditions will be summarized by system organ class (SOC) and preferred term (PT). The tables will be sorted in alphabetic order by SOC and in decreasing frequency based on the total number of reports by preferred terms in each SOC. The number and percentage of subjects with any significant medical history and concurrent medical conditions will be summarized for each SOC and preferred term. The denominator used for calculating the percentages will be the total number of subjects. For the tables, if a subject reports the same preferred term multiple times, then that preferred term will be counted only once for that subject. Similarly, if a subject reports multiple conditions within the same SOC, then that SOC will be counted only once for that subject in the tables.

All medical history and concurrent medical condition data will be listed by site and subject number. The listing will contain subject identifier, treatment, SOC, PT, whether there was any medical history or concurrent condition, and if yes, a detail of the medical history or concurrent condition.

7.8 MEDICATION HISTORY AND CONCOMITANT MEDICATIONS

Summaries of medication history and concomitant medications will be tabulated based on the FAS.

Medication history information to be obtained and recorded on the eCRF includes any medication relevant to eligibility criteria that stopped at or within 30 days prior to signing of informed consent. The CD prior biologic medication which have been stopped are recorded on the eCRF as well.

Concomitant medications are recorded on the eCRF and include any medication other than study drug taken at any time between the times of informed consent through the end of the study. Any ongoing CD biologic medications are included with the Concomitant Medications.

Medication history, CD prior biologic medications, and concomitant medications will be coded using the WHODrug dictionary (Version 01March 2015 or higher).

Concomitant medications will be summarized by therapeutic classification and preferred medication name and will include only those medications taken at any time between the times of informed consent and on or prior to the last dose date of study drug. Concomitant medications will be classified and summarized separately as follows:

- Concomitant medications that started and stopped prior to baseline: any medication stopped after time of informed consent and prior to the first dose of the study medication.
- Concomitant medications that started prior to and were ongoing at baseline: any medication that started before and was not stopped prior to the first dose of the study medication.
- Concomitant medications that started after baseline: any medication that started at or after the first dose of the study medication.

- Concomitant medications that were ongoing and started after baseline: any medication that started before and was not stopped prior to the first dose of the study medication or any medication that started at or after the first dose of the study medication.

The tables for medication history and CD prior biologic medications will present the number and percentage of subjects by preferred medication name using the total number of subjects in the treatment arm as the denominator. Preferred medication names are sorted by decreasing frequency based on the total number of subjects.

Separate listings for medication history, CD prior biologic medications, and concomitant medications will be produced by site and subject number. The listing for medication history will contain site number, subject number, treatment, WHODrug preferred medication name, dose, frequency, unit, route, end date, and whether the medication was ongoing. The listing for CD prior biologics medications which have been stopped will contain site number, subject number, treatment, WHODrug preferred medication name, dose, unit, frequency, route, start date, end date, reason for discontinuation, and primary reason for intolerance. The listing for concomitant medication will contain site number, subject number, treatment, WHODrug preferred medication name, dose, unit, frequency, route, start date, end date, study day, and whether the medication was given to treat PTE/AE.

7.9 Study Drug Exposure and Compliance

Study drug exposure will be summarized based on the FAS and the FAS-Extension.

Exposure will be presented as the frequency and percentage of subjects who received complete infusions. A subject has received complete infusion if the total amount was infused as per data collected in eCRF.

Duration of exposure will be calculated as (date of last dose – date of first dose) + 127. Duration of exposure will be summarized continuously and categorically. For Study Part A, duration of exposure will be summarized in the following categories: <20 Weeks, 20 – <24 Weeks, 24 - <32 Weeks, 32 – <40 Weeks, and ≥ 40 Weeks. For Study Part B, duration of exposure will be summarized in the following categories: <56 Weeks, 56 - <64 Weeks, and ≥ 64 Weeks.

Since all doses will be administered at in-clinic visits compliance will not be presented.

All study drug administration and accountability data will be listed by site and subject number. The following variables will be listed: subject number, treatment, dose dates and times, dose interruption dates and times (if applicable), and completion status of infusion and reason for incomplete infusion.

7.10 Efficacy Analysis

This section describes the analyses to be conducted on the primary, secondary, and additional efficacy endpoints.

All proportion-based efficacy endpoints will be summarized by presenting the point estimate and 2-sided 95% confidence intervals (CIs) for the proportion. All subjects with missing data for determination of endpoint status will be considered as a non-responder in the analysis.

All change from Baseline-based efficacy endpoints will be summarized descriptively by time point for observed and change from Baseline values. Missing data will be imputed using the LOCF method.

7.10.1 Primary Efficacy Endpoint

Primary efficacy analysis will be summarized based on the FAS.

The primary endpoint is the proportion of subjects achieving endoscopic remission, defined as a total SES-CD score of ≤ 4 at Week 26. The proportion of subjects with endoscopic remission and its 2-sided 95% CI will be calculated using the Clopper-Pearson method.

Subjects with a missing SES-CD score at Week 26 will be considered as non-responders.

All SES-CD score components will be listed by site and subject number for each bowel segment.

7.10.1.1 Sensitivity Analyses for Primary Efficacy Endpoint

To assess the robustness of the primary efficacy analysis, the following additional analyses will be performed for the primary endpoint.

- The proportion of subjects with endoscopic remission and its 2-sided 95% CI will be calculated excluding subjects with a Screening SES-CD score <7.
- The proportion of subjects with endoscopic remission and its 2-sided 95% CI will be calculated using the PPS (if applicable).
- The proportion of subjects with endoscopic remission and its 2-sided 95% CI will be calculated using the LOCF method.

7.10.1.2 Summaries of Primary Efficacy Endpoint within Subgroups

The primary efficacy endpoint of endoscopic remission will be summarized for the following subgroups using the FAS, and the PPS (if applicable):

- Baseline Disease Activity (CDAI) (≤330, > 330)
- Duration of CD (<1 year, 1 – <3 years, 3 – <7 years, ≥7 years)
- Geographic Region (North America, Western / Northern Europe, Central Europe, Eastern Europe, Africa / Asia / Australia)
- Baseline CRP (≤5 mg/L, >5 mg/L; ≤10 mg/L, >10 mg/L)
- Baseline Fecal Calprotectin (≤250 µg/g, >250 µg/g; ≤500 µg/g, >500 µg/g)
- Prior TNF-alpha Status (Naïve, Failure)
- Baseline SES-CD (<7, 7 to 15 (Moderate), >15 (Severe))

7.10.2 Secondary Efficacy Endpoints

Secondary efficacy analyses will be summarized based on the FAS and FAS-Extension. Subgroup analyses will be performed using prior TNF-alpha status (naïve, failure).

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for the observed and change from baseline values for the segmental SES-CD scores, the overall SES-CD score, and the CDAI score will be presented.

The details collected on each of the below endpoints will be listed.

7.10.2.1 Complete Mucosal Healing

The proportions of subjects with ulcerations at Baseline who achieve complete mucosal healing at Week 26 and Week 52 and their 2-sided 95% CI will be calculated. Complete mucosal healing is defined as the absence of ulceration, which is demarcated as an SES-CD variable 'Size of Ulcers' score of 0 (Appendix B), from the presence of ulceration at Baseline. Subjects with any missing 'Size of Ulcers' score at Week 26 or Week 52 will be considered as non-responders.

Complete mucosal healing will also be summarized for the subgroups listed in section 7.10.1.2 based on the FAS, FAS-Extension, PPS, and PPS-Extension.

7.10.2.2 Endoscopic Remission

Endoscopic remission at Week 14 and Week 52 will be analyzed following a similar approach outlined in section 7.10.1.

7.10.2.3 Endoscopic Response

The proportions of subjects with endoscopic response (defined as SES-CD reduction by at least 50% from baseline) at Week 14, Week 26, and Week 52 and their CIs will be calculated by bowel segment and overall. Subjects with a missing SES-CD at Week 14, Week 26, and/or Week 52 will be considered as non-responders. A sensitivity analysis will be performed for the proportion of subjects with endoscopic response and its 2-sided 95% CI using the LOCF method.

Analyses for endoscopic response will also be performed overall and by prior TNF-alpha status (naïve, failure) based on the PPS and PPS-Extension.

7.10.2.4 Clinical Response

The proportions of subjects achieving clinical response (CDAI score decrease from baseline of at least 100 points) at Week 10, Week 26, and Week 52 and their CIs will be calculated. Subjects with a missing CDAI score at Week 10, Week 26, and/or Week 52 will be considered as non-responders.

Analyses for clinical response will also be performed overall and by prior TNF-alpha status (naïve, failure) based on the PPS and PPS-Extension.

7.10.2.5 Clinical Remission

The proportions of subjects achieving clinical remission (CDAI score of at most 150) at Week 10, Week 26, and Week 52 and their CIs will be calculated. Subjects with a missing CDAI score at Week 10, Week 26, and/or Week 52 will be considered as non-responders.

Analyses for clinical remission will also be performed overall and by prior TNF-alpha status (naïve, failure) based on the PPS-Extension.

7.10.2.6 Durable Clinical Remission

The proportion of subjects in Study Part B with durable clinical remission (defined as clinical remission at Week 26 and Week 52) at Week 52 and its CI will be calculated. Subjects with a missing CDAI score at Week 52 will be considered as non-responders.

Analyses for durable clinical remission will also be performed overall and by prior TNF-alpha status (naïve, failure) based on the PPS-Extension.

7.10.3 Additional Efficacy Endpoints

Additional efficacy analyses will be summarized based on the FAS, FAS-Extension, FAS-MREn, and FAS-MREn-Extension, as applicable. Subgroup analyses will be performed using prior TNF-alpha status (naïve, failure).

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for the observed and change from baseline values for the ileal, colonic, and total Global Histological Disease Activity Scores (GHAS) will be presented.

The correlation between subjects' SES-CD scores and MaRIA scores by study visit will be explored by bowel segment and overall using scatter plots. The correlation between subjects' CDAI score and global MaRIA score by study visit will be explored using scatter plots.

The relationship between the various remission statuses, as defined by CDAI (i.e., clinical response and clinical remission), endoscopic (i.e., endoscopic response, endoscopic remission, and complete mucosal healing), imaging (i.e., ileocolonic remission by MREn, overall remission by MREn, ileocolonic response by MREn, and overall response by MREn), and histological (i.e., total GHAS ≤ 4) assessments, will also be explored using Pearson's correlation coefficient in the following combinations:

- Clinical Response and Endoscopic Response
- Clinical Response and Endoscopic Remission
- Clinical Response and Ileocolonic Remission by MREn
- Clinical Response and Overall Remission by MREn
- Clinical Response and Total GHAS ≤ 4
- Clinical Remission and Endoscopic Response
- Clinical Remission and Endoscopic Remission

- Clinical Remission and Ileocolonic Remission by MREn
- Clinical Remission and Overall Remission by MREn
- Clinical Remission and Total GHAS ≤ 4
- Endoscopic Response and Ileocolonic Remission by MREn
- Endoscopic Response and Overall Remission by MREn
- Endoscopic Response and Total GHAS ≤ 4
- Endoscopic Remission and Ileocolonic Remission by MREn
- Endoscopic Remission and Overall Remission by MREn
- Endoscopic Remission and Total GHAS ≤ 4
- Complete Mucosal Healing and Ileocolonic Remission by MREn
- Complete Musocal Healing and Ileocolonic Response by MREn
- Ileocolonic Remission by MREn and Total GHAS ≤ 4
- Overall Remission by MREn and Total GHAS ≤ 4

The correlation between subjects' change from Baseline in CDAI, change from Baseline in SES-CD, change from Baseline in MaRIA, and change from Baseline in GHAS by study visit will be explored using scatter plots.

The details collected on each of the below endpoints will be listed.

7.10.3.1 MREn Parameters

Only original read MREn parameters will be utilized for analyses.

Continuous individual MREn parameters (i.e., relative contrast enhancement, wall thickness, global MaRIA score, and segmental MaRIA score) for each ileocolonic segment (i.e., ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and terminal ileum) and more proximal bowel segments (i.e., jejunum J-1, jejunum J-2, proximal ileum PI-1, and proximal ileum PI-2), if evaluable, will be summarized descriptively at Baseline, each post-Baseline visit, and change from Baseline to each post-Baseline visit.

Shifts in categorical individual MREn parameters (i.e., ulceration, edema, presence of fistulas, fistulas description, presence of obstructive lesions, fluid collections, fluid collection change, inflammatory mass, and inflammatory mass change) between baseline and each post-baseline visit for each ileocolonic segment and more proximal bowel segments, if evaluable, will be presented as cross-tabulations of responses with missing, if applicable, and total categories. Scheduled visits for MREn are at Baseline, Week 26, and Week 52.

Missing data will not be imputed. Original read and re-read MREn parameters will be listed.

7.10.3.2 MaRIA Scores

The proportions of subjects achieving segmental MaRIA score <7 at Baseline, Week 26, and Week 52 and their CIs will be calculated. The proportions of subjects achieving segmental MaRIA score <11 will be calculated similarly. In addition, the proportion of subjects achieving ileocolonic remission and response by MREn and overall remission and response by MREn at Baseline, Week 26, and Week 52 and their CIs will be calculated. The MREn-based measures of interest are defined as follows:

- Ileocolonic remission is defined as a post-Baseline segmental MaRIA score <7 in every ileocolonic segment from a Baseline segmental MaRIA score ≥7 in any ileocolonic segment.
- Overall remission is defined as a post-Baseline segmental MaRIA score <7 in every segment, whether ileocolonic or proximal, from a Baseline segmental MaRIA score ≥7 in any segment.
- Ileocolonic response is defined as a post-Baseline segmental MaRIA score <11 in every ileocolonic segment from a Baseline segmental MaRIA score ≥11 in any ileocolonic segment.
- Overall response is defined as a post-Baseline segmental MaRIA score <11 in every segment, whether ileocolonic or proximal, from a Baseline segmental MaRIA score ≥11 in any segment.

The proportion of subjects with 25%, 50%, and 75% reduction in ileocolonic MaRIA score at Week 26 and Week 52 and their CIs will be calculated by ileocolonic bowel segment.

In addition, the correlation between the SES-CD size of ulcers parameter and the MaRIA ulceration parameter (Yes/No) at Baseline, Week 26, and Week 52 will be explored by bowel segment using the chi-squared test. For comparison purposes between SES-CD, GHAS, and MaRIA, the following assumptions will be taken:

- The SES-CD size of ulcers parameter will be dichotomized with ‘None’ and ‘Aphthous ulcers’ as ‘Aphthous or None’ and ‘Large ulcers’ and ‘Very large ulcers’ as ‘Ulcers > 0.5 cm’.
- The MaRIA ulceration parameter for the descending colon and sigmoid colon will be combined into ‘descending and sigmoid colon’, where a ‘No’ response requires a lack of ulceration in both the descending colon and the sigmoid colon.
- The MaRIA scores for the descending colon and sigmoid colon will be added together to create ‘descending and sigmoid colon’ for continuous comparisons.

7.10.3.3 SES-CD Score Reduction

The proportions of subjects with 25% and 75% reduction of SES-CD at Week 14, Week 26, and Week 52 and their CIs will be calculated by bowel segment and overall.

7.10.3.4 Granulocyte Presence

The proportion of subjects with no granulocytes present in the bowel biopsy at Baseline, Week 26, and Week 52 and their CIs will be calculated. The presence of granulocytes is defined by the presence of lamina propria neutrophils and/or neutrophils in the epithelium, which are described in Section 7.10.3.5. In addition, the proportion of subjects with no granulocytes present in the bowel biopsy at Week 26 and Week 52 will be presented for subjects with granulocytes present at Baseline.

7.10.3.5 Histology Change

Histology parameters, classified as features of chronicity or features of activity, are given a score by a pathologist as follows:

Classification	Parameter	Score	
Features of Chronicity	Structural (Architectural) Change	0	None
		1	Not severe
		2	Severe
	Chronic Inflammatory Infiltrate	0	None
		1	Increased but not very dense infiltrate
		2	Very dense infiltrate
Features of Activity	Lamina Propria Neutrophils	0	None
		1	Some but not readily detectable
		2	Easily detectable at low magnification
	Neutrophils in Epithelium	0	None
		1	In surface epithelium
		2	In crypt epithelium, with or without abscesses
	Epithelial Damage	0	None
		1	Some degenerative or regenerative changes, less than half of epithelium, irrespective of surface or crypts
		2	Some degenerative or regenerative changes, more than half of epithelium, irrespective of surface or crypts
	Erosion or Ulceration	0	None
		1	Strictly defined by the presence of granulation tissue
	Epithelioid Granuloma	0	None
		1	Present

The modified GHAS is calculated as the sum of all individual scores for each parameter listed above, for each individual biopsy [4]. The features of chronicity GHAS, features of activity GHAS, and total segmental GHAS will be calculated for each bowel segment using the highest total score in that segment. The ileal GHAS (IGHAS) is defined as the segmental GHAS for the ileum. The colonic GHAS (CGHAS) is defined as the highest segmental GHAS amongst the rectum, descending/sigmoid colon, transverse colon, and ascending colon. The features of chronicity score ranges between 0 and 4, and the features of activity score ranges between 0 and 8. The IGHAS, CGHAS, and segmental GHAS range between 0 and 12.

The proportions of subjects meeting the following criteria will be presented:

- IGHAS ≤ 4 at Baseline, Week 26, and Week 52 and their CIs
- CGHAS ≤ 4 at Baseline, Week 26, and Week 52 and their CIs
- Both IGHAS and CGHAS ≤ 4 at Baseline, Week 26, and Week 52 and their CIs

The proportions listed above will also be presented for subjects who had a modified GHAS score > 4 at Baseline.

The proportions of subjects with an IGHAS or CGHAS ≤ 4 and no neutrophils, defined as no lamina propria neutrophils and no neutrophils in the epithelium, at Baseline, Week 26, and Week 52 and their CIs will be calculated. Also, the proportions of subjects with an IGHAS or CGHAS ≤ 4 and no neutrophils at Week 26 and Week 52 will be presented for subjects with a modified GHAS score > 4 or neutrophils at Baseline.

Change from baseline in features of chronicity GHAS, features of activity GHAS, total segmental GHAS, and CGHAS will be presented using descriptive statistics.

7.10.3.6 Normalization of CRP

The proportions of subjects with elevated CRP at Baseline (CRP > 2.87 mg/L) who achieve normalization of CRP (CRP ≤ 2.87 mg/L) at Week 10, Week 26, Week 38, and Week 52 and their CIs will be calculated.

CRP results will be summarized at Baseline, each post-Baseline visit, and change from Baseline to each post-Baseline visit. Scheduled visits collection for CRP are at Baseline, Week 10, Week 26, Week 38, and Week 52.

7.10.3.7 Fecal Calprotectin

Fecal calprotectin results from stool samples will be summarized at Baseline, each post-Baseline visit, and change from Baseline to each post-Baseline visit. Scheduled visits for stool sample collection for fecal calprotectin evaluation are at Baseline, Week 14, Week 26, Week 38, and Week 52.

7.10.3.8 Positive for AVA

A positive AVA subject is defined as a subject who has at least 1 positive AVA result in any postbaseline sample. The proportions of subjects positive for AVA at Baseline, Week 26, Week 52, and the Postdose 18 Week Safety Follow-up Visit and their CIs will be calculated.

7.10.3.9 Positive Neutralizing AVA

A positive neutralizing AVA is defined as a sample that was evaluated as positive in the neutralizing AVA assay. The proportions of subjects with positive neutralizing AVA at Baseline, Week 26, Week 52, and the Postdose 18 Week Safety Follow-up Visit and their CIs will be calculated.

7.10.3.10 Clinical Response

Clinical response at Week 38 and Week 46 will be analyzed following a similar approach outlined in section 7.10.2.4.

7.10.3.11 Clinical Remission

Clinical remission at Week 38 and Week 46 will be analyzed following a similar approach outlined in section 7.10.2.5.

7.10.3.12 Corticosteroid-Free Remission

The proportions of subjects with any corticosteroid use at Baseline who discontinue all corticosteroids by Week 10, Week 14, Week 26, and Week 52 and their CIs will be calculated.

The proportions of subjects with corticosteroid-free remission at Week 10, Week 14, Week 26, and Week 52 and their CIs will be calculated. Corticosteroid-free remission is defined as the achievement of clinical remission with the discontinuation of corticosteroid use post-Baseline from the use of corticosteroids at Baseline.

7.11 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

There is no pharmacokinetic or pharmacodynamic analysis planned for this study.

7.12 OTHER OUTCOMES

The patient reported outcomes (PRO) analysis includes the change from baseline in QOL measures that will be summarized descriptively overall and by endoscopic remission status. Subjects will complete the IBDQ, EQ-5D, and WPAI-CD health related QOL questionnaires at Baseline, Week 14, Week 26, Week 38, and Week 52. The QOL questionnaires will be summarized at Baseline, each post-Baseline visit, and change from Baseline to each post-Baseline visit. Missing data will be imputed using the LOCF method.

Derivation guidelines for IBDQ, EQ-5D, and WPAI-CD are documented in Appendix G of the SAP.

The responses collected on each of the QOL questionnaires will be listed.

7.12.1 IBDQ

The IBDQ is a valid and reliable instrument used to assess quality of life in adult patients with IBD. It includes 32 questions on 4 domains of health-related quality of life (HRQOL): Bowel Systems (10 items), Emotional Function (12 items), Social Function (5 items), and Systemic Function (5 items). Patients are asked to recall symptoms and quality of life from the last 2 weeks and rate each item on a 7-point Likert scale (higher scores equate to higher quality of life). A total IBDQ score is calculated by summing the scores from each domain; the total IBDQ score ranges from 32 to 224.

7.12.2 **EQ-5D Questionnaire**

The EQ-5D questionnaire, developed by EuroQol, is a simple, valid, and reliable instrument used to measure general health-related quality of life in patients and includes five domain items - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients choose the level of health problems they currently have on each item as "None", "Moderate", or "Extreme" and are scored a 1, 2, or 3, respectively. A composite EQ-5D score can be calculated from the individual scores to assess overall HRQOL. The EQ-5D VAS score is a self-assigned rating of overall health using a 20 cm visual, vertical scale, with a score of 0 as the worst and 100 as best possible health. The EQ-5D total score and EQ-5D VAS score have been shown in many studies to be valid and reliable instruments for measuring HRQOL in patients with GI diseases.

7.12.3 **WPAI-CD**

The WPAI questionnaire is a valid and reliable 6-item instrument that consists of four metrics: absenteeism (the percentage of work time missed because of one's health in the past seven days), presenteeism (the percentage of impairment experienced while at work in the past seven days because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health in the past seven days). WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. WPAI-CD is the specific disease version of the questionnaire for Crohn's Disease.

7.13 SAFETY ANALYSIS

Safety analyses include AEs, clinical laboratory values, vital signs, and ECGs. All safety summaries will be based on the FAS and FAS-Extension. The analysis of safety data will be restricted to descriptive statistics only, unless otherwise specified.

7.13.1 **Adverse Events**

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study, but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. Pretreatment events and AEs will be coded using MedDRA Version 19 or higher. AEs will be summarized using the MedDRA SOC, high level term (HLT), and PT.

Treatment-emergent adverse events (TEAEs) will be defined as any AE that occurs after the first dose of study drug and up to the last dose or early termination plus applicable follow up (i.e., 18 weeks).

If the onset date of an AE is equal to the date of first dose of study medication and the AE was documented as a PTE on the eCRF, the AE will be classified as a PTE. Otherwise, the AE will be flagged as a TEAE.

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or HLT or PT when multiple TEAEs are coded to the same SOC or HLT or PT. Thus, if a subject has two distinct AEs, each of which corresponds to a distinct PT but both of which correspond to the same HLT, then that subject will be counted once at that HLT subject-count summary level and once at each of the two preferred-term subject-count summary levels within an HLT. This same logic is extended to all PT nested within HLT that is in-turn nested within an SOC. For the intensity summaries, if a subject reports multiple treatment-emergent AEs coded to the same SOC or HLT or PT then the TEAE with maximum intensity will be included in the summary.

TEAEs with missing intensity will be listed as such in the TEAE listings, however, will be summarized as severe in summary tables. If the relationship of a TEAE is missing, the relationship for the TEAE will be considered to have been related. In the cases where a subject has multiple TEAEs with the same SOC or HLT or PT, the TEAE with the maximum intensity or strongest relationship will be summarized.

Most frequent TEAEs are defined as events that occur in at least 3% of subjects within the treatment group.

TEAEs will include the number and percentage of subjects as follows:

- Overview of Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term
- Subject Mappings of Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by System Organ Class
- Treatment-Emergent Adverse Events by High Level Term
- Treatment-Emergent Adverse Events by Preferred Term
- Treatment-Emergent Adverse Events by Baseline AVA Status, System Organ Class, High Level Term, and Preferred Term
- Most Frequent Treatment Emergent Adverse Events by Preferred Term
- Most Frequent Non-Serious Treatment Emergent Adverse Events by Preferred Term
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class, High Level Term, and Preferred Term
- Intensity of Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term
- Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term
- Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class, High Level Term, and Preferred Term

- Subject Mappings for Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation
- Serious Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term
- Subject Mappings for Serious Treatment-Emergent Adverse Events
- Serious Treatment-Emergent Adverse Events by Baseline AVA Status, System Organ Class, High Level Term, and Preferred Term
- Adverse Events Related to Study Procedures by System Organ Class, High Level Term, and Preferred Term
- Treatment-Emergent Infections by System Organ Class, High Level Term, and Preferred Term
- Pretreatment Events by System Organ Class, High Level Term, and Preferred Term
- Pretreatment Serious Events by System Organ Class, High Level Term, and Preferred Term

Data listings will be provided for PTEs, TEAEs, TEAEs leading to study drug discontinuation, SAEs, AEs that resulted in death, and AEs occurring more than 30 days post treatment.

7.13.1.1 Adverse Events of Special Interest

Based on the mechanism of action of vedolizumab, certain adverse events of special interest (AESIs) have been predefined. The categories of adverse events of special interest, and other planned analyses, are described below.

Infusion-Related Reactions (IRRs), including Hypersensitivity Reactions

The clinical database will be searched for possible IRRs during the reporting period using the following MedDRA 19.0 search criteria:

- Anaphylactic/anaphylactoid shock conditions Standard MedDRA Query (SMQ) (broad)
- Angioedema SMQ (broad)
- Hypersensitivity SMQ (broad)
- Infusion related reaction HLT

An AE that is indicated as an infusion site reaction in the eCRF will also be considered an IRR AESI.

Infusion-related AEs will be summarized by SOC, HLT, and PT. In addition, all AEs beginning on, or one calendar day after, the dates of study drug infusions will be similarly analyzed.

Upper Respiratory Tract Infections

The infections retrieved from the clinical database will be evaluated for upper respiratory tract infections during the reporting period using the MedDRA 19.0 search criteria of:

- Upper respiratory tract infections HLT in the Infections and Infestations SOC
- Bronchitis PT
- Influenza PT

Upper respiratory tract infections will be summarized by SOC, HLT, and PT.

Gastrointestinal (GI) Infections

The infection reports retrieved from the clinical database were evaluated for GI infections during the reporting period using the MedDRA 19.0 search criteria of:

- Abdominal and gastrointestinal infections HLT in the Infections and infestations SOC
- Gastrointestinal infections HLT of the Gastrointestinal disorders SOC

GI infections will be summarized by SOC, HLT, and PT.

Suspected Progressive Multifocal Leukoencephalopathy (PML)

The protocol incorporates an active screening program in order to identify and manage any case of PML (Protocol Section 11.1.1). This program is known as the Risk Assessment and Minimization for PML (RAMP). The clinical database will be searched for suspected PML reports received within the Infection and Infestation SOC using the MedDRA 19.0 search criteria of:

- Human polyomavirus infection PT
- JC virus infection PT
- JC virus test positive PT
- Leukoencephalopathy PT
- Polyomavirus test positive PT
- Progressive multifocal leukoencephalopathy PT

Suspected PML will be summarized by SOC, HLT and PT along with the results of the RAMP screening program.

Other Infections, including Opportunistic Infections

The infection reports retrieved from the clinical database, not classified as upper respiratory tract infections (URTIs), GI infections, or suspected PML will be searched using the MedDRA 19.0 search criteria of:

- Infections and Infestations SOC

The following reports will then be excluded:

- Abdominal and gastrointestinal infections HLT
- URTI HLT
- Bronchitis PT

- Influenza PT
- Human polyomavirus infection PT
- JC virus infection PT
- JC virus test positive PT
- Leukoencephalopathy PT
- Polyomavirus test positive PT
- Progressive multifocal leukoencephalopathy PT

Other infections will be summarized by SOC, HLT and PT.

Liver Injury

The clinical database will be searched for reports of liver injury using the following MedDRA 19.0 search criteria:

- 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)

Liver Injuries will be summarized by SOC, HLT and PT.

Malignancies

The clinical database will be searched for reports of malignancy using the MedDRA 19.0 search criteria of:

- Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC.

Malignancies will be summarized by SOC, HLT, and PT.

7.13.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be evaluated and presented using the International System of Units (SI) unless otherwise stated. Refer to Appendix A for scheduled measurements for clinical laboratory tests and to Table 7.i for a list of all Protocol-specified clinical laboratory tests. The central laboratory will perform laboratory tests for serum chemistries, hematology, and urinalysis. All laboratory test parameters will be displayed in individual subject data listings in SI units. For test results not in SI units, the conversion to SI units will be done in the derived analysis data sets using the known conversion factors. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived dataset. All summaries and analyses will be based on the values using these preferred SI units. If a lab test with quantitative results has a value that is reported using a non-numeric qualifier (e.g., less than (<) a

certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

The following summaries of hematology, serum chemistry and urinalysis lab tests will be presented for each scheduled time point (Baseline, each post-Baseline visit, and Final Visit).

The observed and change from Baseline values will be based on a single data value selected according to the window conventions described in Table 7.a, Table 7.b, Table 7.c, and Table 7.d. Note that "character" urinalysis parameters will only be listed.

Shifts in laboratory test values will be presented as cross-tabulations (Baseline versus each post-Baseline visit and Final Visit) of numbers of subjects with low, normal, and high values relative to the normal range used at the central laboratory. This classification will be based on the low, normal, and high alert flags reported by the central laboratory. If a subject has multiple values within a particular visit window, the most extreme result will be used for summary. Shift tables will be produced for all clinical laboratory tests with reference ranges.

Listings of all clinical safety laboratory data will be provided, including hematology, serum chemistry, and urinalysis. Laboratory data outside of the normal reference range will be indicated in the listings. In addition, markedly abnormal values (MAVs) will be flagged. The listing will also include the site, subject number, age (at informed consent), gender, treatment group, study visit, and sample collection date.

Table 7.i Protocol-Specified Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (dipstick)
RBC	ALT	Bilirubin
WBC w/ differential	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Hematocrit	Amylase	Ketones
Platelets	Lipase	Leukocyte esterase
PT/INR	AST	Nitrite
	Total and direct bilirubin	pH
	Total protein	Protein
	Creatinine	Specific Gravity
	Blood urea nitrogen	
	Creatine kinase	
	GGT	
	Potassium	
	Sodium	
	Calcium	
	Chloride	
	Bicarbonate	
	Magnesium	
	Phosphorus	
	Uric Acid	
	Glucose	
	eGFR (for MREn subjects only)	

Other:	
HIV	Beta hCG and Urine Pregnancy hCG
Hepatitis panel, including HBsAg and anti-HCV	(female subjects of childbearing potential)
CRP	FSH, if menopause is suspected
AVA	
Quantiferon for TB	

Stool:
Fecal calprotectin

FSH=follicle-stimulating hormone, GGT= γ-Glutamyl transferase, HBsAg=hepatitis B surface antigen, hCG=human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells.

MAV laboratory results, identified as defined by the criteria in Appendix E, will be tabulated. MAV tables will include all laboratory parameters with available MAV criteria.

Additionally, for each subject with a MAV for a parameter, all the subject's values of that parameter will be listed.

Subject mappings for the MAV summary table will be provided.

7.13.3 Vital Signs

Vital signs, including pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, respiration rate, and weight, will be summarized. Vital sign values will be tabulated at Baseline and at each post-Baseline visit, and change from Baseline will be calculated for each post-Baseline visit and Final Visit. Refer to Appendix A for scheduled measurements for vital signs.

Criteria for MAV vital signs are listed in Appendix F. The number and percentage of subjects who meet MAV vital signs criteria will be summarized.

Vital signs data will be listed by site number and subject number. In addition, markedly abnormal values (MAVs) will be flagged. The listing will include site number, subject number, treatment group, age, gender, study visit, and assessment date.

7.13.4 **12-Lead ECGs**

Overall ECG interpretation category (normal, not clinically significant abnormal, clinically significant abnormal) is collected by eCRF at Screening.

ECG data will be listed by site number and subject number. The listing will include site number, subject number, treatment group, age, gender, study visit, and assessment date.

7.13.5 **Other Observations Related to Safety**

The other safety endpoints to be included in the listings are the liver function tests for increase, sign and symptoms, event history, and test results. Also included are the details of infection, their diagnostic tests, cause/origin, history preceding events, and associated symptoms. The malignancy status based on diagnostic tests, stage, the risk factors, and details will also be listed.

The PML checklist that includes the PML criteria, their response, symptoms, result, and abnormality will be listed by visit. The listings will also include the PML algorithm and the responses by visit.

7.14 INTERIM ANALYSIS

Formal interim analyses will be conducted for final efficacy at Weeks 14, 26, and 52, and for safety using the FAS and FAS-Extension, unless otherwise noted.

The Week 14 interim analysis will include the secondary and additional endpoints along with all safety endpoints, including:

- Disposition of Subjects
- Demographic and Baseline Characteristics
- Medication History and Concomitant Medications
- Study Drug Exposure and Compliance
- Secondary Efficacy Endpoints: endoscopic remission at Week 14, endoscopic response at Week 14, clinical response at Week 10, clinical remission at Week 10
- Additional Efficacy Endpoints: 25% and 75% reduction of SES-CD at Week 14, normalization of CRP at Week 10, change from Baseline to Week 14 in fecal calprotectin, change from Baseline to Week 14 in IBDQ total and subscale scores, change from Baseline to Week 14 in EQ-5D utility score and VAS score, change from Baseline to Week 14 in percent work time missed due to CD, change from Baseline to Week 14 in percent impairment while working due to CD, change from Baseline to Week 14 in percent overall work impairment due to CD, change from Baseline to Week 14 in percent activity impairment due to CD
- Safety Endpoints: AEs, AESIs, laboratory results, vital signs, ECGs

For subjects who have completed the Week 26 visit by the Week 14 interim lock date, the endpoints listed below for Week 26 will be included in the Week 14 interim analysis for publication purposes.

The Week 26 interim analysis will include the endpoints listed above for Week 14 as well as added primary, secondary, and additional endpoints, including:

- Primary Efficacy Endpoint: endoscopic remission at Week 26
- Secondary Efficacy Endpoints: complete mucosal healing at Week 26, endoscopic response at Week 26, clinical response at Week 26, clinical remission at Week 26
- Additional Efficacy Endpoints: 25% and 75% reduction of SES-CD at Week 26, no granulocytes present in bowel biopsy at Week 26, change in histology at Week 26, normalization of CRP at Week 26, change from Baseline to Week 26 in fecal calprotectin, change from Baseline to Week 26 in IBDQ total and subscale scores, change from Baseline to Week 26 in EQ-5D utility score and VAS score, change from Baseline to Week 26 in percent work time missed due to CD, change from Baseline to Week 26 in percent impairment while working due to CD, change from Baseline to Week 26 in percent overall work impairment due to CD, change from Baseline to Week 26 in percent activity impairment due to CD

The Week 52 interim analysis will include the endpoints listed above for Weeks 14 and 26 as well as added secondary and additional endpoints, including:

- Secondary Efficacy Endpoints: complete mucosal healing at Week 52, endoscopic response at Week 52, clinical response at Week 52, clinical remission at Week 52, durable clinical remission
- Additional Efficacy Endpoints: change from Baseline to Week 26 in individual MREn parameters for each ileocolonic segment and for more proximal bowel segments (using the FAS-MREn), change from Baseline to Week 52 in individual MREn parameters for each ileocolonic segment and for more proximal bowel segments (using the FAS-MREn), MaRIA score < 7 at Week 26 and Week 52 globally and on a per segment basis, 25% and 75% reduction of SES-CD at Week 52, no neutrophils present in bowel biopsy at Week 52, change in histology at Week 52, normalization of CRP at Weeks 38 and 52, change from Baseline to Weeks 38 and 52 in fecal calprotectin, AVA positive at Week 52, positive neutralizing AVA at Week 52, clinical response at Weeks 38 and 46, clinical remission at Week 38 and 46, change from Baseline to Weeks 38 and 52 in IBDQ total and subscale scores, change from Baseline to Weeks 38 and 52 in EQ-5D utility score and VAS score, change from Baseline to Week 52 in percent work time missed due to CD, change from Baseline to Week 52 in percent impairment while working due to CD, change from Baseline to Week 52 in percent overall work impairment due to CD, change from Baseline to Week 52 in percent activity impairment due to CD

For the interim analyses outlined above, subgroup analysis of the primary, secondary, and additional efficacy endpoints will be conducted on prior TNF-alpha status (naïve, failure).

7.15 CHANGES IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

8.0 REFERENCES

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2. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004; 60(4):505-12.
3. 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.
4. Geboes K and Dalle I. Influence of treatment on morphological features of mucosal inflammation. Gut 2002; 50 Suppl 3:iii37-iii42.

9.0 APPENDICES

Appendix A Schedule of Study Procedures

	Screening	Treatment										Final Visit or ET	Postdose Follow-up visit
		Part A							Part B				
Study Day/Week:	**Days -28 to -1**	**Day 1**	**Week 2**	**Week 6**	**Week 10**	**Week 14**	**Week 22**	**Week 26 (a)**	**Week 30**	**Week 38**	**Week 46**	**Week 52**	**18 Week Safety Follow-up**
Visit Windows (Days):			±3	±3	±3	±7	±3	±7	±7	±7	±7	±7	±7
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Informed consent	X												
Inclusion/exclusion criteria	X	X (b)											
Demographics /medical and medication history/ concurrent medical conditions	X												
CD prior biologics history (c)	X												
Physical examination	X	X (b)		X (b)	X	X (b)		X	X (b)	X(b)	X (b)	X	X
Vital Signs	X	X (b)	X (g)	X (b)		X (b)	X (b)	X	X(b)	X(b)	X(b)	X	X
Height and weight (d)	X	X		X	X	X		X	X	X	X	X	
CDAI	X (e)	X (f)		X (f)	X	X (f)		X(f)		X(f)	X	X(f)	
Patient diary	X	X	X	X	X	X	X	X	X	X	X	X	
Ileocolonoscopy (g)	X					X		X				X	
MREn (h)	X							X				X	
Sample Collection:													
Fecal calprotectin (i)	X					X		X		X		X	
Tuberculosis screening (j)	X												
Hematology	X (k)	X (b)		X (b)	X	X(b)		X		X(b)		X	X

Footnotes are on last table page.

Study Day/Week:	Screening	Treatment										Final Visit or ET	Postdose Follow-up visit
		Part A							Part B				
	Days -28 to -1	Day 1	Week 2	Week 6	Week 10	Week 14	Week 22	Week 26 (a)	Week 30	Week 38	Week 46	Week 52	18 Week Safety Follow-up
Visit Windows (Days):			±3	±3	±3	±7	±3	±7	±7	±7	±7	±7	±7
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13
Clinical chemistry	X (k)	X (b)						X		X(b)		X	X
Serum creatinine (for MREn)							X (l)				X(l)		
Urinalysis	X							X				X	
AVA		X (b)						X				X	X
CRP	X	X (b)			X			X		X		X	
Pharmacogenomic DNA and RNA samples (m)		X (b)											
Pregnancy testing (n)	X	X (b)	X (b)	X (b)	X	X (b)	X (b)	X	X (b)	X (b)	X (b)	X	X
QOLs		X (b)				X (b)		X		X		X	
WPAI:CD		X (b)				X (b)		X		X (b)		X	
ECG	X												
Dosing (IV)		X	X	X		X	X		X	X	X		
PML Checklist (b)	X	X	X	X	X	X	X	X	X	X	X		X
PML Wallet Card		X						X (o)				X (o)	
Concomitant medications / procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
PTE assessment	X	X(b)											
AE/SAE assessment		X	X	X	X	X	X	X	X	X	X	X	X

Footnotes are on last table page.

(a) Week 26 is the final visit for subjects completing at Week 26 (Study Part A) and for subjects who continue to extension of treatment (Study Part B) this is a standard visit.
(b) Assessment completed or sample taken pre-dose.
(c) Collect prior biologic medications that stopped prior to screening.
(d) Height collected only at the Screening Visit.
(e) The components of the CDAI score to determine eligibility must be completed within 14 days prior to enrollment using hematocrit results collected during Screening.
(f) CDAI score components are to be performed prior to dosing; the total CDAI score will be calculated once results are available for all components.
(g) Biopsies to be collected at Screening, Week 26, and Week 52 for those completing the study.
(h) MREn conducted only at pre-identified sites. During the Screening period MREn should be performed prior to ileocolonoscopy. At Week 26 and Week 52 MREn to be performed prior to ileocolonoscopy either on the same day or at least 7 days before the ileocolonoscopy within the permitted time window for Week 26 or Week 52 procedures. Sites participating in MREn will need to check eGFR prior to procedure at Screening, Week 26, and Week 52 (using eGFR calculated from the Week 22 Visit for the Week 26 MREn and from the Week 46 Visit for the Week 52 MREn).
(i) Stool sample to be collected and sent to central laboratory for evaluation of fecal calprotectin.
(j) QuantiFERON® test or tuberculin skin test only.
(k) Hepatitis and HIV testing only done at the Screening Visit.
(l) Only subjects participating in MREn to have a sample for serum creatinine collected at Week 22 and Week 46. Samples will be sent to central laboratory for evaluation of eGFR.
(m) DNA and RNA samples will be collected on Day 1 only for subjects that have consented to the Pharmacogenomic study.
(n) Serum pregnancy completed at Screening and at the Postdose 18 Week Safety Follow-up Visit; urine pregnancy to be completed at other visits.
(o) Long Term Follow-up Wallet card will be given to subjects at the last clinical visit.

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

	Simple Endoscopic Score for Crohn's Disease values			
Variable	0	1	2	3
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)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Ø, Diameter.

Source: Adapted from Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004; 60(4):505-12 [**2**].

Appendix C Crohn's Disease Activity Index (CDAI)

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:	

Source: 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 [3].

(a) If hematocrit subtotal < 0, enter 0.

(b) If body weight subtotal < -10, enter -10.

Appendix D Geographic Regions

Region	Countries		
North America	Canada	Puerto Rico	United States
Western / Northern Europe	Austria France Ireland Norway Sweden	Belgium Germany Italy Portugal Switzerland	Denmark Iceland Netherlands Spain United Kingdom
Central Europe	Czech Republic Poland Slovak Republic	Greece Romania	Hungary Serbia
Eastern Europe	Bulgaria Latvia Turkey	Estonia Malta Ukraine	Israel Russia
Africa / Asia / Australia	Australia New Zealand Taiwan South Africa	Hong Kong South Korea China	India Malaysia Singapore

Appendix E Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Gender	Age	Conventional Units			Takeda Preferred SI Units	
			Units	Markedly Abnormal Value		Units	Markedly Abnormal Value
Red Blood Cells	Both	Adult	$\times 10^6$ cells/µL	< 0.8 × LLN, > 1.2 × ULN		$\times 10^{12}$ cells/L	< 0.8 × LLN, > 1.2 × ULN
White Blood Cells	Both	Adult	$\times 10^3$ cells/µL	<0.5 × LLN, > 1.5 × ULN		$\times 10^9$ cells/L	< 0.5 × LLN, > 1.5 × ULN
Hemoglobin	Both	Adult	g/dL	< 0.8 × LLN, > 1.2 × ULN		g/L	< 0.8 × LLN, > 1.2 × ULN
Hematocrit	Both	Adult	%	< 0.8 × LLN, > 1.2 × ULN		Fraction of 1	< 0.8 × LLN, > 1.2 × ULN
Platelets	Both	Adult	$\times 10^3$/µL	< 75, > 600		$\times 10^9$ /L	< 75, > 600
MCV	Both	Adult	fL	< 70, > 110		fL	< 70, > 110
Segmented Neutrophils (Absolute)	Both	Adult	$\times 10^3$ cells/µL	< 0.5 × LLN, > 1.5 × ULN		$\times 10^9$ cells/L	< 0.5 × LLN, > 1.5 × ULN
Segmented Neutrophils (Relative)	Both	Adult	%	< 0.5 × LLN, > 1.5 × ULN		Fraction of 1	< 0.5 × LLN, > 1.5 × ULN
Lymphocytes (Absolute)	Both	Adult	$\times 10^3$ cells/µL	< 0.5 × LLN, > 1.5 × ULN		$\times 10^9$ cells/L	< 0.5× LLN, > 1.5 × ULN
Lymphocytes (Relative)	Both	Adult	%	< 0.5 × LLN, > 1.5 × ULN		Fraction of 1	< 0.5 × LLN, > 1.5 × ULN
Monocytes (Absolute)	Both	Adult	$\times 10^3$ cells/µL	> 2 × ULN		$\times 10^9$ cells/L	> 2 × ULN
Monocytes (Relative)	Both	Adult	%	> 2 × ULN		Fraction of 1	> 2 × ULN
Eosinophils (Absolute)	Both	Adult	$\times 10^3$ cells/µL	> 2 × ULN		$\times 10^9$ cells/L	> 2 × ULN
Eosinophils (Relative)	Both	Adult	%	> 2 × ULN		Fraction of 1	> 2 × ULN
Basophils (Absolute)	Both	Adult	$\times 10^3$ cells/µL	> 3 × ULN		$\times 10^9$ cells/L	> 3 × ULN
Basophils (Relative)	Both	Adult	%	> 3 × ULN		Fraction of 1	> 3 × ULN
Reticulocytes (Relative)	Both	Adult	% of erythrocytes	> 3.0		Fraction of 1	> 0.030
PT	Both	Adult	Sec	> 1.5 × ULN		Sec	> 1.5 × ULN
APTT	Both	Adult	Sec	> 1.5 × ULN		Sec	> 1.5 × ULN
INR†	Both	Adult	NA	> 1.5		NA	> 1.5

LLN = lower limit of normal or lower reference limit; ULN = upper limit of normal or upper reference limit
† Values are for subjects without anticoagulation, based on the normal range provided above for PT.

Chemistry—Criteria for Markedly Abnormal Values

Parameter	Gender	Age (years)	Conventional Units			Takeda Preferred SI Units	
			Units	Markedly Abnormal Values		Units	Markedly Abnormal Value
Alanine Aminotransferase	Both	Adult	U/L	>3 × ULN		U/L	>3 × ULN
Albumin	Both	Adult	g/dL	< 2.5		g/L	< 25
Alkaline Phosphatase	Both	>20	U/L	>3 × ULN		U/L	>3 × ULN
Aspartate Aminotransferase	Both	Adult	U/L	>3 × ULN		U/L	> 3 × ULN
Total Bilirubin	Both	Adult	mg/dL	> 2.0		µmol/L	> 34.2
Total Protein	Both	Adult	g/dL	< 0.8 × LLN, > 1.2 × ULN		g/L	< 0.8 × LLN, > 1.2 × ULN
Creatinine	Both	Adult	mg/dL	> 2		µmol/L	> 177
Blood Urea Nitrogen	Both	Adult	mg/dL	> 30		mmol/L	> 10.7
Creatine Kinase	Both	Adult	U/L	>5 × ULN		U/L	>5 × ULN
γ-Glutamyl Transferase	Both	Adult	U/L	>3 × ULN		U/L	>3 × ULN
Potassium (serum)	Both	Adult	mEq/L	< 3.0, > 6.0		mmol/L	< 3.0, > 6.0
Sodium	Both	Adult	mEq/L	< 130, > 150		mmol/L	< 130, > 150
Direct Bilirubin	Both	Adult	mg/dL	>2 × ULN		µmol/L	>2 × ULN
Calcium	Both	Adult	mg/dL	< 7.0, > 11.5		mmol/L	< 1.75, > 2.88
Uric Acid	Both	Adult	mg/dL	> 13.0		µmol/L	> 773
Glucose	Both	Adult	mg/dL	< 50, > 350		mmol/L	< 2.8, > 19.4
Magnesium	Both	Adult	mg/dL	< 1.2, > 3.0		mmol/L	< 0.5, > 1.2
Phosphorus	Both	Adult	mg/dL	< 1.6, > 6.2		mmol/L	< 0.52, > 2.000
Total Cholesterol	Both	Adult	mg/dL	> 300		mmol/L	> 7.72
Triglycerides	Both	Adult	mg/dL	> 2.5 × ULN		mmol/L	> 2.5 × ULN
Chloride	Both	Adult	mEq/L	< 75, > 126		mmol/L	< 75, > 126
HbA1c	Both	Adult	%	> 7		Fraction of 1	> 0.07
Bicarbonate	Both	Adult	mEq/L	< 8.0		mmol/L	< 8.0
Prolactin	Both	Adult	µg/L	>10 × ULN		pmol/L	>10 × ULN
Progesterone	Female	Adult	ng/mL	Progesterone/ Estrogen - 26:1†		nmol/L	Progesterone/ Estrogen - 26:1†

LLN = lower limit of normal or lower reference limit; ULN = upper limit of normal or upper reference limit
†Any abnormal values should be interpreted with the ratio progesterone/estrogen and SHBP values: Higher levels of SHBP lower levels of free progesterone.

Serum Chemistry—Criteria for Markedly Abnormal Values (Continued)

Parameter	Gender	Age (years)	Conventional Units			Takeda Preferred SI Units	
			Units	Markedly Abnormal Values		Units	Markedly Abnormal Value
Thyroid Stimulating Hormone	Both	Adult	mU/L	< 0.8 × LLN, > 2.0 × ULN		mU/L	< 0.8 × LLN, > 2.0 × ULN
Vitamin B12	Both	Adult	pg/mL	< 125		pmol/L	< 92
Folate	Both	Adult	ng/mL	< 2.2, > 17.5		nmol/L	< 5.0, > 39.7
Amylase	Both	Adult	U/L	>2 × ULN		U/L	>2 × ULN
Lipase	Both	Adult	U/L	>3 × ULN		U/L	>3 × ULN

LLN = lower limit of normal or lower reference limit; ULN = upper limit of normal or upper reference limit

†Any abnormal values should be interpreted with the ratio progesterone/estrogen and SHBP values: Higher levels of SHBP lower levels of free progesterone.

Appendix F Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Systolic Arterial Pressure	(mmHg)	< 85	> 180
Diastolic Arterial Pressure	(mmHg)	< 50	> 110
Pulse	(bpm)	< 50	> 120
Body Temperature	^{o}C	< 35.6	> 37.7
	^{o}F	< 96.1	> 99.9

Both the criterion value and the change from Baseline must be met.

Appendix G: Patient Related Outcomes

Quality of Life questionnaire: IBDQ

	Sub-score	Calculation
	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.	

Quality of Life questionnaire: EQ-5D

	Sub-score	Calculation
	EQ-5D mobility component score	Ranging from 1 to 3
	EQ-5D self-care component score	Ranging from 1 to 3
	EQ-5D usual activities component score	Ranging from 1 to 3
	EQ-5D pain/discomfort component score	Ranging from 1 to 3
	EQ-5D anxiety/depression component score	Ranging from 1 to 3
EQ-5D Index Score	1. If any of the 5 components above are missing, the index score is missing. Skip the remaining steps below. 2. Count the number of component scores with a response > 1. If the count is non-zero, subtract 1. If the count is zero, leave it as 0. 3. Count the number of component scores with a response equal to 2. If the count is non-zero, subtract 1. If the count is zero, leave it as 0. 4. Count the number of component scores with a response equal to 3. If the count is non-zero, subtract 1. If the count is zero, leave it as 0. 5. Calculate the index score using the following formula: $EQ-5D\ \text{index score} = 1 - 0.146016 \times (1, \text{if mobility} = 2; 0, \text{if mobility} \neq 2) - 0.557685 \times (1, \text{if mobility} = 3; 0, \text{if mobility} \neq 3) - 0.1753425 \times (1, \text{if self} - \text{care} = 2; 0, \text{if self} - \text{care} \neq 2) - 0.4711896 \times (1, \text{if self} - \text{care} = 3; 0, \text{if self} - \text{care} \neq 3) - 0.1397295 \times (1, \text{if usual activities} = 2; 0, \text{if usual activities} \neq 2) - 0.3742594 \times (1, \text{if usual activities} = 3; 0, \text{if usual activities} \neq 3) - 0.1728907 \times (1, \text{if pain/discomfort} = 2; 0, \text{if pain/discomfort} \neq 2) - 0.5371011 \times (1, \text{if pain/discomfort} = 3; 0, \text{if pain/discomfort} \neq 3) - 0.156223 \times (1, \text{if anxiety/depression} = 2; 0, \text{if anxiety/depression} \neq 2) - 0.4501876 \times (1, \text{if anxiety/depression} = 3; 0, \text{if anxiety/depression} \neq 3) + 0.1395949 \times (\text{result from Step \#2}) - 0.0106868 \times (\text{result from Step \#3})^2 + 0.1215579 \times (\text{result from Step \#4}) + 0.0147963 \times (\text{result from Step \#4})^2$	
EQ5D VAS	On a scale of 0 to 100, where 0 is the worst imaginable health state and 100 is the best imaginable health state.	

Quality of Life questionnaire: WPAI-CD

	Dimension	Calculation
	Absenteeism Percent work time missed due to health	$\frac{Q2}{Q2+Q4}$
	Presenteeism Percent impairment while working due to health	$\frac{Q5}{10}$
	Overall Work Impairment Percent overall work impairment due to health	$\frac{Q2}{Q2+Q4}+\left[\left(1-\frac{Q2}{Q2+Q4}\right)\times\frac{Q5}{10}\right]$
	Daily Activities Impairment Percent activity impairment due to health	$\frac{Q6}{10}$
Note	WPAI-CD dimension scores are multiplied by 100 to be expressed in percentages.	