Statistical Analysis Plan

NCT Number: NCT02764762

Title: An Open-Label, Phase 4 Study to Evaluate the Efficacy and Safety of Triple Combination Therapy With Vedolizumab IV, Adalimumab SC, and Oral Methotrexate in Early Treatment of Subjects With Crohn's Disease Stratified at Higher Risk for Developing Complications

Study Number: Vedolizumab-4006

Document Version and Date: Amendment 2; 21 February 2023

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Vedolizumab-4006

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PHASE 4

Version**:** Amendment 2

Date**:** 21 February 2023

Prepared by:

[redacted]

Based on:

Protocol Version: Amendment 04

Protocol Date: 30 June 2020

1.1 Approval Signatures

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

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3.0 LIST OF ABBREVIATIONS

ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASCA	anti-Saccharomyces cerevisiae antibody
AST	aspartate aminotransferase
BMI	body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
eCRF	electronic case report form
CRO	contract research organization
CRP	C-reactive protein
CV	Conventional units
ECG	Electrocardiogram
EHI	endoscopic healing index
FAS	full analysis set
FSH	follicle-stimulating hormone
GGT	γ-glutamyl transferase
GI	Gastrointestinal
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IBD	Inflammatory bowel disease
IBD-DI	Inflammatory Bowel Disease Disability Index
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
INR	international normalized ratio
IP	Investigational Product
IRT	interactive response technology
IV	Intravenous
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
Monitr CD	Monitr Crohns Disease
nADA	neutralizing antidrug antibodies
PK	Pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PPS	per protocol set
PRO-2	Patient Reported Outcome 2
PROSPECT	Crohn's Disease Personalized Risk and Outcome Prediction Tool
PTE	pretreatment event

SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SC	Subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
TB	Tuberculosis
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary
WPAI-CD	Work Productivity and Activity Impairment - Crohn's Disease

4.0 OBJECTIVES

4.1 Primary Objective

The primary objective is to determine the effect of triple combination therapy with an anti-integrin (vedolizumab intravenous [IV]), a tumor necrosis factor (TNF) antagonist (adalimumab subcutaneous [SC]), and an immunomodulator (oral methotrexate) on endoscopic remission of moderate to severe Crohn's Disease (CD) at Week 26.

4.2 Secondary Objectives

Secondary objectives include:

- To evaluate the effect of vedolizumab IV monotherapy on endoscopic remission at Week 102 following triple combination therapy.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on endoscopic healing at Weeks 26 and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on endoscopic response at Weeks 26 and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on deep remission at Weeks 26 and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on clinical remission by Crohn's Disease Activity Index (CDAI) at Weeks 10, 26, 52, 78, and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on clinical response by CDAI at Weeks 10, 26, 52, 78, and 102.

4.3 Additional Objectives

Additional objectives include:

- To evaluate the pharmacokinetics (PK) of vedolizumab and adalimumab in CD subjects at higher risk for complications at Week 26.
- To assess immunogenicity to vedolizumab and adalimumab over the follow-up period.
- To evaluate C-reactive protein (CRP) levels at Weeks 10 and 26.
- To evaluate fecal calprotectin at Weeks 10, 14, 26, 52, 78, and 102.
- To evaluate the impact of triple combination therapy on health-related quality-of-life (HRQOL) using the Inflammatory Bowel Disease Questionnaire (IBDQ), Work Productivity and Activity Impairment - Crohn's Disease (WPAI-CD), and the Inflammatory Bowel Disease Disability Index (IBD-DI).

- To evaluate endoscopic remission, defined as Monitr Crohn's Disease (Monitr CD) Endoscopic Healing Index (EHI) score ≤20, at Weeks 26 and 102.
- To evaluate Monitr CD EHI score ≤30 or ≤50 at Weeks 26 and 102.

4.4 Safety Objective

The safety objective is to evaluate the safety of triple combination therapy with an anti-integrin, a TNF antagonist, and an immunomodulator over a 26-week period, followed by 76 weeks of monotherapy with an anti-integrin.

4.5 Study Design

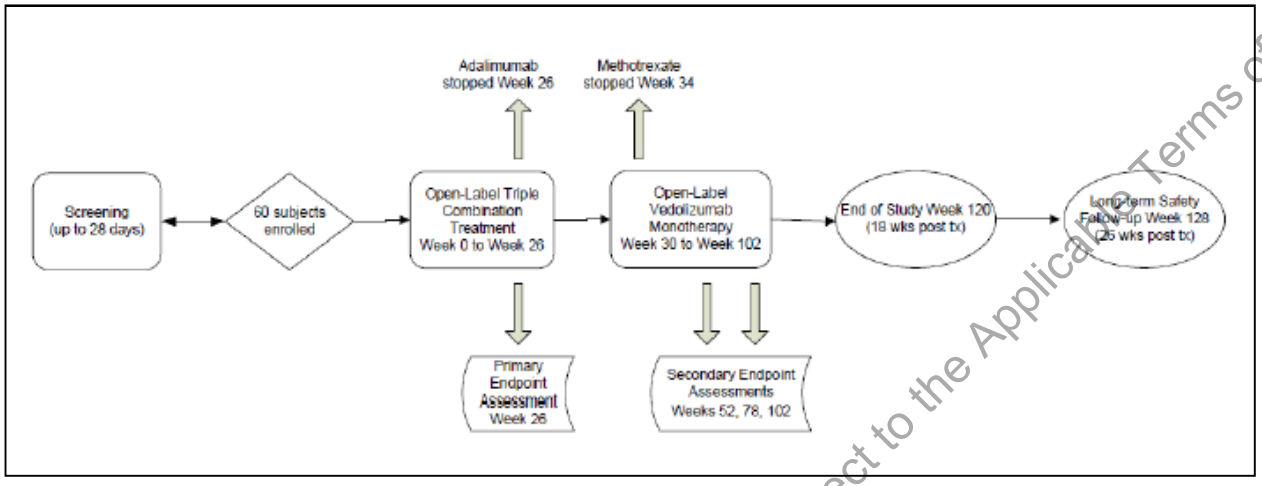
This is a phase 4, open-label, multicenter study in subjects with newly-diagnosed CD at higher risk for complications due to aggressive disease. The study will investigate the efficacy and safety of triple combination therapy (300 mg vedolizumab IV, 160/80/40 mg adalimumab SC, and 15 mg oral methotrexate) over a 26-week treatment phase for induction of clinical endoscopic remission and mucosal healing followed by efficacy and safety of vedolizumab IV monotherapy to maintain remission for 76 weeks, for a total treatment phase of 102 weeks.

Approximately 60 subjects with moderate to severe active CD at higher risk for disease complications will be studied at approximately 65 sites in the United States and Canada. Subjects must be diagnosed with CD within the previous 24 months and be naïve to biologics. Subjects will be determined to be at increased risk of CD complications. Subjects at low risk for CD complications will be excluded. Subjects will be followed for a total of 128 weeks.

The study consists of up to a 4-week screening period, a 26-week triple combination treatment phase, an additional 76-week vedolizumab IV monotherapy treatment phase, and a 26-week follow-up period following last dose (with final efficacy evaluations at Week 120). The duration of the study from screening to final efficacy visit at Week 120 will be approximately 124 weeks. All subjects, including subjects who discontinue early, will participate in a safety follow-up telephone call 26 weeks after last dose, for a total follow-up of 128 weeks.

A schematic of the study design is included as Figure 4.a. A schedule of assessments is listed in Appendix A.

Figure 4.a Schematic of Study Design



5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is the percentage of subjects achieving endoscopic remission (defined as a Simple Endoscopic Score for Crohn's Disease [SES-CD] of 0-2) at Week 26.

5.2 Secondary Endpoints

Secondary endpoints are as follows:

- Percentage of subjects achieving endoscopic healing defined as SES-CD ≤4 AND reduction from baseline SES-CD of at least 2 points AND no individual SES-CD subscore >1 at Week 26.
- Percentage of subjects achieving endoscopic response defined as 50% reduction in SES-CD from baseline at Week 26.
- Change from baseline SES-CD score at Week 26.
- Percentage of subjects achieving deep remission (defined as CDAI <150 and SES-CD 0-2) at Week 26.
- Percentage of subjects achieving clinical remission (defined as CDAI <150) AND endoscopic response as a measure of mucosal healing (defined as 50% reduction in SES-CD from baseline) at Week 26.
- Percentage of subjects achieving clinical remission (CDAI score <150) at Weeks 10 and 26.
- Percentage of subjects achieving clinical response (defined as ≥100 point decrease in CDAI score) at Weeks 10 and 26.
- Change from baseline C-reactive protein (CRP) levels at Weeks 10 and 26.

- Change in fecal calprotectin concentrations from baseline at Weeks 10, 14, 26, 52, 78, and 102.
- Percentage of subjects achieving clinical remission (defined as CDAI <150) AND CRP <5 (in subjects with elevated CRP at baseline) at Weeks 26, 52, 78, and 102.
- Percentage of subjects using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission (CDAI score <150) at Weeks 10, 26, and 102.
- Percentage of subjects maintaining clinical remission (defined as CDAI <150) at Weeks 52, 78, and 102.
- Percentage of subjects maintaining clinical response (defined as ≥100 point decrease in CDAI score from baseline) at Weeks 52, 78, and 102.
- Percentage of subjects maintaining endoscopic remission (defined as SES-CD of 0-2) at Week 102.
- Percentage of subjects maintaining deep remission (defined as CDAI <150 and SES-CD 0-2) at Week 102.
- Percentage of subjects maintaining endoscopic healing defined as SES-CD ≤4 AND reduction from baseline SES-CD of at least 2 points AND no individual SES-CD subscore >1 at Week 102.
- Percentage of subjects maintaining endoscopic response defined as 50% reduction in SES-CD from baseline at Week 102.
- Percentage of subjects maintaining clinical remission (defined as CDAI <150) AND endoscopic response as a measure of mucosal healing (defined as 50% reduction in SES-CD from baseline) at Week 102.
- Percentage of subjects with first exacerbation of CD after 26 weeks (defined as a CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, objective evidence of disease activity by colonoscopy AND CRP above normal, OR fecal calprotectin >250 μg/g alone).

5.3 Additional Endpoints

Additional endpoints include the following:

- Change from baseline IBDQ score at Weeks 14, 26, 52, 78, and 102.
- Change from baseline WPAI-CD score at Weeks 14, 26, 52, 78, and 102.
- Change from baseline in IBD-DI score at Weeks 14, 26, 52, 78, and 102.
- Percentage of subjects achieving normalization of CRP defined as <5 mg/L at Week 26 (in those elevated at baseline).
- Trough concentration of vedolizumab and adalimumab at Week 26.

- Change from baseline CDAI score at Weeks 26, 52, 78, and 102.
- Change from baseline of Patient Reported Outcome 2 (PRO-2) score at Weeks 26, 52, 78, and 102.
- Change from Week 26 CDAI score at Weeks 52, 78, and 102.
- Change from Week 26 PRO-2 score at Weeks 52, 78, and 102.
- Change from Week 26 CRP levels at Weeks 52, 78, and 102.
- Percentage of subjects with positive antidrug antibodies (ADAs) to vedolizumab and adalimumab, and neutralizing ADAs (nADAs) to vedolizumab. (Percentage of subjects with nADAs to adalimumab is optional if deemed necessary for the interpretation of the data).
- Time to major CD-related events (hospitalizations, bowel surgeries, and CD-related procedures).
- Percentage of subjects hospitalized from Day 1 to Week 102.
- Percentage of subjects hospitalized due to CD from Day 1 to Week 102.
- Percentage of subjects requiring surgery other than seton placement for perianal fistula from Day 1 to Week 102.
- Percentage of subjects achieving a PRO-2 score ≤75 AND an SES-CD ≤4 AND a reduction from baseline SES-CD of at least 2 points AND no individual SES-CD subscore >1 at Weeks 26 and 102.
- Percentage of subjects assessed at screening as having moderate-high risk CD with ≥20% chance of disease complication by Year 2 as calculated by the Crohn's Disease Personalized Risk and Outcome Prediction Tool (PROSPECT [2, 3]) for subjects for whom that tool was used.
- Percentage of subjects developing a CD related complication by Week 102 who were assessed at screening as having moderate-high risk CD with ≥20% chance of disease complication by Year 2 as calculated by the PROSPECT predictive tool for those for whom that tool was used.
- Percentage of subjects with an EHI score ≤20 at Weeks 26 and 102.
- Percentage of subjects with an EHI score ≤30 at Weeks 26 and 102.
- Percentage of subjects with an EHI score ≤50 at Weeks 26 and 102.
- Change from baseline in EHI score at Weeks 26 and 102.

5.4 Safety Endpoints

Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs), serious adverse events (SAEs), AEs leading to discontinuation, vital signs, physical examination,

and results of standard laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis).

6.0 DETERMINATION OF SAMPLE SIZE

The sample size was based on an estimate of precision. A sample size of 60 subjects will generate 95% confidence intervals for endoscopic remission (defined as SES-CD of 0-2) rate at Week 26 with a half width no wider than 12.7% and expected remission of 50%. If the expected remission rate is different from 50%, a required sample size would be smaller.

7.0 METHODS OF ANALYSIS AND PRESENTATION

This statistical analysis plan (SAP) is written based on the study protocol Amendment 4, 30 June 2020 [1].

7.1 General Principles

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

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment phase. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

All confidence intervals, statistical tests, and resulting p-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (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.

7.1.1 Study Definitions

Study specific definitions are listed below:

Term	Definition
Endoscopic remission	SES-CD of 0-2.
Endoscopic healing	SES-CD ≤4 and reduction from baseline SES-CD of at least 2 points and no individual SES-CD subscore >1.
Endoscopic response	50% reduction in SES-CD from baseline.
Deep remission	CDAI <150 and SES-CD 0-2.
Clinical remission	CDAI <150.
Clinical response	≥100 point decrease in CDAI score from baseline.
First exacerbation of CD after 26 weeks	CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, or objective evidence of disease activity by colonoscopy and CRP above normal, or fecal calprotectin >250 μg/g alone.
Normalization of CRP	CRP <5 mg/L.
Endoscopic remission (based on Monitr CD)	EHI ≤20.
Triple combination therapy phase	The day of first dose of study medication (Day 1) up to and including the end of the Week 26 study window or the day of last dose, whichever occurs earlier.
Monotherapy phase	The day after the Week 26 study window up to and including the day of last dose of study medication.
Follow-up phase	The day after the last dose up to and including Week 120 EOS/ET.

7.1.2 Definition of Study Days

Study Day 1 (Day 1) is defined as the day on which a subject is administered their first dose of the study medication in the triple combination therapy phase. Other study days are defined relative to the Day 1.

The study day prior to the first dose of study drug will be calculated as:

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

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

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

7.1.3 Definition of Baseline Values

Baseline values will be defined as the last observed value before the first dose of study medication. Any procedures performed on the same day as the first dose of study medication will be assumed to have been performed prior to the administration of the study medication.

7.1.4 Definition of Screen Failure

Screen failure subjects are subjects who signed the informed consent form (ICF) and were not enrolled in the triple combination therapy phase of the study. The primary reason for screen failure was 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 Definition of Study Visit Windows

Study day will be calculated relative to the date of the first dose of study drug in the triple combination therapy phase of the study. The study day prior to the first dose of study drug will be calculated as:

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

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

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

Baseline values are defined in Section 7.1.3. The visit windows for postbaseline visits are defined in Table 7.a through Table 7.d. If a subject has more than 1 non-missing measurement in the same visit window, the measurement closest to the target day will be used. In case of ties between measures located on different sides of the target day, the measurement that occurs later will be used. In case of ties located on the same side of the target day (i.e., two or more measurements occur on the same day), the average of the values will be used.

Table 7.a Visit Windows for Triple Combination Therapy Phase: CDAI, Safety Laboratory Parameters, Vital Signs, ADA and Serum/Urine hCG

Visit	Target Study Day	Study Day Range	
		CDAI, Safety Laboratory Parameters Vital Signs, ADA	Serum/Urine hCG
Baseline	1	≤1	≤1
Week 2	15	2-29	2-29
Week 6	43	30-57	30-57
Week 10	71	58-85	58-85
Week 14	99	86-127	86-113
Week 18	127	NA	114-141
Week 22	155	128-169	142-169
Week 26	183	170-197	170-197

Table 7.b Visit Windows for Triple Combination Therapy Phase: Other Endpoints

Visit	Target Study Day	Study Day Range					
		PRO-2	SES-CD, Monitr CD Test	CRP	Fecal calprotectin	IBDQ, WPAI, IBD-DI	Health outcomes, CD-related events
Baseline	1	≤1	≤1	≤1	≤1	≤1	NA
Week 2	15	NA	NA	NA	NA	NA	2-29
Week 6	43	NA	NA	NA	NA	NA	30-57
Week 10	71	NA	NA	2-127	2-85	NA	58-85
Week 14	99	NA	NA	NA	86-141	2-141	86-127
Week 22	155	NA	NA	NA	NA	NA	128-169
Week 26	183	170-197	170-267	128-197	142-197	142-197	170-197

Note: The Week 26 visit window for SES-CD and Monitr CD is extended beyond day 197 due to a data review identifying procedures delayed due to the COVID-19 pandemic.

Table 7.c Visit Windows for Monotherapy Phase: CDAI, Safety Laboratory Parameters, Serum/Urine hCG, Vital Signs, and ADA

Visit	Target Study Day	Study Day Range			
		CDAI, Safety Laboratory Parameters, Health Outcomes, CD-related events	Serum/Urine hCG	Vital Signs	ADA
Week 30	211	*198-239	198-225	198-225	NA
Week 34	239	NA	226-253	226-253	NA
Week 38	267	240-295	254-281	254-281	198-323
Week 42	295	NA	282-309	282-309	NA
Week 46	323	296-351	310-337	310-337	NA
Week 50	351	NA	338-365	338-358	NA
Week 52	365	352-372	NA	359-372	NA
Week 54	379	373-407	366-393	373-393	324-435
Week 58	407	NA	394-421	394-421	NA
Week 62	435	408-463	422-449	422-449	NA
Week 66	463	NA	450-477	450-477	NA
Week 70	491	464-519	478-505	478-505	436-547
Week 74	519	NA	506-533	506-533	NA
Week 78	547	520-575	534-561	534-561	NA
Week 82	575	NA	562-589	562-589	NA
Week 86	603	576-631	590-617	590-617	548-659
Week 90	631	NA	618-645	618-645	NA
Week 94	659	632-687	646-673	646-673	NA
Week 98	687	NA	674-701	674-701	NA
Week 102	715	≥688	≥702	≥702	≥660

*For safety laboratory parameters, only hematology is scheduled.

Table 7.d Visit Windows for Monotherapy Phase: Other Endpoints

Visit	Target Study Day	Study Day Range		
		PRO-2	SES-CD, Monitr CD Test	CRP, Fecal calprotectin, IBDQ, WPAI, IBD-DI
Week 52	365	352-372	NA	198-456
Week 78	547	520-575	NA	457-631
Week 102	715	≥688	≥268	≥632

Data identified on the eCRF as coming from an "unscheduled" visit will be eligible for windowing. There will not be a separate "unscheduled" categorization for the reporting of these

observations. Data from the End-of Study or Early Termination visit (Week 120) and LTFU Phone Call visits (Week 128) will not be included in the visit windows; they will be identified from the visit entered in the eCRF and appear in summary tables as "Week 120, EOS/ET" visit.

The study visit window conventions 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 CDAI Scores

The CDAI consists of 8 components: number of liquid or very soft stools, abdominal pain, general well-being, extra-intestinal manifestations of CD, use of Lomotil/Imodium/opiates for diarrhea, abdominal mass, hematocrit level and body weight. The CDAI total score is derived from the 8 components as described below (refer to Appendix B for a tabular summary of the derivation).

The CDAI will be derived at each scheduled visit utilizing the most recent available patient reported components (number of liquid or very soft stools, abdominal pain, general well-being and use of Lomotil/Imodium/opiates for diarrhea are self-reported by subjects via eDiary on a daily basis), physician reported outcomes components (extra-intestinal manifestations of CD, abdominal mass) and body weight, and hematocrit values as described below:

1. Identify the completion date of the physician reported CDAI components and set it as the CDAI calculation/assessment date.
2. Calculate the 3 eDiary sub-scores (liquid/soft stool frequency, abdominal pain and general well-being) as follows:
   a) Select the diary data from 10 days prior to the CDAI calculation date identified in (1).
   b) Exclude the day before, day of and day after colonoscopy.
   c) Take 7 most recent days of diary data.
   d) If less than 4 days of diary are non-missing for a component, then the respective component sub-score cannot be calculated and is set to missing.
   Otherwise:
      i. If 4 to 6 days of diary are non-missing, calculate the average of non-missing diary days (sum over non-missing entries/number of non-missing entries), multiply by 7, then multiplying by the factor appropriate for the respective component sub-score (x2 for liquid/soft stools, x5 for abdominal pain, x7 for general well-being) and round to the nearest integer.
      ii. If 7 or more days of diary are non-missing, calculate the sum of the most recent 7 days of non-missing diary and multiply the sum by the factor appropriate for the respective component sub-score (see above).
3. Extra-intestinal manifestations of CD sub-score:
   Count the number of check boxes ticked for extra-intestinal manifestations of CD and multiply that count by a factor of 20.

4. Lomotil/Imodium/opiates for diarrhea sub-score:
   If use of Lomotil/Imodium/opiates for diarrhea is reported ("Yes"), then the subscore is 30; otherwise ("No"), the sub-score is 0. Information on Lomotil/Imodium/opiates use was recorded by the subject daily in the eDiary. Therefore the following rule will be applied:
   a) Select the diary data from 10 days prior to the CDAI calculation date identified in (1).
   b) Exclude the day before, day of and day after colonoscopy.
   c) Take 7 most recent days of diary data.
   d) If any use of Lomotil/Imodium/opiates for diarrhea is reported on those days, then the subscore is 30; if no use is reported on those days, the sub-score is 0.
      If no information on use of Lomotil/Imodium/opiates is available for the last 10 days, then the sub-score is set to missing.
5. Abdominal Mass sub-score:
   Responses "Definite", "Questionable" and "None" will be assigned sub-scores of 50, 20, and 0, respectively.
6. Hematocrit sub-score:
   a) Identify the corresponding hematocrit result using the visit windows and rules defined in Section 7.1.5.
   b) Subtract hematocrit value (in %) from 47 for males and from 42 for females, multiply result by a factor of 6 and round to the nearest integer.
      If the hematocrit sub-score is <0, set it to 0.
7. Body Weight sub-score:
   a) Identify the corresponding body weight result using the visit windows and rules defined in Section 7.1.5.
   b) Identify the standard weight based on subject's gender and baseline height (cm) as follows:
      i. Standard weight for men in kilogram = $(\text{height in cm}/100)^2 \times 22.1$
      ii. Standard weight for women in kilogram = $(\text{height in cm}/100)^2 \times 20.8$
   c) Calculate the maximum of {(1 – (Body weight/Standard Weight)) ×100, -10}; the value rounded to the nearest integer is the body weight sub-score.
8. The total CDAI score is the sum of the 8 sub-scores above. If any of the sub-scores are missing, the total CDAI score is set to be missing.

7.1.7 Convention for Calculation of PRO-2 Score

The PRO-2 score will be derived at each scheduled visit utilizing liquid/soft stool frequency and abdominal pain scores from 7 days prior to the same visit. The sub-scores are calculated in a similar way to CDAI subscores (see Section 7.1.6 step 2), however the 7 day average is

calculated rather than the 7 day total and the same multiplication factors used (x2 for liquid/soft stools, x5 for abdominal pain). The PRO-2 score is the sum of the two sub-scores. If either of the sub-scores are missing, the PRO-2 score is set to be missing.

7.1.8 Convention for Calculation of IBDQ Sub-domain and Total Score

The IBDQ is a widely used, health-related quality of life questionnaire used for subjects with ulcerative colitis and Crohn's disease. The questionnaire is regarding the subject's bowel problems and how they affected his or her life during the past 2 weeks. The IBDQ consists of 32 questions, with each question response ranging from 1 to 7, where 1 indicates worse IBD and 7 indicates better IBD. Four sub-domains and a total score will be derived.

IBDQ Sub-domain	Calculation
Bowel symptoms score	Sum of (Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, Q29). Ranging from 10 to 70. 10 questions.
Emotional function score	Sum of (Q3, Q7, Q11, Q15, Q19, Q21, Q23, Q25, Q27, Q30, Q31 and Q32). Ranging from 12 to 84. 12 questions.
Social function score	Sum of (Q4, Q8, Q12, Q16 and Q28). Ranging from 5 to 35. 5 questions.
Systemic symptoms score	Sum of (Q2, Q6, Q10, Q14 and 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.	

To calculate the IBDQ total score, the scores for Bowel symptom, Emotion function, Social function, and Systemic symptoms are summed. The IBDQ total score ranges from 32 to 224, with a higher score indicating better quality of life. If any of the component score is missing at a visit, the imputed value will be set to missing.

7.1.9 Convention for Calculation of WPAI-CD Sub-scores

The WPAI-CD consists of 6 questions that evaluate absenteeism (work time missed), presenteeism (reduced work productivity), overall work impairment, and activity impairment. Each subscore is expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

WPAI-CD subscore	Calculation
Percentage of work time missed because of CD in the past seven days [Absenteeism]	Q2/(Q2+Q4)
Percentage of impairment experienced while at work in the past seven days because of CD [Presenteeism]	Q5/10
Overall work productivity loss	Q2/(Q2+Q4)+ [(1- Q2/(Q2+Q4))×Q5/10]
Percentage of impairment in daily activities due to CD in the past seven days [Activity impairment]	Q6/10

7.1.10 Convention for Calculation of IBD-DI

The IBD-DI consists of 14 questions that focus on body functions, body structures, activities and participation, and environmental factors. Twelve of the 14 items are based on a five-point Likert scale (no limitation, slight limitation, moderate limitation, severe limitation, extreme limitation), one item (arthritis) is a binary response, and the number of liquid stools is a continuous value. The IBD-DI score will be calculated as the sum of the values for the 14 questions:

- The response for Arthritis is scored as 0 if the response is "no" and 4 if the response is "yes".
- The number of liquid stools is categorized as follows: 0 is grouped together and other values are categorized into quartiles.
- The responses to all other questions are rescaled to range from 0 to 4.

A subject at a specific time point should normally not answer both questions 12a and 12b of the 14-item IBD-DI questionnaire. Should this situation occur, i.e., if a subject has answered both 12a and 12b (with a value 0 to 4), the primary analysis approach will use the answer to question 12b if age at visit <19 years and the answer to question 12a if age at visit ≥19 years. As a sensitivity analysis, the worst case scenario (with a value 0 to 4) approach will be utilized, i.e. choose the answer with the most severe limitation.

If <20% of the questions have missing values for a subject, the IBD-DI score will be rescaled from 0 to 100 using the following formula: score×100/(p×4), where p represents the number of answered items. If ≥20% of the questions have missing values for a subject, the IBD-DI score will be set to missing.

Scores range between 0 to 100, with 0 to 20 indicating no disability, 20 to 35 mild disability, 35 to 50 moderate disability, and 50 to 100 severe disability.

7.1.11 Conventions for Missing Adverse Event 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 when first study medication date is missing).
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 15th 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, if 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 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.

7.1.12 Conventions for Missing Concomitant Medication 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:

1. If the start date is partial or unknown:
   - If the day is missing, the start day will be the first day of the month.
   - If the month is missing,
     - If the year is the same as the date of first dose of study drug, the start month will be the month corresponding to 90 days prior to the date of first dose of study drug with exception that the month of first dose is Jan, Feb, or Mar.
     - If the year is the same as the year of first dose of study drug and the month of first dose is Jan, Feb, or Mar, the start month will be Jan.
     - If the year is not the same as the year of first dose of study drug, the start month will be Jan.

- 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 unknown:
  - If eCRF indicates that the medication ended prior to the informed consent date, then the medication start date will be imputed to the informed consent date minus one day.
  - Otherwise the start date will be the minimum of the date of first dose of study drug and the medication end date.

2. If the stop date is partial, unknown or "ongoing":
   - If the day is missing, the stop day will be the last day of the month reported. If the eCRF indicates the medication ended prior to informed consent, and month is the month of informed consent, the day should be imputed to informed consent date minus one day.
   - If the month is missing:
     - If the year is the same as the date of last assessment, then the stop month will be to the month during which the last assessment occurred.
     - If the year is not the same as the year of the last assessment, then the end month will be Dec.
   - If the year is missing or the entire date is unknown or if the medication is "ongoing", the stop year will be the year in which the last assessment occurred. If information collected on the eCRF indicate that the medication ended prior to the informed consent date, then the medication end date will be imputed to the informed consent date minus one day.

7.1.13 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 (Day 1):

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

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.

7.2 Analysis Sets

The following analysis sets will be used for analysis and presentation of the study data:

- The safety analysis set (SAF): All subjects who received at least 1 dose of study drug will be included in the SAF.
- The full analysis set (FAS): All subjects who received at least 1 dose of study medication and have a post enrollment efficacy assessment will be included in the FAS.
- The per protocol set (PPS): All FAS subjects who do not violate the protocol in a way that would impact the primary efficacy will be included in the PPS. All decisions to exclude subjects from the PPS will be made prior to the database lock. The hierarchy of reasons for exclusion is as follows: inclusion and exclusion criteria violations, study medication dosing errors, receiving forbidden concomitant medications such as oral corticosteroids without tapering and refusal for Week 26 endoscopy.
- The PK analysis set: All subjects who receive at least 1 dose of study drug and have sufficient blood sampling to allow for PK evaluation.

In addition, the population of "all enrolled subjects" may be used for particular data summaries. All treated subjects (i.e., the SAF) will be presented in the subject listings.

7.3 Disposition of Subjects

Subject disposition will be summarized and provided in listings. The following summaries will be produced:

- 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), World Health Organization Drug Dictionary (WHODrug) and SAS® versions used for reporting.
- Summary of screen failures including:
  - total number of screen failures
  - descriptive statistics for age
  - counts and percentages for gender, ethnicity, race and the primary reason for screen failure.
- Summary of study subjects enrolled by site and country.

- Summary of subject disposition including:
  - number of subjects completing or prematurely discontinuing study drug along with the primary reason for study drug discontinuation (vedolizumab, adalimumab and methotrexate will be presented separately)
  - number of subjects completing all study drugs in triple combination therapy phase
  - number of subjects completing or not completing all planned study visits, specifically Weeks 26, 52, 78 and 102 with the reason for discontinuation of the planned study visits
- Summary of significant protocol deviations as captured on the eCRF.
- Summary of reasons for exclusion from PPS.
- Summary of number of subjects in each analysis set defined in Section 7.2.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the SAF. The variables that will be tabulated are listed in Table 7.e.

Table 7.e Summary of Demographic and Baseline Characteristics

Demography (unit)	Summarized as	Categories
Age (years)	Continuous and categorical	<35, >=35 <65, >=65
Gender	Categorical	Male Female
Ethnicity	Categorical	Hispanic or Latino Non-Hispanic and Latino Not Collected
Race[a]	Categorical	American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Multiracial
Height (cm)	Continuous	
Weight (kg)	Continuous	
Body Mass Index (BMI) (kg/m^2)	Continuous	
Smoking Classification	Categorical	Never-smoker Current smoker 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.

CD-related baseline characteristics will be summarized for the SAF. If there is a large difference between the SAF and the FAS (e.g. >5%) then CD related baseline characteristics will be summarized for both analysis sets. The characteristics that will be tabulated are listed in Table 7.f. For categorical responses, a "Missing" category will be added, as needed.

Table 7.f Summary 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 SES-CD	Continuous and Categorical	4-6 7-15 (Moderate) >=16 (Severe)
Baseline CDAI Activity	Continuous and Categorical	≤220 >220 to ≤330 >330
Baseline C-reactive protein (CRP) (mg/L)	Continuous and Categorical	≤2.87 mg/L >2.87 mg/L to ≤5 mg/L >5 mg/L to ≤10 mg/L >10 mg/L
Baseline fecal calprotectin (FC) (µg/g)	Continuous and Categorical	≤250 µg/g >250 µg/g to ≤500 µg/g >500 µg/g
Has the patient had any acute exacerbations within the past 12 months?	Categorical	Yes No
Number of acute exacerbations	Continuous	
Has the patient had any hospitalizations for Crohn's disease within the past 12 months?	Categorical	Yes No
Number of hospitalizations	Continuous	
Has the patient had a colonoscopy within the last 12 months?	Categorical	Yes No
Location of Crohn's Disease	Categorical	Ileum Colon Rectal Involvement Other Each location tabulated separately as well as the following combination: Ileal Colonic Ileocolonic
Has the patient had surgery for Crohn's disease?	Categorical	Yes No
How many surgeries?	Continuous	

Table 7.f Summary of CD-Related Baseline Characteristics

Characteristics (unit)	Summarized as	Categories
Has the patient had any extraintestinal manifestations?	Categorical	Yes No
Types of Extraintestinal manifestations	Categorical	Arthritis/Arthralgia Iritis/Uveitis Erythema nodosum Pyoderma gangrenosum Aphthous stomatitis Anal fissure Anal fistula Abscess Other fistula Fever over 37.8°C during the past week
Estimated number of weeks of corticosteroid use over the last 12 months	Continuous	
Concomitant use of baseline corticosteroids	Categorical	Yes No
Method of Complication Risk Assessment (primary)	Categorical	PI Clinical Assessment 2014 AGA CD Clinical Care Pathway PROSPECT Tool
Method of Complication Risk Assessment (all)	Categorical	PI Clinical Assessment 2014 AGA CD Clinical Care Pathway PROSPECT Tool
Baseline PROSPECT risk score at 2 years	Continuous	
Baseline ulcer size (ileum)	Categorical	None Aphthous Large Very large
Baseline ulcer size (colon)	Categorical	None Aphthous Large Very large
Baseline ulcer size (rectum)	Categorical	None Aphthous Large Very large

7.5 Medical History and Concurrent Medical Conditions

A subject's medical history will include any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. All medical history and concurrent medical conditions will be summarized and listed for the SAF.

Concurrent medical conditions are significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at the screening or baseline examination. The condition (e.g., diagnosis) should be described.

Medical history and concurrent medical conditions will be coded using the latest version of MedDRA. The number and percentage of subjects with any significant medical history and any concurrent medical conditions will be summarized for each MedDRA system organ class (SOC) and preferred term (PT). The tables will include numbers and percentages of subjects and will be sorted alphabetically by SOC and descending frequency of PT. A subject will only be counted once within a SOC or PT even if he/she has multiple conditions/symptoms for that SOC or PT.

All medical history and concurrent medical condition data will be listed separately by site and subject number.

7.6 Medication History and Concomitant Medications

All outputs described in this section will be generated for the SAF. Accordingly, the denominator for all percentages is the number of subjects included in the SAF.

Medication history information includes any medication relevant to eligibility criteria which was stopped at or within 30 days prior to the signing of informed consent.

Medication history is captured on the Medication History/Concomitant Medications eCRF page. Medication history will be coded using WHODrug and will be summarized by therapeutic classification, and preferred medication name. Therapeutic classification will be sorted alphabetically and preferred medication names by decreasing frequency using the total number of subjects as the denominator. If a subject reports taking 2 medications belonging to the same class, he/she will only be counted once within that class.

In addition, a history of any medications taken for the treatment of CD, including the reason for discontinuation, that stopped at or prior to signing of informed consent is collected at screening. Any prior CD treatment is captured on the Prior CD Treatment eCRF. The prior CD medications are not coded; they will be summarized by verbatim term. Verbatim terms will be sorted alphabetically.

Concomitant medications will be summarized by therapeutic classification and preferred medication name and will include only those medications taken at any time between informed consent and on or prior to the end of study (Week 120) or early termination. 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 were ongoing after 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 and on or before the end of study (Week 120) or early termination.

Concomitant medications will be coded using WHODrug and summarized by therapeutic classification and preferred medication name using the total number of subjects in the SAF for the denominator. The concomitant medications that were ongoing after baseline or started during the treatment period will be summarized separately for each treatment phase; the denominator for each phase will be the number of SAF subjects entering that treatment phase. Therapeutic classification will be sorted alphabetically and preferred medication names by decreasing frequency based on the total number of subjects. Separate listings for medication history, CD prior medications and concomitant medications will be produced by site and subject number.

7.7 Study Drug Exposure and Compliance

The SAF will be used for all summaries in this section. Study drug exposure and compliance will be summarized by study drug and treatment period.

The exposure to each treatment will be calculated separately as the duration between the first and last dose of study drug plus approximately 5 times the half-life of the study drug. Given that the mean terminal half-life of vedolizumab, adalimumab and methotrexate is approximately 25.2 days, 2 weeks and 9 hours respectively, the extent of exposure will be calculated as follows:

- Vedolizumab: Date of last dose of vedolizumab – Date of first dose of vedolizumab + 1 + 126 days (18 weeks).
- Adalimumab: Date of last dose of adalimumab – Date of first dose of adalimumab + 1 + 70 days (10 weeks).
- Methotrexate: Date of last dose of methotrexate – Date of first dose of methotrexate + 1 + 2 days.

The adalimumab SC dosing is recorded in the eCRF for clinic visits and electronic diaries (e-diaries) for at-home dosing. Duplicate entries will be handled as follows prior to summarizing:

- If a clinic visit SC dose is also recorded in the e-diary, data will be taken from the eCRF for analysis.
- If an e-diary contains multiple dosing records on a single date, the record with the most drug injected (complete vs partial) will be used for analysis, regardless of time or location.

The number of completed doses and the number of completed or partial doses will also be summarized by study drug and treatment period. Study drug administration data for vedolizumab, adalimumab, methotrexate and folic acid (the companion supplement) will be presented in data listings.

7.8 Efficacy Analysis

This section describes the summaries to be provided for the primary, secondary and additional efficacy endpoints. Summaries of the efficacy data will be based on the FAS. Summaries of the primary endpoint will also be based on the PPS and on observed cases (FAS subset to those with a Week 26 colonoscopy).

All subjects with missing data for the determination of binary endpoint status will be considered as a value of 'NO' in the analysis. In summary tables, the number of subjects not achieving the endpoint (a true 'NO') will be tabulated as well as the number of total "NO" (true "NO" plus imputed "NO").

Categorical secondary and additional endpoints will be summarized using the number and percentage of subjects and corresponding 95% CI calculated using the Wald asymptotic method, unless otherwise noted.

Continuous secondary and additional efficacy endpoints will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum).

7.8.1 Primary Efficacy Endpoint(s)

The primary endpoint is the percentage of subjects achieving endoscopic remission, defined as a SES-CD score of 0-2, at Week 26. The number and percentage of subjects achieving/not-achieving endoscopic remission and corresponding 95% CIs will be summarized by triple combination therapy.

7.8.2 Secondary Efficacy Endpoint(s)

Categorical endpoints listed in Section 5.2 will be summarized by the treatment phase in which they are measured, that is, endpoints measured up to week 26 will be summarized in the triple combination therapy phase and endpoints after week 26 will be summarized in the monotherapy phase. The denominator for each treatment phase, is the number of subjects in the FAS that take a dose of study medication in that treatment phase.

For the following secondary endpoints that are the maintenance of a result after Week 26, the corresponding analysis will be based on the number of subjects in the FAS that achieved the endpoint at Week 26 and continued into the monotherapy phase, e.g. the subject has to meet the criterion at both Week 26 and the specified post-Week 26 visit to be considered as a value of "YES" in the analysis:

- maintaining clinical remission.
- maintaining clinical response.
- maintaining endoscopic remission.
- maintaining deep remission.
- maintaining endoscopic healing.

- maintaining endoscopic response.
- clinical remission and endoscopic response.

For the secondary endpoint of the first exacerbation of CD after 26 weeks, the eCRF is only completed for subjects starting at Week 30; therefore, the denominator for the summary will be the FAS subjects that receive a dose of study medication in the monotherapy phase.

For each of the continuous endpoints listed in Section 5.2, the change from baseline will be calculated and summarized for each post baseline visit the endpoint is scheduled to be measured.

7.8.3 Additional Efficacy Endpoint(s)

7.8.3.1 Categorical Endpoints

Categorical endpoints listed in Section 5.3 will be summarized by the treatment phase in which they are measured, that is, endpoints measured up to week 26 will be summarized in the triple combination therapy phase and endpoints after week 26 will be summarized in the monotherapy phase. The denominator for each treatment phase, is the number of subjects in the FAS that take a dose of study medication in that treatment phase. The exception are the following endpoints that will be summarized by planned study visit across both treatment phases combined:

- Subjects assessed at screening as having moderate-high risk CD with ≥20% chance of disease complication by Year 2 as calculated by the PROSPECT predictive tool for those for whom that tool was used.
- Subjects developing a CD related complication by Week 102 who were assessed at screening as having moderate-high risk CD with ≥20% chance of disease complication by Year 2 as calculated by the PROSPECT predictive tool for those for whom that tool was used.

7.8.3.2 Continuous Endpoints

For the IBDQ (total and sub-scores), WPAI-CD (total and sub-domains), IBD-DI score, CDAI score, PRO-2 score, and EHI the change from baseline will be calculated for each post-baseline assessment and summarized by visit for the entire study. The visits through Week 26 will be summarized in the triple combination therapy phase and visits after Week 26 will be summarized in the monotherapy phase. The denominator for each treatment phase, is the number of subjects in the FAS that take a dose of study medication in that treatment phase.

For the CDAI score, PRO-2 score, and CRP levels, the change from Week 26 will be calculated for each post-Week 26 assessment and summarized by visit for the monotherapy treatment phase.

If baseline and Week 26 CDAI and PRO-2 scores and their changes from baseline and changes from Week 26 are approximately normally distributed, then these changes will be summarized using descriptive statistics.

7.8.3.3 Time to Event Endpoints

The time from the date of first dose to major CD-related events (a single endpoint including either hospitalizations, bowel surgeries or procedures) will be analyzed descriptively using Kaplan-Meier product limit methods. The time to event will be summarized by estimates of 25th, 50th (median), and 75th percentiles with 95% CI, and the range (Min, Max). Kaplan-Meier plots will be presented over the entire study period. The number of subjects at risk, number and percentage of subjects with major CD-related events will be presented for Week 26 and Week 102. The number of subjects at risk will be counted as the subjects that are still in the study (on treatment) at the start of the visit window for that visit. The number of events will be assessed at the end of the visit window for that visit.

A subject that does not have any major CD-related events during the study will be censored using the date of last visit.

7.8.4 Subgroup Analysis

The following subgroups will be defined:

- baseline SES-CD [<=15, >=16]
- baseline ulcer size (ileum) [none, aphthous ulcers, large/very large ulcers]
- baseline ulcer size (colon) [none, aphthous ulcers, large/very large ulcers - defined using the worst category (largest size) out of the right, transverse and left colon locations]
- baseline ulcer size (rectum) [none, aphthous ulcers, large/very large ulcers]
- baseline CDAI [<=220, >220-<=330, >330]
- disease location [ileal, colonic, ileocolonic]
- baseline fecal calprotectin [<=500, >500]
- baseline CRP [<=5, 5-10, >10]
- ADA status [positive AVA only, positive ADA only, positive AVA and ADA, negative AVA and ADA] over 26 weeks
- ADA status [positive AVA only, positive ADA only, positive AVA and ADA, negative AVA and ADA] over 102 weeks.

The primary endpoint endoscopic remission as well as endoscopic healing and endoscopic response at Week 26 will be analysed by all subgroups excluding baseline CDAI and ADA status over 102 weeks. Clinical remission and clinical response at Week 26 will be analysed by all subgroups excluding baseline SES-CD, baseline ulcer size and ADA status over 102 weeks. The combined endpoint of clinical remission and endoscopic response at Week 26 will be analysed by all subgroups excluding ADA status over 102 weeks.

The maintenance of endoscopic healing and maintenance of endoscopic response at Week 102 will be analysed by all subgroups excluding baseline CDAI and ADA status over 26 weeks.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Pharmacokinetic analysis will be done using the PK analysis set.

7.9.1 Pharmacokinetic Analysis

Blood samples are to be collected for vedolizumab PK analysis on Day 1 and Weeks 6, 10, 14, 26, 38, 54, 70, 86, and 102. Blood samples are to be collected for adalimumab PK analysis on Day 1 and Weeks 6, 10, 14, 22, and 26. Measured serum vedolizumab and adalimumab concentrations will be summarized by time and treatment phase using descriptive statistics. Individual serum concentration versus time data will be presented in a data listing.

C_{trough}, trough serum concentrations (measured concentration at the end of a dosing interval at steady state), will be derived directly before next administration. Ctrough for each medication will be summarized using descriptive statistics (number of non-missing values, mean, SD, %CV, median, minimum, and maximum).

Additionally, all PK analyses will be analysed by the ADA status subgroups as defined in Section 7.8.4.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

The proportion of subjects with positive antidrug antibodies (ADA) (transient and persistent) and the proportion of subjects with positive neutralizing ADA during the study will be summarized by treatment phase. A positive ADA subject is defined as a subject who has at least 1 positive ADA result in any postbaseline sample, and is further categorized as:

- Transiently positive: subjects with at least one confirmed positive ADA sample at a postdose visit (excluding last available) and no consecutive positive ADA samples.
- Persistently positive: subjects with confirmed positive ADA in 2 or more consecutive ADA samples postdose with positive result or last available postdose ADA sample with positive result.

The impact of ADA on efficacy, PK and safety will be examined by subgroup analyses described in Section 7.8.4, 7.9.1 and 7.11.1.2, respectively.

7.11 Safety Analysis

Safety analyses include AEs, clinical laboratory values, vital signs and ECGs. All safety summaries will be presented by treatment phase for the subjects included in the SAF.

7.11.1 Adverse Events

A pretreatment event 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. An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug. Pretreatment events and AEs will be coded using MedDRA. 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 on or after the first dose of study drug and up to the last dose of study drug plus 18 weeks follow up or early termination. TEAEs with a start day ≤ Day 197 will be assigned to the triple combination therapy, TEAEs with a start day >Day 197 and on or before the study day of the last dose of study medication will be assigned to the monotherapy treatment period, and TEAEs starting after the study day of the last dose of study medication will be assigned to the follow-up period.

In summaries containing the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC, HLT or PT when multiple TEAEs are coded to the same SOC, 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.

AEs will be summarized by intensity (mild, moderate and severe). AEs with missing intensity will be presented as such in the AE listings, however, will be summarized as severe in summary tables. AEs will also be summarized by the relationship to study drug (related or not related). If the relationship of an event is missing, the relationship for the event will be considered to have been related, but it will be presented as missing in the AE listings. In the cases where a subject has multiple AEs with the same SOC or HLT or PT, the AE with the maximum intensity or strongest relationship will be summarized.

In the summary tables, SOCs and HLTs will be sorted in alphabetical order. Within a SOC and a HLT, adverse events will be sorted in descending order of total number of subjects with the PT.

All AEs, not just those which are treatment-emergent, will be presented in listings. Special listings for TEAEs leading to study discontinuation, SAEs and deaths will also be presented.

7.11.1.1 Treatment-Emergent Adverse Events

An overview of TEAEs will be provided. The summary will include relatedness, severity, TEAEs leading to discontinuation, SAEs including relatedness and those leading to discontinuation, and deaths. The number of events will be displayed as well and the number and percentage of subjects experiencing the event.

The number and percentage of subjects experiencing TEAEs will be summarized as follows:

- TEAEs by SOC, HLT, and PT.
- Intensity of TEAEs and by SOC, HLT, and PT.
- Relationship of TEAEs to study drug and by SOC, HLT, and PT.
- Intensity of Drug-Related TEAEs and by SOC, HLT and PT.

- TEAEs leading to study drug discontinuation by SOC, HLT and PT.
- Most frequent non-serious TEAEs (i.e., AEs occurring in ≥5% of subjects in any treatment phase) by SOC, HLT and PT in descending order of frequency.

The number and percentage of subjects experiencing SAEs will be summarized as follows:

- SAEs by SOC, HLT and PT.
- SAEs by severity and by SOC, HLT and PT.
- SAEs by relationship to the investigational product and by SOC, HLT and PT.

7.11.1.2 TEAEs of Special Interest

Adverse events of special interest are defined as serious infections, opportunistic infection such as PML, liver injury, malignancies, infusion-related reactions or systemic reactions and hypersensitivity; see Appendix C for details.

The number and percentage of subjects experiencing treatment-emergent AESIs will be summarized as follows:

- AESI by SOC, HLT, and PT.
- AESIs by severity and by SOC, HLT and PT.
- AESIs by relationship to the investigational product and by SOC, HLT and PT.

Specifically for hypersensitivity and infusion-related reactions, analyses by SOC, HLT and PT will additionally be analysed by the ADA status subgroups as defined in Section 7.8.4.

7.11.1.3 Pretreatment Events

The number and percentage of subjects experiencing pretreatment events will be summarized as follows:

- Pretreatment Events by SOC, HLT, PT.
- Serious Pretreatment Events by SOC, HLT, PT.

7.11.2 Clinical Laboratory Evaluations

The laboratory parameters for serum chemistries, hematology, stool and urinalysis shown in Table 7.g were recorded in this study. Refer to Appendix A for scheduled measurements for clinical laboratory tests.

Clinical laboratory tests will be evaluated and presented by treatment period using conventional units (CV). All laboratory test parameters will be displayed in individual subject data listings in CV 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), then the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

Clinical laboratory tests with numeric results will be tabulated using summary statistics for observed and change from baseline values at each scheduled time point (baseline and each post baseline visit).

Markedly abnormal values (MAV), defined by the criteria in Appendix C and Appendix E, will be tabulated. MAV tables will include all laboratory parameters with available MAV criteria. If both the baseline and on-treatment values of a parameter are beyond the MAV limit for that parameter, then the on-treatment value will be considered a MAV only if it is more extreme than the baseline value.

The number and percentage of subjects with Liver Function Test (LFT) abnormalities will be presented by period and treatment group. LFT abnormalities are defined as follows:

- ALT or AST >8 × ULN, or
- ALT or AST >5 × ULN and persists for more than 2 weeks, or
- ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
- ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia.

The laboratory data will be listed in full. Laboratory data outside of the normal reference range will be flagged in the listing. In a separate listing, for each subject with a MAV for a parameter, all the subject's values of that parameter will be listed.

Table 7.g Clinical Laboratory Tests

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

Other:		
HIV	ASCA IgA	
Hepatitis panel, including HBsAg and anti-HCV	ASCA IgG	
	Anti-CBir1 IgG	
	ANCA	
	NOD2 genotype test	

Serum	Urine	Stool
CRP	hCG (for pregnancy in female subjects of childbearing potential only)	Fecal calprotectin
PK samples		*C difficile* (b)
ADA/nADA		
QuantiFERON for TB		
beta hCG (for pregnancy in female subjects of childbearing potential only)		
FSH, if menopause is suspected (Screening Visit only)		
Monitr CD Test (biomarker panel using serum to measure hsCRP, SAA 1, CEACAM 1, VCAM 1, ANG 1, ANG 2, IL-7, TGFα, EMMPRIN, MMP 1, MMP 2, MMP 3, and MMP 9)		

Abbreviations: ADA,antidrug antibodies; ALT, alanine aminotransferase; ASCA, anti-Saccharomyces cerevisiaeantibody; AST, aspartate aminotransferace; anti-CBir1, anti-flagellin; CRP, C-reactive protein; FSH, follicle-stimulating hormone;GGT, γ-glutamyl transferase; HBsAg, hepatitis B surface antigen; hCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ANCA, antineutrophil antibody;IgA, immunoglobulinA; IgG, immunoglobulin G; nADA, neutralizing antidrug antibodies; NOD2, nucleotide-binding oligomerization domain-containing protein;PK, pharmacokinetic; PT, prothrombin time; RBCs, red blood cells; TB, tuberculous; WBC, white blood cell; ULN, upper limit of normal; hsCRP, high-sensitivity C-reactive protein; SAA 1, serum amyloid A 1; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1: VCAM 1, vascular cell adhesion molecule 1; IL-7, interleukin-7; TGFα, transforming growth factor α; EMMPRIN, extracellular matrix metalloproteinase inducer; MMP, matrix metalloproteinase (a) WBC differential to include lymphocytes, monocytes, basophils, eosinophils, and neutrophils. (b) Not done at screening; only done if subject experiences a flare during the study.

7.11.3 Vital Signs

Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, body temperature, weight and respiration rate will be measured (refer to Appendix A for a schedule of vital signs measurements). For each vital sign parameter, the observed values at each time point, change from baseline, and percent change from baseline at each post baseline visit will be summarized by descriptive statistics.

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

Vital signs data will be listed with MAVs flagged.

7.11.4 12-Lead ECGs

Overall ECG interpretation category (normal, not clinically significant abnormal, clinically significant abnormal) was collected at Screening. ECG data will be listed by site number and subject number.

7.11.5 Other Observations Related to Safety

Physical examination findings, PML checklist, and LTFU data will be listed.

7.12 Interim Analysis

An interim analysis will be conducted for the purpose of publication when all subjects have completed the 26 week combination treatment phase (i.e. Week 26 Visit or early termination (ET) Visit). No study decisions will be made based on the interim results and subjects will continue to the monotherapy treatment phase. All available data will be included in the interim analysis. Data which can be considered final at Week 26 (all data except AEs, concomitant medications, and any data post-Week 26) will be cleaned and locked prior to the analysis. The primary endpoint is measured at Week 26 so there is no alpha adjustment required in the statistical analyses. The interim analysis will follow all methodology outlined in this Statistical Analysis Plan (SAP) and all data will be summarized.

The following data may be included in the interim analysis:

1. Disposition.
2. Demographic and other baseline characteristics.
3. Medical history and concurrent medical conditions.
4. Medication history and concomitant medications.
5. Study drug exposure excluding compliance.
6. Efficacy.
    a) Primary endpoint: Endoscopic remission.
    b) Secondary endpoints defined through Week 26.

7. Adverse events.

7.13 Changes in the Statistical Analysis Plan

The following items were not included in the protocol but will be analysed:

- The secondary endpoint maintaining clinical response based on CDAI has been added to address the secondary objective.
- Hospitalizations due to CD related issues from Day 1 to Week 102 has been added to the summary of additional endpoints.
- Change from baseline CDAI score at post-baseline visits has been added to the summary of additional endpoints. Whilst it is not specifically described in the protocol as an endpoint, it is discussed within the statistical analyses of the protocol.

The following change was made to the planned analyses described in the protocol:

- Changes from baseline and changes from Week 26 for CDAI and PRO-2 scores will be analysed descriptively rather than using a non-parametric method as data exploration suggests that the data are approximately normally distributed.

The following revisions were made after SAP version Final 1.0 was approved:

- Study phase definitions updated in Section 7.1.11.
- Serum/urine hCG added in Table 7.a and Table 7.c.
- SES-CD added in Table 7.b and Table 7.d.
- Time windows for Monitr CD updated in Table 7.b and Table 7.d.
- Time windows for ADA updated in Table 7.c.
- Category labels for baseline SES-CD updated in Table 7.f.
- Concomitant medications during the follow-up phase summarized with concomitant medications started after baseline in Section 7.6.
- Observed case analysis for the primary endpoint added to Section 7.8.
- Compliance excluded from interim analysis in Section 7.12.

The following revisions were made after SAP version Amendment 1 was approved:

- CDAI derivation Steps 2 and 4 updated in Section 7.1.6 to remove the diary data from the day before, day of and day after colonoscopy.
- PRO-2 derivation updated to use 7 day average (per protocol) in Section 7.1.7.
- Calculation of IBD-DI adjusted and sensitivity analysis added in Section 7.1.10 due to multiple answers to Q12.
- Completion of all drugs in triple combination therapy phase added in Section 7.3.

- Additional details provided for location of Crohn's disease combination and method of complication risk assessment, baseline PROSPECT risk score at 2 years and baseline ulcer sizes also added in Table 7.d.
- Compliance simplified in Section 7.7 to the number of complete or partial doses.
- Section 7.8.4 added to describe subgroups and the efficacy analyses to which these will be applied. Subgroup descriptions also added in Sections 7.9.1, 7.10, 7.11.1.2.
- Appendix D updated to be consistent with Vedolizumab-4014.

8.0 REFERENCES

1. An Open-Label, Phase 4 Study to Evaluate the Efficacy and Safety of Triple Combination Therapy With Vedolizumab IV, Adalimumab SC, and Oral Methotrexate in Early of Subjects With Crohn's Disease Stratified at Higher Risk for Developing Complications Takeda Development Center Americas, Inc., One Takeda Parkway, Deerfield, IL 60015.
2. Siegel CA, Horton H, Siegel LS, Thompson KD, Mackenzie T, Stewart SK, et al. A validated web-based tool to display individualised Crohn's disease predicted outcomes based on clinical, serologic and genetic variables. Aliment Pharmacol Ther 2016;43(2):262-71.
3. Siegel C, Siegel L, Hyams J, Kugathasan S, Markowitz J, Rosh J, et al. Real-time tool to display the predicted disease course and treatment response for children with Crohn's disease. Infllamm Bowel Dis 2011;17(1):30-8.

9.0 APPENDICES

Appendix A Schedule of Study Procedures

Induction Phase (Screening Through Week 26)											
	Screening	Treatment									
Study Week		Wk 0	Wk 2	Wk 4 (r)	Wk 6	Wk 8 (r)	Wk 10	Wk 14	Wk 18 (r)	Wk 22	Wk 26
Study Day ± Visit Window (Days)	Day -28 to Day -1	1	15 ±3	n/a	43 ±3	n/a	71 ±3	99 ±3	n/a	155 ±7	183 ±7
Visit Number:	1	2	3	n/a	4	n/a	5	6	n/a	7	8
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demographics/medical and medication history/ concurrent medical conditions	X										
CD History	X										
Physical examination	X	X	X		X		X	X		X	X
Vital signs (a)	X	X	X		X		X	X		X	X
Access IRT to obtain subject ID	X										
Access IRT to register visit		X	X		X			X		X	X
ASCA IgA, ASCA IgG, Anti-CBir1 IgG, ANCA, NOD2 genotype test	X										
CDAI		X	X		X		X	X		X	X
PRO-2	X	X									X
Ileocolonoscopy (b)	X										X
SES-CD	X										X
CRP	X	X					X				X
Fecal calprotectin (c)	X						X	X			X

Appendix A Schedule of Study Procedures (continued)

Induction Phase (Screening Through Week 26) (continued)											
	Screening	Treatment									
Study Week		Wk 0	Wk 2	Wk 4 (r)	Wk 6	Wk 8 (r)	Wk 10	Wk 14	Wk 18 (r)	Wk 22	Wk 26
Study Day ± Visit Window (Days)	Day -28 to Day -1	1	15 ±3	n/a	43 ±3	n/a	71 ±3	99 ±3	n/a	155 ±7	183 ±7
Visit Number:	1	2	3	n/a	4	n/a	5	6	n/a	7	8
Tuberculosis QuantiFERON or skin test (d)	X										
Chemistry, Hematology, Urinalysis	X	X	X		X		X	X		X	X
Hepatitis, HIV	X										
Pharmacogenomic DNA and RNA samples (f)		X									
PK samples for vedolizumab (g)		X			X		X	X			X
PK samples for adalimumab (h)		X			X		X	X		X	X
ADAs samples, vedolizumab		X			X			X			X
ADAs samples, adalimumab		X	X		X		X	X		X	X
Pregnancy test (hCG) (i)	X										
Urine pregnancy test (i)		X	X		X		X	X		X	X
Home pregnancy test (j)									X		
ECG	X										
Vedolizumab (IV) (k)		X	X		X			X		X	
Adalimumab (SC) (l)		X (m)	X (m)	X	X (m)	X	X	X (m)	X	X (m)	X
Methotrexate (PO) (n)		X	X	X	X	X	X	X	X	X	X
Folic acid (PO) (o)		X	X	X	X	X	X	X	X	X	X

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Induction Phase (Screening Through Week 26) (continued)											
	Screening	Treatment									
Study Week		Wk 0	Wk 2	Wk 4 (r)	Wk 6	Wk 8 (r)	Wk 10	Wk 14	Wk 18 (r)	Wk 22	Wk 26
Study Day ± Visit Window (Days)	Day -28 to Day -1	1	15 ±3	n/a	43 ±3	n/a	71 ±3	99 ±3	n/a	155 ±7	183 ±7
Visit Number:	1	2	3	n/a	4	n/a	5	6	n/a	7	8
AE/SAE assessment		X	X		X		X	X		X	X
Concomitant medications/ procedures	X	X	X		X		X	X		X	X
PML checklist (p)	X	X	X		X			X		X	
PML wallet card		X									
IBDQ		X						X			X
WPAI		X						X			X
IBD-DI		X						X			X
Health outcomes, CD-related events			X		X		X	X		X	X
Patient diary	X	X	X	X	X	X	X	X	X	X	X
C difficile test (q)											
CD Risk by clinical assessment, PROSPECT Tool or 2014 AGA CD Care Pathway	X										
Monitr CD Test		X									X

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Maintenance Phase (Week 30 Through Week 128)															
	Treatment														
Study Week	**Wk 30**	**Wk 34 (s)**	**Wk 38**	**Wk 42 (s)**	**Wk 46**	**Wk 50 (s)**	**Wk 52**	**Wk 54**	**Wk 58 (s)**	**Wk 62**	**Wk 66 (s)**	**Wk 70**	**Wk 74 (s)**	**Wk 78**	**Wk 82 (s)**
Study Day ± Visit Window (Days)	211 ±7	239 ±7	267 ±7	295 ±7	323 ±7	351 ±7	365 ±7	379 ±3	407 ±7	435 ±7	463 ±7	491 ±7	519 ±7	547 ±7	575 ±7
Visit Number:	**9**	**9b**	**10**	**10b**	**11**	**11b**	**12**	**13**	**13b**	**14**	**14b**	**15**	**15b**	**16**	**16b**
Physical examination	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
Vital signs (a)	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
Access IRT to register visit	X	X (s)	X	X (s)	X	X (s)		X	X (s)	X	X (s)	X	X (s)	X	X (s)
CDAI	X		X		X		X	X		X		X		X	
PRO-2							X							X	
Ileocolonoscopy (b)															
SES-CD															
CRP							X							X	
Fecal calprotectin (c)							X							X	
Chemistry, Hematology, Urinalysis	X (e)		X		X		X	X		X		X		X	
PK samples for vedolizumab (g)			X					X				X			
ADAs samples, vedolizumab			X					X				X			
ADAs samples, adalimumab			X					X				X			
Pregnancy test (hCG) (i)	X														

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Maintenance Phase (Week 30 Through Week 128)															
	Treatment														
Study Week	**Wk 30**	**Wk 34 (s)**	**Wk 38**	**Wk 42 (s)**	**Wk 46**	**Wk 50 (s)**	**Wk 52**	**Wk 54**	**Wk 58 (s)**	**Wk 62**	**Wk 66 (s)**	**Wk 70**	**Wk 74 (s)**	**Wk 78**	**Wk 82 (s)**
Study Day ± Visit Window (Days)	211 ±7	239 ±7	267 ±7	295 ±7	323 ±7	351 ±7	365 ±7	379 ±3	407 ±7	435 ±7	463 ±7	491 ±7	519 ±7	547 ±7	575 ±7
Visit Number:	**9**	**9b**	**10**	**10b**	**11**	**11b**	**12**	**13**	**13b**	**14**	**14b**	**15**	**15b**	**16**	**16b**
Urine pregnancy test (i)	X		X		X			X		X		X		X	
Home pregnancy test (j)		X		X		X			X						
Vedolizumab (IV) (k)	X	X (s)	X	X (s)	X	X (s)		X	X (s)	X	X (s)	X	X (s)	X	X (s)
Methotrexate (PO) (n)	X	X													
Folic acid (PO) (o)	X	X													
AE/SAE assessment	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
Concomitant medications/procedures	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
PML checklist (p)	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
PML wallet card															
IBDQ							X							X	
WPAI							X							X	
IBD-DI							X							X	
Health outcomes, CD-related events	X		X		X		X	X		X		X		X	
Patient diary	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
LTFU questionnaire															
C difficile test (q)															

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Maintenance Phase (Week 30 Through Week 128) (continued)							
	Treatment					EOS or ET	LTFU Phone Call
Study Week	Wk 86	Wk 90 (s)	Wk 94	Wk 98 (s)	Wk 102 EOT	Wk 120 (18 wks post tx)	Wk 128 (26 wks post tx)
Study Day ± Visit Window (Days)	603 ±7	631 ±7	659 ±7	687 ±7	715 ±7	841 ±7	897 ±7
Visit Number:	17	17b	18	18b	19	20	21
Physical examination	X	X (s)	X	X (s)	X	X	
Vital signs (a)	X	X (s)	X	X (s)	X	X	
Access IRT to register visit	X	X (s)	X	X (s)	X	X	
CDAI	X		X		X	X	
PRO-2					X		
Ileocolonoscopy (b)					X	X (ET only)	
SES-CD					X		
CRP					X		
Fecal calprotectin (c)					X		
Chemistry, Hematology, Urinalysis	X		X		X	X	
PK samples for vedolizumab (g)	X				X		
ADAs samples, vedolizumab	X				X		
ADAs samples, adalimumab	X				X		
Pregnancy test (hCG) (i)						(X)	
Urine pregnancy test (i)	X		X		X	X	
Home pregnancy test (j)							
Vedolizumab (IV) (k)	X	X (s)	X	X (s)	X		

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Maintenance Phase (Week 30 Through Week 128) (continued)							
	Treatment					**EOS or ET**	**LTFU Phone Call**
Study Week	**Wk 86**	**Wk 90 (s)**	**Wk 94**	**Wk 98 (s)**	**Wk 102 EOT**	**Wk 120 (18 wks post tx)**	**Wk 128 (26 wks post tx)**
Study Day ± Visit Window (Days)	603 ±7	631 ±7	659 ±7	687 ±7	715 ±7	841 ±7	897 ±7
Visit Number:	**17**	**17b**	**18**	**18b**	**19**	**20**	**21**
Methotrexate (PO) (n)							
Folic acid (PO) (o)							
AE/SAE assessment	X	X (s)	X	X (s)	X	X	
Concomitant medications/procedures	X	X (s)	X	X (s)	X	X	
PML checklist (p)	X	X (s)	X	X (s)	X		
PML wallet card					X		
IBDQ					X		
WPAI					X		
IBD-DI					X		
Health outcomes, CD-related events	X		X		X	X	
Patient diary	X	X (s)	X	X (s)	X		
LTFU questionnaire							X
***C difficile* test (q)**							
Monitr CD Test					X	X (ET only)	

Abbreviations; AE, adverse event; ADA, antidrug antibodies; ANCA, perinuclear antineutrophil antibody; ASCA, anti-Saccharomyces cerevisiae antibody; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; ET, early termination; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; IBD-DI, Inflammatory Bowel Disease Disability Index; IBDQ, Inflammatory Bowel Disease Questionnaire; ID, identification; IgA, immunoglobin; IRT, interactive response technology; IV, intravenous; LTFU, long-term follow-up; n/a=not applicable; NOD2, nucleotide-binding oligomerization domain-containing protein 2; PK, pharmacokinetic; PML, progressive multifocal leukoencephalopathy; PO, oral; PRO-2, patient-reported outcome 2; RNA, ribonucleic acid; SAE, serious adverse event; SC, subcutaneous; SES-CD, simple endoscopic score for Crohn's disease; tx, treatment; WPAI,Work Productivity and Activity Impairment.

(a) Height collected only at the screening visit. Weight will be measured at every site visit where CDAI is calculated.

(b) Endoscopy to be collected at screening, Weeks 26 and 102, or early termination for central read. Biopsies will also be collected. All biopsies collected per protocol will be centrally stored and analyzed at the end of the study. Although it is permissible for the investigator to take additional biopsy samples as deemed necessary for standard of care

management of the patient during the protocol required colonoscopy, these will be considered as occurring outside the protocol. Such collection, handling, and analyses of the additional samples will be and remain the responsibility of the investigator.
(c) Stool sample to be collected from the first bowel movement in the morning and sent to central laboratory.
(d) QuantiFERON test or tuberculin skin test only.
(e) Hematology only.
(f) DNA and RNA samples will be collected on Day 1.
(g) PK samples for vedolizumab to be collected predose on dosing days Day 1 and Weeks 6, 10, 14, 26, 38, 54, 70, 86, and 102. at visits where study drug is given.
(h) PK samples for adalimumab to be collected predose on dosing days (prior to vedolizumab dosing) on Day 1 and Weeks 6, 10, 14, 22, and 26. For Weeks 6, 14, and 22, when the subject is self-administering adalimumab at home, the adalimumab PK samples will be collected on the day of vedolizumab PK collection, prior to vedolizumab infusion.
(i) Women of childbearing potential only. Urine pregnancy testing will be conducted at the site and serum pregnancy testing will be conducted by the central laboratory. Serum pregnancy completed at screening and Week 30 or Early Termination if stopped prior to Week 30; urine pregnancy to be completed at other visits.
(j) Women of childbearing potential only. When site visits shift from every 4 weeks to every 8 weeks, women of childbearing potential will need to take a home pregnancy test every other month (in between visits) up until Week 58 and report the results to the site. If the subject experiences an exacerbation and switches to Q4W dosing, then no home pregnancy test is required as subject will have urine pregnancy test performed on site before infusion.
(k) Vedolizumab IV 300 mg at Week 0, 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, and 102. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion for monitoring hypersensitivity reactions.
(l) Adalimumab SC 160 mg at Week 0, 80 mg at Week 2, then 40 mg every 2 weeks for a total of 27 weeks. Self injection or caregiver may inject using either the Pen or prefilled syringe if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique. Adalimumab will be self-administered at home at Weeks 2, 4, 8, 10, 12, 16, 18, 20, 24, and 26.
(m) At Weeks 0, 2, 6, 14, and 22, adalimumab will be administered 1 day after the vedolizumab infusion. For Week 0, the subject should return to the site the day after (or within a 3-day window of) the vedolizumab infusion to self-administer the adalimumab SC injection while instructed and observed by site staff or to have the injection administered by qualified site staff. Subsequent doses will be self-administered at home starting at Week 2.
(n) Methotrexate 15 mg (six 2.5-mg tablets) PO once weekly for total of 34 weeks.
(o) Daily folic acid (1 mg PO capsule or tablet) must be taken during the 34-week period of methotrexate treatment.
(p) PML checklist must be administered at screening and prior to vedolizumab dosing at every vedolizumab dosing visit.
(q) A C difficile test will be done only if a subject experiences a flare up during the study.
(r) Not a clinic visit. Home dosing with adalimumab and methotrexate only.
(s) Optional 4-week vedolizumab dosing visit. If a subject has a first exacerbation of CD after 26 weeks (defined as a CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, objective evidence of disease activity by colonoscopy and CRP above normal, OR fecal calprotectin >250 µg/g alone), then frequency of vedolizumab infusions will be changed to vedolizumab 300 mg IV every 4 weeks (instead of every 8 weeks) for the remainder of treatment. Subjects should be monitored for 1 hour after each infusion for hypersensitivity reactions.

Appendix B 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)		x 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)		x 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)		x 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		x 20	
Lomotil/Imodium/opiates for diarrhea	Yes = 1 No = 0		x 30	
Abdominal mass	None = 0 Questionable = 2 Definite = 5		x 10	
Hematocrit (%) (a)	Males: subtract value from 47 Females: subtract value from 42		x 6	
Body Weight (b)	(1 – (Body weight/ Standard Weight)) × 100		x 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.
(a) If hematocrit subtotal <0, enter 0.
(b) If body weight subtotal <-10, enter -10.

Appendix C Adverse Events of Special Interest (AESI)

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

Appendix D Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology – Criteria for Markedly Abnormal Values

	Conventional Units		Takeda Preferred SI Units	
Parameter	**Units**	**Markedly Abnormal Value**	**Units**	**Markedly Abnormal Value**
RBC count	$\times 10^6$ cells/µL	<0.8 × LLN, >1.2 × ULN	$\times 10^{12}$ cells/L	<0.8 × LLN, >1.2 × ULN
WBC count	$\times 10^3$ cells/µL	<3.0	$\times 10^9$ cells/L	<3.0
Hemoglobin	g/dL	<8	g/L	<80
Hematocrit	%	<0.8 × LLN, >1.2 × ULN	Fraction of 1	<0.8 × LLN, >1.2 × ULN
Platelet count	$\times 10^3$/µL	<100, >1200	$\times 10^9$ /L	<100, >1200
Lymphocytes	$\times 10^3$ cells/µL	<0.5	$\times 10^9$ cells/L	<0.5
PT	Sec	>3 × ULN	Sec	>3 × ULN
INR†	NA	>2.5 x ULN	NA	>2.5 x ULN

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.

Appendix D Criteria for Identification of Markedly Abnormal Laboratory Values (continued)

Serum Chemistry – Criteria for Markedly Abnormal Values

	Conventional Units		Takeda Preferred SI Units	
Parameter	**Units**	**Markedly Abnormal Values**	**Units**	**Markedly Abnormal Value**
ALT	U/L	>3 × ULN	U/L	>3 × ULN
Albumin	g/dL	<3.5	g/L	<35
Alkaline Phosphatase	U/L	>3 × ULN	U/L	>3 × ULN
AST	U/L	>3 × ULN	U/L	>3 × ULN
Amylase	U/L	>3 x ULN	U/L	>3 x ULN
Bicarbonate	mEq/L	<21, >33	mmol/L	<21, >33
Total Bilirubin	mg/dL	>2.2	µmol/L	>37.6
Total Protein	g/dL	<2.0, >9.0	g/L	<20, >90
Creatinine	mg/dL	>2 x ULN	mmol/L	>2 x ULN
Blood Urea Nitrogen	mg/dL	>2 x ULN	mmol/L	>2 x ULN
Creatine Kinase	U/L	>3 × ULN	U/L	>3 × ULN
GGT*	U/L	>3 × ULN	U/L	>3 × ULN
Lipase	U/L	>3 × ULN	U/L	>3 × ULN
Potassium	mEq/L	<2.8, >6.3	mmol/L	<2.8, >6.3
Sodium	mEq/L	<117, >160	mmol/L	<117, >160
Calcium	mg/dL	<6.1, >12.9	mmol/L	<1.52, >3.22
Uric Acid	mg/dL	>2 x ULN	µmol/L	>2 x ULN
Glucose	mg/dL	<50, >450	mmol/L	<2.5, >25
Phosphorus	mg/dL	<2.5	mmol/L	<0.81

LLN = lower limit of normal or lower reference limit; ULN = upper limit of normal or upper reference limit; * GGT = γ-Glutamyl Transferase.

Appendix E Criteria for Identification of Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Systolic Blood Pressure	mmHg	<85	>180
Diastolic Blood Pressure	mmHg	<50	>110
Pulse	bpm	<50	>120
Body Temperature	°C	<35.6	>37.7

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	27-Feb-2023 15:27 UTC