Clinical Study Protocol

NCT Number: NCT04804540

Title: A Multicenter, Single-arm, Open-label, Phase 4 Study to Evaluate the Safety and Efficacy of Vedolizumab in Indian Patients With Ulcerative Colitis and Crohn's Disease

Study Number: Vedolizumab-4020

Document Version and Date: Version 4.0, 09 November 2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

A Multicenter, Single-arm, Open-label, Phase 4 Study to Evaluate the Safety and Efficacy of Vedolizumab in Indian Patients With Ulcerative Colitis and Crohn's Disease

Vedolizumab to treat Ulcerative Colitis and Crohn's Disease

Sponsor: Takeda Biopharmaceuticals India Pvt. Ltd.
6th Floor, Building 8,
Tower C, DLF Cyber City,
Gurgaon 122002, Haryana, India

Study Number: **Vedolizumab-4020**

IND Number: Not Applicable

Compound: Vedolizumab

Date: 09 November 2022 **Version Number:** 4.0

Amendment History:

Date	Amendment Number	Region
24 May 2018	Initial version	India
19 October 2019	01	India
09 October 2020	02	India
30 March 2021	03	India
09 November	04	India

Takeda except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the study.

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given below and relevant guidelines provided to the site.

Contact Type/Role	India Contact
Serious adverse event and pregnancy reporting	Cognizant Email address: eupv@tgrd.com Fax number: +1-224 554 1052
Takeda Medical Monitor	Dr [redacted] [redacted] 6th Floor, Building No – 8, Tower – C DLF Cyber City, DLF Phase – II, Gurgaon Haryana, India [redacted]
Takeda Responsible Medical Director	Dr [redacted] [redacted] 6th Floor, Building No – 8, Tower – C DLF Cyber City, DLF Phase – II, Gurgaon Haryana, India [redacted]
Project Management	Dr [redacted] [redacted] 6th Floor, Building No – 8, Tower – C DLF Cyber City, DLF Phase – II, Gurgaon Haryana, India, [redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council For Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council For Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations as per latest New Drugs and Clinical Trials Rule 2019, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator Appendix B.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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Not Applicable</td><td>EudraCT No.:
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<tr><td colspan="4">Study Design:
This is an open-label, single-arm, prospective, Phase 4 study to be conducted at multiple sites in India to evaluate the safety and efficacy of vedolizumab 300 mg intravenous (IV) infusion in patients with moderately to severely active ulcerative colitis (UC) or Crohn's Disease (CD).
Approximately 150 patients with moderately to severely active UC or CD who have demonstrated inadequate response to, loss of response to, or intolerance to either conventional therapy or tumor necrosis factor-alpha (TNFα) antagonist will be enrolled in this study. At least 30% of the total recruited patients will be enrolled in each UC or CD group.
The total duration of the study for each patient will be up to 74 weeks, consisting of a 4-week screening period (Days -28 to -1), a 46-week treatment period, and 16-week (ie, 5 vedolizumab half-lives) safety follow-up period after the last dose of study drug. Additionally, patients will be required to participate in a long-term follow-up safety survey through telephonic visit at 6 months after the last dose of study drug i.e. 8 weeks after 16-week follow-up visit.
Patients who meet all the inclusion criteria and none of the exclusion criteria will be administered vedolizumab 300 mg IV at the site. Patients will visit the site for dosing at Weeks 0 (Day 1), 2, 6, 10(CD Patients who have not shown a response can receive a dose at 10 week),14, 22, 30, 38 and 46.
Patients will be evaluated for safety and efficacy from initiation of vedolizumab treatment until 46 weeks (the treatment period), or until discontinuation of vedolizumab, whichever occurs earlier. All patients will be observed further for safety assessments for 16 weeks after the study treatment period or discontinuation of vedolizumab for post-treatment adverse event (AE) monitoring. In addition, patients will participate in the long-term follow-up safety survey through telephonic visit at 6 months after the last dose i.e. 8 weeks after the 16-week follow-up visit, during which information will be collected on events such as infections resulting in hospitalizations, cancer, UC or CD related surgeries, and development of progressive multifocal leukoencephalopathy.</td></tr>
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• To assess the safety of vedolizumab IV in patients with UC or CD in India.</td></tr>
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Adult patients aged between 18 to 65 years both inclusive, with moderately to severely active UC or CD.</td></tr>
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150</td><td colspan="2">Number of Sites:
Approximately 20+ Sites in India</td></tr>
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Vedolizumab IV 300 mg</td><td colspan="2">Route of Administration:
Intravenous</td></tr>
<tr><td colspan="2">Duration of Treatment:
46-weeks</td><td colspan="2">Period of Evaluation:
The study includes a 4-week screening period, a 46-week treatment period, and a follow-up period of 6 months which includes first</td></tr>
</table>

	follow-up visit at 16 weeks and second telephonic follow-up visit at 6 months after the last dose. The duration of the study for each patient will be approximately 74 weeks.

Main Criteria for Inclusion:

Adult patients aged 18 to 65 years both inclusive, diagnosed with moderately to severely active UC or CD for at least 3 months prior to screening with a Full Mayo Score of 6-12 for UC or a Harvey Bradshaw Index score of ≥8 for CD at the time of enrollment, and have demonstrated an inadequate response to, loss of response to, or intolerance to either conventional therapy or tumor necrosis factor-alpha (TNFα) antagonist.

Main Criteria for Exclusion:

- Any evidence of an active infection during Screening
- Patients who have received any biologics within 60 days (or 5-half-lives of the drug) of enrollment
- Patients who have had prior exposure to vedolizumab, natalizumab, efalizumab, or rituximab

Main Criteria for Evaluation and Analyses:

Primary endpoint

The primary endpoint includes:

- Incidence of adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), adverse drug reactions (ADRs), and unexpected ADRs

Secondary endpoints

The secondary endpoints include:

- Proportion of patients with clinical response at Weeks 14, 30, and 46 in UC and CD groups
- Proportion of patients with clinical remission at Weeks 14, 30, and 46 in UC and CD groups
- Proportion of patients with vedolizumab discontinuation in UC and CD groups
- Proportion of patients with mucosal healing/endoscopic response at Week 46 in UC and CD groups
- Change in the patient-reported Quality of Life (Short Inflammatory Bowel Disease Questionnaire) from baseline to Weeks 14, 30, and 46

Statistical Considerations:

Exposure-adjusted incidence rates and 95% confidence intervals (CIs) by Poisson method will be calculated for each safety endpoint based on total number of incident events and person-time at risk.

The number and percentage of patients with treatment-emergent AEs (TEAEs; defined as any AEs, regardless of relationship to study drug), AEs leading to discontinuation, AESIs, and SAEs that occur on or after the first dose date and up to 6 months after the last dose date of the study drug, will be summarized by MedDRA system organ class, high level term, and preferred term overall, by severity, and by relationship to study drug.

Treatment efficacy outcomes will be analyzed using descriptive statistics.

Cox regression models may be used to explore predictors of time to treatment discontinuation.

Sample Size Justification:

The sample size of 150 patients was recommended by the Drugs Controller General of India (DCGI). At least 30% of the total recruited patients will be enrolled in each UC or CD group. This sample size will enable a serious infection rate of 6 per 100 person-years to be measured with a precision of ±3.8 with 95% CI based on a normal approximation of the annualized proportion of patients to be infected. This anticipated serious infection rate is based on observed rates in a post hoc pooled analysis of Indian sites participating in the vedolizumab global Phase 3 Studies C13006 and C13007 and open label extension (Study C13008) of these studies.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of special interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
β-hCG	beta human chorionic gonadotropin
CD	Crohn's Disease
CI	Confidence Interval
CMV	Cytomegalovirus
CRO	Contract Research Organization
CRP	C-reactive Protein
DCGI	Drugs Controller General of India
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Collection
ET	Early termination
GCP	Good Clinical Practice
GI	Gastrointestinal
HBI	Harvey-Bradshaw Index
HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface antigen
HCP	Healthcare professional
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLT	High-Level Term
HRQoL	Health-related quality of life
IAC	Independent Adjudication Committee
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
JC	John Cunningham
LAR	Legally acceptable representative
MAdCAM-1	Mucosal Addressin Cell Adhesion Molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
PAC	Patient alert card
PV	Pharamacovigilance
PML	Progressive multifocal leukoencephalopathy

PPAS	Per-Protocol Analysis Set
PT	Preferred Term
PTE	Pretreatment Event
QoL	Quality of Life
RAMP	Risk Minimization Action Plan for PML
SAE	Serious Adverse Event
SAS	Safety analysis set
SCCAI	Simple Clinical Colitis Activity Index
SES-CD	Simple Endoscopic Score for Crohn's Disease
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TDC	Takeda Development Center
TNF-α	Tumor Necrosis Factor-alpha
UC	Ulcerative Colitis
ULN	Upper limit of normal
WBC	White blood cells

4.0 INTRODUCTION

4.1 Background

4.1.1 The Inflammatory Bowel Diseases: Ulcerative Colitis and Crohn's Disease

Inflammatory bowel disease (IBD) encompasses ulcerative colitis (UC) and Crohn's disease (CD), both of which are chronic, relapsing, and remitting inflammatory diseases. UC affects the colonic mucosa and submucosa, and CD may involve any portion of the gastrointestinal (GI) tract from mouth to anus, in a transmural fashion from mucosa to serosa. UC and CD are lifelong diseases that cause considerable morbidity in a relatively young patient population. The highest reported annual prevalence of UC and CD in North America was 249 per 100,000 persons and 319 per 100,000 persons, respectively. In Europe, the highest annual reported prevalence of UC and CD was 505 per 100,000 persons and 322 per 100,000 persons, respectively [1].

Incidence and prevalence in the Asia-Pacific region is comparatively lower, but reported to be rising rapidly [2]. Although, India is reported to have one of the highest incidence rates of UC in the Asia-Pacific region [2], there is still a paucity of recent prevalence and incidence data for IBD in India. A community-based study conducted in the year 1999 to 2000 [3] in Punjab, North India, reported an incidence and prevalence of UC of 6.02 per 100,000 patients (95% confidence interval [CI] 1.2 to 17.6) and 44.3 per 100,000 patients (95% CI 29.4 to 66.6) respectively [3]. Epidemiological data for CD in the Indian population is lacking. Higher rates of IBD have been observed among South Asian migrants (Indians, Bangladeshis and Pakistanis) compared with indigenous populations and other resident ethnic groups in studies in the United Kingdom, Singapore, and Malaysia, suggesting a genetic predisposition to IBD, particularly UC, among South Asians [2,4,5,6].

While current conventional and biologic therapies have been effective for many patients with UC or CD, they have numerous limitations for patients with moderate to severe disease, posing a significant unmet medical need for safer and more effective therapies. Conventional therapies for UC and CD include 5-aminosalicylic acids, corticosteroids, and immunomodulators such as azathioprine, 6-mercaptopurine, and methotrexate. Biologic therapy is largely limited to tumor necrosis factor-alpha (TNF-α) antagonists which represent an important addition to the pharmacologic armamentarium. However, TNF-α antagonists are effective in only a subset of patients, with approximately two-thirds of patients in controlled trials failing treatment at the end of the first year of therapy [7,8,9].

Therefore, it is clear that current treatments do not sufficiently address the unmet need in this population, with many patients still requiring frequent hospitalization, serial bowel resections, colectomies, and enteral nutrition, and regularly experiencing fistulae, GI abscesses, refractory diarrhea, and rectal bleeding. These patients are often unable to function normally in society.

4.1.2 Vedolizumab

Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody directed against the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue through adhesive interactions with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa. Vedolizumab exclusively targets the $\alpha_4\beta_7$ integrin, antagonizing its adherence to MAdCAM-1 and thus impairing the migration of leukocytes into GI mucosa [10]. By virtue of its

gut-selective mechanism of action, vedolizumab is expected to have anti-inflammatory activity without the generalized immunosuppression found with current treatments for UC or CD.
Detailed information regarding nonclinical and clinical pharmacology, toxicology, and clinical studies of vedolizumab is found in package insert.

4.1.2.1 Trial Data for UC

The safety and efficacy of vedolizumab intravenous (IV) for the treatment of patients with moderately to severely active UC (Complete Mayo Score 6 to 12 with endoscopic subscore ≥2) was demonstrated in a randomized, double-blind, placebo-controlled study, comprising 2 phases and evaluating efficacy endpoints at Weeks 6 and 52 (C13006). Enrolled subjects had failed treatment with corticosteroids, immunomodulators, and/or TNF-α antagonists.

Vedolizumab IV subjects with UC had a statistically significant improvement in clinical response, clinical remission, mucosal healing, durable clinical response, durable clinical remission, and corticosteroid-free remission compared with placebo. The beneficial effect of vedolizumab IV on clinical remission was observed both in UC subjects with no prior TNF-α antagonist exposure, as well as in those who had failed prior TNF-α antagonist therapy.

4.1.2.2 Trial Data for Crohn's Disease

The safety and efficacy of vedolizumab IV for the treatment of patients with moderately to severely active CD (Crohn's Disease Activity Index score of 220 to 450) was evaluated in 2 studies (C13007 and C13011). Study C13007 was a randomized, double-blind, placebo-controlled study comprising 2 phases that evaluated efficacy endpoints at Weeks 6 and 52. Study C13011 was a randomized, double-blind, placebo-controlled study that evaluated efficacy at Weeks 6 and 10 in the subgroup of subjects defined as having failed TNF-α antagonist therapy, as well as in the overall population, which included subjects naïve to TNF-α antagonist therapy.

In Study C13007, overall, a significantly higher proportion of vedolizumab IV subjects with CD, achieved clinical remission at Week 52, compared with placebo subjects. In Study C13011, the subset of vedolizumab IV subjects who had failed prior TNF-α antagonist therapy did not demonstrate significant benefit relative to placebo by Week 6. However, by Week 10, a higher proportion of vedolizumab IV subjects with CD who had failed prior TNF-α antagonist therapy achieved clinical remission.

4.1.2.3 Safety Profile for UC and CD

In the pivotal Phase 3 study in UC (C13006), 12% of vedolizumab IV-treated subjects experienced a serious adverse event (SAE), compared with 11% of placebo-treated subjects. The most frequent SAE was UC, which occurred in 8% and 7% of vedolizumab- and placebo-treated subjects, respectively. Two percent of vedolizumab IV-treated subjects had at least 1 SAE in the infections and infestations system organ class (SOC), as compared with 3% of the placebo-treated subjects. The most common adverse drug reactions (ADRs) occurring in ≥3% of vedolizumab IV subjects, and in excess of 1% over placebo subjects included nasopharyngitis, headache, and cough.

In the pivotal Phase 3 study of induction and maintenance in CD (C13007), 24% of vedolizumab IV-treated subjects experienced at least 1 SAE, compared with 16% of placebo-treated subjects. GI disorders were very common (16% of vedolizumab- and 12% of placebo-treated subjects), with CD being the most common SAE (12% and 9%, respectively). SAEs within the infections and infestations SOC were also common (6% and 3%, respectively), with anal abscess being the most

common SAE reported within this SOC (2% and <1%, respectively). The most common of the ADRs occurring in more than 3% of vedolizumab IV subjects and in excess of ≥1% over placebo subjects in Study C13007 were pyrexia, nasopharyngitis, nausea, and arthralgia.

In a pivotal Phase 3, placebo-controlled study of vedolizumab IV induction treatment in CD (C13011), subjects received vedolizumab 300 mg IV or placebo at Weeks 0, 2, and 6. The majority of subjects had failed therapy with at least 1 TNF-α antagonist before enrollment. Safety data observed in the TNF-α antagonist failure safety subpopulation were generally similar to those observed in the overall safety population.

An open-label study of vedolizumab 300 mg IV, every 4 weeks, is ongoing to evaluate long-term safety in subjects with CD or UC who had previously been enrolled in a vedolizumab IV study (rollover patients); de novo subjects (not previously enrolled in vedolizumab studies) were also enrolled. Results from an interim analysis of the safety data from rollover subjects appear to be consistent with the data from placebo-controlled clinical studies of vedolizumab IV.

In pivotal Phase 3 studies, other reported SAEs, including extraintestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis), were uncommon (<1%). Malignancy was diagnosed in 15 subjects receiving vedolizumab IV across all clinical studies (9 subjects with UC and 6 subjects with CD). Patients with IBD have an increased risk for colon cancer [1], and colon cancer was reported in 4 vedolizumab IV-treated subjects; carcinoid tumor of the appendix was diagnosed in 1 vedolizumab IV-treated subject. One case of B-cell lymphoma was reported in a subject who had received 21 infusions of vedolizumab IV.

4.1.2.4 Indian Experience

A total of 92 subjects from India were enrolled in studies C13006 and C13007. Sixty-four Indian subjects (40 subjects with UC and 24 subjects with CD) received vedolizumab during these clinical studies. Post hoc descriptive subgroup analyses of efficacy in these trials showed similar favorable changes in disease status associated with vedolizumab treatment among subjects with UC and CD. This supports the use of vedolizumab in adult Indian patients as an efficacious therapeutic option for UC and CD.Post hoc analysis of safety data for the Indian subjects demonstrated no significant differences in the types of adverse events (AEs)/SAEs observed compared with the overall global population. Overall, 84% of the global subjects and 61% of the Indian subjects who received vedolizumab experienced at least 1 AE. Interim analysis (data cut off 08 May 2015) of an ongoing long-term open-label safety study (C13008) showed the safety profile in global and Indian subjects to be consistent with that seen in the pivotal studies.

4.2 Rationale for the Proposed Study

The Drugs Controller General of India (DCGI) , has, as a requirement for the vedolizumab marketing authorization approval in India, requested a study to generate data on the safety of vedolizumab in India. Accordingly, the current study has been planned with the primary safety endpoint to provide such data.

4.3 Benefit/Risk Profile

Data on the safety profile of vedolizumab is somewhat limited in India. This Phase 4 study is designed to gather important information on the safety and efficacy of vedolizumab in patients with UC and CD. The dosing and administration regimen and study population in this study are consistent with the approved vedolizumab IV label. Overall, vedolizumab has been well tolerated in clinical studies. The procedures performed during the study are part of usual clinical practice. Taking into account

the risks associated with procedures and the disease worsening in this population, the benefit-risk profile remains positive for vedolizumab in this study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary objective

- To assess the safety of vedolizumab IV in patients with UC or CD in India

5.1.2 Secondary objective

- To assess the efficacy of vedolizumab IV in patients with UC or CD in India

5.2 Endpoints

5.2.1 Primary endpoint

The primary endpoint include:

- Incidence of AEs, SAEs, AEs of special interest (AESIs), ADRs, and unexpected ADRs

(Definitions are provided in Section 10.0).

5.2.2 Secondary endpoints

The secondary endpoints include:

- Proportion of patients with clinical response at Weeks 14, 30, and 46 in UC and CD groups
- Proportion of patients with clinical remission at Weeks 14, 30, and 46 in UC and CD groups
- Proportion of patients with vedolizumab discontinuation in UC and CD groups
- Proportion of patients with mucosal healing/endoscopic response at Week 46 in UC and CD groups
- Change in the patient-reported Quality of Life (Short Inflammatory Bowel Disease Questionnaire [SIBDQ]) from baseline to Weeks 14, 30, and 46

(Definitions are provided in Section 9.1.9).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is an open-label, single-arm, prospective, Phase 4 study to be conducted at multiple sites in India to evaluate the safety and efficacy of vedolizumab 300 mg IV infusion in patients with moderately to severely active UC or CD.

Approximately 150 patients with moderately to severely active UC or CD who have demonstrated inadequate response to, loss of response to, or intolerance to either conventional therapy or tumor necrosis factor-alpha (TNFα) antagonist will be enrolled in this study. At least 30% of the total recruited patients will be enrolled in each UC or CD group.

The total duration of the study for each patients will be up to 74 weeks, consisting of a 4-week screening period (Days -28 to -1), a 46-week treatment period, and 16-week (ie, 5 vedolizumab half-lives) safety follow-up period after the last dose of study drug. Additionally, patients will be required to participate in a long-term follow-up safety survey through telephonic visit at 6 months after the last dose of study drug i.e. 8 weeks after the 16-week follow-up visit.

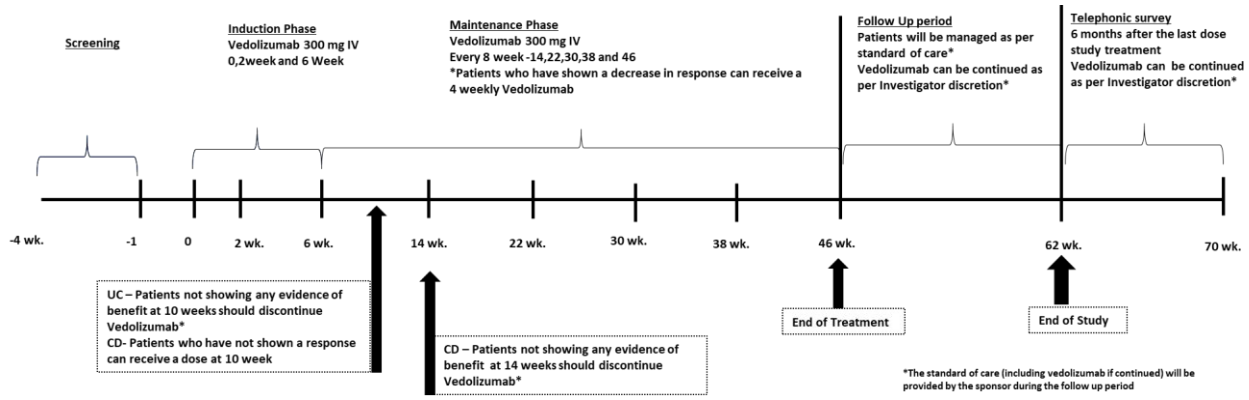
Patients who meet all the inclusion criteria and none of the exclusion criteria will be administered vedolizumab 300 mg IV at the site. Patients will visit the site for dosing at Weeks 0 (Day 1), 2, 6, 10 (CD- Patients who have not shown a response can receive a dose at 10 week),14, 22, 30, 38, and 46.

Patients will be evaluated for safety and efficacy from initiation of vedolizumab until 46 weeks (the treatment period), or until discontinuation of vedolizumab, whichever occurs earlier. All patients will be observed further for safety assessments for 16 weeks after the study treatment period or discontinuation of vedolizumab for post-treatment AE monitoring.

In addition, patients will participate in the long-term follow-up safety survey through telephonic visit at 6 months after the last dose i.e. 8 weeks after the 16-week follow-up visit, during which information will be collected on events such as infections resulting in hospitalizations, cancer, UC or CD related surgeries, and development of progressive multifocal leukoencephalopathy (PML).

A schematic of the study design is included as **Figure 6-a**. A Schedule of Study Procedures is listed in **Appendix A**.

Figure 6-a: **Schematic of Study Design.**



6.2 Justification for Study Design, Dose, and Endpoints

The study is being undertaken to collect data on the safety and efficacy of vedolizumab in Indian patients with moderately to severely active UC or CD for regulatory submission. DCGI has granted marketing authorization for vedolizumab in India based on efficacy studies of vedolizumab in UC and CD conducted across the globe; and so, safety data of vedolizumab in Indian patients needs to be submitted to DCGI. A Phase 4 study design is the most appropriate design to generate such data, as the focus of the study is primarily to collect information on safety and to additionally explore the clinical efficacy of the study drug.

Vedolizumab 300 mg IV infusion is approved for the indications planned to be studied. The safety and treatment efficacy endpoints are similar to those used in other outcome studies in UC and CD. The study period of 74 weeks includes a 4 weeks screening period, 46 weeks treatment period and 6 months safety monitoring period (16 weeks follow-up visit and 6 months telephonic visit). This study duration will help us in reporting safety endpoints of interest including AEs, SAEs, ADRs, and AESIs.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the vedolizumab, such that the risk/benefit is no longer acceptable for patients participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises patient safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF PATIENTS

All entry criteria, including test results, need to be confirmed prior to the first dose.

7.1 Inclusion Criteria

Patient eligibility is determined according to the following criteria before entry into the study:

1. In the opinion of the investigator, the patient (or, when applicable, the patient's legally acceptable representative) is capable of understanding and complying with the protocol requirements and able to provide a signed and dated written informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures.
2. The patient is aged between 18 to 65 years both inclusive at the screening visit.
3. The patient has a diagnosis of moderately to severely active UC or CD at least 3 months prior to screening, with a Full Mayo Score of 6-12 for UC and a Harvey Bradshaw Index (HBI) score of ≥8 for CD at the time of enrollment.
4. The patient has UC or CD with involvement of the ileum and/or colon that has been assessed by colonoscopy/ileo-colonoscopy as applicable within 30 days before or at the time of screening.
5. Patients with extensive colitis or pancolitis of >8 years duration or left-sided colitis >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial Screening Visit (if not performed in previous 12 months, must be performed during Screening).
6. The patient has demonstrated, an inadequate response to, loss of response to, or intolerance to at least 1 of the following agents:
    a. Conventional therapy
    b. TNF-α alpha antagonist
7. A male patient who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 16 weeks after last dose.
8. A female patient of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 16 weeks after last dose. Female patient not of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an appropriate clinical profile [ie, age appropriate, history of vasomotor symptoms] , confirmed before any study drug is implemented).

*Definitions and highly effective methods of contraception are defined in Section 9.1.14 and pregnancy reporting responsibilities are defined in Section 9.1.15.

7.2 Exclusion Criteria

Any patient who meets any of the following criteria will not qualify for entry into the study:

1. The patient has an evidence of abdominal abscess at the screening visit.

2. The patient has a history of extensive colon resections, subtotal or total colectomy.
3. The patient has undergone an ileostomy, colostomy, or has known fixed symptomatic stenosis of the intestine.
4. The patient has active or latent tuberculosis (TB).
5. The patient has hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
6. The patient has evidence of active *Clostridium difficile* infection or is having treatment for *C. difficile* infection or other intestinal pathogens during Screening or has evidence of an active infection during Screening.
7. The patient currently requires or has a planned surgical intervention for the indication to be studied during the study. Patients who had a surgical procedure requiring general anesthesia within 30 days prior to screening or are planning to undergo major surgery during the study period will also be excluded from the study.
8. The patient has received any investigational compound within 60 days of enrollment.
9. The patient has received any live vaccinations within 30 days prior to enrollment.
10. The patient has received any biologics within 60 days (or 5-half-lives of the drug) of enrollment.
11. The patient has had a prior exposure to vedolizumab or a history of hypersensitivity or allergies to vedolizumab, natalizumab, efalizumab, or rituximab.
12. The patient has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, an active psychiatric problem, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety.
13. The patient has a history of malignancy.
14. The patient has any of the following laboratory abnormalities during the Screening Period:
    a. Hemoglobin level <8 g/dL
    b. White blood cell (WBC) count $<3 \times 10^9$/L
    c. Platelet count $<100 \times 10^9$/L or $>1200 \times 10^9$/L
    d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x the upper limit of normal (ULN)
    e. Serum creatinine >2 x ULN
15. The patient has a history of any major neurological disorder, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease
16. The patient has a positive PML subjective symptom checklist during screening or prior to the administration of study drug on Day 1 (Appendix J).
17. The patient has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to enrollment.

18. If female, the patient is pregnant or lactating or intending to become pregnant before, during, or within 16 weeks after completion of participation in the study; or intending to donate ova during such time period.
19. If male, the patient intends to donate sperm during the course of this study or for 16 weeks thereafter.
20. The patient is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
21. The patient has conditions which, in the opinion of the investigator, may interfere with the patient's ability to comply with the study procedures.

7.3 Permitted Medications

The medication that is permitted and can be co-administered with vedolizumab for the treatment of UC or CD should be consistent with prescribing information of vedolizumab.

7.3.1 Oral Corticosteroid Dosing and Tapering

The maximum dose of oral corticosteroids for the treatment of UC or CD that may be co-administered with vedolizumab as a long-term regimen is prednisone 30 mg/day or budesonide 9 mg/day with 6 mg/day for maintenance (or equivalent) as long as they have been stable for at least 4 weeks prior to enrollment or for 2 weeks prior to enrollment if being tapered. Short-term use (≤4 weeks) of higher doses is acceptable; however, patients who require consistent higher doses should be withdrawn from the study.

7.4 Criteria for Discontinuation or Withdrawal of a Patient

The primary reason for discontinuation or withdrawal of the patient from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure patients, refer to Section 9.1.19.

1. Pretreatment event (PTE) or AE. The patient has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the patient's health or the patient is unwilling to continue because of the PTE or AE (Refer to Section 10.1 for definitions of AEs).
2. Liver Test Abnormalities.

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status, see Section 9.1.12), if the following circumstances occur at any time during study drug treatment:

- 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 (>5%).

3. Significant protocol deviation. If patient failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the patient's health.
4. Lost to follow-up. The patient did not return to the clinic and attempts to contact the patient were unsuccessful. Attempts to contact the patient must be documented in the patient's source documents.
5. Voluntary withdrawal. The patient (or patient's legally acceptable representative) wants to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy).
6. Study termination. The sponsor, IRB/IEC, or regulatory agency terminates the study.
7. Pregnancy. The patient is found to be pregnant.

   Note: If the patient is found to be pregnant, the patient must be withdrawn immediately. The procedure is described in Section 9.1.15.
8. Lack of efficacy. The investigator has determined that the patient is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the patient. Lack of efficacy is defined as evidence of active inflammation despite an adequate course of treatment (3 induction doses) eg, no change or even elevation of scores above baseline (Simple Clinical Colitis Activity Index [SCCAI] for UC and HBI for CD).

   Note:-

   - CD Patients not showing any evidence of benefit at 14 weeks should discontinue Vedolizumab
   - UC Patients not showing any evidence of benefit at 10 weeks should discontinue Vedolizumab

9. Others.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Patient

The investigator may discontinue a patient's study participation at any time during the study when the patient meets the study termination criteria described in Section 7.4. In addition, a patient may discontinue his or her participation without giving a reason at any time during the study. Should a patient's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, all procedures scheduled for the Early Termination Visit should be done. Discontinued or withdrawn patients will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Vedolizumab IV

The study sites will be supplied by the sponsor with the following drug in an open-label manner: vedolizumab (Kynteles) IV 300 mg/vial, for single use, in 20 mL vials. The study drug will be provided in a glass vial as a white to off-white lyophilized solid formulation for reconstitution using sterile water. Each vial will be packaged in an appropriately labeled single vial carton, as per the New Drugs and Clinical Trials Rule, 2019.

Each carton will have a single-panel package insert that will contain, but will not be limited to the following: sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, drug identification number, patient information, caution statement, directions for use, and storage conditions.

Each carton will also contain patient alert card (PAC) along with package insert. This PAC will be distributed to the patients by the healthcare professional (HCP). The objective of providing PAC is to alert patients about the early signs and symptoms of PML and to remind patients that they may be at risk of infections and should consult HCP if they are unwell.

Vedolizumab lyophilized powder must be reconstituted with sterile water for injection and diluted in 250 mL of sterile 0.9% sodium chloride injection prior to administration. After the infusion is complete, 30 mL of sterile 0.9% sodium chloride injection will be flushed. Refer to vedolizumab package insert for detailed instructions on reconstitution and dilution.

8.1.2 Storage

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

Vedolizumab IV must be stored at 2ºC to 8ºC (36ºF to 46ºF). A daily temperature log of the drug storage area must be maintained every working day. Refer to vedolizumab label for details on storage of reconstituted and diluted solutions.

8.1.3 Dose and Regimen

The dose and dosing regimen for all patients is provided below.

Treatment Group	Dose	Treatment Description
All patients	Vedolizumab IV 300mg	Induction Phase: Weeks 0 (Day 1), 2, and 6 Maintenance Phase: Weeks 14, 22, 30, 38, 46

Note:-

CD Patients who have not shown a response can receive a dose (300 mg IV) at 10 week

Patients who have shown a decrease in response can receive a 4 weekly Vedolizumab 300 mg IV

No dose modifications will be allowed during the study.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that which is assigned to that individual patient according to the study protocol. All cases of overdose (with or without associated AEs) will be documented on an overdose page of the eCRF, in order to capture the important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE page of eCRFs according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.3.

In the event of drug overdose, the patient should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

Since this is an open-label single-arm study, randomization procedures will not be applicable for this study. Patients will receive treatment sequentially as they enter the study and according to the study schedule. The patient identification number will be entered in to the eCRF.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to patients enrolled in the study. To document appropriate use of sponsor-supplied drug (vedolizumab IV 300 mg), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each patient, and return to the sponsor or designee. Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the drug is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file. The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed with the drug identification used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed including initials, seal, or signature of the person dispensing the drug.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, patients are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the patient entering into the study, and before any protocol-directed procedures are performed.

A unique patient identification number (patient number) will be assigned to each patient at the time of screening; this patient number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History

At screening, demographic information to be obtained will include date of birth and sex. Patient's smoking and alcohol intake history will also be collected.

Medical history to be obtained will include any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions will be considered concurrent medical conditions (see Section 9.1.13).

Medication history will include any medication relevant to eligibility criteria, concomitant medication, and medications stopped at or within 30 days prior to signing of informed consent.

In addition, all prior biologic medication history for the treatment of UC or CD with the reason for discontinuation will be collected for patients where possible.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (12) others. All subsequent physical examinations will assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight and Height

A patient should have weight and height measured while wearing indoor clothing and with shoes off. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place.

9.1.5 Vital Sign Procedures

Vital signs will include body temperature, respiratory rate, blood pressure, and pulse (beats per minute). If the vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hours before or after the scheduled blood draw. On dosing days, vitals are taken predose.

9.1.6 Ulcerative colitis/Crohn's Disease Presentation at Screening/Baseline

- UC/CD disease activity assessment at Screening: Full Mayo Score (UC patients) and HBI (CD patients). The components of the Full Mayo Score and HBI to determine eligibility must be completed within 14 days prior to enrollment.
- UC/CD disease activity assessment at baseline: Simple Clinical Colitis Activity Index (SCCAI) (UC patients) and HBI (CD patients).
- Endoscopic or imaging assessments: For UC, endoscopy is scored using the Mayo Score (Appendix E). For CD, endoscopy is scored using the Simple Endoscopic Score for Crohn's Disease (SES-CD) (Appendix H).

9.1.6.1 Full Mayo Score

The Full Mayo Score evaluates ulcerative colitis stage, based on four parameters: stool frequency, rectal bleeding, endoscopic evaluation, and Physician's global assessment. Each parameter of the score ranges from zero (normal or inactive disease) to 3 (severe activity) [11]. The scores 0-2 are considered as clinical remission, 3-5 mild, 6-10 moderate, and 11-12 severe (Appendix E).

9.1.6.2 Simple Clinical Colitis Activity Index

SCCAI is composed of six domains: bowel frequency (during the day) ranging from 0 to >9; bowel frequency (during the night) ranging from 0 to 6; urgency of defecation ranging from none to incontinence; blood in stool ranging from none to usually frank (>50% of defecation); general well-being ranging from very well to terrible; and a number of defined extracolonic features of UC (ie. arthritis, erythema nodosum, pyoderma gangrenosum, and uveitis). The score of <5 is considered as inactive disease and score of ≥5 is active disease [12] (Appendix G).

9.1.6.3 Harvey Bradshaw Index

The HBI was conceived in 1980 as a simplified version of the Crohn's Disease Activity Index to foster a systematic collection of clinical data related to CD. The index evaluates five clinical parameters: general well-being, abdominal pain, number of liquid stools per day, abdominal mass, and complications [13]. The score <5 is considered as clinical remission, 5-7 mild, 8-16 moderate, and >16 severe disease (Appendix F).

9.1.6.4 Simple Endoscopic Score for Crohn Disease Score

The SES-CD assesses the size of mucosal ulcers, the ulcerated surface, the endoscopic extension, and the presence and type of narrowings in each bowel segment (ileum, [right/transverse/left] colon, and rectum). Each of the four SES-CD variables is scored from 0 to 3, with the sum of the scores for each variable ranging from 0 to 15 yielding a total SES-CD score of 0–60. More specifically, ileocolonoscopic findings can be scored according to SES-CD as following: presence and size of ulcers (none = 0; diameter 0.1–0.5 cm = 1; 0.5–2 cm = 2; >2 cm = 3); extent of ulcerated surface (none = 0; <10% = 1; 10%–30% = 2; >30% = 3); extent of affected surface (none = 0; <50% = 1; 50%–75% = 2; >75% = 3); and presence and type of narrowings (none = 0; single, can be passed = 1; multiple, can be passed = 2; cannot be passed = 3) [14]. The score 0-2 is considered as clinical remission, 3-6 mild, 7-15 moderate, and >15 severe (Appendix H).

9.1.7 Principal Investigator Reported Outcome Measures

The investigator will complete the Full Mayo Score and HBI questionnaires at the time of screening to assess the UC/CD disease activity for enrollment.

The investigator will also complete the SCCAI and HBI questionnaires at the time points specified in the Schedule of Study Procedures post-screening to assess UC/CD disease activity for efficacy assessments.

9.1.8 PML Checklist

Clinic staff will administer the subjective PML checklist during screening to exclude patients with positive responses from enrolling into the study. The subjective PML checklist will be administered (prior to dosing) at each visit, as shown in Appendix J, to evaluate symptoms suggestive of PML. Any patients reporting signs or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation, as described in the Risk Assessment and Minimization for PML (RAMP) Algorithm referenced in Section 11.1.1. The symptoms from a positive PML checklist will be recorded as an AE. Additional information and tools for the RAMP can be found in the Study Manual.

9.1.9 Efficacy measurements

Terms	Definitions
Vedolizumab discontinuation	Vedolizumab discontinuation is defined as ceasing vedolizumab, or a treatment gap ≥90 days between consecutive doses.
Clinical remission	Clinical remission is defined as SCCAI [12] of ≤2 with no individual score >1 (UC patients) or a HBI ≤4 (CD patients) [13].
Clinical response	Clinical response is defined as a decrease in SCCAI of ≥3 from baseline or by physician assessment of clinical response (UC patients) [12] or a decrease in HBI of ≥3 points from baseline* (CD patients) [13].
Mucosal healing**	Mucosal healing is based on endoscopic evidence of no inflammation and healing of the mucosa as defined by a Mayo endoscopic subscore of ≤1 point [15] or SES-CD 0-2 or SES-CD ≤4 and at least a 2 point reduction from baseline with no sub-score >1 [16].
Endoscopic response**	Endoscopic response is defined as decrease in Mayo endoscopic subscore of ≥1 point in UC [15] and >50% decrease in SES-CD in CD [16].
Patient-reported QoL	A score will be computed for the SIBDQ [17]. Linguistically validated translations of the SIBDQ are available in local languages.

CD= Crohn's disease, HBI= Harvey Bradshaw Index, SES-CD= Simple Endoscopic Score for Crohn Disease, SCCAI= Simple Clinical Colitis Activity Index, SIBDQ= Short Inflammatory Bowel Disease Questionnaire, QoL= Quality of life, UC= Ulcerative colitis

* Baseline is defined as the assessment prior to first dose of study.

** Colonoscopy/ Ileo-colonoscopy is not mandatory except screening visit, however if performed will be used to assess mucosal healing and endoscopic response.

9.1.10 Patient Reported Outcome Measures

Patients will complete the SIBDQ at the time points specified in the Schedule of Study Procedures.

9.1.10.1 Short Inflammatory Bowel Disease Questionnaire

The SIBDQ is a valid and reliable [17] instrument used to assess quality of life in adult patients with IBD. It is a 10-item questionnaire that includes questions on 4 domains of health-related quality of life (HRQoL): Bowel systems, emotional function, social function, and systemic function and is

scored on a 7-point Likert scale from 1 (severe problem) to 7 (no problems at all). A total SIBDQ score is calculated by summing the scores from each domain; the total SIBDQ score ranges from 10 (poor HRQoL) to 70 (optimum HRQoL).

9.1.11 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the patient over the counter. Concomitant medication is not provided by the sponsor. At each study visit, patients will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.12 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures at the time points specified in the Schedule of Study Procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9. a lists the tests that will be obtained for each laboratory specimen.

Table 9. a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells White blood cells Hemoglobin Hematocrit Platelets	ALT Albumin Total bilirubin AST Total protein Creatinine Blood urea nitrogen	Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific Gravity

Serum	Urine
HIV test Hepatitis panel, including HBsAg and anti-HCV β-hCG (for pregnanacy) (female patients of childbearing potential) CRP	Urine pregnancy test (female patients of childbearing potential)
Mantoux test/Interferon gamma release assay and Chest X-ray for Tuberculosis	
Stool: Fecal calprotectin *Clostridium difficile* Test	

ALT=Alanine aminotransferase, anti-HCV= anti-hepatitis C virus, AST=Aspartate aminotransferase, CRP= C-reactive protein, HBsAg= Hepatitis B surface antigen, β-hCG= beta human chorionic gonadotropin, HIV= Human Immunodeficiency Virus

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If patients experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma glutamyl transferase, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted (refer to Section 7.4 and Section 10.2.4 for the appropriate guidance on reporting abnormal liver tests).

If ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant patient details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.4).

9.1.13 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those 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 (screening/baseline) examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.14 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 16 weeks after last dose of study drug, nonsterilized** male patients who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. From signing of informed consent, throughout the duration of the study, and for 16 weeks after last dose of study drug, female patients of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females not of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an appropriate clinical profile [ie, age appropriate, history of vasomotor symptoms], confirmed before any study drug is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are included the only acceptable methods of contraception are:

Intrauterine devices:	**Hormonal contraceptives:**
Copper T PLUS condom or spermicide	Implants
Progesterone T PLUS condom or spermicide	Hormone shot/injection
	Combined pill
	Minipill
	Patch
	Vaginal ring PLUS male condom and spermicide

Barrier methods (eg, male condom PLUS spermicide, cap [plus spermicidal cream or jelly] PLUS male condom and spermicide, diaphragm [plus spermicidal cream or jelly] PLUS male condom and

spermicide) can be used each time the patient has intercourse in addition to methods listed in the table above to ensure acceptable protection level.

Patients will be provided with information on acceptable methods of contraception as part of the patient informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular serum/urine hCG pregnancy tests will be performed only for women of childbearing potential and patients will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures (Appendix A). In addition to a negative serum β-hCG pregnancy test at Screening, patients also must have a negative urine pregnancy test at Week 0 Day 1, during the treatment phase, Week 46/ET and at the 16-week safety follow-up visit.

9.1.15 Pregnancy

If any patient is found to be pregnant during the study, the patient should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male patient during the study or for 16 weeks after the last dose, should also be recorded following authorization from the patient's partner.

If the pregnancy occurs during administration of study drug or within 16 weeks of the last dose of study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0. If the female patient and/or female partner of a male patient agrees to the primary care physician being informed, the investigator should notify the primary care physician that the patient/female partner of the patient was participating in a clinical study at the time she became pregnant and provide details of treatment the patient received. All pregnancies in patients on active study drug will be followed up to the final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.16 ECG Procedure

A standard 12-lead ECG will be recorded at the time points specified in the Schedule of Study Procedures (Appendix A). The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

9.1.17 Tuberculosis Screening

All patients will complete TB screening to determine eligibility. All patients must complete a diagnostic tests of Mantoux test/Interferon gamma release assay and Chest X-ray during screening as per the decision of investigator and the feasibility of the site. Patients will be excluded from the study if they have active or latent TB, regardless of treatment history, as defined in Section 7.2.

9.1.18 Harvey Bradshaw Index/Mayo Score

A HBI/Mayo Score will be evaluated during screening to determine eligibility. A HBI/SCCAI score will also be derived at the time points specified in the Schedule of Study Procedures and at any unscheduled visit(s) due to disease exacerbation (See Appendix A).

9.1.19 Documentation of Screen Failure

Investigators must account for all patients who sign informed consent. If the patient is found to be not eligible after screening, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal (specify reason)
- Others (specify reason)

Patient numbers assigned to patients who fail screening should not be reused.

9.1.20 Documentation of Study Entrance

Only patients who meet all of the inclusion criteria and none of the exclusion criteria are eligible for enrolment into the treatment phase.

If the patient is found to be not eligible for treatment phase, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Patient Treatment Compliance

If a patient is persistently noncompliant with the study drug administration visits, it may be appropriate to withdraw the patient from the study. All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A.

Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Patients will be screened within 28 days prior to 1st dose. Patients will be screened in accordance with predefined inclusion and exclusion criteria as described in Sections 7.1 and 7.2, respectively. See Section 9.1.19 for procedures for documenting screening failures.

Procedures to be completed at Screening can be found in the Schedule of Study Procedures (Appendix A).

9.3.2 Rescreening

Automatic rescreening of the patients is not allowed. If the investigator believes in the appropriateness of the patient for the study, and considers a rescreen, permission for the same must be obtained from the Medical Monitor. Rescreening at the investigator's discretion without prior approval from the Medical Monitor is not allowed.

9.3.3 Enrollment

Enrollment will take place on Day 1. If the patient has satisfied all of the inclusion criteria and none of the exclusion criteria, the patient will be enrolled. Patients will be instructed on when the first dose of investigational drug will be given as described in Section 6.1.

9.3.4 Treatment Phase

The treatment phase will be of 46 weeks. The study drug doses will be given at Week 0 (Day 1), 2, 6, 10 (CD- Patients who have not shown a response can receive a dose at 10 week), 14, 22, 30, 38, and 46.

9.3.5 End of Treatment Visit or Early Termination

The end of treatment visit will be performed on Week 46 or at early terimation.

For all patients receiving study drug, the investigator must complete the end of treatment eCRF page.

9.3.6 Postdose 16-Week Safety Follow-up

Upon receipt of the last dose of study drug (completers and ETs), all patients will complete a safety follow-up visit 16 weeks postdose. Assessments will be completed per the Schedule of Study Procedures for the postdose 16-week safety follow-up visit and end of study eCRF page must be completed. During this 16 week follow up period patients will be managed as per standard of care which includes Vedolizumab (an approved treatment in India for the current study patient population) or any other treatment per investigator discretion and it will be provided by the sponsor. Vedolizumab treatment during this follow period shall not be considered as study treatment as vedolizumab is an approved product and part of standard of care for this patient population. Any adverse event in patients receiving Vedolizumab as a part of standard of care during the follow up period will be compensated for medical management by the sponsor only if found to be related to the study treatment, as assessed by study investigator.

9.3.7 Poststudy Long-term Follow-up

Upon completion of treatment phase or early termination from the study, all patients will participate in a long-term follow-up safety survey through telephonic visit. The survey will be administered at 6 months after the last dose of study drug i.e. 8 weeks after the 16-week follow-up visit, and the information will be collected on events such as infections resulting in hospitalizations, cancer, UC or CD related surgeries, and development of PML. During this follow up period patients will be managed as per standard of care which includes Vedolizumab (an approved treatment in India for the current study patient population) or any other treatment per investigator discretion and it will be provided by the sponsor. Vedolizumab treatment during this follow period shall not be considered as study treatment as vedolizumab is an approved product and part of standard of care for this patient population. Any adverse event in patients receiving Vedolizumab as a part of standard of care during the follow up period will be compensated for medical management by the sponsor only if found to be related to the study treatment, as assessed by study investigator.

9.3.8 Unscheduled Visits Due to Disease Exacerbation

Patients who are seen by the investigator or site staff at a time point not required by the protocol (ie, unscheduled visit) due to disease exacerbation will undergo the following procedures:

- Physical examination
- Vital signs assessment
- Collection of concomitant medications and procedures
- Collection of AEs and SAEs
- Serum chemistry and hematology, as indicated
- Other (per investigator discretion and approval by Sponsor)

There is no minimum time for repeat evaluation by unscheduled visits in order to determine if a patient meets the criteria for disease exacerbation. In general, however, enough time should be provided for clinically meaningful change to occur (eg, 1 week).

9.3.9 Post Study Care

The patient should be returned to the care of a physician and standard therapies as required. If the Investigator decides to continue Vedolizumab or any other treatment during the follow up period i.e. following the end of treatment phase (46 weeks) or Early Termination, the same will be provided by the sponsor. . Vedolizumab treatment during this follow period shall not be considered as study treatment as vedolizumab is an approved product and part of standard of care for this patient population. Any adverse event in patients receiving Vedolizumab will be compensated for medical management by the sponsor only if found to be related to the study treatment, as assessed by study investigator.

10.0 PRETREATMENT EVENTS, ADVERSE EVENTS, ADVERSE DRUG REACTIONS, UNEXPECTED ADVERSE DRUG REACTIONS

10.1 Definitions

10.1.1 Pretreatment events

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

10.1.2 Adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a drug; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.
- Necessitate therapeutic intervention
- Require an invasive diagnostic procedure
- Require discontinuation or a change in dose of study drug or a concomitant medication
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should not be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should not be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays, etc) should not be recorded as PTEs unless related to study procedures. However, if the patient experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a patient has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy), any occurrence of an episode should be captured as a PTE/AE only if the condition becomes more frequent, serious, or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a patient has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the patient experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the patient experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs /PTEs:

- If the patient experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the patient's medical condition should not be recorded as PTEs or AEs, but should be documented in the patient's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should not be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are not considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the patient to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda medically significant AE List (Table 10. a).

Table 10. a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Adverse events of special interest

A special interest adverse event (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

AESIs in this study are listed in Section 10.2.2.

10.1.6 Adverse drug reactions

An ADR is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

10.1.7 Unexpected Adverse drug reactions

An unexpected ADR is an ADR with the nature, severity, or outcome which is not consistent with the Product Insert.

10.1.8 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the patient.

Moderate: The event causes the patient discomfort and interrupts the patient's usual activities.

Severe: The event causes considerable interference with the patient's usual activities.

10.1.9 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.10 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.11 Start Date

The start date of the AE/PTE is the date at which the first signs/symptoms were noted by the patient and/or investigator.

10.1.12 Stop Date

The stop date of the AE/PTE is the date at which the event resolved/recovered with or without sequelae or the patient died.

10.1.13 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.14 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the patient died, dosing with study drug was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose interrupted – the dose was interrupted due to the particular AE.

10.1.15 Outcome

- Recovered/Resolved – Patient returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the patient died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the patient died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the patient recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cerebrovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.

- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the patient's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE, AE, and ADR Collection Period

Collection of PTEs will commence from the time the patient signs the informed consent to participate in the study and continue until the patient is first administered study drug or until screen failure. For patients who discontinue prior to study drug administration, PTEs are collected until the patient discontinues study participation.

Collection of AEs will commence from the time that the patient is first administered study drug. Routine collection of AEs will continue until 16 weeks (safety follow-up period) followed by a telephonic survey 6 months (long-term follow-up period) after the last dose of study drug .

10.2.1.2 PTE, AE, and ADR Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Patients may report AEs occurring at any other time during the study. Patients experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All patients experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

SIBDQ will be used in this study. It will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.1.3 Adverse Event Collection Involving Medically Anticipated Clinical Events

UC or CD is associated with certain characteristic signs and symptoms including diarrhea, rectal bleeding, and abdominal pain that may be present at baseline and persist or fluctuate based on the individual patient's disease history during the course of the study. These signs and symptoms will not be collected as AEs. These characteristics of disease activity will be regularly captured in the SCCAI score/HBI.

Exacerbations of disease activity (eg, increase in the daily amount of rectal bleeding or abdominal pain beyond the patient's normal fluctuation, new signs and symptoms) will be collected as AEs and reported according to regulatory reporting requirements.

Extra-intestinal manifestations of the patient's disease (eg, arthralgia, arthritis, uveitis) that develop or worsen during the study are considered AEs.

10.2.2 Adverse event of special interest reporting

If an AESI, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be recorded in the Special Interest AE eCRF or SAE Form. The applicable form should be completed and reported to the SAE reporting contact in Section 1.1 within 24 hours. The list of AESIs are as follows:

Serious infections

Serious infection is defined as any event coded to a Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT) within the MedDRA SOC of infections and infestations that meet the 'serious' definition (see Section 10.1.4).

Opportunistic infections

This is defined as infections included in the United States Center for Disease Control's list of opportunistic infections. This includes TB and PML.

Opportunistic infections include:

- Candidiasis of bronchi, trachea, esophagus, or lungs: This is defined as any event coded to a MedDRA term for candidiasis of the bronchi, trachea, esophagus, or lung.
- Coccidioidomycosis: This is defined as any event coded to a MedDRA term for coccidioidomycosis, pulmonary coccidioidomycosis, cutaneous coccidioidomycosis, or extrapulmonary coccidioidomycosis.
- Cryptococcosis: This is defined as any event coded to a MedDRA term for cryptococcosis, pulmonary cryptococcosis, extrapulmonary cryptococcosis, disseminated cryptococcosis, and recurrent cryptococcosis.
- Cryptosporidiosis: This is defined as any event coded to a MedDRA term for cryptosporidiosis or recurrent cryptosporidiosis.

- Cytomegalovirus (CMV) disease: This is defined as events coded to a MedDRA term for CMV disease, including CMV chorioretinitis, colitis, duodenitis, enteritis, gastritis, hepatitis, mononucleosis, mucocutaneous ulcer, myelomeningoradiculitis, myocarditis, esophagitis, pancreatitis, pericarditis, proctocolitis, urinary tract infection, encephalitis, CMV pneumonia, and CMV syndrome.
- Encephalopathy-related infections: This is defined as encephalitis or encephalopathy due to infections, excluding those transmitted by arthropod (such as Japanese B encephalitis) or rodents, or due to influenza, measles, mumps, polio, or rabies. Includes PML (see below).
- Herpes simplex: This is defined as events coded to MedDRA terms for herpes simplex esophagitis, bronchitis, or pneumonitis, or to herpes esophagitis, bronchitis, or pneumonia.
- Histoplasmosis: This is defined as events coded to any MedDRA term for histoplasmosis and includes both acute and chronic infections of any site.
- Isosporiasis, chronic intestinal: This is defined as events coded to MedDRA terms forisosporiasis of the MedDRA high-level term (HLT) isospora infection.
- Kaposi's sarcoma: This is defined as events coded to the MedDRA HLT Kaposi sarcoma.
- *Mycobacterium avium* complex: This is defined as events coded to the MedDRA term *Mycobacterium avium* complex infection.
- TB: This is defined as all events coded to the MedDRA HLT TB infections, including new infections and reactivation of latent infections, of pulmonary and extra pulmonary sites.
- *Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii* pneumonia): This is defined as events coded to the MedDRA term *Pneumocystis jiroveci* pneumonia Pneumonia, recurrent. This is defined as events coded to the MedDRA term pneumonia recurrent.
- PML: All reports of suspected PML (Appendix J) (reports coded to the following MedDRA PTs: human polyomavirus infection, John Cunningham (JC) virus infection, JC virus test positive, leukoencephalopathy, polyomavirus test positive, progressive multifocal leukoencephalopathy) will be reviewed by PML Independent Adjudication Committee (IAC) and assessed against the PML diagnostic criteria of the American Academy of Neurology [18]. Where incomplete information is provided, the physician shall seek to obtain all relevant information).

  Investigators will be provided with the vedolizumab HCP educational brochure and instructed to monitor patients for any new onset or worsening of neurological signs and symptoms, consistent with standard of care clinical practice and the information contained in the approved prescribing information, which describes the typical signs and symptoms of PML and recommended action if PML is suspected. The patient will be given vedolizumab Patient Alert Card.
- Salmonella septicemia, recurrent: This is defined as events coded to the MedDRA terms Salmonella sepsis or Salmonella septicemia.
- Toxoplasmosis of brain: This is defined as events coded to MedDRA term cerebral toxoplasmosis.

Other rare infections that are not normally seen in immunocompetent persons may also be considered as opportunistic infections.

GI infections

This is defined as events within the infections and infestation SOC that are coded to the MedDRA HLT GI infections. The treating physician should record and report all GI infections, including those occurring as a result of UC or CD.

Respiratory infections

This is defined as events within the respiratory, thoracic and mediastinal disorders SOC that are coded to the MedDRA HLT respiratory tract infection. As respiratory infections are common and often mild in nature, the treating physician should ask study participants at each clinic visit if they have had any respiratory infections since last visit, and collect all relevant information.

Other clinically significant infections

This is defined as events within the infections and infestation SOC that are not included in any of the above categories, are classified as moderate or severe (Section 10.1.8), and require anti-infective treatment.

Malignancies

All malignant and benign neoplasms should be recorded on the eCRF. The analyses will focus on malignancies and include all events within the MedDRA Malignant tumors Standardised MedDRA Queries (SMQ). This SMQ includes all malignancies and carcinomas in situ.

The treating physician should seek all available clinical and histopathology information on the malignancy, including site, cell type, size, stage, and grade (including nodal status and metastases), clinical history, prior history of malignancy or premalignant disorders, family history, history of screening and diagnostic tests, and history of risk factors and medication history.

Infusion-related reactions and hypersensitivity

All suspected cases of infusion reactions, hypersensitivity, and anaphylaxis should be reported on the eCRF, regardless of time since last drug exposure.

Events that are coded to PTs in the following will be considered as suspected reports of hypersensitivity:

- Anaphylactic reaction (narrow SMQ)
- Anaphylactic/anaphylactoid shock conditions (narrow SMQ)
- Hypersensitivity (narrow SMQ)
- Angioedema (narrow SMQ)

All suspected reports will be adjudicated by a Takeda or contract research organization (CRO) pharmacovigilance (PV) physician using the hypersensitivity criteria of the National Institute of Allergy & Infectious Diseases [19].

The physician shall seek all information on clinical history, presenting signs and symptoms, time interval between biologic exposure and onset of symptoms, and treatments received.

Hepatic injury

Events coded to PTs in the following MedDRA SMQs (narrow) will be considered as suspected reports of liver injury:

- Cholestasis and jaundice of hepatic origin (narrow SMQ)
- Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions (narrow SMQ)
- Hepatitis non-infectious (narrow SMQ)
- Liver related investigations, signs, and symptoms (narrow SMQ)

The treating physician shall seek all relevant information on the hepatic injury, including signs and symptoms, initial and follow-up laboratory results (including serology results), time course of the hepatic injury, diagnosis, concurrent medications and doses, pre-existing liver disease, infections, suspected etiology (and treating physician to rule out alternative etiologies), and outcome.

10.2.3 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

The SAE page of the eCRF must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Patient identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

In the event that electronic data collection (EDC) is unavailable, a paper SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

If reporting by fax, the site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.

If reporting by email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day.

Once EDC is available, the SAE should immediately be entered into the SAE form within EDC.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of serious PTEs will follow the procedure described for SAEs.

10.2.4 Reporting of Abnormal Liver Tests

If a patient is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant patient details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.12 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should enter this information into the SAE form page of the eCRF or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs/IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including investigators and IRBs/IECs, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB/IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No data safety monitoring committee, or clinical endpoint committee will be used in this study.

11.1 Adjudication Committee

Considering PML is an AESI, a PML IAC will be implemented for this study. The PML IAC will consist of a panel of leading PML experts, including a neurologist, neuroradiologist, and a virologist.

11.1.1 Risk Minimization Action Plan for PML (RAMP Program)

Natalizumab (TYSABRI), another integrin receptor antagonist, has been associated with PML, a rare and often fatal opportunistic infection of the central nervous system. PML is caused by the JCV and typically only occurs in patients who are immunocompromised [20,21]. Natalizumab is a pan-α_4 integrin antagonist that binds to both the $\alpha4\beta1$ and $\alpha4\beta7$ integrins and inhibits cellular adhesion to VCAM-1 and MAdCAM-1 [22,23]. In contrast, vedolizumab binds to the $\alpha4\beta7$ integrin only [24] and inhibits adhesion to MAdCAM-1, but not VCAM-1. However, a risk of PML cannot be ruled out.

To address the theoretical risk of the development of PML in patients treated with vedolizumab, the sponsor, with input from renowned PML experts, has developed a Risk Minimization Action Plan for PML, the RAMP. The complete description of the RAMP program, including materials and instructions for its implementation and monitoring, is included in the Study Manual.

The RAMP is focused on early clinical detection and management of that specific safety risk, including the discontinuation of study drug, if applicable. Patients are assessed for signs and symptoms of PML prior to the administration of each dose of study drug using a PML subjective symptom checklist. Patients with a positive PML subjective symptom checklist at any time after enrollment in a vedolizumab clinical study will be evaluated according to a prespecified algorithm (the PML Case Evaluation Algorithm). The next dose of study drug will be held until the evaluation is complete and results are available. Subsequent doses of study will be administered only if the possibility of PML is definitively excluded, as described in the RAMP algorithm. An IAC has been stabled as part of the RAMP program to review new neurological signs and symptoms potentially consistent with PML, and will provide input regarding patient evaluation and management as defined in the IAC charter.

To ensure success of the RAMP program, site personnel will be trained to recognize the features of PML, and patients will be trained to report specific neurological signs and symptoms without delay. Educational materials for teaching site personnel and patients about PML and the RAMP procedures will be distributed to all sites and are included in the study manual. Formal teaching and training will be performed for site personnel prior to the start of the study. Patients will receive training and educational materials prior to receiving treatment. The ICF will contain specific information on the hypothetical risk of PML.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, ADRs, medical history, and concurrent conditions will be coded using MedDRA. Drugs will be coded using the World Health Organization drug dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each patient who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

This section provides information on the statistical analysis approach. All analyses will be performed using standard software such as SAS (Version 9.3 or later).

All analyses will be performed separately by IBD disease type (CD and UC). Missing data will not be imputed for analyses.

13.1.1 Analysis Sets

- The safety analysis set (SAS) will include all enrolled patients who receive at least 1 dose of study drug.
- The per-protocol analysis set (PPAS) is a subset of the SAS and consists of all patients who do not violate the terms of the protocol in a way that would impact the study outcome significantly.

Significant protocol violations and significant protocol deviations will be identified prior to database lock.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, with consulting a medical expert as needed. If necessary, the handling rules for analysis data will be supplemented with new handling rules that were not discussed at the planning stage. The Handling Rules for Analysis Data must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics, including numbers of observations (n), means (SD), and medians (10th to 90th percentiles) for continuous variables, and frequency (n) and percentages for categorical variables will be used to examine patient baseline characteristics.

13.1.3 Primary (Safety) Analysis

Analyses will present 1) all AEs and SAEs, regardless of association with vedolizumab, and 2) all ADRs and Unexpected ADRs, which is the subset of AEs where the physician believes there is reasonable suspicion of a causal relationship between vedolizumab and the AE (Section 10.1).

Exposure-adjusted incidence rates and 95% CIs by Poisson method will be calculated for each safety endpoint using the total numbers of incident events and person-time at risk. Two separate incidence calculations will be used: incidence rates for events that occur while on vedolizumab therapy, and incidence rate for events that occur after discontinuation of vedolizumab.

The number and percentage of patients with treatment-emergent adverse events (TEAEs; defined as any AEs, regardless of relationship to study drug), AEs leading to discontinuation, and SAEs that occur on or after the first dose date and up to 6 months after the last dose date of the study drug, will be summarized by MedDRA SOC, HLT, and PT overall, by severity, and by relationship to study drug.

13.1.3.1 Infections

The analysis of new infections will be based on the first occurrence of an infection event after initiation of vedolizumab. Patients with a history of a chronic infection of interest before study entry

will be excluded from the analysis for that AE to enable the analyses to focus on incident events only. For acute infections, all patients will be included except those with the infection of interest at study entry.

Analysis of reactivation of latent infections will include patients with a history of that infection.

Cases of PML as confirmed by the IAC will be included in the analyses. Unconfirmed cases of PML will be listed in the study report but not in the main analyses.

13.1.3.2 Malignancies

Analyses will focus on incident malignant neoplasms and carcinomas in situ. Benign neoplasms will be listed in the study report but not in the main analyses. Analyses will examine all malignancies pooled, then separately for each of the most common malignancies.

13.1.3.3 Infusion-Related Reaction and Hypersensitivity

Currently, vedolizumab is available for infusion only. Infusion-related reaction, as determined by the treating physician, will be included in the analyses. Suspected cases not confirmed by the treating physician will be listed in the study report but not in the main analyses. A risk window covering the infusion day and the day after the infusion will be used for infusion-related reactions and hypersensitivity.

13.1.3.4 Hepatic Injury

Cases of drug-induced liver injury adjudicated as "Related" will be included in the analyses, as these are the events most likely to be due to drug-related hepatotoxicity. Cases adjudicated as "Unrelated" will be listed in the study report but not in the main analyses.

13.1.4 Analysis of Treatment Efficacy Endpoints

Descriptive statistics, including means, standard deviations, quartiles, frequencies (n) and percentages will be presented for the efficacy and QoL endpoints. The results at Week 14, Week 30 and Week 46 for treatment efficacy endpoints and QoL assessments will be summarized. More specifically, for binary endpoints, proportions and associated 95% CIs by exact method will be provided. For changes from baseline in continuous endpoints, paired t-test will be used if normality assumption holds based on the Shapiro–Wilk test, or the Wilcoxon signed rank test will be used if otherwise.

Cox regression models may be used to explore predictors (including UC/CD presentation at baseline) of time to treatment discontinuation.

13.1.5 Subgroup Analyses

Subgroups to be explored include

- Biologic-naïve patients
- Biologic-experienced patients

The details of the subgroup analysis will be detailed in the statistical analysis plan.

The interim analysis will be performed after all subjects completes week 14 weeks assessment. All statistical testing at Week 14 will be two-sided and will be performed using a significance (alpha)

level of 0.05. A separate Interim analysis plan will be prepared for elaborative discussion about the analysis plan and mocks for interim assessment

13.2 Determination of Sample Size

The study will recruit 150 patients. This sample size was recommended by the DCGI on approval of vedolizumab as a new drug. At least 30% of the total recruited patients will be enrolled in each UC or CD group.

This sample size will enable a serious infection rate of 6 per 100 person-years to be measured with a precision of ±3.8 with 95% CI based on a normal approximation of the annualized proportion of patients to be infected. This anticipated serious infection rate is based on observed rates in a post hoc pooled analysis of data from Indian sites participating in the vedolizumab global Phase 3 C13006 and C13007 clinical studies and open label extension (Study C13008) of these studies.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB/IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study drug, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB/IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB/IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment. Significant protocol deviations will be entered into the eCRF, which is reviewed by the study sponsor or designee.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the drug is stored and prepared, and any other facility used during the study. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki (DOH), and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB/IEC Approval

IRBs/IECs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB/IEC. If any member of the IRB/IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB/IEC for the protocol's review and approval. This protocol, the Package Insert, a copy of the ICF, and, if applicable, patient recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB/IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB/IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification, no protocol activities including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB/IEC. This may include notification to the IRB/IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB/IEC, and submission of the investigator's final status report to IRB/IEC. All IRB/IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB/IEC and sponsor.

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB/IEC approval of the ICF and if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB/IEC and the sponsor prior to use.

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB/IEC. In the event the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the patient, or the patient's legally acceptable representative, determines he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and prior to the patient entering into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent and prior to patient entering into the study.

Once signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be given to the patient.

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will only be linked to the sponsor's clinical trial database or documentation via a patient identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs/IECs to review the patient's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy

reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, patient name, address, and other identifier fields not collected on the patient's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document as per ICMJE. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's

designee will obtain clinical study insurance against the risk of injury to study patients. Refer to the study site agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A: Schedule of Study Procedures

	Screening		Treatment								Follow-up		
Study Day/Week	**Days -28 to -1 (a)**	**(Day 1) (a) Week 0**	**Week 2**	**Week 6**	**Week 10**	**Week 14**	**Week 22**	**Week 30**	**Week 38**	**Week 46 End of treatment Visit or ET (b)**	**Safety Follow-up (16weeks postdose)**	**Long-term Follow-up (l) (6 months postdose)**	**Unscheduled visit**
Visit Windows (Days):			±3	±3	±3	±3	±7	±7	±7	±7	±7		
Visit Number:	1	2	3	4	5	6	7	8	9	10	11		
Informed consent	X												
Inclusion/exclusion criteria	X	X											
Demographics /medical and medication history/concurrent medical conditions	X												
CD or UC prior biologics history	X												
Physical examination	X	X	X	X	X	X	X	X	X	X	X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X		X
Height and weight (c)	X	X	X	X	X	X	X	X	X	X			X
IBD and other medications	X	X	X	X	X	X	X	X	X	X	X		
Dosing		X	X	X	X[m]	X	X	X	X	X			
Full Mayo Score/SES-CD/SCCAI/HBI assessments	X (d)	X (e)				X (e)		X (e)		X (e)			
PML Checklist	X	X	X	X	X	X	X	X	X	X	X		
QoL (SIBDQ)	X	X				X		X		X	X		
Inflammatory biomarkers (CRP if measured)	X					X		X		X			
Inflammatory biomarkers (Fecal calprotectin if measured)	X					X		X		X			
Colonoscopy/ Ileo-colonoscopy	X (f)					X (g)				X (g)			
ECG	X									X			
Sample Collection:													
Clostridium difficile	X												
Tuberculosis screening (h)	X												
Hepatitis test (i)	X												
HIV test (i)	X												
Serum chemistry and hematology	X					X		X		X			X (j)
Urinalysis	X					X		X		X			
Pregnancy test (k)	X	X	X	X	X	X	X	X	X	X	X		X
PTE/AE/SAE/AESIs collection	X	X	X	X	X	X	X	X	X	X	X	X	X

AE= Adverse event, AESI= Adverse event of special interest, anti-HCV= anti-hepatitis C virus, CD= Crohn's disease, CRP= C-reactive protein, ECG= Electrocardiogram, ET= Early Termination, HBI= Harvey Bradshaw Index, HBsAg= Hepatitis B surface antigen, HIV= Human Immunodeficiency Virus, IBD= Inflammatory bowel disease, PML= Progressive multifocal

leukoencephalopathy, PTE= Pretreatment event, QoL= Quality of life, SAE= Serious adverse event, SCCAI= Simple Clinical Colitis Activity Index, SIBDQ= Short Inflammatory Bowel Disease Questionnaire, UC= Ulcerative colitis

a) The day of first study drug administration for treatment period is Day 1. The day before first study drug administration for Treatment period is Day -1.
b) The end of treatment visit or ET is defined as the date of the last visit (Week 46) of the patient or until discontinuation of vedolizumab.
c) Height data collected only at the Screening Visit.
d) Full Mayo Score for UC and HBI score for CD will be calculated at the time of screening. The components of the Full Mayo score and HBI to determine eligibility must be completed within 14 days prior to enrollment. The investigator will complete the Full Mayo Score and HBI questionnaires at the time of screening. SES-CD score will be calculated at the time of screening in CD patients.
e) SCCAI/HBI will be calculated at the baseline (Day 1 prior to dosing/Week 0) and at Weeks 14, 30, and 46 for efficacy assessments. The investigator will complete the SCCAI and HBI questionnaires at the time of visit.
f) Colonoscopy/Ileo-colonoscopy should have been performed within 30 days before the patient enrollment or at the time of screening.
g) Colonoscopy/ Ileo-colonoscopy is not mandatory, however if performed will be used to assess mucosal healing and endoscopic response using Mayo endoscopic subscore in UC patients and SES-CD score in CD patients.
h) Mantoux test/Chest X-ray/Interferon gamma release assay as per the feasibility of the site and investigator's decision.
i) Hepatitis panel, including HBsAg and anti-HCV and HIV testing done only at the Screening Visit.
j) Serum chemistry and hematology will be done at investigator's decision.
k) Serum pregnanacy (β-hCG) test will be done at Screening, and only urine pregnancy test will be done at other visits.
l) Patients will participate in the long-term follow-up safety survey by telephonic visit
m) Patients who have not shown a response can receive a dose at 10 week
.

Appendix B: Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to International Conference on Harmonisation E6 Good Clinical Practice (ICH GCP) and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential patients, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each patient who participates in the study, and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an serious adverse event (SAE), notify the sponsor within 24 hours.

Appendix C: Elements of the Patient Informed Consent

In seeking informed consent, the following information shall be provided to each patient:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the patient's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of patients involved in the study.
7. A description of the patient's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment.
10. A description of the possible side effects of the treatment that the patient may receive.
11. A description of any reasonably foreseeable risks or discomforts to the patient and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the patient or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the patient, the patient should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the patient will be maintained, and a note of the possibility that regulatory agencies, auditor(s), Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and the monitor may inspect the records. By signing a written informed consent form, the patient or the patient's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the patient for participating in the study.
17. The anticipated expenses, if any, to the patient for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), patient's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the patient.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient otherwise is entitled, and that the patient (or the patient's legally acceptable representative) may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.
20. The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient.

21. A statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.
22. A statement that the patient (or the patient's legally acceptable representative) will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the study.
23. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
24. The foreseeable circumstances or reasons under which the patient's participation in the study may be terminated.
25. A written patient authorization (either contained within the informed consent form or provided as a separate document) describing to the patient the contemplated and permissible uses and disclosures of the patient's personal information (including personal health information) for purposes of conducting the study. The patient authorization must contain the following statements regarding the uses and disclosures of the patient's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer patients the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and efficacy of the study drug, studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that patients agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the patient's identity will remain confidential in the event that study results are published.
26. Female patients of childbearing potential (eg, nonsterilized, premenopausal female patients) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study, and for 16 weeks after last dose. Regular pregnancy tests will be performed throughout the study for all female patients of childbearing potential. If a patient is found to be pregnant during study, study drug will be discontinued and the investigator will offer the patient the choice to receive unblinded treatment information.
27. Male patients must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 16 weeks after last dose. If the partner or wife of the patient is found to be pregnant during the study, the investigator will offer the patient the choice to receive unblinded treatment information.

28. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D: Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners
- Business partners assisting Takeda, its affiliates, and licensing partners
- Regulatory agencies and other health authorities
- Institutional Review Board

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies
- Management, monitoring, inspection, and audit of the study
- Analysis, review, and verification of the study results
- Safety reporting and pharmacovigilance relating to the study
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners
- Archiving and audit of study records
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E: Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

Component	Score
Stool Frequency	
Normal	0
1–2 stools/day more than normal	1
3–4 stools/day more than normal	2
>4 stools/day more than normal	3
Rectal Bleeding	
None	0
Visible blood with stool less than half the time	1
Visible blood with stool half of the time or more	2
Passing blood alone	3
Physician Rating of Disease Activity	
Normal	0
Mild	1
Moderate	2
Severe	3
Endoscopic Findings	**Score**
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern, mild friability)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe disease (spontaneous bleeding, ulceration)	3
Full Mayo Score	**(sum)**

Assessments	
Mucosal healing	Mayo endoscopic subscore of ≤1 point
Endoscopic response	Decrease in Mayo endoscopic subscore of ≥1 point
Clinical remission	0-2
Mild	3-5
Moderate	6-10
Severe	11-12

Source: [25]

Appendix F: Harvey-Bradshaw Index for Crohn's Disease

Component	Score
General Well-Being	
Very well	0
Slightly below average	1
Poor	2
Very poor	3
Terrible	4
Abdominal Pain	
None	0
Mild	1
Moderate	2
Severe	3
Number of Liquid Stools per Day	(#)
Abdominal Mass	
None	0
Dubious	1
Definite	2
Tender	3
Complications	
Arthralgia	1
Uveitis	1
Erythema nodosum	1
Aphthous ulcers	1
Pyoderma gangrenosum	1
Anal fissures	1
New fistula	1
Abscess	1
Total	**(sum)**

Assessments	
Clinical remission	≤4
Clinical response	Decrease in HBI of ≥3 points from baseline
Mild disease	5-7
Moderate disease	8-16
Severe disease	>16

Source: [26].

Appendix G: Simple Clinical Colitis Activity Index (SCCAI)

Symptoms refer to the previous week:

Component	Score
Bowel frequency (day), n (1 per occurrence)	
0-3	0
4-6	1
7-9	2
>9	3
Bowel frequency (night)	
0	0
1-3	1
4-6	2
Urgency of defecation	
None	0
Hurry	1
Immediately (toilet nearby)	2
Incontinence	3
Blood in stool	
None	0
Trace	1
Occasionally frank (<50% of defecation)	2
Usually frank (>50% of defecation)	3
General well-being (0-10)	
≥7 (very well)	0
6 (slightly below par)	1
5 (poor)	2
4 (very poor)	3
<4 (terrible)	4
Extracolonic features (1 per manifestation)	
Arthritis	
Yes	1
No	0
Uveitis	
Yes	1
No	0
Erythema nodosum	
Yes	1
No	0
Pyoderma gangrenosum	
Yes	1

Component		**Score**
No		0
Total		**(sum)**

Assessments	
Inactive UC	SCCAI score of <5
Active UC	SCCAI score of ≥5
Clinical response	Decrease in SCCAI ≥3 from baseline
Clinical remission	SCCAI score of ≤2 with no individual subscore >1

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

Definition - scoring of elementary lesions considered:

	SES-CD values (evaluated for each of the 5 ileo-colonic segments			
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%
Stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed

	Ileum	Right Colon	Transverse Colon	Left Colon	Rectum	Total
Presence and size of ulcers (0-3)	0-3	0-3	0-3	0-3	0-3	0-15
Extent of ulcerated surface (0-3)	0-3	0-3	0-3	0-3	0-3	0-15
Extent of affected surface (0-3)	0-3	0-3	0-3	0-3	0-3	0-15
Presence and type of narrowings	0-3	0-3	0-3	0-3	0-3	0-15
					SES -CD =	**0-60**

Assessments	
Mucosal healing	SES-CD 0-2 or SES-CD ≤4 and at least a 2 point reduction from baseline with no sub-score >1
Endoscopic response	>50% decrease in SES-CD

Source: [27].

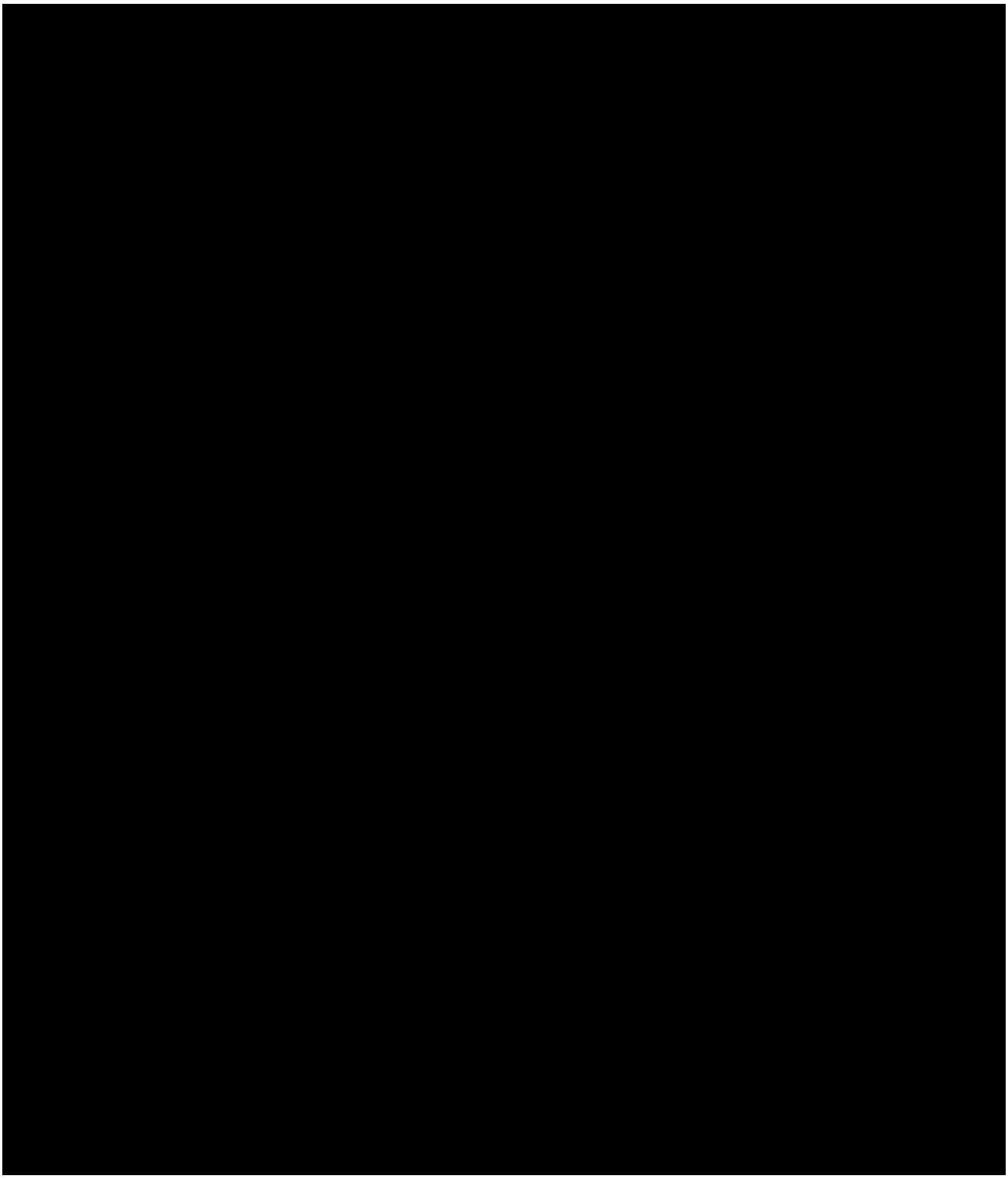
Appendix I: Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

[redacted]

[redacted]

[redacted]

Appendix J: Progresive Multifocal Leukoencephalopathy (PML) Symptom Checklist



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