Title: A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST)

NCT Number: NCT02790138

Protocol Approve Date: 14 September 2020

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

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

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

PROTOCOL AMENDMENT

A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST)

Vedolizumab IV 300 mg in the Treatment of Chronic Pouchitis

Sponsor: Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015

Takeda Development Centre Europe, Ltd.
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Study Number: Vedolizumab-4004

IND Number: 009125 **EudraCT Number:** 2015-003472-78

Compound: Vedolizumab IV

Date: 14 September 2020 **Amendment Number:** 04

Amendment History:

Date	Amendment Number	Amendment Type	Region
12 February 2016	Initial Protocol	Not applicable	Global
01 June 2016	01	Non-substantial	Global
20 October 2016	02	Substantial	Global
21 April 2017	03	Substantial	Global
14 September 2020	04	Non-substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda Development Center (TDC) sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	United States/Canada Contact	Europe/Rest of World Contact
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protoco and compound) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD	

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 Conference on 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.

Electronic Signatures may be found on the last page of this document.

PPD

1.3 Protocol Amendment 04 Summary of Changes

Rationale for Amendment 04

This document describes the changes in reference to the Protocol Incorporating Amendment No. 04.

The primary reason for this amendment is to add exploratory objectives and endpoints for the CCI

[redacted]

Minor grammatical, editorial and formatting changes, for clarification purposes only, are not listed below nor in Appendix J. For specific description of text changes and where the changes are located, see Appendix J.

Changes in Amendment 04

CCI

[redacted]

3. Added centrally read endoscopic assessments of the pouch.

CCI

[redacted]

7. Clarified that prior medication history includes all prior medications for the treatment of UC/pouchitis.
8. Corrected acute histologic inflammation descriptors for score of 0 in Appendix E for clarification of PDAI scoring.
9. Deleted duplicated text describing analysis set for primary analysis.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, the vedolizumab IV (Entyvio) 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 subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, 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 Clinical 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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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. Takeda Development Centre Europe, Ltd	**Compound:** Vedolizumab IV	
Title of Protocol: A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST)	**IND No.:** 009125	**EudraCT No.:** 2015-003472-78
Study Number: Vedolizumab-4004	**Phase:** 4	

Study Design:

Phase 4, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vedolizumab 300 mg intravenous (IV) infusion during a 34-week treatment period (with last dose at Week 30) using pouch endoscopy. Approximately 110 subjects with a proctocolectomy and ileal pouch anal anastomosis (IPAA) for ulcerative colitis (UC) who have developed chronic or recurrent pouchitis will be enrolled.

Chronic or recurrent pouchitis is defined as a modified Pouchitis Disease Activity Index (mPDAI) score ≥5 assessed as the average from 3 days immediately prior to the Baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either:

(a) ≥3 recurrent episodes within 1 year prior to the Screening visit, each treated with ≥2 weeks of antibiotic or other prescription therapy, or

(b) requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately prior to the Baseline Endoscopy Visit.

Subjects will be randomized in a 1:1 ratio to either the approved UC vedolizumab dose regimen or placebo treatment at Day 1, Weeks 2, 6, 14, 22, and 30. All subjects will receive concomitant antibiotic treatment with ciprofloxacin 500 mg twice daily from randomization through Week 4. Efficacy will be assessed at Week 14 and Week 34.

Primary Objective:

To compare the efficacy of vedolizumab IV and placebo in terms of the percentage of subjects with chronic or recurrent pouchitis achieving clinically relevant remission.

Secondary Objectives:

To assess the efficacy of vedolizumab IV by:

- Percentage of subjects achieving mPDAI <5 and a reduction of overall score by ≥2 points from Baseline.
- Percentage of subjects achieving PDAI <7 and a reduction of overall score by ≥3 points from Baseline.
- Time to remission (defined as a PDAI score <7 and a decrease in PDAI score of ≥3 points from Baseline).
- Percentage of subjects achieving a partial response (defined as reduction of mPDAI score by ≥2 points from Baseline).
- Change in PDAI endoscopic subscore.
- Change in PDAI histologic subscore.
- Change in total PDAI.
- Change in Inflammatory Bowel Disease Questionnaire (IBDQ), and Cleveland Global Quality of Life (CGQL, Fazio Score, 3 items).

Exploratory Objectives:

CCI [redacted]

CCI [redacted]

Safety Objective:

To assess the safety of vedolizumab IV in chronic or recurrent pouchitis.

Subject Population: Adult subjects with a proctocolectomy and IPAA for UC, that was completed at least 1 year before the Day 1 (Randomization) Visit, who have developed chronic or recurrent pouchitis, defined as a mPDAI score ≥5 assessed as the average from 3 days immediately prior to the Baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either:

(a) ≥3 recurrent episodes within 1 year prior to the Screening visit, each treated with ≥2 weeks of antibiotic or other prescription therapy, or

(b) requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately prior to the Baseline Endoscopy Visit

Number of Subjects:	**Number of Sites:**
Approximately 110 subjects will be randomly assigned in a 1:1 ratio to receive vedolizumab IV (n=55) or placebo (n=55).	Approximately 40 sites in North America and Europe.
Dose Level(s): Group 1: Vedolizumab IV 300 mg at Day 1, Weeks 2, 6, 14, 22, and 30. Group 2: Placebo IV at Day 1, Weeks 2, 6, 14, 22, and 30. All subjects will receive ciprofloxacin 500 mg twice daily through Week 4.	**Route of Administration:** Intravenous
Duration of Treatment: 34 weeks (with last dose at Week 30)	**Period of Evaluation:** The study includes up to a 4-week Screening Period, a 34-week Treatment Period (with last dose at Week 30), and an 18-week Follow-up Period following last dose. The duration of the study from the start of screening to 18 weeks post last dose at Week 30 will be approximately 52 weeks. All subjects will participate in a long-term follow-up (LTFU) safety survey by telephone 26 weeks after their last dose.

Main Criteria for Inclusion:

- Male or female subjects aged 18 to 80 years, inclusive.
- History of IPAA for UC completed at least 1 year prior to the Day 1 (Randomization) Visit.
- Pouchitis that is chronic or recurrent, defined by an mPDAI score ≥5 assessed as the average from 3 days immediately prior to the Baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either (a) ≥3 recurrent episodes within 1 year prior to the Screening Period treated with ≥2 weeks of antibiotic or other prescription therapy, or (b) requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately prior to the Baseline Endoscopy Visit.

Main Criteria for Exclusion:

- Crohn's disease (CD), CD of the pouch, irritable pouch syndrome (IPS), isolated or predominant cuffitis, diverting stoma, or mechanical complications of the pouch.
- Previous treatment with vedolizumab, natalizumab, efalizumab, rituximab, etrolizumab, or anti-mucosal

addressin cell adhesion molecule-1 (MAdCAM-1) therapy.

- Any investigational or approved biologic or biosimilar agent within 60 days of randomization.
- Nonbiologic investigational therapy within 30 days prior to randomization.
- Active or latent tuberculosis.
- Chronic hepatitis B virus (HBV) infection or chronic hepatitis C virus (HCV) infection or a known history of human immunodeficiency virus (HIV) infection (or is found to be seropositive at Screening) or subject is immunodeficient.
- Active, severe infection.
- Positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist at Screening.

Main Criteria for Evaluation and Analyses:

The primary efficacy endpoint is the percentage of subjects with chronic or recurrent pouchitis achieving clinically relevant remission after 14 weeks of treatment. Clinically relevant remission will be defined as an mPDAI score <5 and a reduction in overall score by ≥2 points from Baseline.

Secondary efficacy endpoints are:

- Percentage of subjects achieving mPDAI score <5 and a reduction of overall score by ≥2 points from Baseline after 34 weeks of treatment (last dosing at week 30).
- Percentage of subjects achieving PDAI score <7 and a reduction of overall score by ≥3 points from Baseline PDAI score after 14 weeks of treatment and after 34 weeks of treatment (last dosing at Week 30).
- Time to remission (defined as a PDAI score <7 and a decrease in PDAI score of ≥3 points from Baseline).
- Percentage of subjects achieving a partial response (defined as a reduction in mPDAI score by ≥2 points from Baseline) after 14 and after 34 weeks of treatment (last dosing at week 30).
- Change in PDAI endoscopic subscore at Weeks 14 and 34 compared to Baseline.
- Change in PDAI histologic subscore at Weeks 14 and 34 compared to Baseline.
- Change in total PDAI score at Weeks 14 and 34 compared to Baseline.
- Change in IBDQ, and CGQL (Fazio Score, 3 items) at Weeks 14, 22, and 34 compared to Baseline.

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Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs), serious adverse events (SAEs), vital signs, and results of standard laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis).

Statistical Considerations:

The primary efficacy endpoint is the percentage of subjects who achieve clinically relevant remission at Week 14 (defined as an mPDAI score <5 and a decrease in mPDAI score of ≥2 points from Baseline). Subjects who withdraw early for any reasons will be included in the denominator for the estimation of this percentage. At the final analysis, the difference between the percentages of subjects achieving remission at Week 14 in each treatment group will be assessed by the chi-squared test. The null hypothesis, that the percentage of subjects achieving remission at Week 14 in each treatment group is the same, will be tested against the alternative hypothesis that the 2 percentages are not the same.

The primary efficacy analysis will be based on the full analysis set (FAS) including all randomized subjects. Analysis will also be performed on the PP population for confirmatory purposes.

The secondary endpoint of time to remission (defined as a PDAI score <7 and a decrease in PDAI score of ≥3 points from Baseline), will be analyzed by survival analysis procedures. Remission rates from the time of randomization over the 34-week study period will be estimated by Kaplan-Meier product limit methods. The log-rank test will be applied to compare the 2 treatment groups. Cox proportional hazards regression will be performed to explore the effect of prognostic factors. Adjustments for baseline imbalances on key prognostic factors will be made using Cox regression. As this is a multicenter clinical study, heterogeneity of treatment effect across the participating centers will be explored.

Statistical tests will be 2-sided and performed at the 0.05 level of significance.

A single futility analysis will be performed when 25 patients per treatment arm have been recruited and completed their Week 14 assessment for primary efficacy. The purpose of this analysis will be to assess for futility, and at this point simulations will be performed to determine the posterior probability of achieving a treatment difference of at least 25% between the active and placebo treatment arms. On the basis of the posterior probability of success, a decision will be made to continue or terminate the study on the grounds of futility. It is not intended to stop the study on the grounds of efficacy; hence, no adjustment to the statistical significance level used for testing at the final analysis is necessary.

Safety analyses will be based on the safety (SAF) analysis set. All subjects who received at least 1 dose of study drug will be included in the safety analysis set. No formal statistical tests will be performed for safety analyses.

Sample Size Justification:

The sample size is calculated on the basis of remission rate at 14 weeks. The remission rate in subjects treated with placebo is estimated to be 15%. An effect size of at least 25% would be considered clinically meaningful (ie, a remission rate of 40% in subjects maintained on vedolizumab IV). Therefore, a total of 98 evaluable subjects (49 per treatment group) will be required to detect a 25% difference in the remission rate at the 2-sided 0.05 level of significance with 80% power. To account for attrition, 110 subjects will be randomized (55 per treatment group).

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 document. The vendors identified in the template 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

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATZ	anal transitional zone
eCRF	electronic case report form
CD	Crohn's disease
CGQL	Cleveland Global Quality of Life
CIMS	Central Image Management Solutions
CRA	clinical research associate
CRO	contract research organization
CCI	[redacted]
ECG	electrocardiogram
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ET	early termination
FAP	familial adenomatous polyposis
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
G6PD	glucose-6-phosphate dehydrogenase
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBsAg	hepatitis B virus surface antigen
hCG	human chorionic gonadotropin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
IAC	Independent Adjudication Committee
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IB	Investigator's Brochure
ICH	International Conference on Harmonisation

IEC	independent ethics committee
IgG1	immunoglobulin G1
INR	international normalized ratio
IPAA	ileal pouch anal anastomosis
IPS	irritable pouch syndrome
IRB	institutional review board
IRR	infusion-related reaction
IV	intravenous
IWRS	interactive web response system
JCV	John Cunningham virus
LFT	liver function tests
LTFU	long-term follow-up
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
Med ID	medication identification number
MedDRA	Medical Dictionary for Regulatory Activities
mPDAI	modified Pouchitis Disease Activity Index
PC	product complaint
PD	pharmacodynamics
PDAI	Pouchitis Disease Activity Index
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PP	per-protocol
PTE	pretreatment event
Q8W	once every 8 weeks
RAMP	Risk Minimization Action Plan for PML
CCI	[redacted]
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
CCI	[redacted]
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reactions
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis
ULN	upper limit of normal
WBC	white blood cell
WHODRUG	World Health Organization Drug Dictionary

3.4 Corporate Identification

TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease and Current Treatments for Chronic or Recurrent Pouchitis

The surgical treatment of choice for patients with ulcerative colitis (UC) is removal of the colon followed by construction of an ileal pouch anal anastomosis (IPAA). Inflammation of the "pouch," commonly called pouchitis, is the most common long-term complication in these patients and is characterized by watery, sometimes bloody stool associated with urgency, incontinence, abdominal cramps, malaise, and fever. In addition to these abnormalities, biopsy of the pouch shows chronic inflammatory changes with intense infiltration of both acute and chronic inflammatory cells.

Pouchitis is a poorly understood condition, with a reported cumulative frequency of 23% to 46% over 10 to 11 years in patients who underwent an ileoanal pouch procedure [1, 2]. The etiology of pouchitis is likely multi-factorial. Pouchitis may be due in part to exposure of the ileal mucosa of the pouch to noxious components of feces, such as short chain fatty acids and bile acids, to which it may never be completely adapted. Altered immunoregulation, previously undiagnosed Crohn's disease (CD) affecting the ileum, and ischemia caused by decreased mucosal blood flow may also be involved in the etiology of pouchitis [3].

The clinical response of pouchitis to treatment with antibiotics such as metronidazole or ciprofloxacin, as well as probiotics including *Lactobacilli*, suggests that fecal stasis, *C difficile* infection, bacterial overgrowth, or dysbiosis (altered proportions among fecal bacterial populations) may be triggers. Other therapeutic agents tested for the treatment of pouchitis with mixed success include mesalamine, corticosteroids, nutritional agents (short-chain fatty acids, glutamine, or soluble fiber administered per suppository or enema), immunomodifying agents, cigarettes and transdermal nicotine, bisthmus-containing agents, and allopurinol [3]. Importantly, none of these therapies have been shown to be effective in clinical trials. Furthermore, due to their nonspecific mechanism of action, use of some of these therapies may place patients at risk for infection complications.

Results from 3 clinical trials of the probiotic agent VSL#3 for the primary and secondary prophylaxis of pouchitis have been published [4-6] and showed efficacy around 85% to 90%. However, long-term efficacy in routine care could not be reproduced in another study [7].

While pouchitis usually responds to short-term antibiotic therapy, some patients experience recurrent pouchitis and require chronic antibiotic therapy to sustain remission or the more drastic option of surgical removal of the pouch. Chronic or recurrent pouchitis is often managed with long-term antibiotic administration, with metronidazole and ciprofloxacin being the antibiotics most often prescribed [8]. There are presently no approved drugs for the treatment or prevention of pouchitis in the United States or Europe. Thus, a large unmet medical need exists in the management of refractory pouchitis.

Although many patients respond to antibiotic therapy, there is also evidence to suggest that aberrant regulation of the mucosal immune system might play a part in the pathogenesis of

pouchitis arising from an abnormal mucosal immune response to a dysbiosis of the pouch microbiota [9]. For example, pouchitis rarely occurs in patients with familial adenomatous polyposis (FAP) who have undergone a colectomy with creation of IPAA [10]. There are known genetic risk factors for the development of pouchitis associated with a dysregulation of the mucosal immune system [11]. The interleukin-1 receptor antagonist gene allele 2, tumor necrosis factor gene allele 2, and NOD2/CARD15 polymorphisms have all been associated with pouchitis [12-15].

Herfarth et al conducted a systematic review of the use of biologics in the treatment of pouchitis [16]. Well-controlled clinical studies of tumor necrosis factor-alpha (TNF-α) antagonist therapy in the treatment of pouchitis were not available. However, the available data for infliximab suggests potential clinical effectiveness in the treatment of antibiotic refractory or fistulizing pouchitis. The data for adalimumab are more limited and sufficient long-term outcomes were lacking. There are no published data available related to the efficacy of certolizumab, golimumab, natalizumab, or vedolizumab in patients with antibiotic refractory pouchitis or fistulizing and/or pouch complications [16]. Subjects with pouchitis were excluded from the pivotal phase 3 clinical studies for vedolizumab.

4.1.2 Vedolizumab

Vedolizumab (also called MLN0002) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin mediates lymphocyte trafficking to gastrointestinal (GI) mucosa and gut-associated lymphoid tissue (GALT) through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [17-20]. Vedolizumab binds the $\alpha_4\beta_7$ integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing lymphocytes into GI mucosa. As a result, vedolizumab acts as a gut-selective immunomodulator [21].

Vedolizumab IV (also known as ENTYVIO; KYNTELES; or MLN0002 IV) has been granted marketing approval in several regions, including the United States, European Union, and several other countries worldwide. Vedolizumab IV is approved for the treatment of adult patients with moderately to severely active UC or CD, who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy (corticosteroids, immunomodulators) or a TNF-α antagonist. The approved dosing regimen is 300 mg vedolizumab IV infused intravenously at Weeks 0, 2, and 6, then once every 8 weeks (Q8W) thereafter.

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pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of vedolizumab in healthy subjects and subjects with UC or CD.

4.1.2.1 Nonclinical

No nonclinical studies have been conducted to evaluate vedolizumab specifically for chronic pouchitis in UC.

Nonclinical in vitro and in vivo studies have been conducted with vedolizumab and its murine homologue, Act-1. Act-1 has demonstrated clinical and histomorphologic evidence of efficacy in a cotton-top tamarin model of inflammatory bowel disease (IBD). Extensive nonclinical evaluations of the cardiovascular, acute, local, subchronic, chronic, immunologic, and reproductive toxicity of vedolizumab in pharmacologically responsive species (New Zealand white rabbits and cynomolgus monkeys) have been conducted and support its clinical development. Nonclinical studies also show that vedolizumab does not antagonize $\alpha_4\beta_1$ integrin [21].

4.1.2.2 Human Experience

As of 19 November 2016, approximately 4200 subjects (309 healthy subjects, 1811 subjects with UC, 2138 subjects with CD, 3 subjects undergoing allo-HSCT, 1 subject with pouchitis, and 2 subjects with melanoma) have received at least 1 dose of vedolizumab across completed and ongoing company-sponsored interventional clinical studies (see Investigator's Brochure [IB], Edition 19). Vedolizumab exposure has extended for ≥12 months in 1832 subjects, ≥24 months in 1379 subjects, ≥36 months in 1169 subjects, ≥48 months in 862 subjects, ≥60 months in 645 subjects, ≥72 months in 308 subjects, ≥84 months in 32 subjects, and ≥96 months in 22 subjects. Based on drug shipment data, the global cumulative postmarketing patient exposure to vedolizumab IV globally is estimated to be approximately 77,382 patient-years.

In the 52-week pivotal phase 3 studies (C13006 and C13007), the most common (≥5% and at a higher incidence than placebo) adverse events in subjects administered vedolizumab IV were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most serious adverse events (SAEs) were related to exacerbations or complications of the underlying UC or CD. For those infections that were reported more frequently in vedolizumab-treated subjects, the sites of these infections correlate with the known tissue distribution of MAdCAM-1 binding sites. Anal abscess, abdominal abscess, and gastroenteritis were the most frequently reported serious infections. Extraintestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis) occurred at low frequency (<1%). Concomitant use of corticosteroids and/or conventional immunomodulators did not appear to be associated with any increased rate of infections based on the comparative rates of infections in the phase 3 clinical studies among subjects. One death occurred in a vedolizumab-treated subject during Study C13006 and 5 deaths occurred during Study C13007, including 1 death in a placebo-treated subject. Results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab treatment. No cases of progressive multifocal leukoencephalopathy (PML) were reported in these studies.

Overall, 4% of subjects treated with vedolizumab IV and 3% of subjects treated with placebo experienced a treatment-emergent adverse event (TEAE) defined by the investigator as an infusion-related reaction (IRR). The most frequently observed IRR events in the subjects treated with vedolizumab (by preferred term and reported more than twice) were nausea, headache,

pruritus, dizziness, fatigue, IRR, pyrexia, urticaria, and vomiting. The majority of IRRs were mild or moderate in intensity, and few resulted in discontinuation of study treatment. Observed IRRs generally resolved with no or minimal intervention following the infusion.

Overall, vedolizumab was well tolerated in clinical studies. For additional safety related information from the clinical trials experience, see the current edition of the IB.

4.2 Rationale for the Proposed Study

There are presently no approved drugs for the treatment or prevention of pouchitis in the United States or Europe. Thus, a large unmet medical need exists in the management of pouchitis.

While pouchitis usually responds to short-term antibiotic therapy, approximately 5% to 19% of patients with acute pouchitis develop refractory or rapidly relapsing forms of the disease [22, 23]. Chronic or recurrent pouchitis is often managed with long-term antibiotic administration, with metronidazole and ciprofloxacin being the antibiotics most often prescribed [8]. The disease course of antibiotic-responsive pouchitis may evolve into antibiotic-dependent pouchitis and then antibiotic-refractory pouchitis. In cases where chronic or recurrent pouchitis does not respond to therapy, this may necessitate the drastic option of surgical removal of the pouch.

Although many patients respond to antibiotic therapy, there is also evidence to suggest that aberrant regulation of the mucosal immune system might play a part in the pathogenesis of pouchitis arising from an abnormal mucosal immune response to a dysbiosis of the pouch microbiota [9].

The humanized mAb vedolizumab is effective for induction and maintenance therapy of UC and CD [24-28]. Vedolizumab abrogates the interaction of $\alpha_4\beta_7$ integrin on memory T and B cells with MAdCAM-1 expressed on the vascular endothelium in the gut [19, 20]. MAdCAM-1 levels are elevated in IBD [19]. This mechanism of action suggests that vedolizumab may be effective in the treatment of other chronic inflammatory diseases of the GI tract, such as chronic or recurrent pouchitis. It is hypothesized that vedolizumab IV will effectively and safely achieve clinically relevant remission in subjects with chronic or recurrent pouchitis. This study will establish whether vedolizumab IV may be an effective therapy for chronic or recurrent pouchitis.

4.3 Benefit-Risk Assessment

The proposed study (Vedolizumab-4004) is designed to evaluate the efficacy and safety of vedolizumab IV in the treatment of adult subjects with chronic or recurrent pouchitis. Currently, no drugs have been approved in the United States or Europe for the treatment or prevention of pouchitis, indicating that a high unmet medical need exists for this patient population.

Inhibition of the interaction of the $\alpha_4\beta_7$ integrin on memory T and B cells with MAdCAM-1 expressed on the vascular endothelium in the gut may be effective in the treatment of chronic inflammatory diseases of the GI tract, such as chronic or recurrent pouchitis. All subjects will receive concomitant antibiotic treatment with ciprofloxacin 500 mg twice daily through Week 4. Additional courses of antibiotics will be allowed, as needed, for flares after Week 14.

The dosing and administration regimen of vedolizumab are consistent with the approved vedolizumab IV label. The proposed protocol will include safety measures similar to those conducted in the vedolizumab IV UC and CD clinical programs, including sufficient safety measures, evaluations, and discontinuation criteria to assure safety in the individual subjects in the planned study.

Overall, vedolizumab IV has been well tolerated in clinical studies and the benefit-risk profile is positive.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to compare the efficacy of vedolizumab IV to placebo in terms of the percentage of subjects with chronic or recurrent pouchitis achieving clinically relevant remission

5.1.2 Secondary Objectives

The secondary objectives are to assess the efficacy of vedolizumab IV by:

- Percentage of subjects achieving mPDAI <5 and a reduction of overall score by ≥2 points from Baseline mPDAI.
- Percentage of subjects achieving PDAI <7 and a reduction of overall score by ≥3 points from Baseline PDAI.
- Time to remission (defined as a PDAI score <7 and a decrease in PDAI score of ≥3 points from Baseline).
- Percentage of subjects achieving a partial response (defined as reduction mPDAI score by ≥2 points from Baseline).
- Change in PDAI endoscopic subscore.
- Change in PDAI histologic subscore.
- Change in total PDAI.
- Change in Inflammatory Bowel Disease Questionnaire (IBDQ), and Cleveland Global Quality of Life (CGQL, Fazio Score, 3 items).

5.1.3 Exploratory Objectives

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[redacted]

5.1.4 Safety Objective

The safety objective is to assess the safety of vedolizumab IV in chronic or recurrent pouchitis.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary efficacy endpoint is the percentage of subjects with chronic or recurrent pouchitis achieving clinically relevant remission after 14 weeks of treatment. Clinically relevant remission is defined as an mPDAI score <5 and a reduction of overall score by ≥2 points from Baseline.

5.2.2 Secondary Endpoints

Secondary efficacy endpoints are:

- Percentage of subjects achieving an mPDAI score <5 and a reduction of overall score by ≥2 points from Baseline after 34 weeks of treatment (last dosing at Week 30).
- Percentage of subjects achieving PDAI score <7 and a reduction of overall score by ≥3 points from Baseline PDAI score after 14 weeks of treatment and after 34 weeks of treatment (last dosing at Week 30).
- Time to remission (defined as a PDAI score <7 and a decrease in PDAI score of ≥3 points from Baseline).
- Percentage of subjects achieving a partial response (defined as reduction in mPDAI score by ≥2 points from Baseline) after 14 and after 34 weeks of treatment (last dosing at Week 30).
- Change in PDAI endoscopic subscore at Weeks 14 and 34 compared to Baseline.
- Change in PDAI histologic subscore at Weeks 14 and 34 compared to Baseline.
- Change in total PDAI score at Weeks 14 and 34 compared to Baseline.
- Change in IBDQ, and CGQL (Fazio Score, 3 items) at Weeks 14, 22, and 34 compared to Baseline.

5.2.3 Exploratory Endpoints

CCI

[redacted]

CCI

5.2.4 Safety Endpoints

Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs), SAEs, vital signs, and results of standard laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

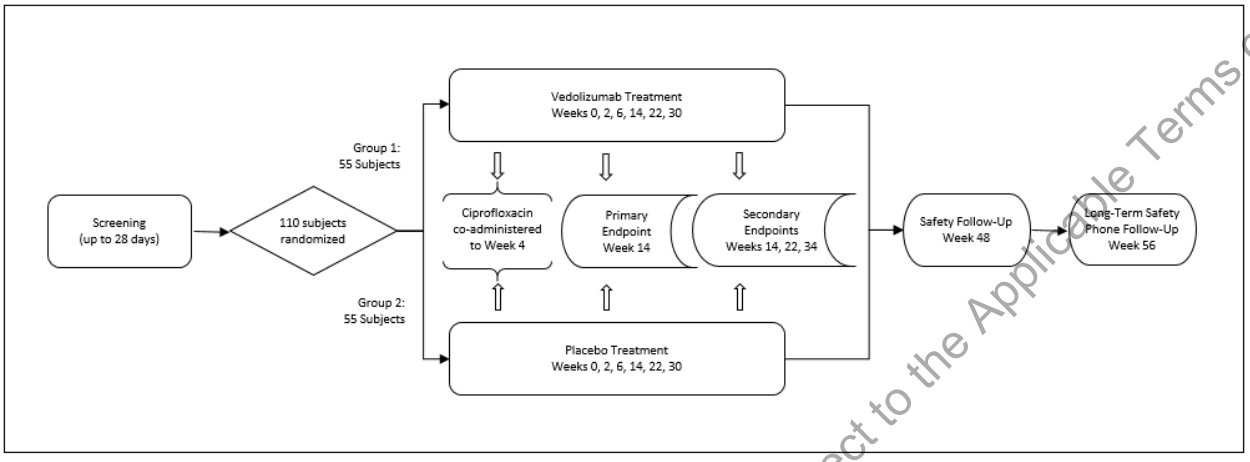
This is a phase 4, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vedolizumab IV 300 mg over a 34-week treatment period (with the last dose at Week 30) in subjects with a proctocolectomy and IPAA for UC who have developed chronic or recurrent pouchitis.

Approximately 110 adult subjects with chronic or recurrent pouchitis will be randomized to this study. Subjects must have developed chronic or recurrent pouchitis, defined as a modified Pouchitis Disease Activity Index (mPDAI) score ≥5 assessed as the average from 3 days immediately prior to the Baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either (a) ≥3 recurrent episodes within 1 year prior to the Screening visit, each treated with ≥2 weeks of antibiotic or other prescription therapy, or (b) requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately prior to the Baseline Endoscopy Visit.

After the Screening Period of up to 28 days, subjects will be randomized at Day 1 in a 1:1 ratio to either vedolizumab IV or placebo treatment. Subjects will receive their assigned infusion (vedolizumab or placebo) at Day 1, Weeks 2, 6, 14, 22, and 30 (final dose). All subjects will receive concomitant antibiotic treatment with ciprofloxacin 500 mg twice daily through Week 4. Additional courses of antibiotics will be allowed, as needed, for flares after Week 14. Final efficacy assessments will be measured 4 weeks after the last study dose (Week 34). Additional safety follow-ups will occur 18 weeks after the last study dose (Week 48) and subjects will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 26 weeks after the last dose of study drug (Week 56).

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

In 1310 patients who had an IPAA for chronic UC, 559 patients had at least 1 episode of pouchitis. Approximately 70% of those patients who had at least 1 attack of pouchitis had a second episode [29]. There are currently no approved drugs for the treatment of chronic or recurrent pouchitis. Chronic pouchitis is often managed with long-term antibiotic administration; however, long-term antibiotic use can lead to antibiotic resistance. The treatment of antibiotic refractory pouchitis is also often challenging. While a prolonged course of combined antibiotic agents is often used, maintenance of remission in this group of patients after induction treatment with combined antibiotics remains challenging and represents an unmet need [30]. Existing data suggests infliximab may be clinically effective for antibiotic-refractory pouchitis, but well-controlled studies are not presently available for any TNF-α antagonist therapies [16]. The mechanism of action of vedolizumab suggests that it may be effective in the treatment of chronic inflammatory diseases of the GI tract, such as pouchitis. Based on these considerations it is proposed that vedolizumab IV may be efficacious in achieving disease remission in the study population defined.

Since there are no approved drugs for chronic or recurrent pouchitis, the placebo-controlled design was selected. The dose and administration regimen selected for the vedolizumab IV treatment group is consistent with the approved label for UC [31, 32].

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 (ET) 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 vedolizumab, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- At the futility analysis, if the probability of success does not meet the pre-determined futility threshold and the study is stopped for futility at this point.

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 an study site, a study-specific procedure for ET 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 SUBJECTS

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

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is male or female and aged 18 to 80 years, inclusive.
4. The subject has a history of IPAA for UC completed at least 1 year prior to the Day 1 (Randomization) Visit.
5. The subject has pouchitis that is chronic or recurrent, defined by an mPDAI score ≥5 assessed as the average from 3 days immediately prior to the Baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either (a) ≥3 recurrent episodes within 1 year prior to the Screening Period treated with ≥2 weeks of antibiotic or other prescription therapy, or (b) requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately prior to the Baseline Endoscopy Visit
6. The subject agrees to take ciprofloxacin (500 mg twice daily) on Day 1 and through Week 4, regardless of the previous treatment and to stop any previous antibiotic therapy on Day 1 of the study. (Additional courses of antibiotics will be allowed, as needed, for flares after Week 14.)
7. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use a barrier method of contraception (eg, condom with spermicide)* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose. The female partner of a male subject should also be advised to use a highly effective method of contraception*.
8. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use a highly effective method of contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.

*Definitions and highly effective methods of contraception are defined in Section 9.1.21 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.22 Pregnancy.

7.2 Exclusion Criteria

The exclusion criteria are divided into 3 categories: GI exclusion criteria, infectious disease exclusion criteria, and general exclusion criteria. Subjects meeting any of the following criteria will not qualify for entry into the study:

7.2.1 Gastrointestinal Exclusion Criteria

1. The subject has CD or CD of the pouch. Subjects will be excluded if the investigator suspects, on the basis of the screening endoscopy, that the pattern of inflammation may be due to CD.
2. The subject has irritable pouch syndrome (IPS).
3. The subject has isolated or predominant cuffitis.
4. The subject has mechanical complications of the pouch (eg, pouch stricture or pouch fistula).
5. The subject currently requires or has a planned surgical intervention for UC during the study.
6. The subject has diverting stoma.

7.2.2 Infectious Disease Exclusion Criteria

1. The subject has evidence of an active infection (eg, sepsis, cytomegalovirus, or listeriosis) during Screening.
2. The subject has active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following:
   a) A diagnostic TB test performed within 30 days of Screening or during the Screening Period that is positive, as defined by:
      i. A positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests ***OR***
      ii. A tuberculin skin test reaction ≥10 mm (≥5 mm in subjects receiving the equivalent of >15 mg/day prednisone) ***OR***
   b) Chest X-ray within 3 months prior to Day 1 that is suspicious for pulmonary TB, and a positive or 2 successive indeterminate QuantiFERON test within 30 days prior to Screening or during the Screening Period.

      Note: if the subject has a negative diagnostic TB test documented in the previous 3 months, screening testing does not need to be repeated provided subject has no risk factors for exposure.
3. The subject has chronic hepatitis B virus (HBV) infection* or chronic hepatitis C virus (HCV) infection** or a known history of human immunodeficiency virus (HIV) infection (or is found to be seropositive at Screening) or subject is immunodeficient (eg, due to organ transplantation, history of common variable immunodeficiency, etc).

   * Subjects who are positive for hepatitis B virus surface antigen (HBsAg) will be excluded. For subjects who are negative for HBsAg but are positive for either surface antibodies and/or core antibodies, HBV DNA polymerase chain reaction will be performed and if any test result meets or exceeds detection sensitivity, the subject will be excluded.
   ** If subject is HCV antibody positive, then a viral load test will be performed. If the viral load test is positive, then the subject will be excluded.
4. The subject has evidence of **active** infection with *C difficile* during Screening (to be confirmed by laboratory test).

7.2.3 General Exclusion Criteria

1. The subject has any prior exposure to vedolizumab, natalizumab, efalizumab, rituximab, etrolizumab, or anti-MAdCAM-1 therapy.
2. The subject has a history of hypersensitivity or allergies to vedolizumab or its components.
3. The subject has allergies to and/or contraindications for ciprofloxacin, a history of tendon disorders related to quinolone administration and/or glucose-6-phosphate dehydrogenase (G6PD) deficiency. Further conditions requiring precautions for use of ciprofloxacin have to be considered based on local prescribing information.
4. The subject is taking, has taken, or is required to take any excluded medications (as listed in Section 22).
5. The subject has received any investigational or approved biologic or biosimilar agent within 60 days prior to Randomization
6. The subject has received an investigational nonbiologic therapy within 30 days prior to Randomization.
7. The subject has received an approved nonbiologic therapy (including 5-aminosalicylate [5-ASA], corticosteroid, azathioprine, 6-mercaptopurine [6-MP], etc.) in an investigational protocol within 30 days prior to Randomization.
8. The subject has received any live vaccinations within 30 days prior to randomization.
9. The subject has a positive PML subjective symptom checklist at Screening.
10. *[Previous criterion #10 incorporated into criterion #3 in amendment number 3*].
11. The subject has had a kidney, heart, or lung transplant.
12. *[Previous criterion #12 deleted in amendment number 3*].
13. The subject has a history of malignancy, except for the following: adequately-treated nonmetastatic basal cell skin cancer; squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to the Screening visit; and history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to Screening. Subjects with a remote history of malignancy (eg, >10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the sponsor on a case-by-case basis prior to enrollment.
14. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, demyelinating, or neurodegenerative disease.
15. The subject has conditions which, in the opinion of the investigator, may interfere with the subject's ability to comply with the study procedures.
16. The subject has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurologic,

or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise subject safety.

17. The subject has any of the following laboratory abnormalities during the Screening Period:
    i. Hemoglobin level <8 g/dL.
    ii. White blood cell (WBC) count $<3 \times 10^9$/L.
    iii. Lymphocyte count $<0.5 \times 10^9$/L.
    iv. Platelet count $<100 \times 10^9$/L or $>1200 \times 10^9$/L.
    v. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN).
    vi. Alkaline phosphatase >3 × ULN.
    vii. Serum creatinine >2 × ULN.
18. If female, the subject is pregnant or lactating or intending to become pregnant or nurse before, during, or within 18 weeks after the last dose of study drug; or intending to donate ova during such time period.
19. If male, the subject intends to donate sperm or father a child during the course of this study or for 18 weeks after the last dose of study drug.
20. The subject 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 subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening.
22. *[Previous criterion #22 incorporated into criterion #3 in amendment number 3*].

7.3 Excluded Medications

The following medications are excluded from use during the study until Week 34 unless specified otherwise:

1. Any treatment for pouchitis other than those listed below in Section 7.3.1 (either approved or investigational).
2. Antibiotic therapy for pouchitis from Week 4 through Week 14 of the study. (Antibiotics will be allowed after Week 14, as needed, for flares.)
3. Tizanidine, methotrexate, and zolpidem from Randomization to Week 4 (contraindication to ciprofloxacin)
    – Several drugs might interfere with ciprofloxacin when administered concomitantly. Use with caution or monitoring (especially drugs metabolized by CYP1A2) may be required (as detailed in local prescribing information).

4. Oral corticosteroids for pouchitis, except as described in Section 7.3.1.1.
5. Within 30 days prior to Randomization and throughout study until Week 34, any of the following for the treatment of pouchitis:
   - Nonbiologic therapies (eg, cyclosporine, thalidomide) other than those specifically listed in Section 7.3.1.
   - An investigational nonbiologic therapy.
   - An approved nonbiologic therapy in an investigational protocol.
6. NSAIDS (if used continuously for ≥2 weeks) within 30 days prior to Randomization (Day 1) and throughout the study until Week 34
   - Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgia, menstrual cramps etc. and daily use of low dose (≤100 mg acetylsalicylic acid for cardiovascular prophylaxis are permitted).
7. Any investigational or approved biologic or biosimilar agent within 60 days prior to Randomization (Day 1) and throughout the study until Week 34.
8. All live vaccines within 30 days prior to randomization, throughout the study treatment period and for at least 6 months after the last dose of study drug.
9. Either approved or investigational biologic agents for the treatment of non-IBD conditions, other than localized injections (eg, intra-ocular injections for wet macular degeneration).
10. Rectal products (enemas and suppositories including 5-ASA and corticosteroids) within 15 days prior to Randomization (Day 1) and throughout the study until Week 34.

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

7.3.1 Permitted Medications and Treatments

The following medications for pouchitis are permitted during the study:

1. Ciprofloxacin (500 mg twice daily for 4 weeks, starting at Randomization) is mandatory therapy in this study. If subjects are receiving other antibiotics at Randomization, they will be switched to ciprofloxacin and continue on this for the first 4 weeks of the study.
2. Additional antibiotics will be allowed, as needed, for flares after Week 14.
3. Oral 5-ASA if taken at a stable dose for at least 2 weeks prior to randomization and throughout the study until Week 34.
4. Anti-diarrheals for control of **chronic** diarrhea, with stable dose for at least 2 weeks prior to Randomization and throughout the study until Week 34.
5. Antibiotic therapy for pouchitis if taken before Screening should be kept at a stable dose for 2 weeks prior to Randomization.

6. Oral corticosteroid therapy for pouchitis if taken at a stable dose for at least 4 weeks prior to Randomization and with mandatory tapering after Week 4 (Visit 4) of the study as described in Section 7.3.1.1.
7. Probiotics (eg, *Saccharomyces boulardii)* and/or immunomodulators (azathioprine, 6-MP), if taken at a stable dose for at least 8 weeks prior to Randomization and throughout the study until Week 34.

7.3.1.1 Oral Corticosteroid Dosing and Tapering

The maximum dose of oral corticosteroids for the treatment of pouchitis that may be co-administered with vedolizumab IV is 20 mg/day prednisone or 9 mg/day budesonide or 5 mg/day beclomethasone dipropionate (or equivalent) as long as they have been used at a stable dose for at least 4 weeks prior to Randomization.

It is required that subjects receiving oral corticosteroids begin a tapering regimen by Week 4 (Visit 4) of the study. Tapering should be finished by Week 8, if possible.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.23.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires ET because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

   - Liver Function Test (LFT) Abnormalities.

     Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.17), 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%).

   - Leukopenia or lymphopenia: WBC and lymphocyte counts will be monitored for all subjects. Azathioprine, 6-MP, if applicable, should be discontinued and the dose of vedolizumab held for an absolute lymphocyte count $<0.5\times10^9$/L at any point in the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of vedolizumab can be administered only if the absolute

lymphocyte count is $\geq 0.5\times10^9$/L. If the absolute lymphocyte count remains $<0.5\times10^9$/L, study drug should be discontinued and the subject withdrawn from the study.

2. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes 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 should not be recorded in the *voluntary withdrawal* category. Similarly, lack of efficacy should not be recorded in the *voluntary withdrawal* category).
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.22.
7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.
8. Other.

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

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the ET Visit and post-treatment follow-up visit and safety phone call (18 and 26 weeks post-treatment). Discontinued or withdrawn subjects will not be replaced. Refer to Section 9.3.9 for appropriate Post-Study Care procedures.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication 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 clinical trial material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Vedolizumab IV and Placebo

The study sites will be supplied by the sponsor with the following medication in an open-label manner: vedolizumab IV 300 mg/vial, for single use, in 20 mL vials. The study drug will be provided in a glass vial as a lyophilized solid for reconstitution using 4.8 mL of sterile water for injection and further dilution (5.0 mL) in 250 mL of sterile 0.9% sodium chloride. Each vial will be packaged in an appropriately labeled single vial carton.

The placebo infusion will be 250 mL of commercially available sterile 0.9% sodium chloride provided by the clinical study center. For both active vedolizumab and placebo infusions, the unblinded investigational pharmacist or designee will mask the IV bags after preparation in order to maintain the study blind.

Additional reference information and administration instructions can be found in the pharmacy manual.

8.1.1.2 Companion Medication

Treatment with ciprofloxacin is required per protocol from Day 1 until Week 4 (Visit 4). Ciprofloxacin 500 mg twice daily must be prescribed by the investigator as per the local label. Ciprofloxacin will not be provided by the sponsor but will be reimbursed.

8.1.2 Storage

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study 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.

8.1.3 Dose and Regimen

The study drug regimen for both randomized groups is provided in Table 8.a. The vedolizumab IV or placebo/sodium chloride infusion will be administered intravenously over 30 minutes. Instructions for reconstitution and blinded administration will be provided in the pharmacy manual. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion.

All subjects will receive the antibiotic ciprofloxacin from Day 1 through Week 4 (Visit 4).

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description
1	300 mg vedolizumab IV	IV infusion with vedolizumab at Weeks 0, 2, 6, 14, 22, 30
2	0.9% sodium chloride (250 mL)	IV infusion with placebo at Weeks 0, 2, 6, 14, 22, 30

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject 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 this 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 in addition be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

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

8.2 Study Drug Assignment and Dispensing Procedures

The investigator or the investigator's designee will access the interactive web response system (IWRS) at Screening to obtain the study-specific subject identification number (subject number). The investigator or the investigator's designee will utilize the IWRS to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening. At drug-dispensing visits, the investigator or designee will again contact the IWRS to register the visits. At Day 1, Weeks 2, 6, 14, 22, and 30 for all subjects in both treatment groups, the IWRS will provide email notification to the unblinded site pharmacist/nurse. If the subject is randomized to vedolizumab IV, a medication identification number (Med ID) will be assigned by IWRS and provided to the unblinded site pharmacist/nurse by email notification. If the subject was randomized to receive placebo, the IWRS will provide email notification to the unblinded site pharmacist/nurse, but no Med ID will be assigned. To maintain the blind the IWRS will ensure the investigator or designee is unaware if a Med ID has been assigned or not. If sponsor-supplied drug (active vials) is lost or damaged, the site can request a replacement from IWRS by the unblinded site pharmacist/nurse. Refer to IWRS manual provided separately.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel. Subjects will be randomized in a 1:1 ratio to either vedolizumab or placebo treatment using an IWRS. Randomization will be stratified to achieve equal distribution of patients using maintenance antibiotic therapy at a stable dose for at least 4 weeks prior to randomization and those having had at least 3 episodes of pouchitis despite treatment (with pulse antibiotics or other prescription therapy) during the 1 year prior to baseline endoscopy.

8.4 Drug Blind Maintenance

The study drug blind will be maintained using the IWRS. All subjects and study personnel except for those directly involved with study drug preparation will be blinded to study drug assignment for the entire study. In order to maintain the blind, unblinded individuals preparing study drug will cover the product in a blinding bag prior to dispensing. All unblinded dosing information must be maintained in a secured area, accessible only by unblinded personnel, and separate from blinded information.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

The investigator can perform emergency unblinding using the IWRS, if medically necessary. In all scenarios, the sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel (with the exception of the dispensing pharmacist or unblinded site pharmacy personnel/nurse) are unblinded, study drug must be stopped immediately, and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator and investigator's designated site pharmacy must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (vedolizumab IV), the investigator pharmacy must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the designated site pharmacy must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, designated site pharmacy personnel should acknowledge the receipt of the shipment by signing bottom half of the

packing list and by recording in IWRS. 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's designated site pharmacy 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:

- Monitoring expiration dates (monitored via IWRS).
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the drug accountability log is completed for the Medication ID 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 IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator's designated site pharmacy must record the current inventory of all sponsor-supplied drugs (vedolizumab IV) 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, expiry date and amount dispensed, and amount returned to the pharmacy (if applicable) including initials, seal, or signature of the person dispensing the drug. The log should include all required information as a separate entry for each subject (by subject identifier) to whom sponsor-supplied drug is dispensed.

The investigator's designated site pharmacy staff must complete an individual subject accountability log to document if infusion was complete or if incomplete and study drug was returned to the pharmacy, including the date and amount returned to the pharmacy, including the initials, seal, or signature of the person administering the infusion. Only unblinded designated site pharmacy personnel and unblinded clinical research associates (CRAs) can perform drug accountability and only unblinded designated site pharmacy staff and unblinded clinical CRAs can process drug returns in order to preserve blinding.

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, subjects 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 process are described in Section 15.2 and Appendix C.

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

A unique subject identification number (subject number) will be assigned to each subject through the IWRS system at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age, sex, Hispanic ethnicity (as applicable), race as described by the subject, height, weight, and smoking/nicotine usage status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.16).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 60 days prior to signing of informed consent.

In addition, all prior medication history for the treatment of UC/pouchitis, with the reason for discontinuation, is to be collected for subjects where possible.

9.1.3 Ulcerative Colitis and Pouchitis History

UC history will include details of UC diagnosis, disease severity, surgery including IPAA date, hospitalizations, and extraintestinal manifestations.

9.1.4 Physical Examination Procedure

A Visit 1 (Screening) physical examination 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 (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment performed prior to first dose of study drug.

9.1.5 Weight, Height

A subject 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.

9.1.6 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, supine blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (resting more than 5 minutes).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained at least 0.5 hours before or after the scheduled blood draw.

9.1.7 PML Checklist

Site staff will administer the subjective PML checklist during Screening to exclude subjects 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 A, to evaluate symptoms suggestive of PML. Any subjects reporting signs or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation. The symptoms from a positive PML checklist obtained after randomization will be recorded as an AE. Additional information and tools will be found in the Investigator Site File.

9.1.8 ECG Procedure

A standard 12-lead electrocardiogram (ECG) will be recorded. 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. A copy of the ECG trace should be kept with the subject's notes.

9.1.9 Primary Efficacy Measurement

The primary efficacy measure is having achieved clinically relevant remission after 14 weeks of treatment. Clinically relevant remission will be defined as a mPDAI score <5 and a decrease in mPDAI score of ≥2 points from Baseline.

9.1.10 Pouchitis Endoscopy

Endoscopy will be performed at Screening (baseline endoscopy), Week 14, and Week 34.

All study endoscopies will be video-recorded using the Robarts Central Image Management Solutions (CIMS). All study videos will be subject to central review to ensure consistent grading. Central reviewer's assessment will stand as final assessment for eligibility, if different from the site's.

Central reviewers will score endoscopic findings by using a defined list of descriptors defined in the Endoscopy Image Review Charter. These include the mPDAI/PDAI descriptors. Additionally, CCI , number of ulcers (total, aphthous, and non-aphthous), and proportion of surface area

ulcerated (excluding aphthous ulcers) in the pouch will be scored for Screening, Week 14, and Week 34/Early Termination videos.

At each endoscopy, a total of 4 to 5 pieces of biopsy will be obtained from the distal, mid, and proximal pouch body. Biopsies will be assessed for the presence of inflammation by trained, central histopathologists. Work Instructions will detail the requirements for study endoscopy, biopsy and histopathology. Subject preparation for endoscopy should follow the site's usual clinical practice (such as phosphate enema or polyethylene glycol).

9.1.11 PDAI

The PDAI was developed as an objective, and quantitative criteria for pouch inflammation after IPAA. The 18-point overall score is calculated from 3 separate 6-point scales based on clinical symptoms (0 to 6), endoscopic findings (0 to 6) and histologic changes (0 to 6). The PDAI incorporates histologic features of acute inflammation, along with symptom and inflammation on endoscopy, and establishes a cutoff of 7 for differentiation between 'pouchitis' (≥7 points) and 'no pouchitis' (<7 points) [33]. See Appendix E.

Clinically relevant remission in this study is defined as a PDAI score <7 and a reduction of ≥3 points compared to Baseline.

Although the standard PDAI remains an optimal way to diagnose pouchitis, the mPDAI, consisting of symptom and endoscopy scores from the PDAI but omitting histology scores, offers similar sensitivity and specificity in diagnosing patients with acute or acute relapsing pouchitis. A cutoff of 5 differentiates patients with pouchitis (mPDAI ≥5) from patients without pouchitis (mPDAI <5) [34]. See Appendix F.

Clinically relevant remission in this study is defined as an mPDAI score <5 and a reduction of ≥2 points from Baseline.

A partial response is defined as a reduction of mPDAI score of ≥2 points from Baseline.

The clinical part of the PDAI score (patient reported symptoms) will be assessed as the average from the 3 days immediately prior to Baseline endoscopy (or bowel preparation for endoscopy). Recording will be facilitated by a paper diary.

CCI

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[redacted]

9.1.14 Patient Reported Outcome Measures

Subjects will complete the IBDQ and the CGQL quality of life questionnaires at the time points specified in the schedule of events (Appendix A).

9.1.14.1 IBDQ

The IBDQ is a valid and reliable [37-39] instrument used to assess quality of life in adult patients with IBD. It includes 32 questions on 4 domains of Health-Related Quality-of-Life (HRQOL): Bowel Systems (10 items), Emotional Function (12 items), Social Function (5 items), and Systemic Function (5 items). Subjects are asked to recall symptoms and quality of life from the last 2 weeks and rate each item on a 7-point Likert scale (higher scores equate to higher quality of life). A total IBDQ score is calculated by summing the scores from each domain; the total IBDQ score ranges from 32 to 224. See Appendix I.

9.1.14.2 Cleveland Global Quality of Life (CGQL) Instrument (Fazio Score)

The CGQL (Fazio Score) was developed as a quality-of-life indicator specifically for patients with ileal pouch-anal anastomosis [40]. Subjects rate 3 items (current quality of life, current quality of health, and current energy level), each on a scale of 0 to 10 (0, worst; 10, best). The scores are added, and the final CGQL utility score is obtained by dividing this result by 30 [40].

Fazio score will be assessed as the average from 3 days immediately prior to endoscopy (or bowel preparation for endoscopy). Recording will be facilitated by a paper diary.

9.1.15 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 subject over the counter. Concomitant medication is not provided by the sponsor (including ciprofloxacin). At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through Week 48), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.16 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, ECG, or physical examination abnormalities noted at Screening/baseline examination, according to the judgement of the investigator. The condition (ie, diagnosis) should be described as current on the Medical History eCRF.

9.1.17 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 20 mL, and the approximate total volume of blood for the study is 75 mL. Details of these procedures, specimen handling and required safety monitoring will be given in the laboratory manual.

Table 9.a Clinical Laboratory Tests

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

Other:		
HIV Hepatitis panel, including HBsAg and anti-HCV		
Serum	**Urine**	**Stool**
QuantiFERON for TB CRP	hCG (for pregnancy in female subjects of childbearing potential only)	Fecal calprotectin
beta hCG (for pregnancy in female subjects of childbearing potential only) FSH, if menopause is suspected (Screening visit only)		*C difficile*

*WBC differential to include lymphocytes, monocytes, basophils, eosinophils, and neutrophils.
FSH =follicle-stimulating hormone, GGT= γ-Glutamyl transferase, hCG =human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells.

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

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

(Please refer to Section 7.4 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the 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 subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

CCI [redacted]

9.1.19 *Clostridium Difficile* Sample Collection

A stool sample will be collected during Screening for the analysis of *C difficile*.

9.1.20 Tuberculosis Screening

All subjects will complete TB screening to determine eligibility as described in Section 7.2.2, unless a negative test result is available from within 3 months prior to Screening and subject has no risk factors for exposure. All subjects must complete a diagnostic test during Screening either a QuantiFERON test or a tuberculin skin test. Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history.

9.1.21 Contraception and Pregnancy Avoidance Procedure

9.1.21.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study drug, nonsterilized** male subjects 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. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below.

9.1.21.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (from the list below).

In addition, they must be advised not to donate ova during this period.

9.1.21.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential (ie, fertile) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (ie, younger than age 45) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those that, alone or in combination, result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
    - Non-hormonal methods:
        - Intrauterine device (IUD).
        - Bilateral tubal occlusion.
        - Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success).
    - Hormonal methods:
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
            - Oral.
            - Intravaginal (eg, ring).
            - Transdermal.
        - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter until she has been on contraceptive for 3 months;

- Oral.
- Injectable.
- Implantable.

2. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
3. Subjects will be provided with information on highly effective methods of contraception as part of the subject 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.
4. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a. Contraceptive requirements of the study.
   b. Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   c. Assessment of subject compliance through questions such as:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")?
      iv. Is there a chance you could be pregnant?
5. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses) and a negative urine hCG pregnancy test prior to receiving each IV dosing.

9.1.21.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- Assessment of subject compliance through questions such as:
    - Have you used the contraception consistently and correctly since the last visit?
    - Have you forgotten to use contraception since the last visit?
    - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
    - Is there a chance you could be pregnant?

9.1.22 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and sponsor-supplied treatment should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 18 weeks after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug, eg, after Visit 1 or within 18 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug including placebo will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.23 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible, the investigator should complete the eCRF. The IWRS should be contacted as a notification of screen failure.

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

1. PTE/AE.
2. Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
3. Significant protocol deviation.
4. Lost to follow-up.
5. Voluntary withdrawal (specify reason).
6. Study termination.
7. Other, specify.

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.24 Documentation of Randomization

Randomization will be performed through the IWRS system. Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

9.2 Monitoring Subject Treatment Compliance

A study drug dispensing log, including records of drug received from the sponsor and volume of vedolizumab dispensed to each subject intravenously, will be maintained by the site.

If a subject is persistently noncompliant with the study drug, it may be appropriate to withdraw the subject from the study.

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

Subjects will be screened within 28 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.23 for procedures for documenting screening failures.

Procedures to be completed at Screening (Visit 1) can be found in the Schedule of Study Procedures (Appendix A).

9.3.2 Rescreening

Automatic rescreening of a subject is not allowed. If the principal investigator believes in the appropriateness of the subject 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 permitted. Rescreening can be done only once for a patient.

There is a minimum of 28 days from initial screening before rescreening can be done.

If *C difficile* eradication is done, a minimum of 28 days after end of therapy is required before rescreening.

All inclusion and exclusion criteria must be met again at Randomization.

If a patient was randomized, no rescreening or re-enrollment is possible.

9.3.3 Study Randomization

Randomization will take place on Day 1. The Day 1 procedures are documented in Appendix A.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IWRS as described in Section 8.2. Subjects will be instructed on when the first dose of study drug will be given as described in Section 8.1.3. The procedure for documenting Screening failures is provided in Section 9.1.23.

9.3.4 End of Treatment Visit

The End of Treatment (EOT) Visit will be performed at Week 30.

9.3.5 Final Endoscopy Visit or Early Termination

The Final Endoscopy Visit will be performed at Week 34 or at ET.

For all subjects receiving study drug, the investigator must complete the End of Study (EOS) eCRF page.

9.3.6 Safety Follow-Up Visit

Follow-up will begin the first day after the Final Endoscopy Visit or Early Termination Visit and will continue for 18 weeks post-treatment until Week 48. If subject is male or subject is postmenopausal and cannot attend the site for this visit, the visit may be conducted via phone.

9.3.7 Post-Study Follow-Up

Upon completion of or early termination from the study, all subjects will complete a LTFU safety survey by telephone. This questionnaire will be administered at 26 weeks after the last dose of study drug.

9.3.8 Unscheduled Visits Due to Exacerbation/Relapse of Pouchitis

Subjects 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:

1. Physical examination.
2. Urine pregnancy test (for females of childbearing potential).
3. Clinical chemistry and hematology, if indicated.

4. Concomitant medications.
5. AE/SAE assessment.

9.3.9 Post-Study Care

Vedolizumab IV will not be supplied upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

Subject to applicable laws and feasibility and Takeda's decision, access to the study drug may be available to individual subjects for whom no standard therapy exists, and the subject is at risk of significant morbidity or mortality.

10.0 PRETREATMENT EVENTS (PTE) AND ADVERSE EVENTS (AE)

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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 Product Complaints

A product complaint (PC) is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product and/or device (eg, prefilled syringe).

An investigator who is made aware of or identifies a potential PC should immediately report the event to Takeda in accordance with the contact list provided to the site. Whenever possible, the associated product should be maintained in accordance with the instructions pending further guidance from a Takeda representative.

10.1.4 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 preexisting 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 subject 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 subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE 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 subject 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.

Worsening of PTEs or AEs:

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

- If the subject 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 /Serious PTEs:

- If the subject 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 subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject'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.

10.1.5 SAEs

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 subject 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. Is 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 subject 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

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).

10.1.6 AEs of Special Interest

An AESI (serious or nonserious) is an AE 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 for this compound are serious infections including opportunistic infection such as PML, liver injury, malignancies, infusion-related or systemic reactions and hypersensitivity, as described in further detail below.

Injection and/or Infusion Site Reactions and Hypersensitivity

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; hence such

premedications are unlikely to be necessary or beneficial. At the discretion of the investigator, however, subjects may be administered premedication prior to any study drug administration. Corticosteroids, if given as a premedication, should be limited to the day of administration.

Vedolizumab IV should be administered by a health care practitioner prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measure should be available for immediate use. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion.

Subjects and caregivers will be instructed to report the development of rash, hives, pruritus, flushing, urticaria, injections site pain, redness, and/or swelling, etc. that may represent an administration-related reaction (ie, infusion-related reaction) to study drug. Subjects will be asked to report administration-related AEs to the sites immediately as they are experienced. Appropriate treatment and follow-up will be determined by the investigator. If signs or symptoms of an administration-related reaction are observed during the administration of study drug, it should be immediately discontinued and the subject treated as medically appropriate. In the case of a mild reaction, study drug administration may be reinitiated (with appropriate premedication and investigator supervision) at the discretion of the investigator. Subjects with a severe or serious administration-related reaction (eg, shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs, severe injection site reactions) must be withdrawn from the study (see Investigator Site File).

In all cases of administration-related reaction, the medical monitor must be informed as soon as practical. The disposition of subjects with less severe administration-related reactions should be discussed with the medical monitor.

Serious Infections

Subjects will be monitored for signs and symptoms of infection and for lymphopenia during the study. Subjects with signs and symptoms suggestive of infections, including GI infections, will be treated as clinically indicated. Interventions may include antibiotic treatment, if appropriate and/or discontinuation of concomitant immunomodulators. Blood, sputum, urine, and/or stool cultures should be obtained as appropriate for the detection and diagnosis of infection. Withholding or terminating study drug administration may be considered as described in Section 7.4.

Malignancies

All cases of malignancies that are detected during the study will be reported as AEs. Local medical practices for the management of malignances will apply. Subjects with history of malignancy (except for specific cancers) or at high risk for malignancy will be excluded from the study per the exclusion criteria.

Other

Other special interest AEs include liver injury and PML, which are discussed in Sections 10.2.3 and 11.2.1, respectively.

10.1.7 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 subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.8 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.

10.1.9 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.

10.1.10 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator, and the time, if available.

10.1.11 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died, and the time, if available.

10.1.12 Frequency

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

10.1.13 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 subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.14 Outcome

- Recovered/Resolved – Subject 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 subject 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 subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular 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 subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Start of PTE collection:

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Day 1; Visit 2) or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Start of AE collection:

AEs must be collected from the time that the subject is first administered study drug (Day 1; Visit 2). Any drugs provided by the sponsor are considered study drugs, including placebo.

Routine collection of AEs will continue until Week 48 (Visit 10).

10.2.1.2 PTE and AE Reporting

1. Event term.
2. Start and stop date, and time (if available).
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.

PDAI and QOL instruments 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 subject 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 AEs of Special Interest

If an AE of special interest, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria in Section 10.1.6, it should be recorded in an AE of special interest eCRF or SAE Form. The applicable form should be completed and reported to the SAE reporting contact in Section 1.1 within 24 hours.

10.2.2 Collection and Reporting of SAEs

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

A Takeda SAE eCRF or 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 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.
- Subject identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The SAE eCRF should be completed within 24 hours of first onset or notification of the event. However, as a back-up, if required, the SAE form should be completed and reported to Takeda Pharmacovigilance or designee within 24 hours to the attention of the contact listed in Section 1.1.

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.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject 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 subject 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 9.1.17 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

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 complete a follow-up SAE form 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 or 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 the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. 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 or IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No data safety monitoring committee will be used in this study.

11.1 Steering Committee

The Steering Committee will comprise medical experts involved in the study, the sponsor, and an independent statistician. The Steering Committee will remain blinded to treatment assignments throughout the conduct of the study. The Steering Committee will oversee the conduct and reporting of the study, ensuring expert clinical guidance and a high standard of scientific quality, and making any necessary modifications to the protocol. The Steering Committee charter will define the responsibilities of the committee.

11.2 Adjudication Committee

A PML Independent Adjudication Committee (IAC) will be instituted for this study. The PML IAC will consist of a panel of leading PML experts, including a neurologist, neuroradiologist, and a virologist. Adjudication will be done on blinded data.

11.2.1 Risk Assessment and 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 John Cunningham virus (JCV) and typically only occurs in subjects who are immunocompromised [41, 42]. Natalizumab is a pan- α4 integrin antagonist that binds to both the α4β1 and α4β7 integrins and inhibits cellular adhesion to VCAM-1 and MAdCAM-1 [43, 44]. In contrast, vedolizumab binds to the α4β7 integrin only [21] and inhibits adhesion to MAdCAM-1, but not VCAM-1. Although no cases of PML have been reported in clinical trials with vedolizumab to date, a risk of PML cannot be ruled out.

To address the theoretical risk of the development of PML in subjects 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 Investigator Site File.

The RAMP is focused on early clinical detection and management of that specific safety risk, including the discontinuation of study drug, if applicable. Subjects are assessed for signs and symptoms of PML prior to the administration of each dose of study drug using a PML subjective symptom checklist. Subjects 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 drug will be administered only if the possibility of PML is definitively excluded, as described in the RAMP algorithm. An IAC has been established as part of the RAMP program to review new neurological signs and symptoms potentially consistent with PML, and will provide input regarding subject 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 subjects will be trained to report specific neurological signs and symptoms without delay. Educational materials for teaching site personnel and subjects about PML and the RAMP procedures will be distributed to all sites and are included in the Investigator Site File. Formal teaching and training will be performed for site personnel prior to the start of the study. Subjects will receive training and educational materials prior to receiving treatment. The informed consent form will contain specific information on the hypothetical risk of PML. Any documented case of PML will be reported as an SAE, regardless of whether hospitalization occurs.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

12.1 eCRFs

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

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor or delegated contract research organization (CRO) will make arrangements to train appropriate site staff in the use of the eCRF. 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.

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.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal 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.

The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject'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 subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, 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 subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (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

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

All randomized subjects will contribute to the full analysis set (FAS) and be used for the primary analysis population for efficacy. Subjects in the FAS will be analyzed according to the treatment they were randomized to receive.

All FAS subjects who do not have any major protocol violations will be included in the per-protocol (PP) population. Major protocol violations will be specified in the SAP.

All subjects who received at least 1 dose of study drug will be included in the safety analysis set (SAF).

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information will be listed and summarized. For continuous variables, the summary will consist of descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum). For categorical variables, the summary will consist of number and percentage of subjects in each category.

Medical history and concurrent medical conditions will be summarized by system organ class and preferred term. Medication history and concomitant medications will be summarized by preferred term.

13.1.3 Efficacy Analysis

The primary efficacy endpoint is the percentage of subjects who achieve remission after 14 weeks of treatment (defined as a mPDAI score <5 and a reduction of overall score by ≥2 points from Baseline). Subjects who withdraw early for any reasons will be included in the denominator for the estimation of this percentage. At the final analysis, the difference between the percentages of subjects achieving remission at Week 14 in each treatment group will be assessed by the chi-squared test. The null hypothesis, that the percentage of subjects achieving remission at Week 14 in each treatment group is the same, will be tested against the alternative hypothesis that the 2 percentages are not the same.

The secondary endpoint, the time to symptomatic remission (defined as a PDAI score <7 and a decrease in PDAI score of ≥3 points from Baseline), will be analyzed by survival analysis procedures. Remission rates from the time of randomization over the 34-week study period will be

estimated by Kaplan-Meier product limit methods. The log-rank test will be applied to compare the 2 treatment groups. Cox proportional hazards regression will be performed to explore the effect of prognostic factors. Adjustments for baseline imbalances on key prognostic factors will be made using Cox regression. As this is a multicenter clinical study, heterogeneity of treatment effect across the participating centers will be explored.

Other dichotomous secondary endpoints will be analyzed by calculating rates and corresponding 95% confidence intervals, which will be reported by treatment group; rate differences between treatment groups and their 95% confidence intervals will also be reported.

Change from baseline in mPDAI, PDAI, CCI IBDQ, and CGQL scores will be analyzed using Wilcoxon rank-sum tests; the Wilcoxon-Mann-Whitney odds estimator and its 95% CI will also be presented.

The primary efficacy analysis will be based on the FAS population including all randomized subjects. Analysis will also be performed on the PP population for confirmatory purposes.

Statistical tests will be 2-sided and performed at the 0.05 level of significance.

13.1.4 Safety Analysis

Safety analyses will be based on the SAF set. All subjects who received at least 1 dose of study drug will be included in the safety analysis set. No formal statistical tests or inference will be performed for safety analyses. Safety data will be presented by treatment group.

The number and percentage of subjects with AEs (regardless of relationship to study drug), AEs of special interest (ie, serious infections including opportunistic infection such as PML, liver injury, malignancies, infusion-related or systemic reactions, and hypersensitivity), AEs leading to discontinuation, and SAEs that occur on or after the first dose date and up to 18 weeks 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. If a subject experienced more than 1 AE for a given preferred term, intensity is defined as the intensity of the most severe event and relationship to study drug is the relationship of the most related event.

Change from Baseline in clinical laboratory tests, vital signs and weight will be summarized by treatment group. Subjects with markedly abnormal values for laboratory tests and vital signs will be tabulated.

Physical examination findings and PML checklist data will be presented in data listings.

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

13.2 Futility Analysis and Criteria for Early Termination

A single futility analysis will be performed when 25 patients per treatment arm have been recruited and completed their Week 14 assessment of primary efficacy. The purpose of this analysis will be to assess futility, and at this point simulations will be performed to determine the posterior probability of achieving a treatment difference of at least 25% between the active and placebo treatment arms. On the basis of the posterior probability of success, a decision will be made to

continue or terminate the study on the grounds of futility or to continue the study to completion. It is not intended to stop the study on the grounds of efficacy; hence, no adjustment to the statistical significance level used for testing at the final analysis is necessary.

13.3 Determination of Sample Size

The sample size is calculated based on the remission rate at 14 weeks. The previous sample size was based on the observed remission rate in GEMINI 1 in patients with moderate to severe ulcerative colitis: the placebo group remission rate was 8%, the vedolizumab group rate was 23%; an effect size of 15%.

However, pouchitis is different from UC and a new assessment using published data was made to evaluate what would be a significant treatment effect. On the basis of 2 recent papers using the mPDAI as the primary endpoint [45, 46], a placebo rate of 15% was estimated. A clinically significant effect was estimated to be of 25%, an average of the remission (complete response) observed in the 2 aforementioned papers (32% and 21% post-induction response, respectively) evaluating the effect of infliximab using the mPDAI.

An effect size of at least 25% would be considered clinically meaningful (ie, a remission rate of 40% in subjects maintained on vedolizumab IV). Therefore, a total of 98 evaluable subjects (49 per treatment group) will be required to detect a 25% difference in the remission rate at the 2-sided 0.05 level of significance with 80% power. To account for attrition, 110 subjects will be randomized (55 per treatment group).

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 or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), 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 subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (prospectively approved deviations) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

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 medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). 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, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, 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 and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local 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 or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, the vedolizumab IV (Entyvio) package insert, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject 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 or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site 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 trial. Until the site receives notification no protocol activities, including screening may occur.

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

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject 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 informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject 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 informed consent form 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 or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

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

The subject, or the subject'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 subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject'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 informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject'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 subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject'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 its monitor or designee's monitor, 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 and IECs to review the subject'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 subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject'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. 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 and/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 study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects 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 subject 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 the sponsor providing this information to callers must provide the sponsor 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 subject in the study must be insured in accordance with the regulations applicable to the site where the subject 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 subjects. Refer to the study site agreement regarding the sponsor's policy on subject 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							Final Endoscopy Visit or ET	Safety Follow-Up (a)	Post-Study
Study Day/Week:	**Days -28 to -1**	**Wk0/ Day 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 14**	**Wk 22**	**Wk 30 (EOT)**	**Wk 34 (EOS)**	**Wk 48 (or 18 weeks post-tx if ET)**	**Phone Wk 56 (or 26 weeks post-tx if ET)**
Visit Windows (Days):			±2	±2	±2	±3	±7	±7	±7	±7	±7
Visit Number:	**1 (b)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 (c) /ET**	**10**	**11**
Informed Consent (d)	X										
Inclusion/Exclusion Criteria	X	X									
Demographics	X										
Medical/Surgical History	X (e)										
UC/Pouchitis Disease History	X										
Concomitant Medications/Procedures (f)	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X	X	X	X	X	X	X	X	X		
Weight & Height	X (g)	X	X	X	X	X	X	X	X		
Vital Signs	X	X	X	X	X	X	X	X	X		
ECG	X										
IBDQ		X				X	X		X		
CGQL		X				X	X		X		
mPDAI	X (h)					X			X		
PDAI	X (h)(i)					X			X		
Pouch Endoscopy with Biopsy	X					X			X		
Hematology	X	X				X		X	X		
Serum Chemistry and Other Laboratory Tests	X	X				X		X	X		
HIV/Hepatitis panel	X (j)										
Urinalysis	X	X				X		X	X		
CRP	X	X				X		X	X		
FSH (k)	X										
Tuberculosis QuantiFERON or Skin Test	X										
C difficile test	X										
Serum Pregnancy Test (l)	X								X		
Urine Pregnancy Test (l)		X (m)	X (m)	X	X (m)	X (m)	X (m)	X (m)		X	
Fecal Calprotectin Assay	X	X (m)				X	X	X	X		
Study Drug Dosing (IV) (n)		X	X		X	X	X	X			
Ciprofloxacin		X	X	X (o)		X (o)	X (o)	X (o)			

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screening	Treatment							Final Endoscopy Visit or ET	Safety Follow-Up (a)	Post-Study
Study Day/Week:	**Days -28 to -1**	**Wk0/ Day 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 14**	**Wk 22**	**Wk 30 (EOT)**	**Wk 34 (EOS)**	**Wk 48 (or 18 weeks post-tx if ET)**	**Phone Wk 56 (or 26 weeks post-tx if ET)**
Visit Windows (Days):			±2	±2	±2	±3	±7	±7	±7	±7	±7
Visit Number:	**1 (a)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 (b) /ET**	**10**	**11**
PML Checklist	X	X (m)	X (m)	X	X (m)	X (m)	X (m)	X (m)	X	X	
Provide PML Wallet Card		X							X		
PTE Assessment (f)	X	X									
AE/SAE Assessment (f)		X	X	X	X	X	X	X	X	X	
Long-Term Follow-Up Questionnaire											X
Access IWRS to Obtain Subject ID	X										
Access IWRS for Randomization		X									
Access IWRS to Register Visit	X	X	X		X	X	X	X	X		

Wk=Week.
(a) If subject is male or subject is postmenopausal and cannot attend the site for the safety follow-up visit, the safety follow-up visit may be conducted via phone.
(b) Once informed consent is obtained, listed procedures may be performed at any time during the screening period.
(c) Perform Visit 9 procedures if subject withdraws before Week 34.
(d) Informed consent process can begin prior to Visit 1, for example, if washout from medications is required.
(e) Smoking/nicotine usage status will be captured as part of medical history.
(f) Record adverse events, PTEs, and medications from the time of signing the Informed Consent Form.
(g) Height collected only at Visit 1.
(h) Clinical mPDAI and PDAI scores (patient reported symptoms) will be assessed as average from 3 days immediately prior to baseline endoscopy (or bowel preparation for endoscopy). Recording will be facilitated by a paper diary.
(i) Clinical and endoscopic PDAI scores for Visit 2 will be the scores obtained during Screening, and the histologic score will be added when available to complete the full PDAI score.
(j) Hepatitis and HIV testing only done at the Screening Visit.
(k) Only if menopause is suspected.
(l) Only required for women of child bearing potential.
(m) To be performed before dosing.
(n) Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion for monitoring hypersensitivity reactions.
(o) All subjects will receive ciprofloxacin 500 mg twice daily through Week 4. Additional antibiotics will be allowed, as needed, for flares after Week 14.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on Investigators from the FDA are summarized in the "Statement of Investigator" (Form FDA 1572) which must be completed and signed before the Investigator may participate in this study.

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 (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, 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 IRB/Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, 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 subjects. 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 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject'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 subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject'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 SAE, notify the sponsor within 24 hours.
13. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

Appendix C Elements of the Subject Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject'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 subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject'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 subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject'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 subjects 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 effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects 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 subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. 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.
- IRBs and IECs.

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 The Pouchitis Disease Activity Index (PDAI)

The Pouchitis Disease Activity Index (PDAI)[33]			
Criteria		Score	Subtotal
Clinical	**Stool frequency**		
	Usual postoperative stool frequency	0	
	1-2 stools/day > postoperative usual	1	
	3 or more stools/day > postoperative usual	2	
	Rectal bleeding		
	None or rare	0	
	Present daily	1	
	Fecal urgency or abdominal cramps		
	None	0	
	Occasional	1	
	Usual	2	
	Fever (temperature >37.8 ◦C)		
	Absent	0	
	Present	1	
Endoscopic inflammation	Edema	1	
	Granularity	1	
	Friability	1	
	Loss of vascular pattern	1	
	Mucus exudates	1	
	Ulceration	1	
Acute histologic inflammation	**Polymorphic nuclear leukocyte infiltration**		
	None	0	
	Mild	1	
	Moderate + crypt abscess	2	
	Severe + crypt abscess	3	
	Ulceration per low power field (mean)		
	0%	0	
	<25%	1	
	25-50%	2	
	>50%	3	
			Total PDAI

Based on Sandborn et al. Mayo Clin Proc. 1994; 69(5);409-15.

Appendix F The Modified Pouchitis Disease Activity Index (mPDAI)

The Modified Pouchitis Disease Activity Index (mPDAI)			
Criteria		Score	Subtotal
Clinical	**Stool frequency**		
	Usual postoperative stool frequency	0	
	1-2 stools/day > postoperative usual	1	
	3 or more stools/day > postoperative usual	2	
	Rectal bleeding		
	None or rare	0	
	Present daily	1	
	Fecal urgency or abdominal cramps		
	None	0	
	Occasional	1	
	Usual	2	
	Fever (temperature >37.8 ◦C)		
	Absent	0	
	Present	1	
Endoscopic inflammation	Edema	1	
	Granularity	1	
	Friability	1	
	Loss of vascular pattern	1	
	Mucus exudates	1	
	Ulceration	1	
			Total mPDAI

Based on Shen et al. Dis Colon Rectum 2003:46(6):748-53 [34].

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Appendix I Inflammatory Bowel Disease Questionnaire (IBDQ)

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

On this questionnaire there are 32 questions. Each question has a graded response numbered from I through 7. Please read each question carefully and circle/mark the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

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

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME

6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

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

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

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

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

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

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME

4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

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

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

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

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

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

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME

4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

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

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

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

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

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

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME

4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

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

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

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

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

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

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME

4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

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

Appendix J Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 04 are indicated. The corresponding text has been revised throughout the protocol.

This protocol amendment is considered as non-substantial as the changes made do not significantly or negatively impact the safety or physical or mental integrity of the clinical trial participants nor the scientific value of the trial.

Change 1: CCI [redacted]

The primary change occurs in Section 5.1.3 Exploratory Objectives:

Initial wording: Exploratory objectives are:
CCI [redacted]

Amended or new wording: Exploratory objectives are:
CCI [redacted]

Rationale for Change:
CCI [redacted]

The addition of these exploratory objectives is considered to be non-substantial and does not require new subject procedures nor does it alter the main objectives of this trial.

Section 2.0 STUDY SUMMARY also contains this change.

Change 2: Added exploratory endpoints corresponding to new objectives CCI [redacted]

The primary change occurs in Section 5.2.3 Exploratory Endpoints:

Initial wording: The exploratory endpoints are:
CCI [redacted]

Amended or new wording: The exploratory endpoints are:
CCI [redacted]

Rationale for Change:

To add new exploratory endpoints corresponding to new objectives.

The addition of exploratory endpoints is consistent with changes to the exploratory objectives and is considered to be a non-substantial change; the additional endpoints do not require new subject procedures nor do they alter the main objectives of this trial.

Section 2.0 STUDY SUMMARY also contains this change.

Change 3: CCI [redacted]

The primary change occurs in Section 9.1.10: Pouchitis Endoscopy:

Initial wording:	CCI [redacted]
Amended or new wording:	[redacted]

Rationale for Change:

To clarify centrally read assessments that correspond to the new exploratory endpoints. This change is considered non-substantial because the additional exploratory endpoints do not require new subject procedures nor do they alter the main objectives of this trial.

CCI [redacted]

Added tex[redacted]

Rationale for Change:

[redacted].

Change 5: [redacted]

The primary change occurs in Section 13.1.3 Efficacy Analysis:

Initial wording:	Change from baseline in mPDAI, PDAI, IBDQ, and CGQL scores will be analyzed using Wilcoxon rank sum tests; the Wilcoxon-Mann-Whitney odds estimator and its 95% CI will also be presented.
Amended or new wording:	Change from baseline in mPDAI, PDAI, [redacted] IBDQ, and CGQL scores will be analyzed using Wilcoxon rank sum tests; the Wilcoxon-Mann-Whitney odds estimator and its 95% CI will also be presented.

Rationale for Change:

[redacted]

Rationale for Change:

CCI [redacted]

Change 7: Clarified that prior medication history includes all prior medications for the treatment of UC/pouchitis.

The primary change occurs in Section 9.1.2: Demographics, Medical History, and Medication History Procedure:

Initial wording:	In addition, all prior biologic medication history for the treatment of UC/pouchitis, with the reason for discontinuation is to be collected for subjects where possible.
Amended or new wording:	In addition, all prior ~~biologic~~ medication history for the treatment of UC/pouchitis, with the reason for discontinuation, is to be collected for subjects where possible.

Rationale for Change:

This change clarifies the intent of the study to collect all prior medication for the treatment of UC/pouchitis and not just biologics. This clarification is considered to be a non-substantial change.

10. **Change 8**: Corrected acute histologic inflammation descriptors for score of 0 in Appendix E

CCI [redacted]

The primary change occurs in Appendix E The Pouchitis Disease Activity Index (PDAI)Appendix EAppendix EAppendix EAppendix EAppendix EAppendix EAppendix EAppendix E .

Description of change:	[Added response 0 = None for polymorphic nuclear leukocyte infiltration. Added response 0 = 0% added for ulceration per low power field (mean).]

Rationale for Change:

Corrected table to align with histology scoring used in this study and to be consistent with other text in the protocol.

Change 9: Deleted duplicated text describing analysis set for primary analysis.

The primary change occurs in Section 13.1.3 Efficacy Analysis:

Deleted text:	~~The primary efficacy analysis will be based on the full analysis set (FAS) including all randomized subjects. Analysis will also be performed on the PP population for confirmatory purposes.~~

Rationale for Change:

The same information was written twice within the same section of the protocol. Deleted one of the duplicated statements. This is an editorial correction that does not impact the analysis methods and is a non-substantial change.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	14-Sep-2020 12:51 UTC
	Medical Affairs Approval	14-Sep-2020 13:32 UTC
	Pharmacovigilance Approval	14-Sep-2020 13:36 UTC