Title: An Open-Label, Dose-Finding Study of Vedolizumab IV for Treatment of Steroid-Refractory Acute Intestinal Graft-Versus-Host Disease (GvHD) in Patients who Have Undergone Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT)

NCT Number: NCT02993783

Protocol Approve Date: November 27, 2017

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 or company confidential information.

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

An Open-Label, Dose-Finding Study of Vedolizumab IV for Treatment of Steroid-Refractory Acute Intestinal Graft-Versus-Host Disease (GvHD) in Patients who Have Undergone Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT)

Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA USA 02139
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Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".

Study Number:	Vedolizumab-2004		
IND Number:	127,634	**EudraCT Number:**	2016-002985-30
Compound:	Vedolizumab IV		
Date:	17 May 2017	Amendment Number:	01
	27 November 2017		02

Amendment History:

Date	Amendment Number	Amendment Type	Region
27 July 2016	Initial protocol	Not applicable	Global
17 May 2017	01	Substantial	Sweden
27 November 2017	02	Substantial	Global

1.0 ADMINISTRATIVE

1.1 Contacts

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

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

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	North America	Europe
Serious adverse event and pregnancy reporting	See Section 10.2	See Section 10.2
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Protected Personal Data	

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 clinical 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.

Protected Personal Data

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, 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 10.0 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 C 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)

1.3 Protocol Amendment 02 Summary of Changes

Rationale for Amendment 02

This document describes the changes in reference to the protocol incorporating Amendment No. 02. The primary reasons for this amendment are to change some of the inclusion and exclusion criteria, allowing enrollment of suitable subjects and avoiding unnecessary screen failures, as well as to conduct a single interim analysis that fulfills the goals of this study. In addition, changes made in the Sweden only protocol amendment 01 have been incorporated into the global amendment 02.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific descriptions of text changes and where the changes are located, see Appendix G.

Changes in Amendment 02

1. Clarification that the progressive multifocal leukoencephalopathy (PML) checklist is administered per Section 9.4.8.
2. Clarification to the description of patients with steroid-refractory graft-versus-host disease (GvHD) who are eligible for enrollment to the study.
3. Deletion of the inclusion criterion specifying a required level of creatinine clearance for enrollment in the study.
4. Deletion of the exclusion criterion requiring the occurrence of acute steroid resistant GvHD within 28 days from primary treatment.
5. Addition of viral testing procedures to be conducted at the Screening visit.
6. Correction and specification of the pharmacokinetic (PK) postinfusion sampling times.
7. Correction to the end of treatment (ET) visit.
8. Clarification of the posttreatment follow-up assessments.
9. Clarification to the efficacy analyses.
10. Clarification of the immunogenicity analyses.
11. Deletion of redundant safety analysis text.
12. Modification to the conduct of the interim analysis.
13. Corrections to the Schedule of Events (Appendix A).
14. Update of the signatories.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc.	**Compound:** Vedolizumab IV	
Title of Protocol: An Open-Label, Dose-Finding Study of Vedolizumab IV for Treatment of Steroid-Refractory Acute Intestinal Graft-Versus-Host Disease (GvHD) in Patients who Have Undergone Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT)	**IND No.:** 127,634	**EudraCT No.:** 2016-002985-30
Study Number: Vedolizumab-2004	**Phase:** 2a	

Study Design:

This is a phase 2a, open-label, dose-finding study designed to evaluate the safety, tolerability, and clinical activity of vedolizumab to treat patients who have developed acute intestinal GvHD that is refractory to primary steroid therapy. Clinical GvHD scoring will be used for assessment of response to treatment. Patients with acute intestinal GvHD who have received no systemic therapy for the treatment of acute GvHD (prophylaxis acceptable) other than corticosteroids will be administered vedolizumab.

Eligibility will be determined during the Screening period, which may last for up to 28 days before Day 1 (designation of the day of the first intravenous [IV] infusion of vedolizumab). Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study. Approximately 38 evaluable patients will be enrolled.

Patients will be randomized at a ratio of 1:1 to 2 treatment arms to receive either 300 or 600 mg vedolizumab IV on Days 1, 15, 43, 71, and 99. After approximately 10 patients are enrolled at each dose level and have data available from their Day 28 evaluation, safety, tolerability, efficacy, and pharmacokinetic (PK) results will be assessed from the patients at both vedolizumab dose levels (300 and 600 mg), and a Bayesian statistical approach will be used to facilitate the determination of an appropriate dose for subsequent patients in the study. The cohort at the chosen dose level will then be expanded by approximately 18 additional evaluable patients to further assess the tolerability and effectiveness of vedolizumab. Both dose levels may be expanded based on accumulating results, if necessary.

Upon review and agreement by the medical monitor, patients who respond to and tolerate all 5 planned doses of vedolizumab and who develop recurrent symptoms of intestinal GvHD following discontinuation of therapy (ie, after the fifth dose) may enter an extension phase where they may receive 300 mg vedolizumab IV every 2 weeks for 2 doses followed by every 4 weeks for up to 1 year from the first dose of study drug. A dose other than 300 mg and/or a frequency of administration other than every 4 weeks may be chosen based on accumulating safety, efficacy, and PK results. Patients may receive drug beyond 1 year with the agreement of the investigator and the sponsor if, in the opinion of the investigator, the patient is benefitting from treatment. All patients will be followed for overall survival (OS) every 3 months until death, withdrawal of consent, termination of the study by the sponsor, or for a maximum of 1 year after the last patient is enrolled in the study. Additionally, patients will be required to participate in a long-term follow-up (LTFU) safety survey 6 months after the last dose of study drug.

Vital signs, physical and neurological examinations, adverse event assessments, and laboratory values (chemistry, hematology, and urinalysis) will be obtained to evaluate the safety and tolerability of vedolizumab IV. Another pan-α4 integrin antagonist (blocking α4β7 and α4β1) has been associated with progressive multifocal leukoencephalopathy (PML). α4β7 mediates T cell trafficking to the gastrointestinal tract whereas α4β1 mediates T cell trafficking to the central nervous system (CNS) and is therefore involved in CNS immune surveillance. Because vedolizumab binds to the α4β7 integrin only, it is anticipated to affect T cell trafficking to the gastrointestinal tract. However, given the effects of integrin receptor antagonists, there is a potential risk of PML in patients treated with vedolizumab. To date, no cases of PML have been reported in clinical studies of vedolizumab; however, health care professionals should monitor subjects on vedolizumab for any new onset or worsening of neurological signs and symptoms, and consider neurological referral if they occur. To minimize the risk of PML, a PML checklist will be administered at Screening and before vedolizumab IV administration on Days 1, 15, 43, 71, and 99. Optional endoscopy will be performed to evaluate clinical response to vedolizumab treatment.

Confidential Company Information

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, effective date 14 June 2010.

Primary Objective:

To describe the initial activity, tolerability, and safety and to identify a recommended dose and regimen of vedolizumab IV administered for treatment of steroid-refractory acute intestinal GvHD in patients who have undergone allo-HSCT.

Secondary Objectives:

- To evaluate overall response to vedolizumab treatment at Day 28.
- To determine the nonrelapse mortality at 6 months after treatment with vedolizumab.
- To evaluate OS.
- To determine the GvHD-free, relapse-free survival at 6 and 12 months after treatment with vedolizumab.
- To characterize the PK in patients treated with vedolizumab.

Exploratory Objectives

- Company Confidential Information
-
-
-
-
-
-
-

Subject Population: Adult patients with primary steroid-refractory acute intestinal GvHD who have undergone allo-HSCT.

Number of Subjects:	**Number of Sites:**
Approximately 38 evaluable patients	Approximately 15 in the United States and Europe
Dose Level(s):	**Route of Administration:**
Vedolizumab: Initially, patients will be randomized at a ratio of 1:1 to 2 treatment arms to receive 300 or 600 mg. After approximately 10 patients are enrolled at each dose level, one or both dose levels may be expanded in approximately 18 additional evaluable patients.	Vedolizumab: IV

Duration of Treatment:	**Period of Evaluation:**
Patients will receive up to 5 doses of vedolizumab IV (a single dose on each of Days 1, 15, 43, 71, and 99). Upon review and agreement by the medical monitor, patients who respond to and tolerate all 5 planned doses of vedolizumab and who develop recurrent symptoms of intestinal GvHD following discontinuation of therapy (ie, after the fifth dose) may receive 300 mg vedolizumab IV every 2 weeks for 2 doses followed by every 4 weeks for up to 1 year from the first dose of study drug. A dose other than 300 mg and/or a frequency of administration other than every 4 weeks may be chosen based on accumulating safety, efficacy, and PK results. Patients may receive drug beyond 1 year with the agreement of the investigator and the sponsor if, in the opinion of the investigator, the patient is benefitting from treatment.	Patients may receive vedolizumab unless they experience relapse of the underlying malignancy. Patients will discontinue treatment if they have an unacceptable vedolizumab-related toxicity. All patients will be followed for OS every 3 months until death, withdrawal of consent, termination of the study by the sponsor, or for a maximum of 1 year after the last patient is enrolled in the study. Additionally, patients will be required to participate in an LTFU safety survey 6 months after the last dose of study drug. It is anticipated that this study will last for approximately 36 months.

Main Criteria for Inclusion:

Adult patients aged ≥18 years who have received 1 allo-HSCT and have primary steroid-refractory acute GvHD with intestinal disease involvement with a severity index of B, C, or D using the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)- modified International Bone Marrow Transplant Registry Database (IBMTR) index will be enrolled. Patients should have evidence of myeloid engraftment, an Eastern Cooperative Oncology Group performance status of 0 to 3, and an estimated creatinine clearance based on the Cockcroft-Gault estimate of ≥60 mL/minute/1.73 m^2.

Main Criteria for Exclusion:

Patients who have chronic GvHD, have relapse of underlying malignancy after allo-HSCT, or have received systemic agents other than corticosteroids for treatment of acute GvHD (other than GvHD prophylaxis agents) will be excluded from the study. Patients with active CNS disease, active cytomegalovirus colitis, or signs and symptoms of PML or any history of PML will also be excluded. In addition, patients with severe hepatic veno-occlusive disease/sinusoidal obstruction syndrome will be excluded.

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study are overall response (partial response+very good partial response+complete response) at Day 28 and the number and percentage of patients who experience serious adverse events from administration of the first dose of vedolizumab IV through Day 28.

Statistical Considerations:

Statistical analyses will be primarily descriptive and graphical in nature. A Bayesian statistical approach will be used for the PK and efficacy data summary to facilitate decision making. A formal statistical analysis plan will be developed and finalized before database lock.

Sample Size Justification:

Approximately 38 evaluable patients will be enrolled to identify an active and tolerable vedolizumab dose level with sufficient PK sampling to determine the PK parameters in this patient population. Sample size determination is mainly based on clinical considerations and on the primary objective of determining a recommended dose and regimen and to describe the initial activity, tolerability, and safety of vedolizumab IV administered for the treatment of primary steroid-refractory acute intestinal GvHD.

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 Clinical Study Supplier List. The identified vendors 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 medication, 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

Term	Definition
AE	adverse event
allo-HSCT	allogeneic hematopoietic stem cell transplantation
AVA	anti-vedolizumab antibodies
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRO	contract research organization
C_{trough}	observed concentration at the end of a dosing interval
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
EQ-5D	European Quality of Life 5-Dimensional questionnaire
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale
FDA	Food and Drug Administration
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GI	gastrointestinal(ly)
GvHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
IAC	independent adjudication committee
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBMTR	International Bone Marrow Transplant Registry Database
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IL	interleukin
IRB	institutional review board
IRT	interactive voice or web response technology
IV	intravenous(ly)
LTFU	long-term follow-up

Term	Definition
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
PTE	pretreatment event
PVC	polyvinyl chloride
Q4W	once every 4 weeks
Q8W	once every 8 weeks
RAMP	Risk Assessment and Minimization of PML
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOE	schedule of event(s)
ST2	suppressor of tumorigenicity 2
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis
US	United States
VCAM-1	vascular cell adhesion molecule 1
VGPR	very good partial response
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease Under Treatment

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important therapy that is used to treat hematologic malignant disorders and hematologic genetic diseases, but its use is limited by the major complication of graft-versus-host disease (GvHD) [1]. The common complication of GvHD following allo-HSCT is a major cause of morbidity and mortality. The risk of GvHD is variable and depends on patient factors, donor factors, the degree of histocompatibility between donor and recipient, the conditioning regimen, and the GvHD prophylaxis strategy employed [2-4]. GvHD prophylaxis is employed for all patients undergoing allo-HSCT using various strategies such as calcineurin inhibitors, methotrexate, and in vivo or ex vivo T-cell depletion; however, despite GvHD prophylaxis, GvHD still develops in 30% to 50% of allo-HSCT recipients [2,3]. First-line treatment for patients with acute GvHD (Grade II or higher) is corticosteroids such as methylprednisolone. Although first-line treatment is effective in more than 50% of patients, durable responses (defined as a complete response [CR] by Day 28 that remains at 6 months after onset) are observed in only one-third of patients [5]. In patients who do not respond to primary treatment with steroids, acute GvHD is associated with a high rate of morbidity and mortality, primarily from infections and/or multi-organ failure [6,7]. Despite this, there are no approved or agreed-upon standard treatments for steroid-refractory GvHD, which remains largely an untreatable disease with limited survival, representing a major unmet therapeutic need.

Acute GvHD that occurs after allo-HSCT involves the skin, liver, and gut in the most severe and life-threatening cases. Acute skin GvHD is generally not life-threatening with existing therapies, which are usually effective, and the incidence of Stage 3 or 4 liver GvHD is around 2% [2]. While the incidence of Stage 3 or 4 intestinal GvHD has decreased in recent years, most courses of treatment remain unsuccessful, with most fatal cases of GvHD involving the gastrointestinal (GI) tract [2]. Lower intestinal GvHD presents with secretory, protein-rich diarrhea (in excess of 1.5 liters per day in severe cases), abdominal pain from gut distention, inflammation of the small intestine and colon, mucosal ulceration, and bleeding. A recent study of patients who received allo-HSCT showed that 7.9% of patients developed Stage 3 or 4 intestinal GvHD at a median time to onset of 35 days after transplant [8]. Of these patients, 73% developed corticosteroid resistance before or within 14 days of onset of Stage 3 or 4 intestinal GvHD. Significant risk factors for mortality include corticosteroid resistance, age >18 years, increased serum bilirubin, and overt GI bleeding.

4.1.2 Vedolizumab IV

Vedolizumab (also called MLN0002) is a humanized immunoglobulin G1 monoclonal antibody directed against the human lymphocyte integrin α4β7. The α4β7 integrin mediates lymphocyte trafficking to 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 [9-12]. Vedolizumab binds the α4β7

integrin, antagonizing its adherence to MAdCAM-1 and, as such, impairs the migration of gut-homing leukocytes into GI mucosa. As a result, vedolizumab acts as a gut-selective immunomodulator [13]. Vedolizumab has been developed as a treatment for ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by inflammation of the GI tract.

Vedolizumab IV (Entyvio®) is a lyophilized solid that, after appropriate reconstitution and dilution, is intended for intravenous (IV) infusion; it has been granted marketing approval in several regions, including the United States (US) and European Union. 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 a tumor necrosis factor-alpha (TNF-α) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. The approved dosing and administration regimen for UC and CD consists of 300 mg vedolizumab infused IV over approximately 30 minutes at Weeks 0, 2, and 6, then once every 8 weeks (Q8W) thereafter. Previously conducted clinical studies in healthy subjects and patients with UC and CD have characterized the efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and immunogenicity of vedolizumab.

4.1.2.1 Nonclinical

Several key nonclinical studies have been published that support the use of vedolizumab for the treatment of GvHD [14-16]. Extensive nonclinical evaluations of the cardiovascular, acute, local tolerance, 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 [13], which has been implicated in the development of progressive multifocal leukoencephalopathy (PML).

4.1.2.2 Human Experience

As of 19 May 2015, approximately 3600 subjects have received at least 1 dose of vedolizumab across all studies in the clinical development program (see current Investigator's Brochure [IB]). Phase 3, placebo-controlled studies enrolled 2427 subjects with UC or CD, of whom 1434 were administered 300 mg of vedolizumab for induction followed by once every 4 weeks (Q4W) or Q8W for up to a total of 52 weeks, and 488 subjects were administered 300 mg vedolizumab for induction only [17-19]. As of May 2015, vedolizumab exposure has extended for ≥12 months in 1667 subjects, ≥24 months in 1306 subjects, ≥36 months in 935 subjects, ≥48 months in 676 subjects, ≥60 months in 267 subjects, and ≥72 months in 26 subjects. Based on the most recent drug shipment data (19 November 2015), the cumulative patient exposure to vedolizumab since its marketing approval in May 2014 is estimated to be approximately 25,831 patient-years.

In subjects with moderately to severely active CD (phase 3 Study C13007), including subjects who had failed treatment with 1 or more therapies including TNF-α antagonists, vedolizumab 300 mg infusion at Week 0 and Week 2 (induction) followed by either Q4W or Q8W from Week 6 through Week 52 (maintenance) demonstrated statistically significant differences in efficacy compared

with placebo for both the induction phase and maintenance phase. The study met its primary endpoint for the induction phase, clinical remission at Week 6, but did not meet the second primary endpoint of enhanced clinical response (Crohn's Disease Activity Index [CDAI-100]; a ≥100-point decrease in the CDAI score) at Week 6 in the overall population, although the treatment difference favored vedolizumab. The study did meet its primary endpoint for the maintenance phase, clinical remission at Week 52, and important secondary endpoints, including enhanced clinical response at Week 52 and corticosteroid-free clinical remission at Week 52 [18].

In the phase 3 Study C13011, vedolizumab (300 mg infusion at Weeks 0, 2, and 6) was administered to subjects with moderately or severely active CD who had failed conventional therapies, including TNF-α antagonists. The primary endpoint of clinical remission at Week 6 in the TNF-α antagonist failure intent-to-treat population was not met; however, a treatment difference was observed at Week 10 in this population. Similar treatment differences favoring vedolizumab were also demonstrated for the overall population and in the subgroup of subjects who were TNF-α antagonist naïve [19].

Study C13008 is an ongoing, phase 3, open-label, single-arm study. Interim efficacy results with a cutoff date of 16 July 2012 were analyzed from 1822 subjects (704 UC and 1118 CD) enrolled from previous qualifying vedolizumab studies. Enrolled subjects received 300 mg vedolizumab IV Q4W starting at Week 0, and efficacy was assessed using partial Mayo scores (UC subjects) or the Harvey-Bradshaw Index (CD subjects). The interim efficacy results suggest persistence of benefit with continued maintenance treatment in subjects with UC and CD.

Vedolizumab has shown an acceptable safety profile based on an analysis of safety data from both completed and ongoing studies (see current version of the IB). In phase 1 and 2 clinical trials (7 completed phase 1 studies in healthy subjects and 8 completed phase 1b/2 studies in UC or CD patients), there was no consistent evidence of any dose–toxicity relationships, and vedolizumab was well tolerated. The majority of the safety data is from 3 well-controlled, phase 3 clinical studies that evaluated the safety of vedolizumab for up to 12 months in subjects with UC (Study C13006 [52 weeks]) or CD (Studies C13007 [52 weeks] and C13011 [10 weeks]). In addition, an interim assessment of safety was performed for the ongoing, uncontrolled extension study (Study C13008).

Vedolizumab exhibits target-mediated drug disposition as characterized by linear and nonlinear processes of elimination after single-dose administration. Following IV dosing, vedolizumab concentrations fell in a biexponential fashion until concentrations reached approximately 1 to 10 µg/mL with a serum terminal elimination half-life of approximately 25 days. Thereafter, vedolizumab concentrations fell in a nonlinear fashion. Similar PK was observed in healthy subjects and in subjects with UC or CD.

Vedolizumab has shown an acceptable and consistent safety profile in clinical trials. In the pivotal phase 3 studies (Studies C13006 and C13007), the most common (≥5% and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most serious adverse events (SAEs) have been 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 correlated 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 a low frequency (<1%). A total of 4% of vedolizumab-treated subjects and 3% of placebo-treated subjects experienced an infusion-related reaction. In Studies C13006 and C13007, 10% of subjects were positive for anti-vedolizumab antibodies 16 weeks following the last dose of vedolizumab. Results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab treatment. Overall, the safety profile following long-term treatment with vedolizumab in Study C13008 is consistent with safety in the completed studies.

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 trials among subjects who had and had not received these medications.

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 and typically occurs only in patients who are immunocompromised [20,21]. MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T-lymphocytes to tissues within the GI tract, while vascular cell adhesion molecule-1 (VCAM-1) mediates trafficking to the central nervous system. Natalizumab is a pan-α_4 integrin antagonist that binds to both the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins and inhibits cellular adhesion to VCAM-1 and MAdCAM-1 [22,23]. In contrast, vedolizumab binds to the $\alpha_4\beta_7$ integrin only [13] 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 minimize the risk of the development of PML in patients treated with vedolizumab, the sponsor, with input from PML experts, has developed a Risk Minimization Action Plan for PML, the RAMP (see Section 10.7).

As of 19 May 2015, a total 26 subjects (0.7%) who participated in vedolizumab clinical studies have died during the study or up to 2 years following the last dose of study drug (Studies C13004, C13006, C13007, and C13008); 4 of the deaths were considered by the investigator to be related to study drug. Twenty-five of the 26 subjects who died were administered vedolizumab, including 12 subjects each with UC or CD and 1 subject who was diagnosed with both UC and CD. There was no pattern or consistent cause of death identified in these patients; detailed information can be found in the current version of the IB.

Overall, vedolizumab was well tolerated in clinical studies.

4.2 Rationale for the Proposed Study

Acute GvHD is mediated by immunocompetent donor T cells, which migrate to lymphoid tissues soon after infusion, recognize host alloantigens, and become activated upon interaction with host antigen-presenting cells [24]. On the basis of the safety profile of vedolizumab that has been established in patients with inflammatory bowel disease (IBD), it is expected that vedolizumab will have acceptable tolerability in patients with steroid-refractory intestinal GvHD following allo-HSCT because of the specific mechanism of action of vedolizumab and targeted effects on

lymphocytes in the GI tract. A published case series of 6 patients suggests promising activity and tolerability of off-label use of vedolizumab for the treatment of acute steroid-refractory intestinal GvHD [25]. In this case series, all patients exhibited clinical responses within 7 to 10 days after starting treatment with vedolizumab with a decrease in abdominal pain and watery diarrhea. In addition, the patients had gradual macroscopic and histological improvement in the GI tract. In the proposed study, administration of vedolizumab to patients who have developed intestinal GvHD after undergoing allo-HSCT may reduce trafficking of alloreactive T cells to the GI mucosa, reducing ongoing tissue damage from acute intestinal GvHD.

Vedolizumab will be administered to patients with acute intestinal GvHD who have received no systemic therapy for the treatment of acute GvHD (prophylaxis acceptable) other than corticosteroids. Patients will be randomized at a ratio of 1:1 to 2 treatment arms to receive either 300 or 600 mg vedolizumab IV on Days 1, 15, 43, 71, and 99. After approximately 10 patients are enrolled at each dose level and have data available from their Day 28 evaluation, safety, tolerability, efficacy, and PK results will be assessed from the patients at both vedolizumab dose levels (300 and 600 mg), and a Bayesian statistical approach will be used to facilitate the determination of an appropriate dose for subsequent patients in the study.

The cohort at the chosen dose level will then be expanded by approximately 18 additional evaluable patients to further assess the tolerability and effectiveness of vedolizumab. Both dose levels may be expanded based on accumulating results, if necessary.

Upon review and agreement by the medical monitor, patients who respond to and tolerate all 5 planned doses of vedolizumab and who develop recurrent symptoms of intestinal GvHD following discontinuation of therapy (ie, after the fifth dose) may receive 300 mg vedolizumab IV every 2 weeks for 2 doses and Q4W for up to 1 year. A dose other than 300 mg and/or a frequency other than Q4W may be chosen based on accumulating safety, efficacy, and PK results. Patients may receive drug beyond 1 year with the agreement of the investigator and the sponsor if, in the opinion of the investigator, the patient is benefitting from treatment.

Dose Selection

The dose and schedule of vedolizumab IV approved for the treatment of UC or CD is 300 mg IV at Weeks 0, 2, and 6, then Q8W [26]. The doses and schedule of vedolizumab IV proposed for this study are 300 and 600 mg IV on Days 1, 15, 43, 71, and 99.

In the phase 2, placebo-controlled, double-blind, multiple dose study in subjects with active UC (Study C13002), vedolizumab was administered as weight-adjusted doses, ranging from 2.0 to 10.0 mg/kg [27,28]. In this study, vedolizumab was administered for 12 weeks to 11 patients at 10.0 mg/kg which approximates a 760 mg fixed dose, ranging from 420 mg to 950 mg (C13002 CSR). These patients then entered a long-term safety of vedolizumab in the phase 2, open-label Study C13004 in patients with UC or CD. In the combined phase 1b and phase 2 UC and CD patient population across the vedolizumab clinical development program, there was no apparent dose response in adverse events (AEs) by system organ class (SOC) with weight-adjusted doses up to 10.0 mg/kg.

A published case series of 6 patients suggests promising activity and tolerability of off-label use of vedolizumab for the treatment of acute steroid-refractory intestinal GvHD [25]. In this case series, results showed that a patient who did not achieve remission early required chronic administration of vedolizumab to prevent symptom recurrence whereas patients who were treated effectively with vedolizumab early in the acute GvHD course were able to discontinue vedolizumab without recurrence of symptoms (personal communication). This suggests that it may be critical that clinical remission is achieved early in the course of treatment with vedolizumab.

Exposure/response analysis from the phase 3 Study C13006 in adult patients with active CD at Week 6 indicated that higher efficacy can be achieved with higher trough concentrations of vedolizumab [18].

Based on these considerations, 300 and 600 mg vedolizumab IV administered on Days 1, 15, 43, 71, and 99 (equivalent to Weeks 0, 2, 6, 10, and 14) are the proposed doses and schedule to test in this study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to describe the initial activity, tolerability, and safety and to identify a recommended dose and regimen of vedolizumab IV administered for treatment of steroid-refractory acute intestinal GvHD in patients who have undergone allo-HSCT.

5.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate overall response to vedolizumab treatment at Day 28.
- To determine the nonrelapse mortality at 6 months after treatment with vedolizumab.
- To evaluate overall survival (OS).
- To determine the GvHD-free, relapse-free survival at 6 and 12 months after treatment with vedolizumab.
- To characterize the PK in patients treated with vedolizumab.

5.1.3 Additional/Exploratory Objectives

The additional/exploratory objectives are:

- Company Confidential Information
-
-
-
-
-
-
-

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

- The proportion of subjects with overall response (partial response [PR]+very good partial response [VGPR]+CR) at Day 28 (refer to Appendix D).

- The number and percentage of patients who experience SAEs from administration of the first dose of vedolizumab IV through Day 28.

5.2.2 Secondary Endpoints

The secondary endpoints are:

- The proportion of subjects who have died in the absence of primary malignancy relapse after allo-HSCT at 6 months.
- The proportion of subjects with CR at Day 28.
- The proportion of subjects with intestinal overall response at Day 28.
- OS at 6 and 12 months.
- The proportion of subjects alive without GvHD or relapse of primary malignancy at 6 and 12 months.
- The number and percentage of patients who experience treatment-emergent adverse events (TEAEs) from administration of the first dose of vedolizumab IV through 18 weeks after administration of the last dose of vedolizumab IV.
- The number and percentage of patients who experience SAEs from administration of the first dose of vedolizumab IV through 18 weeks after administration of the last dose of vedolizumab IV.
- Mean serum concentrations of vedolizumab before dosing (C_{trough}) on Day 99.
- The total dose of steroids administered (mg/kg/day of methylprednisolone or equivalent) from the start of the first IV infusion of vedolizumab through both 6 and 12 months.

5.2.3 Additional/Exploratory Endpoints

The exploratory endpoints are:

- Company Confidential Information
- [redacted]

- Company Confidential Information
- [redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a phase 2a, open-label, dose-finding study designed to evaluate the safety, tolerability, and clinical activity of vedolizumab to treat patients who have developed acute intestinal GvHD that is refractory to primary steroid therapy. Clinical GvHD scoring will be used for assessment of response to treatment [31]. Patients with acute intestinal GvHD who have received no systemic therapy for the treatment of acute GvHD (prophylaxis acceptable) other than corticosteroids will be administered vedolizumab.

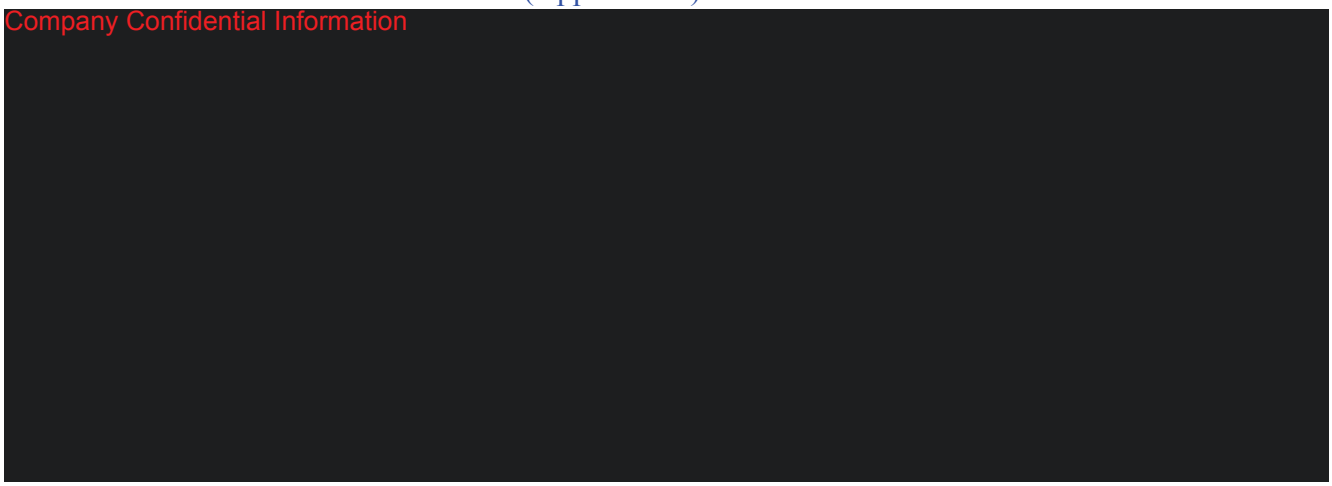
Eligibility will be determined during the Screening period, which may last for up to 28 days before Day 1 (designation of the day of the first IV infusion of vedolizumab). Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study. Approximately 38 evaluable patients will be enrolled.

Patients will be randomized at a ratio of 1:1 to 2 treatment arms to receive either 300 or 600 mg vedolizumab IV on Days 1, 15, 43, 71, and 99. After approximately 10 patients are enrolled at each dose level and have data available from their Day 28 evaluation, safety, tolerability, efficacy, and PK results will be assessed from the patients at both vedolizumab dose levels (300 and 600 mg), and a Bayesian statistical approach will be used to facilitate the determination of an appropriate dose for subsequent patients in the study. The cohort at the chosen dose level will then be expanded by approximately 18 additional evaluable patients to further assess the tolerability and effectiveness of vedolizumab. Both dose levels may be expanded based on accumulating results, if necessary

Upon review and agreement by the medical monitor, patients who respond to and tolerate all 5 planned doses of vedolizumab and who develop recurrent symptoms of intestinal GvHD following discontinuation of therapy (ie, after the fifth dose) may enter an extension phase where they may receive 300 mg vedolizumab IV every 2 weeks for 2 doses followed by Q4W for up to 1 year from the first dose of study drug. A dose other than 300 mg and/or a frequency of administration other than Q4W may be chosen based on accumulating safety, tolerability, efficacy, and PK results. Patients may receive drug beyond 1 year with the agreement of the investigator and the sponsor if, in the opinion of the investigator, the patient is benefitting from treatment. All patients will be followed for OS every 3 months until death, withdrawal of consent, termination of the study by the sponsor, or for a maximum of 1 year after the last patient is enrolled in the study. Additionally, patients will be required to participate in a long-term follow-up (LTFU) safety survey 6 months after the last dose of study drug.

Vital signs, physical and neurological examinations, AE assessments, and laboratory values (chemistry, hematology, and urinalysis as specified in Section 9.4.14) will be obtained to evaluate the safety and tolerability of vedolizumab IV, as described in the Schedule of Events (Appendix A). Another pan-α4 integrin antagonist (blocking α4β7 and α4β1) has been associated with PML. α4β7 mediates T cell trafficking to the GI tract whereas α4β1 mediates T cell trafficking to the central nervous system (CNS) and is therefore involved in CNS immune surveillance. Because vedolizumab binds to the α4β7 integrin only, it is anticipated to affect T cell trafficking to the

gastrointestinal tract. However, given the effects of integrin receptor antagonists, there is a potential risk of PML in patients treated with vedolizumab. To date, no cases of PML have been reported in clinical studies of vedolizumab; however, health care professionals should monitor subjects on vedolizumab for any new onset or worsening of neurological signs and symptoms, and consider neurological referral if they occur. To minimize the risk of PML, a PML checklist will be administered at Screening and before vedolizumab IV administration on Days 1, 15, 43, 71, and 99. Optional endoscopy will be performed to evaluate clinical response to vedolizumab treatment as described in the Schedule of Events (Appendix A).



Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010 [38].

6.2 Number of Patients

Approximately 20 patients will be enrolled to determine the appropriate dose for subsequent patients in the study. The cohort at the chosen dose level then will be expanded by approximately 18 additional evaluable patients to further assess the tolerability and effectiveness of vedolizumab. A total of approximately 38 evaluable patients will be enrolled in this study from approximately 10 to 15 study centers in the United States and Europe. Enrollment is defined as when patients are assigned their first dose of study drug in the interactive voice or web response technology (IRT) system.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may receive vedolizumab unless they experience relapse of the underlying malignancy. Patients will discontinue treatment if they have an unacceptable vedolizumab-related toxicity.

All patients will receive 5 doses of vedolizumab IV (a single dose on each of Days 1, 15, 43, 71, and 99); however, some patients who respond to and tolerate vedolizumab and who develop recurrent symptoms of intestinal GvHD following discontinuation of therapy (ie, after the fifth dose) may enter an extension phase where they may receive 300 mg vedolizumab IV every

2 weeks for 2 doses followed by Q4W for up to 1 year from the first dose of study drug (see Section 6.1).

Patients may receive drug beyond 1 year with the agreement of the investigator and the sponsor if, in the opinion of the investigator, the patient is benefitting from treatment. All patients will be followed for OS every 3 months until death, withdrawal of consent, termination of the study by the sponsor, or for a maximum of 1 year after the last patient is enrolled in the study. Additionally, patients will be required to participate in an LTFU safety survey 6 months after the last dose of study drug.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final analyses for the primary endpoint and clinical study report will be conducted following the end of the study. The estimated timeframe for study completion (first patient in to last patient last visit) is approximately 36 months.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Please refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Maximum Time Frame
Primary:	
• The proportion of subjects with overall response (PR+VGPR+CR) at Day 28.	Up to 28 days
• The number and percentage of patients who experience SAEs from administration of the first dose of vedolizumab IV through Day 28.	Up to 28 days
Secondary:	
• The proportion of subjects who have died in the absence of primary malignancy relapse after allo-HSCT at 6 months.	Up to 6 months
• The proportion of subjects with CR at Day 28.	Up to 28 days
• The proportion of subjects with intestinal overall response at Day 28.	Up to 28 days
• OS at 6 and 12 months.	Up to 1 year
• The proportion of subjects alive without GvHD or relapse of primary malignancy at 6 and 12 months.	Up to 12 months
• The number and percentage of patients who experience TEAEs from administration of the first dose of vedolizumab IV through 18 weeks after administration of the last dose of vedolizumab IV.	Up to 32 weeks
• The number and percentage of patients who experience SAEs from administration of the first dose of vedolizumab IV through 18 weeks after administration of the last dose of vedolizumab IV.	Up to 32 weeks
• Mean serum concentrations of vedolizumab before dosing (C_{trough}) on Day 99.	Up to 14 weeks
• The total dose of steroids administered (mg/kg/day of methylprednisolone or equivalent) from the start of the first IV infusion of vedolizumab through both 6 and 12 months.	Up to 12 months

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 36 months.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Male or female patients aged 18 years or older.
2. Recipient of 1 allo-HSCT but not more than 1 allo-HSCT.
3. Patients with primary steroid-refractory GvHD. Steroid-refractory disease is defined as worsening or no improvement in 5 to 7 days of treatment with methylprednisolone 2 mg/kg or equivalent or lack of a CR after 14 days of primary treatment with methylprednisolone 2 mg/kg or equivalent. Note that patients who develop intestinal GvHD while receiving systemic therapy for other GvHD are still eligible after 5 to 7 days, even if the intestinal GvHD has not been present for the entire duration. Patients who may have received an increase in their steroid dose treatment (eg, increased methylprednisolone from 1 mg/kg to 2 mg/kg) before enrollment will be eligible, provided the patient has met the definition of steroid refractory above. Patients who develop toxicity on corticosteroids or who are otherwise medically unable to be dosed to this level, will also be eligible.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3 (refer to Appendix E).
5. Acute GvHD with intestinal disease involvement with a severity index of B, C, or D using the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)-modified International Bone Marrow Transplant Registry Database (IBMTR) index (See Appendix F). Note that other organ involvement from acute GvHD is also allowed.
6. Evidence of myeloid engraftment defined by absolute neutrophil count $\geq 0.5 \times 10^9$/L on 3 consecutive days.
7. This inclusion criterion is deleted in amendment 02.
8. Sufficient cognitive ability to reliably complete the PML checklist at Baseline.
9. Female patients who:
   - Are postmenopausal for at least 1 year before the Screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice one highly effective method of contraception and one additional effective (barrier) method at the same time, from the time of signing the informed consent through 18 weeks after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 18 weeks after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

10. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
11. Suitable venous access for the study-required blood sampling, including PK and biomarker sampling. Patients with a planned central venous access device will be allowed.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Presence of chronic GvHD at Screening (including acute-chronic overlap syndrome).
2. Relapsed disease after allo-HSCT.
3. Patients with hyperacute GvHD defined as onset of GvHD within the first 15 days following hematopoietic stem cell infusion.
4. Received systemic agents other than corticosteroids for treatment of acute GvHD. GvHD prophylaxis agents (eg, calcineurin inhibitors) may be continued.
5. This exclusion criterion is deleted in amendment 02.
6. Patients with a positive PML subjective checklist must be evaluated by a neurologist for possible PML before enrollment (see Section 10.7). Patients will be excluded if PML cannot be ruled out.
7. Evidence of encephalopathy at Screening.
8. Evidence of severe hepatic veno-occlusive disease/sinusoidal obstruction syndrome.
9. Life expectancy of <3 weeks.
10. History of any major neurological disorders, including multiple sclerosis or neurodegenerative disease. Patients with a history of stroke or brain tumor within the past 3 years are also excluded.
11. Patients with active cytomegalovirus (CMV) colitis (see Section 8.5.3).
12. The patient has chronic hepatitis B (HBV) or hepatitis C (HCV) infection indicated by testing for positive HBV surface antigen, and/or HCV RNA.

13. Any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
14. Positive Clostridium difficile toxin test on a stool sample or evidence of other intestinal pathogens (eg, adenovirus) during Screening.
15. Evidence of uncontrolled active systemic infection.
16. Any serious medical or psychiatric condition that could, in the investigator's or medical monitor's opinion, potentially interfere with the completion of treatment according to this protocol.
17. 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 or medical monitor, would confound the study results or compromise patient safety.
18. History of hypersensitivity or allergies to vedolizumab or its components.
19. If female, the patient is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after participating in this study; or intending to donate ova during such time period.
20. If male, the patient intends to donate sperm during the course of this study or for 18 weeks thereafter.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

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 medication will be provided in a glass vial as a lyophilized solid formulation for reconstitution using sterile water for injection. Each vial will be packaged in an appropriately labeled single vial carton.

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

All infusions will be administered IV over approximately 30 minutes. Longer infusion times of up to 60 minutes may be used based on study observations. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion in a room where appropriate treatment for infusion-related reactions is available. The subject should be considered clinically stable by the investigator or designee prior to discharge.

Additional reference information and administration instructions can be found in the Pharmacy Manual.

8.2 Excluded Concomitant Medications and Procedures

All prescription and over-the-counter medications, including influenza vaccines, taken by a patient as of the first study drug administration through 18 weeks from the last dose will be recorded on the designated electronic case report form (eCRF). Patients must be instructed not to take any medications, including over-the-counter medications and herbal supplements, without first consulting with the investigator.

The following medications and procedures are prohibited during the study:

- Any investigational agent other than vedolizumab.
- Any additional systemic agent other than vedolizumab or corticosteroids for the treatment of acute GvHD. GvHD prophylaxis agents (eg, calcineurin inhibitors) may be continued.
- Approved or investigational biological agents for the treatment of other conditions (eg, rheumatoid arthritis), other than localized injections (eg, intra-ocular injections for wet macular degeneration).

8.3 Permitted Concomitant Medications and Procedures

Other medications considered necessary for the safety and wellbeing of the patient may be administered at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

8.4 Precautions and Restrictions

8.4.1 Criteria for Dosing on Days 15, 43, 71, and 99

After receiving the first dose of vedolizumab IV on Day 1, patients may not receive the second, third, fourth, and/or fifth dose on Days 15, 43, 71, and 99 if they meet any of the following criteria:

1. The patient has a positive PML subjective checklist before the administration of study drug.
2. The patient has suspected CMV colitis. If suspected, endoscopic biopsy is required to rule out CMV colitis before the next dose.
3. The patient has a positive Clostridium difficile test on a stool sample or evidence of other intestinal pathogens (eg, adenovirus).
4. The patient experienced an anaphylactic reaction to vedolizumab.

Patients may continue to receive vedolizumab IV after these criteria have been resolved (refer to Section 8.5).

8.4.2 Reproductive Effects

It is not known what effects vedolizumab has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients in the reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified in the following.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the Screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form (ICF) through 18 weeks after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 18 weeks after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

8.5 Management of Clinical Events

8.5.1 Hypersensitivity Reactions

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to patients receiving vedolizumab; hence, such premedications are unlikely to be necessary or beneficial. At the discretion of the investigator, however, patients may be administered premedication before any study drug administration. Vedolizumab should be administered by a health care professional prepared to manage hypersensitivity reactions, including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use. Patients should be observed during the infusion and until the infusion is complete.

Patients should be instructed to report the development of rash, hives, pruritus, flushing, urticaria, etc that may represent an infusion-related reaction to study medication. If signs or symptoms of infusion-related reaction are observed during the administration of study drug, it should be immediately discontinued and the patient treated as medically appropriate. In the case of a mild reaction, study drug administration may be reinitiated (with appropriate premedication) at the discretion of the investigator. Patients with severe or serious infusion-related reactions (eg, stridor, angioedema, life-threatening change in vital signs) must be withdrawn from the study.

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

8.5.2 Leukopenia or Lymphopenia

Leukocyte and lymphocyte counts will be monitored for all patients with a hematological panel (see Section 9.4.14). Blood samples for analysis of hematological parameters will be obtained as specified in the Schedule of Events (Appendix A).

8.5.3 CMV Colitis

Regular assessments will include symptom-directed assessment for GI toxicity and weekly polymerase chain reaction (PCR) monitoring for CMV reactivation. Preemptive CMV therapy will be initiated per institutional standards for patients with CMV titers ≥500 copies/mL and rising on serial PCR. Subjects with active CMV colitis during Screening will be excluded from the study, and subjects with confirmed CMV colitis during the study will require dosing hold. In patients

with suspected CMV colitis, the subject will require endoscopy and histologic analyses of intestinal biopsy specimens before any additional dosing with vedolizumab.

8.5.4 Malignancy

All cases of malignancies that are detected during the study, including relapse of primary disease, will be reported as AEs.

8.5.5 Other Clinical Events

All patients will be screened for new neurological signs and symptoms potentially consistent with PML using the PML subjective symptom checklist (see Section 9.4.8) before dosing with vedolizumab. Any patients reporting signs or symptoms of PML will undergo objective testing. If a patient demonstrates a neurologic deficit related to PML upon administration of the specific test(s) on the objective checklist, no further doses of vedolizumab should be administered to that patient. The patient should be referred to the study neurologist for further testing, and the sponsor must be notified of this action.

Subsequent doses of study drug will be administered only if the possibility of PML is definitively excluded, as described in the RAMP algorithm.

8.6 Dose Modification or Treatment Delay for Vedolizumab-Related Toxicity

Dosing of vedolizumab should be withheld for Grade 3 or higher vedolizumab-related toxicities. See Section 8.5 for management of vedolizumab dosing for specific clinical events. The medical monitor should be contacted before any vedolizumab dose modification for any patient in the study.

8.7 Blinding and Unblinding

This is an open-label study. Patients will be randomized at a ratio of 1:1 to 2 treatment arms to receive either 300 or 600 mg vedolizumab IV on Days 1, 15, 43, 71, and 99. The investigator or investigator's designee will access the IRT system at Screening to obtain the subject study number. The investigator or the investigator's designee will use the IRT 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. The medication identification (ID) number of the investigational drug to be dispensed will then be provided by the IRT. If sponsor-supplied drug is lost or damaged, the site can request a replacement from IRT. Refer to the IRT manual provided separately. At subsequent drug-dispensing visits, the investigator or designee will again contact the IRT to request additional investigational drug for a subject. The medication ID number of the investigational drug to be dispensed will be provided by the IRT.

8.8 Description of Investigational Agent

Vedolizumab IV drug product is a sterile lyophilized solid formulation provided in a single vial, where each vial nominally contains 300 mg of vedolizumab antibody. Reconstituted

vedolizumab IV drug product contains 60 mg/mL of active vedolizumab antibody, 50 mM histidine/histidine HCl, 125 mM arginine HCl, 100 mg/mL sucrose, and 0.6 mg/mL polysorbate 80, with a pH of 6.3.

Each vial will be reconstituted with sterile water for injection according to the instructions in the Pharmacy Manual.

8.9 Preparation, Reconstitution, and Dispensation

The investigational pharmacist will prepare the study treatment under standard aseptic conditions. For preparation of the active vedolizumab treatment, each vial of vedolizumab will be reconstituted according to the Pharmacy Manual with 4.8 mL of sterile water for injection. For the 300 mg dose, 5.0 mL will be removed from each vial and diluted into 0.9% sodium chloride to an approximate volume of 250 mL. For the 600 mg dose, 5.0 mL will be removed from each of 2 vials and diluted into 0.9% sodium chloride to an approximate volume of 250 mL. Additional details on the preparation of vedolizumab are provided in the Pharmacy Manual.

Because vedolizumab is a biological protein and, therefore, subject to denaturation upon shaking, reconstituted vials and IV solution bags should not be shaken. Vials are for single-use administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

8.10 Packaging and Labeling

Vedolizumab IV will be supplied in single-use, 20 mL vials. The injection vials will be packaged into individual kits containing one 20 mL vial of active vedolizumab. Both the primary and secondary label information will fulfill all requirements specified by local governing regulations. Additional details are provided in the Pharmacy Manual.

8.11 Storage, Handling, and Accountability

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

Vedolizumab IV must be stored at 2°C to 8°C (36°F-46°F). A daily temperature log of the drug storage area must be maintained every working day.

8.12 Other Protocol-Specified Materials

The following supplies will also be required for study treatment administration and are to be provided by the clinical study center:

- Bottled sterile water for injection (for vedolizumab reconstitution).
- 250 mL 0.9% sodium chloride for injection in polyvinyl chloride (PVC) IV bag(s) or 250 mL 0.9% sodium chloride in alternative IV bags or bottles listed in the Pharmacy Manual.

- PVC infusion line or alternative infusion line listed in the Pharmacy Manual.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the medical monitor for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, the IRT provider, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC).

9.3 Treatment Group Assignments

Patients will be randomized at a ratio of 1:1 to 2 treatment arms to receive either 300 or 600 mg vedolizumab IV on Days 1, 15, 43, 71, and 99. The investigator or investigator's designee will access the IRT system at Screening to obtain the subject study number (see Section 8.7). If a patient discontinues from study drug, the randomization code will not be reused, and the patient will not be allowed to re-enter the study. The sponsor may opt to replace patients who discontinue before Day 28 for reasons other than vedolizumab-related safety events.

9.4 Study Procedures

Refer to the Schedule of Events (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow. Evaluations during the Screening period are to be conducted within 28 days before administration of the first dose of study drug. Unless otherwise noted, evaluations during the Treatment period must occur before study drug administration. Tests and procedure should be performed on schedule for all visits. The timing of PK assessments is specified in the Pharmacokinetic Sample Breakdown table.

9.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.4.2 Patient Demographics

The date of birth or age, race (where allowed), ethnicity, and sex of the patient are to be recorded during Screening.

9.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will include the background of the patient's malignancy and prior therapies for it, and the background of the patient's transplant and post-transplant course. In addition, concomitant medications will be recorded as specified in Section 9.4.10.

9.4.4 Physical Examination

Physical examinations will be completed per standard of care at the times specified in the Schedule of Events (Appendix A).

9.4.5 Neurological Examination

A neurological examination, including assessments of cranial nerves, motor and sensory function, coordination, and mental status, will be performed at the time points specified in the Schedule of Events (Appendix A). Completed neurological forms will be stored by the sponsor and sent to the CRO. Clinically significant findings from the neurological examination will be recorded as medical history during Screening, and new clinically significant findings will be recorded as AEs after the first dose of study drug.

9.4.6 Patient Height and Weight

Height will be recorded only during Screening (within 28 days before the first dose of vedolizumab). Body weight will be recorded at the visits specified in the Schedule of Events (Appendix A).

9.4.7 Vital Signs

Vital signs, including heart rate, respiratory rate, systolic and diastolic blood pressure, and temperature, will be recorded at the visits specified in the Schedule of Events (Appendix A). On dosing days, vital signs will be obtained before and within 60 minutes of completion of the infusion.

9.4.8 PML Checklist

Clinic staff will administer the subjective PML checklist during Screening to exclude patients with positive responses from enrolling into the study. The subjective PML checklist will be administered (before dosing, if applicable) at the time points specified in the Schedule of Events (Appendix A) to probe for symptoms suggestive of PML. The checklist must be administered by appropriate clinic staff as it is not designed as a patient questionnaire. A patient who reports a new and persistent change(s) per the subjective checklist must have the corresponding objective test(s) administered and may be referred to a neurologist for a full evaluation, as described in the RAMP algorithm. The PML checklist and the RAMP algorithm and tools are included in the Study Manual. See Section 10.7 for additional details regarding the RAMP program.

9.4.9 Pregnancy Test

A serum or urine pregnancy test will be performed for women of childbearing potential at Screening and within 4 days before the first dose of study drug. The results from these tests must be available and negative before the first dose of study drug is administered.

9.4.10 ECOG Performance Status

The ECOG performance status (see Appendix E) will be assessed at the times specified in the Schedule of Events (Appendix A).

9.4.11 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the eCRF from the first dose of study drug through 18 weeks after the last dose of study drug. See Section 8.2 and Section 8.3 for a list of medications and therapies that are prohibited and/or allowed during the study.

9.4.12 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

9.4.13 Enrollment

Enrollment is defined as when patients are assigned their first dose of study drug in the IRT system. Procedures for completion of the enrollment information are described in the Study Manual.

9.4.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Results of hematology and clinical chemistry safety labs must be available and reviewed by the investigator before enrollment and administration of any study drug. Handling of clinical laboratory samples will be outlined in the Study Manual. Clinical laboratory evaluations will be performed as outlined below.

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the Schedule of Events (Appendix A). Hepatitis and human immunodeficiency virus testing are to be performed only at the Screening visit.

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase (ALP)	Gamma glutamyl transferase (GGT)
Leukocytes with differential	Alanine aminotransferase (ALT)	Glucose
Neutrophils (absolute neutrophil count [ANC])	Aspartate aminotransferase (AST)	Lactate dehydrogenase (LDH)
Platelet (count)	Bilirubin (total)	Magnesium
	Blood urea nitrogen (BUN) (a)	Phosphate
	Calcium	Potassium
	Carbon dioxide (CO_2)	Sodium
	Creatinine	Urate

(a) Blood urea (in mmol/L)=BUN(in mg/dL)×0.357.

PCR monitoring for CMV reactivation will be performed on a weekly basis (see Section 8.5.3) per standard of care. Additionally, blood samples for measurement of anti-vedolizumab antibodies will be obtained as specified in the Schedule of Events (Appendix A).

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

9.4.15 Disease Assessment

Acute GvHD will be assessed as specified in the Schedule of Events (Appendix A) using the BMT CTN-modified IBMTR index for staging and grading acute GvHD (see Appendix F). All cases of malignancies that are detected during the study, including relapse of primary disease, will be reported as AEs (see Section 8.5.4). In addition, other measures such as stool volume, oral intake, and total parenteral nutrition requirement will be collected.

9.4.16 Endoscopy

Endoscopy (optional) will be performed as specified in the Schedule of Events (Appendix A) only for patients already planned for the procedure and will be read locally for efficacy analysis. Biopsy specimens, if available, will be collected for these patients for other histologic analyses, including changes in lymphocyte recruitment patterns.

Detailed instructions for handling and shipping samples are provided in the Laboratory Manual.

9.4.17 PK Measurements

Blood samples (one 5 mL sample per scheduled time) for PK analysis of vedolizumab will be collected into red stopper vacutainers according to the Pharmacokinetic Sample Breakdown table. Note: if done via peripheral vein, PK samples should not be collected from the arm where the vedolizumab infusion was administered. All PK samples should be collected within 10% of nominal time; however, samples collected outside this margin will not be considered protocol deviations. Predose samples should be collected within 0.5 hours before the start of infusion and end of infusion samples should be collected at 30 ± 5 minutes, 1 hour ± 10 minutes; 2 hours ± 20 minutes; 12 ± 2 hours; and 24 hours ± 60 minutes. The exact dates and times of administration of vedolizumab (start and end of infusion) and the exact dates and times of collection of all PK samples will be recorded on the appropriate eCRF.

Detailed instructions for the handling and shipping of samples are provided in the Laboratory Manual.

9.4.18 Company Confidential Information

Confidential Company Information

9.4.19 Company Confidential Information

Confidential Company Information

9.4.20 Company Confidential Information

Confidential Company Information

9.4.21 Immunogenicity

A blood sample will be taken to evaluate the presence of anti-vedolizumab antibodies in serum at the time points specified in the Schedule of Events (Appendix A).

Detailed instructions for the handling and shipping of samples are provided in the Laboratory Manual.

9.4.22 Fecal Microbiome Samples

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[redacted]

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they received all 5 intended doses of vedolizumab IV on Days 1, 15, 43, 71, and 99. In addition, patients will be considered to have completed study treatment if they discontinue study drug for any of the reasons outlined in Section 9.7.

9.6 Completion of Study (for Individual Patients)

In addition to completion or discontinuation of study drug treatment, patients will be considered to have completed the study if they withdraw from the study for any of the reasons outlined in Section 9.8.

For all subjects receiving study medication, the investigator must complete the end-of-study (EOS) eCRF page.

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Treatment with study drug may be discontinued for any of the following reasons:

- AE.
- Protocol deviation.
- Unsatisfactory therapeutic response.
- Progression of underlying malignancy.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

The sponsor may opt to replace patients who discontinue before Day 28 for reasons other than those related to safety. Once study drug has been discontinued, all study procedures outlined for the ET visit will be completed as specified in the Schedule of Events (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

9.8 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up.

- Study terminated by sponsor.
- Withdrawal by subject.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

9.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

9.10 Posttreatment Follow-up Assessments

Patients will be followed for survival and assessment of symptoms of acute and chronic GvHD or relapse of primary malignancy during clinic visits at 4, 5, 6, 9, and 12 months or until the patient's death or withdrawal of consent, or termination of the study by the sponsor. Patients who complete the study will attend a 12-month follow-up visit (EOS).

All patients will be followed for OS every 3 months after the 12 month follow-up visit, until death, withdrawal of consent, termination of study by the sponsor, or for a maximum of 1 year after the last patient is enrolled in the study. In addition, the start of another systemic therapy for treatment of GvHD or for the primary malignancy will be collected. The EOS visit is to be completed when the patient discontinues from the follow-up period. Additionally, patients will be required to participate in an LTFU safety survey 6 months after the last dose of study drug. See the Schedule of Events (Appendix A) for appropriate assessments during follow-up.

NOTE: Related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

A PTE is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the

development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [38]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

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Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [38]. The criteria are provided in the Study Manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study drug?"

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 18 weeks after administration of the last dose of study drug and recorded in the eCRFs.
- Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to the first dose of study drug, but will not be recorded in the eCRF.
- Related and unrelated SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 18 weeks after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided below.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email addresses provided below.

Call center	Phone number	E-mail	Fax
DLSS	Company Confidential Information		

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Company Confidential Information (refer to Section 10.2).

10.6 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, 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 an 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 an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.7 Risk Minimization Action Plan for PML (RAMP Program)

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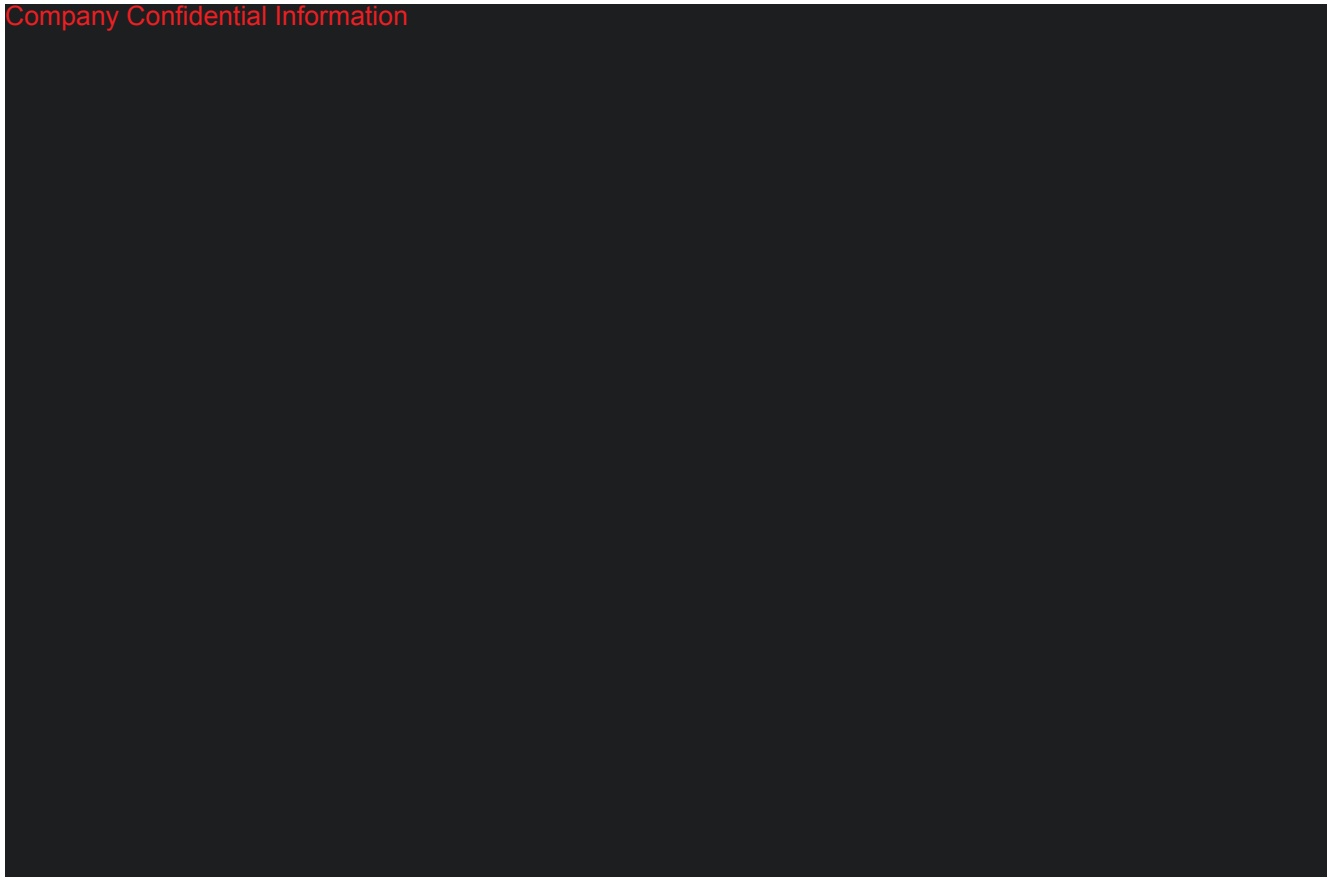

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study. Review of patient safety throughout the study will occur during regular meetings between the sponsor and investigators.

An IAC has been identified 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.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

Completed eCRFs are required for each subject who receives study drug.

The sponsor or its designee will supply investigative sites with access to eCRFs and 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, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs 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.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. 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 principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the 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 ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs 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, 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 Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical 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 before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, patient evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- Safety population: The population of patients evaluable for vedolizumab safety is defined as all patients who receive any amount of study drug.
- Efficacy population: Defined as all patients from the safety set who have completed their Day 28 assessment.
- Per-protocol population: Defined as all patients from the efficacy set who do not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the medical monitor.
- PK population: Defined as patients from the safety set with at least 1 postdose PK sample collected.
- Biomarker population: Defined as patients from the safety set with at least 1 biomarker sample collected.

13.1.2 Procedures for Handling Missing, Unused, and Spurious Data

All available safety, tolerability, efficacy, PK, and biomarker data will be included in data listings and tabulations. No imputation of values for missing data will be performed. The relevance of missing sample data will be assessed.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

13.1.3 Analysis of Demographics and Other Baseline Characteristics

Demographic (age, sex, and other parameters as appropriate) and baseline characteristics (weight, height, and other parameters, as appropriate) will be summarized by dose level.

13.1.4 Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects with overall response (PR+VGPR+CR) in GvHD at Day 28.

Secondary efficacy endpoints include:

- The proportion of subjects who have died in the absence of primary malignancy relapse after allo-HSCT at 6 months.
- The proportion of subjects with acute GvHD CR at Day 28.
- The proportion of subjects with intestinal overall response at Day 28. Symptoms of acute intestinal GvHD will be measured using the BMT CTN-modified IBMTR index (See Appendix F).
- OS at 6 and 12 months.
- The proportion of subjects alive without GvHD or relapse of primary malignancy at 6 and 12 months.
- The total dose of steroids administered (mg/kg/day of methylprednisolone or equivalent) from the start of the first IV infusion of vedolizumab through both 6 and 12 months.

Safety, PK, and efficacy data will be used in decision making. For efficacy evaluation, a Bayesian statistical approach will be used where posterior probability that PR+VGPR+CR rate is at least 70% will be derived from this distribution. If this probability is at least 75% ("75% level of proof at 70%"), this will be considered a positive proof-of-concept in efficacy. Efficacy signals will be evaluated using the initial cohorts and will be updated using the expansion cohort. A flat noninformative prior probability distribution will be assumed in the Bayesian analysis.

In addition, patients will be followed for OS. OS is defined as the time from the date of enrollment to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

13.1.5 Resource Utilization and Patient-Reported Outcome Analysis

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[redacted]

13.1.6 PK Analysis

Concentrations of vedolizumab will be summarized by dose level and by nominal time using descriptive statistics. Individual concentration–time profiles will be presented in data listings. PK parameters will be derived using standard noncompartmental methods. PK parameters of

vedolizumab will be summarized using descriptive statistics. Other PK parameters may be calculated if necessary.

PK parameters will be summarized by dose level. A detailed plan will be provided in the SAP.

13.1.7 Biomarker Analysis

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[redacted]

13.1.8 Immunogenicity Analyses

Immunogenicity (anti-vedolizumab antibodies [AVA]) will be descriptively summarized. The effect of anti-vedolizumab antibodies on safety and efficacy will be explored. The proportion of subjects with positive AVA (transient and persistent) and proportion of subjects with positive neutralizing AVA during the study will be summarized at each visit. Further information about the immunogenicity analyses will be provided in the SAP.

13.1.9 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to study drug will be summarized, and reasons for discontinuation will be tabulated. Safety will be summarized by dose level.

TEAEs will be tabulated. Treatment-emergent is defined as any AE that occurs after administration of the first dose of study drug and up through 18 weeks after the last dose of study medication.

AEs will be tabulated according to MedDRA by SOC, high-level terms, and preferred terms and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 TEAEs.
- Grade 4 TEAEs.
- Grade 5 TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs.
- SAEs.

Listings of PML checklist data and TEAEs resulting in study drug discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters. Descriptive statistics for the actual values (and/or the change from baseline) of vital signs, weight, and blood pressure time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value.

Concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term in the safety analysis set. In addition, the number and percentage of patients receiving blood transfusions will be tabulated in the safety analysis set.

13.2 Interim Analysis

There will be 1 interim analysis when all patients in the dose finding phase have reached Day 28.

13.3 Determination of Sample Size

Approximately 38 evaluable patients will be enrolled to identify an active and tolerable vedolizumab dose level with sufficient PK sampling to determine the PK parameters in this patient population. Sample size determination is mainly based on clinical considerations and on the primary objective of determining a recommended dose and regimen and to describe the initial activity, tolerability, safety, and activity of vedolizumab IV administered for the treatment of primary steroid-refractory acute intestinal GvHD.

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 medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study 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 (a prospectively approved deviation) 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 EC, 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 US 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 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 American 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 IB, a copy of the ICF, 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, ICF) reviewed; and state the approval date. The sponsor will ship drug 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.

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 ICF, 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 ICF, 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 ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The ICF, 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 ICF, 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 ICF 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 before 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 ICF and subject authorization (if applicable) at the time of consent and before 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 ICF, 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 ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs 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 ICF.

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 study 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, US FDA, United Kingdom Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency of Japan), 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

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 or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's investigators), country, and recruiting status will be registered and available for public viewing.

As needed Takeda and Investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants to find a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods 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 Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, 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 clinical study subjects. Refer to the Clinical 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 Events

Schedule of Events for Dose Finding and Expansion Phases (Screening Through Day 32)

	Screening (a)	Day 1	Day 2	Day 3	Day 5	Day 7	Day 9	Day 11	Day 15	Day 16	Day 18	Day 20	Day 22	Day 24	Day 28	Day 32
Informed consent	X															
Inclusion/exclusion criteria	X	X (b)														
Demographics	X															
Medical history	X	X (c)														
Complete physical examination and neurological assessment	X															
Symptom-directed physical examination		X (b)				X			X (b)				X		X	
Height	X															
Weight	X					X			X				X		X	
Vital signs	X	X (d)				X			X (d)				X		X	
ECOG performance status	X	X				X			X				X		X	
PML checklist	X	X (b)							X (b)							
PML wallet card	X															
EQ-5D	X														X	
FACT-BMT	X														X	
Assessment of GvHD	X	X				X			X				X		X	
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through 18 weeks after the last dose of study drug														
Adverse event reporting		Recorded from first dose of study drug through 18 weeks after the last dose of study drug														
	Serious adverse events (e) will be reported from signing of the ICF through 18 weeks after the last dose of study drug.															
Vedolizumab IV administration (f)		X							X							
Samples/Laboratory Assessments																
Pregnancy test (g)	X1	X1 (b)														

Footnotes are on last table page.

Schedule of Events for Dose Finding and Expansion Phases (Screening Through Day 32) (continued)

	Screening (a)	Day 1	Day 2	Day 3	Day 5	Day 7	Day 9	Day 11	Day 15	Day 16	Day 18	Day 20	Day 22	Day 24	Day 28	Day 32
Hematology/chemistry (l)	X1 (l)	X1 (b)				X1			X1 (b)				X1		X1	
Urinalysis		X1 (b)														
Fecal sample for microbiome analysis (h)	X1	X1							X1						X1	
Blood sample for flow cytometry (i)		X1 (b)	X1			X1			X1 (b)		X1				X1	
Blood sample for serum biomarkers		X1 (b)	X1(j)			X1			X1 (b)		X1				X1	
Blood sample for anti-vedolizumab antibodies (i)		X1 (b)											X1			
Blood sample for PK (k)		See Pharmacokinetic Sample Breakdown Table														

ECOG=Eastern Cooperative Oncology Group, EQ-5D=European Quality of Life 5-Dimensional, FACT-BMT=Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale, GvHD=graft-versus-host disease, ICF=informed consent form, IV=intravenous, PK=pharmacokinetic(s), PML=progressive multifocal leukoencephalopathy, X#=the number of samples required (eg, 2 samples=X2).

Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days, except where otherwise specified) with permission from the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission from the medical monitor.**

(a) Unless otherwise noted, the Screening visit must occur within 28 days before the day of the first dose of study drug (Day 1); however, the ICF may be signed more than 28 days before Day 1.

(b) Assessment/sample collection should be performed predose.

(c) The Day 1 medical history is not required if the screening medical history was obtained within 4 days before administration of the first dose of study drug (Day 1).

(d) Vital signs will be obtained before and within 60 minutes of completion of IV infusion of vedolizumab.

(e) Including serious pretreatment events; See Section 10.2.

(f) Vedolizumab will be administered via an approximately 30 minute IV infusion on Days 1 and 15.

(g) A serum or urine beta-human chorionic gonadotropin pregnancy test will be performed only for patients of childbearing potential during Screening and again on Day 1 (Baseline) if the screening test was performed more than 4 days before the first dose of any study drug. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations.

(h) Sample must be taken from the first bowel movement of the day.

(i) Additional specimens may be collected from any patient who experiences an infusion reaction.

(j) To be collected 24 hours (±3 hours) postdose from the preceding day.

(k) Time points for blood samples for PK analysis will be collected as specified in the Pharmacokinetic Sample Breakdown table.

(l) Hepatitis and human immunodeficiency virus testing are to be performed only at the Screening visit. Negative results of all such tests are required for subject enrollment.

Schedule of Events (Day 36 Through End of Study)

	Day 36	Day 40	Day 43	Day 71	Day 99	Extension Dose Visit (a)	4 Month Follow-up Visit (b)	5 Month Follow-up Visit (b)	6 Month Follow-up Visit (b)	9 Month Follow-up Visit (b)	Unscheduled Visit	12 Month Follow-up/ EOS/ET Visit (b)	OSFU
Symptom-directed physical examination	X		X (d)	X (d)	X (d)	X (d)						X	
Weight	X		X	X	X	X	X	X	X	X	X	X	
Vital signs	X		X (c)	X (c)	X (c)	X	X	X	X	X	X	X	
ECOG performance status	X		X	X	X	X	X	X	X	X		X	
PML checklist			X (d)	X (d)	X (d)	X (d)							
Follow-up phone calls													Q3mo (e)
PML wallet card												X	
EQ-5D			X	X	X	X	X	X	X	X		X	
FACT-BMT			X	X	X	X	X	X	X	X		X	
Assessment of GvHD	X		X	X	X	X	X	X	X	X	X	X	
Monitoring of concomitant medications and procedures	Recorded from first dose of study drug through 18 weeks after the last dose of study drug												
Adverse event reporting	Recorded from first dose of study drug through 18 weeks after the last dose of study drug												
	Serious adverse events (f) will be reported from signing of the ICF through 18 weeks after the last dose of study drug.												
Vedolizumab IV administration (g)			X	X	X	X							
Endoscopy (h)											X		
Samples/Laboratory Assessments													
Hematology/chemistry			X1 (d)	X1 (d)	X1 (d)	X1 (d)	X1	X1	X1			X1	
Fecal sample for microbiome analysis (j)	X1		X1	X1	X1								

Footnotes are on last table page.

Schedule of Events (Day 36 Through End of Study) (continued)

	Day 36	Day 40	Day 43	Day 71	Day 99	Extension Dose Visit (a)	4 Month Follow-up Visit (b)	5 Month Follow-up Visit (b)	6 Month Follow-up Visit (b)	9 Month Follow-up Visit (b)	Unscheduled Visit	12 Month Follow-up/ EOS/ET Visit (b)	OSFU
Blood sample for flow cytometry	X1		X1 (d,k)	X1 (d,k)	X1 (d,k)								
Company Confidential Information													
Blood sample for anti-vedolizumab antibodies (d,k)				X1 (k)	X1 (k)							X1	
LTFU Safety Survey	Safety survey completed for patients in long-term follow-up 6 months after the last dose of study drug.												
Blood sample for PK (l)	See Pharmacokinetic Sample Breakdown table												

ECOG=Eastern Cooperative Oncology Group, EOS=end-of-study, EQ-5D=European Quality of Life 5-Dimensional, ET=early termination, FACT-BMT=Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale, GvHD=graft-versus-host disease, ICF=informed consent form, IV=intravenous, LTFU=long-term follow-up; OSFU=overall survival follow-up, PK=pharmacokinetic(s), PML=progressive multifocal leukoencephalopathy, Q3mo=every 3 months, X#=the number of samples required (eg, 2 samples=X2). Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days, except where otherwise specified) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

(a) Upon review and agreement by the medical monitor, patients who respond to and tolerate all 5 planned doses of vedolizumab and who develop recurrent symptoms of intestinal GvHD following discontinuation of therapy (ie, after the fifth dose) may enter an extension phase where they may receive 300 mg vedolizumab IV every 2 weeks for 2 doses followed by every 4 weeks for up to 1 year from the first dose of study drug. A dose other than 300 mg and/or a frequency of administration other than every 4 weeks may be chosen based on accumulating safety, tolerability, efficacy, and PK results. Patients may receive drug beyond 1 year with the agreement of the investigator and the sponsor if, in the opinion of the investigator, the patient is benefitting from treatment.

(b) Symptoms of acute and chronic GvHD and safety will be assessed during clinic visits at 4, 5, 6, 9, and 12 months after Day 1 or until the patient's death or withdrawal of consent or termination of the study by the sponsor. Patients who complete the study will attend a 12-month follow-up visit (EOS).

(c) Vital signs will be obtained before and within 60 minutes of completion of IV infusion of vedolizumab.

(d) Assessment/sample collection should be performed predose.

(e) Patients will be followed for overall survival (OS) every 3 months after the 12-month follow-up visit until death, withdrawal of consent, termination of study by the sponsor, or for a maximum of 1 year after the last patient is enrolled in the study. OS is defined as the time from the date of enrollment to the date of death.

(f) Including serious pretreatment events; see Section 10.2.

(g) Vedolizumab will be administered via an approximately 30 minute IV infusion on Days 43, 71, and 99.

(h) Endoscopy will be performed to assess response to treatment. This procedure is optional and will only be performed for patients already planned for endoscopy. Biopsy specimens, if available, will be collected for these patients for other histologic analyses, including changes in lymphocyte recruitment patterns.

(i) This footnote is deleted from this schedule of events (SOE) and was moved to appear in the Screening visit.

(j) Sample must be taken from the first bowel movement of the day.

(k) Additional specimens may be collected from any patient who experiences an infusion reaction.

(l) Time points for blood samples for PK analysis will be collected as specified in the Pharmacokinetic Sample Breakdown table.

Pharmacokinetic Sample Breakdown

	Day																			
	1	2	3	5	7	9	11	15	16	18	20	22	24	28	32	36	40	43	71	99
	Serum																			
PK collection on nondosing days (a)			X1	X1	X1	X1	X1			X1	X1	X1	X1	X1	X1	X1	X1			
Predose	X1							X1										X1	X1	X1
30 min postdose (±5 min)	X1																	X1	X1	X1
1 h postdose (±10 min)																		X1	X1	X1
2 h postdose (±20 min)	X1							X1										X1	X1	X1
12 h postdose (±2 h)	X1							X1												
24 h postdose (±60 min)		X1							X1											

PK=pharmacokinetic, X#=the number of samples required (eg, 2 samples=X2).
(a) Once the patient completes the inpatient period (as determined by the investigator), sample collection may be aligned with clinic visits. All PK samples should be collected within 10% of nominal time; however, samples collected outside this margin will not be considered protocol deviations. The total number of collected PK samples should be no greater than the amount outlined in this table.

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 by 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 by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, before 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/IEC that conform to 21 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 ICF 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 ICF 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.

Appendix C 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 medication.
- 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 D Definitions for Assessing Response in Treatment of Acute GvHD

Terminology	Definition
CR	Resolution of all signs and symptoms of acute GvHD.
VGPR	Skin: No rash, or residual erythematous rash involving <25% of the body surface, without bullae (excluding residual faint erythema and hyperpigmentation). Liver: Total serum bilirubin concentration <2 mg/dL or <25% of baseline at enrollment. Gut: • Patient tolerates food or enteral feeding. • Predominantly formed stools. • No overt gastrointestinal bleeding or abdominal cramping. • No more than occasional nausea or vomiting.
PR	Improvement of 1 GvHD stage in 1 or more organs without progression in any organ.

Source: Martin PJ, et al, 2009 [31].

Appendix E Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, et al, 1982 [41].

Appendix F Clinical Stages of Graft-Versus-Host Disease

Acute Graft-Versus-Host Disease Clinical Stage

Stage	Skin	Liver Bilirubin: SI Units (Standard Units)	Intestinal Tract Diarrhea/Day
1	Maculopapular rash <25% of body surface (a)	34-50 µmol/L (2-3 mg/dL)	>500 mL diarrhea/day
2	Maculopapular rash 25%-50% of body surface	51-102 µmol/L (3.1-6 mg/dL)	>1000 mL diarrhea/day
3	Rash >50% of body surface	103-225 µmol/L (6.1-15 mg/dL)	>1500 mL diarrhea/day
4	Generalized erythroderma with bullous formation	>255 µmol/L (>15 mg/dL)	Severe abdominal pain, with or without ileus

From Przepiorka et al, 1995 [42].
SI=International System of Units (Système Internationale d'Unités).
(a) Use the "Rule of Nines" or burn chart to determine the extent of the rash.

Criteria for IBMTR Severity Index for Acute Graft-Versus-Host Disease

	Skin			Liver			Intestinal Tract	
Index	**Stage (max)**	**Extent of Rash**		**Stage (max)**	**Total Bilirubin (µmol/L)**		**Stage (max)**	**Volume of Diarrhea (mL/day)**
A	1	<25%		0	<34		0	<500
B	2	25-50%	*or*	1-2	34-102	*or*	1-2	550-1500
C	3	>50%	*or*	3	103-255	*or*	3	>1500
D	4	Bullae	*or*	4	>255	*or*	4	Severe pain and ileus

From Rowlings et al, 1997 [43].
IBMTR=International Bone Marrow Transplant Registry Database.

Appendix G Amendment 02 Detailed Summary of Changes

THE PRIMARY SECTIONS OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 02 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Change 1: Clarification that the progressive multifocal leukoencephalopathy (PML) checklist is administered per Section 9.4.8.

The primary change occurs in Section 6.1 Overview of Study Design:

Initial wording:	To minimize the risk of PML, a RAMP questionnaire will be administered at Screening and before vedolizumab IV administration on Days 1, 15, 43, 71, and 99.
Amended or new wording:	To minimize the risk of PML, a ~~RAMP questionnaire~~ **PML checklist** will be administered at Screening and before vedolizumab IV administration on Days 1, 15, 43, 71, and 99.

Rationale for Change:

To clarify that it is the PML checklist that is administered to patients and that this named reference is used consistently throughout the protocol and in the SOEs.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 7.1 Inclusion Criteria.
- Section Appendix A Schedule of Events.

Change 2: Clarification to the description of patients with steroid-refractory graft-versus-host disease (GvHD) who are eligible for enrollment to the study.

The primary change occurs in Section 7.1 Inclusion Criteria

Added text: **Patients who develop toxicity on corticosteroids or who are otherwise medically unable to be dosed to this level, will also be eligible.**

Rationale for Change:

To allow patients who have developed sensitivity to corticosteroids and can't be dosed at the designated dose to be enrolled to the study.

Change 3: Deletion of the inclusion criterion specifying a required level of creatinine clearance for enrollment in the study.

The primary change occurs in Section 7.1 Inclusion Criteria:

Initial wording:	7.	Creatinine clearance based on the Cockcroft-Gault estimate of ≥60 mL/minute/1.73 m^2 for patients with serum creatinine concentrations above institutional limits (see Section 9.4.14).
Amended or new wording:	7.	**This inclusion criterion is deleted in amendment 02.** ~~Creatinine clearance based on the Cockcroft-Gault estimate of ≥60 mL/minute/1.73 m^2 for patients with serum creatinine concentrations above institutional limits (see Section 9.4.14)~~.

Rationale for Change:

To prevent unnecessary screen failures for a criterion considered irrelevant to the study.

Section 9.4.14 Clinical Laboratory Evaluations also contains this change (removal of the estimation of creatinine clearance).

Change 4: Deletion of the exclusion criterion requiring the occurrence of acute steroid resistant GvHD within 28 days from primary treatment.

The primary change occurs in Section 7.2 Exclusion Criteria:

Initial wording:	5. Acute steroid-resistant GvHD beyond 28 days from primary treatment.
Amended or new wording:	5. **This exclusion criterion is deleted in amendment 02**. ~~Acute steroid-resistant GvHD beyond 28 days from primary treatment.~~

Rationale for Change:

To allow patients beyond 28 days of primary treatment of acute GvHD to enter the study.

Change 5: Addition of viral testing procedures to be conducted at the Screening visit.

The primary change occurs in Section 9.4.14 Clinical Laboratory Evaluations:

Added text: **Hepatitis and human immunodeficiency virus testing are to be performed only at the Screening visit.**

Rationale for Change:

Improve consistency between the procedure section and the SOE.

Section Appendix A Schedule of Events also contains this change in footnote (l).

Change 6: Correction and specification of the pharmacokinetic (PK) postinfusion sampling times.

The primary change occurs in Section 9.4.17 PK Measurements:

Initial wording:	Predose samples should be collected within 0.5 hours before the start of infusion, and end of the infusion samples should be collected within 5 minutes after the end of infusion.
Amended or new wording:	Predose samples should be collected within 0.5 hours before the start of infusion~~,~~ and end of the infusion samples should be collected ~~within 5 minutes after the end of infusion~~ at **30 ± 5 minutes, 1 hour ± 10 minutes; 2 hours ± 20 minutes; 12 ± 2 hours; and 24 hours ± 60 minutes**.

Rationale for Change:

Improve consistency between the procedure section and the SOE.

Change 7: Correction to the end of treatment (ET) visit.

The primary change occurs in Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement:

Initial wording:	Once study drug has been discontinued, all study procedures outlined for the EOS visit will be completed as specified in the Schedule of Events (Appendix A).
Amended or new wording:	Once study drug has been discontinued, all study procedures outlined for the ~~EOS~~ **ET** visit will be completed as specified in the Schedule of Events (Appendix A).

Rationale for Change:

To correct that the ET visit will be conducted (and all associated procedures) when study drug is discontinued.

Change 8: Clarification of the posttreatment follow-up assessments.

The primary change occurs in Section 9.10 Posttreatment Follow-up Assessments

Initial wording:	Patients will be followed for survival and assessment of GvHD or relapse of primary malignancy for 1 year after enrollment or until the patient's death or withdrawal of consent, or termination of the study by the sponsor. All patients will be followed for OS every 3 months until death, withdrawal of consent, termination of study by the sponsor, or for a maximum of 1 year after the last patient is enrolled in the study.
Amended or new wording:	Patients will be followed for survival and assessment of **symptoms of acute and chronic** GvHD or relapse of primary malignancy **during clinic visits at 4, 5, 6, 9, and 12 months** ~~for 1 year after enrollment~~ or until the patient's death or withdrawal of consent, or termination of the study by the sponsor. **Patients who complete the study will attend a 12-month follow-up visit (EOS).** All patients will be followed for OS every 3 months **after the 12 month follow-up visit,** until death, withdrawal of consent, termination of study by the sponsor, or for a maximum of 1 year after the last patient is enrolled in the study.

Rationale for Change:

To clarify that posttreatment follow-up assessments for survival and GvHD status would be made at 4, 5, 6, 9, and 12 months.

Change 9: Clarification to the efficacy analyses.

The primary change occurs in Section 13.1.4 Efficacy Analysis:

Initial wording:	Safety, PK, and efficacy data will be used in decision making. For efficacy evaluation, a Bayesian statistical approach will be used where posterior probabilities that (a) PR+VGPR+CR rate is >54%, and (b) PR+VGPR+CR rate is at least 70% will be derived from this distribution. If (a) is at least 85% probability ("85% level of proof at 54%"), and (b) is at least 75% ("75% level of proof at 70%"), then this will be considered a positive proof-of-concept in efficacy. Efficacy signals will be evaluated using the initial cohorts and will be verified using the expansion cohort.
Amended or new wording:	Safety, PK, and efficacy data will be used in decision making. For efficacy evaluation, a Bayesian statistical approach will be used where posterior **probability** ~~probabilities~~ that ~~(a)~~ PR+VGPR+CR rate ~~is >54%, and (b) PR+VGPR+CR rate~~ is at least 70% will be derived from this distribution. If ~~(a) is at least 85%~~ **this** probability ~~("85% level of proof at 54%"), and (b)~~ is at least 75% ("75% level of proof at 70%"), then this will be considered a positive proof-of-concept in efficacy. Efficacy signals will be evaluated using the initial cohorts and will be ~~verified~~ **updated** using the expansion cohort.

Rationale for Change:

To clarify the conduct of the efficacy analyses.

Change 10: Clarification of the immunogenicity analyses.

The primary change occurs in Section 13.1.8 Immunogenicity Analyses:

Initial wording:	Immunogenicity (anti-vedolizumab antibodies [AVA]) will be descriptively summarized. The effect of anti-vedolizumab antibodies on safety and efficacy will be explored. The proportion of subjects with positive AVA (transient and persistent) and proportion of subjects with positive neutralizing AVA during the study will be summarized at each visit. A positive AVA subject is defined as a subject who has at least 1 positive AVA result in any post-baseline sample, and is further categorized as: • Transiently positive: defined as subjects with confirmed positive AVA in 1 sample at a post-dose visit. • Persistently positive: defined as subjects with confirmed positive AVA in 2 or more consecutive positive AVA samples at post-dose visits.
Amended or new wording:	Immunogenicity (anti-vedolizumab antibodies [AVA]) will be descriptively summarized. The effect of anti-vedolizumab antibodies on safety and efficacy will be explored. The proportion of subjects with positive AVA (transient and persistent) and proportion of subjects with positive neutralizing AVA during the study will be summarized at each visit. **Further information about the immunogenicity analyses**

will be provided in the SAP.

~~A positive AVA subject is defined as a subject who has at least 1 positive AVA result in any post-baseline sample, and is further categorized as:~~

- ~~Transiently positive: defined as subjects with confirmed positive AVA in 1 sample at a post-dose visit~~.
- ~~Persistently positive: defined as subjects with confirmed positive AVA in 2 or more consecutive positive AVA samples at post-dose visits~~.

Rationale for Change:

To clarify the conduct of the immunogenicity analyses.

Change 11: Deletion of redundant safety analysis text.

The primary change occurs in Section 13.1.9 Safety Analysis:

Deleted text: ~~Patients will be randomized at a ratio of 1:1 to 2 treatment arms to receive either 300 or 600 mg vedolizumab IV on Days 1, 15, 43, 71, and 99. After approximately 10 patients are enrolled at each dose level and have data available from their Day 28 evaluation, safety, tolerability, efficacy, and PK results will be assessed from the patients at both vedolizumab dose levels (300 and 600 mg), and a Bayesian statistical approach will be used to facilitate the determination of an appropriate dose for subsequent patients in the study (See Section 13.2). The cohort at the chosen dose level will then be expanded by approximately 18 additional evaluable patients to further assess the tolerability and effectiveness of vedolizumab. Both dose levels may be expanded based on accumulating results, if necessary.~~

Rationale for Change:

To delete redundant text.

Change 12: Modification to the conduct of the interim analysis.

The primary change occurs in Section 13.2 Interim Analysis:

Initial wording:	There will be 1 interim analysis with early stopping rules for futility when at least 50% of patients in the dose finding phase have reached Day 28, based on preliminary efficacy and biological activity as follows: • The posterior probability for the treatment effect to be greater than the 54% target effect will be estimated using the data from the interim analysis. • If the estimated posterior probability is less than 0.3 then stopping for futility will be considered for this dose regimen following review of all the data collected in this initial cohort (eg, biological activity, PK and tolerability). • If the estimated posterior probability is greater than or equal to 0.3 then this dose regimen will be considered for continued enrollment.
Amended or new wording:	There will be 1 interim analysis ~~with early stopping rules for futility~~ when ~~at least 50% of~~ **all** patients in the dose finding phase have reached Day 28 ~~based on preliminary efficacy and biological activity as follows:~~ ~~• The posterior probability for the treatment effect to be greater than the 54% target effect will be estimated using the data from the interim analysis.~~ ~~• If the estimated posterior probability is less than 0.3 then stopping for futility will be considered for this dose regimen following review of all the data collected in this initial cohort (eg, biological activity, PK and tolerability).~~ ~~• If the estimated posterior probability is greater than or equal to 0.3 then this dose regimen will be considered for continued enrollment.~~

Rationale for Change:

To modify the conduct of the interim analysis to occur when all patients have reached Day 28 in the dose finding phase. This change deleted the need for early stopping rules for futility that had been added in the Sweden only amendment 01.

Change 13: Corrections to the Schedule of Events (Appendix A).

The primary changes occur in Section Appendix A Schedule of Events:

Description of change:	In the SOE for Dose Finding, ***PML checklist*** replaces the previous ~~*RAMP questionnaire*~~. The same change was made in the SOE for Day 36 and beyond.
Description of change:	In the SOE for Dose Finding, in the row *Hematology/chemistry*, added footnote **(l)** to this heading and to the Screening visit.
Description of change:	In the SOE for Dose Finding, added text for footnote **(l)**: **Hepatitis and human immunodeficiency virus testing are to be performed only at the Screening visit. Negative results of all such tests are required for subject enrollment.**
Description of change:	In the SOE for Dose Finding, in the row *Symptom-directed physical examination*, footnote **(b)** was added to Day 1 and Day 15 to align the global amendment 02 with a change made in the Sweden only amendment 01.
Description of change:	In the SOE for Dose Finding, in the row *Blood sample for serum biomarkers*, footnote (j) was deleted next to the header and moved to be collected at Day 2 only.
Description of change:	In the SOE for Day 36 and beyond, in the row *PML checklist*, **X (d)** was added to the Extension Dose Visit.
Description of change:	In the SOE for Day 36 and beyond, in the row *Hematology/chemistry*, footnote (i) has been deleted and moved to the SOE for Dose Finding, in the row *Hematology/chemistry* because it refers to a sample collected at the Screening visit.
Description of change:	In the SOE for Day 36 and beyond, in the *row Blood sample for flow cytometry*, footnote **(d)** has been added to Day 43, Day 71, and Day 99 visits to indicate that these assessments/samples should be collected predose.
Description of change:	In the SOE for Day 36 and beyond, a row for ***LTFU Safety Survey*** has been added, along with text: **Safety survey completed for patients in long-term follow-up 6 months after the last dose of study drug.**
Description of change:	In the SOE describing pharmacokinetic sampling, the window for collection of the 12 hour postdose sample was changed from (~~±30 min~~) to (**±2 h**).

Rationale for Change:

Various changes to the SOEs were made to clarify the procedures or to improve consistency between the SOE and procedure sections.

Change 14: Update of the signatories.

The primary change occurs in Section 1.2 Approval

Initial wording:	Protected Personal Data
Amended or new wording:	Protected Personal Data

Rationale for Change:

To update the signatories, reflecting a change in study personnel.

Amendment 02 to An open-label, dose-finding study of vedolizumab IV for treatment of steroid-refractory acute intestinal graft-versus-host disease (GvHD) in patients who have undergone allogeneic hematopoietic stem cell transplantation (allo-HSCT)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Protected Personal Data	Biostatistics Approval	29-Nov-2017 12:42 UTC
	Clinical Science Approval	29-Nov-2017 12:43 UTC
	Clinical Pharmacology Approval	29-Nov-2017 12:55 UTC