



Title: An Open-Label, Dose-Finding Study of Vedolizumab IV Plus Standard of Care for Graft-Versus-Host Disease (GvHD) Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

NCT Number: NCT02728895

Protocol Approve Date: 13 January 2016

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

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

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



## PROTOCOL

### **An Open-Label, Dose-Finding Study of Vedolizumab IV Plus Standard of Care for Graft-Versus-Host Disease (GvHD) Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**

**Sponsor:** Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited  
40 Landsdowne Street  
Cambridge, MA USA 02139  
Telephone: +1 (617) 679-7000

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-1015

**IND Number:** 127,634 **EudraCT Number:** Not Applicable

**Compound:** Vedolizumab IV

**Date:** 13 January 2016

#### **Amendment History:**

<b>Date</b>	<b>Amendment Number</b>	<b>Amendment Type</b>	<b>Region</b>
04 December 2015	Initial Protocol	Not applicable	Global
13 January 2016	01	Nonsubstantial	Global

#### **CONFIDENTIAL PROPERTY OF TAKEDA**

This document is a confidential communication of Takeda. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Takeda except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the study.

## 1.0 ADMINISTRATIVE

### 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 11.0, 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
Serious adverse event and pregnancy reporting	See Section 11.0

## 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.

PPD



## 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 11.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- [Appendix B](#)– Responsibilities of the Investigator.

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/Province)

---

Location of Facility (Country)

### 1.3 Protocol Amendment No. 01 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 01.

The primary purpose of this amendment is to update the protocol regarding inclusion criteria for the expansion phase of the study and the definitions of dose-limiting toxicity (DLT), details on End-of-Cohort Meetings, and recording of vital signs on the days of study drug infusion.

Justification: The changes in the protocol are based upon communication from the United States Food and Drug Administration received on 28 December 2015.

Minor grammatical and editorial changes are included for clarification purposes only. Full details on changes of text are given in [Appendix I](#). The following is a summary of the changes made in the amendment:

1. Section [8.1.2](#): Updated inclusion criterion in the expansion phase of the study.
2. Section [9.2](#): Clarified the definitions of DLT.
3. Section [10.3.7](#): Updated details on recording of vital signs.
4. Section [12.1](#): Provided additional details on End-of-Cohort Meetings.
5. [Appendix A](#): Updated details on recording of vital signs on Study Days –1, +13, and +42.

## TABLE OF CONTENTS

1.0	ADMINISTRATIVE .....	2
1.1	Contacts.....	2
1.2	Approval.....	3
1.3	Protocol Amendment No. 01 Summary of Changes .....	5
2.0	STUDY SUMMARY .....	11
3.0	STUDY REFERENCE INFORMATION .....	15
3.1	Study-Related Responsibilities.....	15
3.2	Principal Investigator/Coordinating Investigator .....	15
3.3	List of Abbreviations .....	16
3.4	Corporate Identification .....	18
4.0	INTRODUCTION.....	19
4.1	Background .....	19
4.1.1	Disease Under Treatment .....	19
4.1.2	Vedolizumab IV .....	19
4.2	Rationale for the Proposed Study .....	22
5.0	STUDY OBJECTIVES .....	24
5.1	Primary Objective.....	24
5.2	Secondary Objectives.....	24
5.3	Exploratory Objectives .....	24
6.0	STUDY ENDPOINTS.....	25
6.1	Primary Endpoints .....	25
6.2	Secondary Endpoints .....	25
6.3	Exploratory Endpoints .....	25
7.0	STUDY DESIGN .....	27
7.1	Overview of Study Design.....	27
7.2	Number of Patients .....	29
7.3	Duration of Study .....	29
8.0	STUDY POPULATION.....	30
8.1	Inclusion Criteria .....	30
8.1.1	Dose-Finding Phase .....	30
8.1.2	Expansion Phase .....	31
8.2	Exclusion Criteria .....	32
8.2.1	Dose-Finding Phase .....	32
8.2.2	Expansion Phase .....	33

9.0	STUDY DRUG .....	36
9.1	Study Drug Administration .....	36
9.2	Definitions of Dose-Limiting Toxicity .....	36
9.3	Dose Escalation Rules.....	36
9.4	Excluded Concomitant Medications and Procedures .....	38
9.5	Permitted Concomitant Medications and Procedures .....	38
9.6	Precautions and Restrictions .....	38
9.6.1	HSC Source .....	38
9.6.2	Criteria for Dosing on Days +13 and +42 After Allo-HSCT .....	38
9.6.3	Reproductive Effects .....	39
9.7	Management of Clinical Events .....	39
9.7.1	Hypersensitivity Reactions .....	39
9.7.2	Leukopenia or Lymphopenia.....	40
9.7.3	Cytomegalovirus Colitis.....	40
9.7.4	Malignancy .....	40
9.7.5	Other Clinical Events .....	40
9.8	Dose Modification or Treatment Delay for Vedolizumab-Related Toxicity .....	41
9.9	Blinding and Unblinding.....	41
9.10	Description of Investigational Agent.....	41
9.11	Preparation, Reconstitution, and Dispensation.....	41
9.12	Packaging and Labeling .....	41
9.13	Storage, Handling, and Accountability .....	42
9.14	Other Protocol-Specified Materials .....	42
10.0	STUDY CONDUCT.....	43
10.1	Study Personnel and Organizations .....	43
10.2	Arrangements for Recruitment of Patients.....	43
10.3	Study Procedures .....	43
10.3.1	Informed Consent.....	43
10.3.2	Patient Demographics .....	43
10.3.3	Medical History .....	43
10.3.4	Physical Examination.....	44
10.3.5	Neurological Examination.....	44
10.3.6	Patient Height and Weight .....	44
10.3.7	Vital Signs .....	44
10.3.8	Progressive Multifocal Leukoencephalopathy Checklist.....	44



10.3.9	Pregnancy Test.....	44
10.3.10	Concomitant Medications and Procedures .....	44
10.3.11	Adverse Events .....	45
10.3.12	Enrollment .....	45
10.3.13	Clinical Laboratory Evaluations .....	45
10.3.14	Tuberculosis Screening .....	46
10.3.15	Chimerism Analysis .....	46
10.3.16	Disease Assessment.....	46
10.3.17	Pharmacokinetic Measurements .....	46
10.3.18	Pharmacodynamic Measurements.....	47
10.3.19	Immunogenicity .....	47
10.4	Completion of Treatment .....	47
10.5	Completion of Study .....	47
10.6	Discontinuation of Treatment With Study Drug and Patient Replacement .....	47
10.7	Withdrawal of Patients From Study .....	48
10.8	Study Compliance.....	48
10.9	Posttreatment Follow-up Assessments .....	48
11.0	ADVERSE EVENTS .....	49
11.1	Definitions.....	49
11.1.1	Pretreatment Event Definition .....	49
11.1.2	Adverse Event Definition.....	49
11.1.3	Serious Adverse Event Definition .....	49
11.2	Procedures for Recording and Reporting Adverse Events and Serious Adverse Events.....	50
11.3	Monitoring of Adverse Events and Period of Observation.....	51
11.4	Procedures for Reporting Drug Exposure During Pregnancy and Birth Events .....	51
11.5	Procedures for Reporting Product Complaints.....	51
11.6	Risk Minimization Action Plan for PML (RAMP Program) .....	52
12.0	STUDY-SPECIFIC COMMITTEES .....	54
12.1	Dose Escalation and Cohort Expansion Plan .....	54
13.0	DATA HANDLING AND RECORDKEEPING.....	55
13.1	eCRFs.....	55
13.2	Record Retention .....	55
14.0	STATISTICAL METHODS .....	57
14.1	Statistical and Analytical Plans .....	57
14.1.1	Analysis Sets.....	57

14.1.2	Procedures for Handling Missing, Unused, and Spurious Data .....	57
14.1.3	Analysis of Demographics and Other Baseline Characteristics .....	57
14.1.4	Efficacy Analysis .....	57
14.1.5	Pharmacokinetic Analysis .....	58
14.1.6	Pharmacodynamic Analysis .....	58
14.1.7	Immunogenicity Analysis.....	58
14.1.8	Safety Analysis .....	58
14.2	Interim Analysis and Criteria for Early Termination .....	59
14.3	Determination of Sample Size.....	59
15.0	QUALITY CONTROL AND QUALITY ASSURANCE.....	60
15.1	Study-Site Monitoring Visits .....	60
15.2	Protocol Deviations.....	60
15.3	Quality Assurance Audits and Regulatory Agency Inspections .....	60
16.0	ETHICAL ASPECTS OF THE STUDY .....	61
16.1	IRB and/or IEC Approval .....	61
16.2	Subject Information, Informed Consent, and Subject Authorization .....	62
16.3	Subject Confidentiality .....	63
16.4	Publication, Disclosure, and Clinical Trial Registration Policy.....	63
16.4.1	Publication and Disclosure .....	63
16.4.2	Clinical Trial Registration.....	64
16.4.3	Clinical Trial Results Disclosure .....	64
16.5	Insurance and Compensation for Injury.....	64
17.0	REFERENCES.....	65

#### LIST OF IN-TEXT TABLES

Table 10.a	Clinical Chemistry and Hematology Tests.....	45
Table 10.b	Clinical Urinalysis Tests .....	46

#### LIST OF IN-TEXT FIGURES

Figure 7.a	Overview of Study Design From Days –1 to +50 .....	29
------------	--	----

#### LIST OF APPENDICES

Appendix A	Schedule of Events.....	68
------------	-------------------------	----

Appendix B	Responsibilities of the Investigator.....	74
Appendix C	Investigator Consent to Use of Personal Information.....	76
Appendix D	Clinical Stages and Grades of Graft-Versus-Host Disease .....	77
Appendix E	Recommended Tacrolimus + Short-Term Methotrexate Prophylaxis Regimen ...	78
Appendix F	Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status.....	79
Appendix G	Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) Scores .....	80
Appendix H	Grade 4 Regimen-Related Organ Toxicities .....	81
Appendix I	Detailed Description of Amendments to Text.....	82

## 2.0 STUDY SUMMARY

<b>Name of Sponsor(s):</b> Millennium Pharmaceuticals, Inc.		<b>Compound:</b> Vedolizumab IV	
<b>Title of Protocol:</b> An Open-Label, Dose-Finding Study of Vedolizumab IV Plus Standard of Care for Graft-Versus-Host Disease (GvHD) Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)		<b>IND No.:</b> 127,634	<b>EudraCT No.:</b> Not Applicable
<b>Study Number:</b> Vedolizumab-1015		<b>Phase:</b> 1b	
<b>Study Design:</b> <p>This is a phase 1b, open-label, dose-finding study designed to evaluate the safety, tolerability, and clinical activity of adding vedolizumab to standard graft-versus-host disease (GvHD) prophylaxis (tacrolimus plus short-term methotrexate) in adult patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). Vedolizumab dose finding will be cohort based and follow a rule-based dose-finding study design with pharmacokinetic (PK) guidance. After a tolerated dose with acceptable PK has been identified, the cohort at that dose level may be expanded to further assess the tolerability and effectiveness of vedolizumab.</p> <p>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. Study drug will be administered initially on Day –1 before allo-HSCT and then on Days +13 and +42 after allo-HSCT.</p> <p>Approximately 36 evaluable patients will be enrolled in this study. For PK endpoints, an evaluable patient is one who receives vedolizumab and has at least 1 PK sample collected.</p> <p>Patients who remain in remission will be followed for safety and development of acute and chronic GvHD for 1 year after allo-HSCT or until the patient’s death or withdrawal of consent or termination of the study by the sponsor. All patients will be followed for overall survival (OS) 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. Patients will attend a Day +100 visit (±7 days) at which time they will enter posttreatment follow-up.</p> <p>Dose escalation will start with a low-dose cohort receiving vedolizumab at 75 mg IV on Day –1 and on Days +13 and +42 after allo-HSCT. HSC infusion should occur on Day 0 (no sooner than 12 hours after completion of IV infusion of vedolizumab on Day –1). The first patient in each dosing cohort will then be monitored for dose-limiting toxicities (DLTs) from the start of the first IV infusion of vedolizumab on Day –1 to Day +28 after allo-HSCT (the DLT observation period) including assessment for neutrophil recovery by Day +28. If the first patient in the first cohort tolerates vedolizumab IV at 75 mg and engraftment occurs, then 2 more patients will be enrolled in the first cohort. If none of the first 3 patients experience DLTs, the next cohort will receive vedolizumab 300 mg IV on Day –1 and on Days +13 and +42 after allo-HSCT. If the first patient in this cohort tolerates vedolizumab IV at 300 mg and engraftment occurs, then 2 more patients will be enrolled in the second cohort. If the first 3 patients at 300 mg tolerate the treatment without experiencing DLTs, then the decision on whether to increase the vedolizumab IV dose in the next cohort will be guided by the PK results. If 1 of the first 3 patients in the cohort experiences a DLT, then 3 additional patients will be enrolled at the same dose level and monitored for DLTs from Day –1 until Day +28. If none of the additional patients experiences a DLT, then the decision on whether to increase the vedolizumab IV dose in the next cohort will be guided by the PK results. If 2 or more patients in a cohort of either 3 or 6 patients experience a DLT, then the dose of vedolizumab IV for the next cohort of 3 patients will be reduced. These patients will be monitored for DLTs in the same manner that patients in the previous cohort were monitored.</p> <p>After a tolerated dose level with acceptable PK has been identified in patients who are undergoing unrelated-donor myeloablative transplant for the treatment of hematologic malignancies, the cohort at that dose level may be expanded to include approximately 18 additional patients undergoing myeloablative conditioning or reduced-intensity conditioning (RIC) and are receiving either related or unrelated allo-HSCT for the treatment of hematologic malignancies or myeloproliferative neoplasms. This group of patients will allow the further assessment of the</p>			

**CONFIDENTIAL**

tolerability and clinical activity of vedolizumab IV.

Vital signs, physical and neurological examinations, adverse event (AE) assessments, and laboratory values (chemistry, hematology, and urinalysis) will be obtained to evaluate the safety and tolerability of vedolizumab IV. To exclude patients with progressive multifocal leukoencephalopathy (PML), a Risk Assessment and Minimization for PML (RAMP) questionnaire will be administered at Screening and before vedolizumab IV administration on Days -1 before allo-HSCT, and on Days +13 and +42 after allo-HSCT.

Serial blood samples for the evaluation of PK of vedolizumab will be obtained at prespecified time points. PK of vedolizumab will be analyzed for each of the first 3 patients at each dose level. It is expected that the concentration-time profile of vedolizumab will be influenced by the level of  $\alpha_4\beta_7$  target saturation. If  $\alpha_4\beta_7$  is saturated, then vedolizumab clearance would be linear; if  $\alpha_4\beta_7$  is not saturated, then clearance would be nonlinear indicating rapid elimination. If the clearance of vedolizumab is nonlinear at the 300 mg dose, then subsequent dosing for all patients will be increased in approximately 150 mg increments (up to a maximum of 600 mg) until linear PK clearance is achieved.

CCI



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.

**Primary Objective:**

- To describe the initial tolerability and safety and identify a recommended phase 2 dose of vedolizumab IV administered for GvHD prophylaxis along with standard GvHD prophylaxis therapy (tacrolimus plus short-term methotrexate) in patients undergoing allo-HSCT.

**Secondary Objectives:**

- To characterize the PK of vedolizumab in patients on Days -1, +13, and +42 after allo-HSCT.
- To determine the cumulative incidence and severity of acute GvHD at 100 days after allo-HSCT.
- To determine the distribution of maximum severity of acute GvHD throughout the 100-day period after allo-HSCT.

**Exploratory Objectives:**

CCI



<b>Subject Population:</b> Adult patients undergoing allo-HSCT for the treatment of hematologic malignancies or myeloproliferative neoplasms.	
<b>Number of Subjects:</b> Approximately 36 evaluable patients	<b>Number of Sites:</b> Approximately 3 to 4 in the United States
<b>Dose Level(s):</b> Vedolizumab: initially 75 mg on Day –1 before allo-HSCT and on Days +13 and +42 after myeloablative allo-HSCT	<b>Route of Administration:</b> Vedolizumab: intravenous (IV)
<b>Duration of Treatment:</b> Patients will receive up to 3 doses of vedolizumab IV within the first 100 days after allo-HSCT.	<b>Period of Evaluation:</b> Patients who remain in remission will be followed for safety and development of acute and chronic GvHD for 1 year after allo-HSCT 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 until death, withdrawal of consent, termination of the study by the sponsor, or for a maximum of 1 year after the last patient enrolled is enrolled in the study. Additionally, subjects will be required to participate in a long-term follow-up (LTFU) safety survey 6 months after the last dose of study drug. It is anticipated that this study will last for approximately 2 to 3 years.
<b>Main Criteria for Inclusion:</b> In the initial cohort for dose finding, patients who are undergoing unrelated-donor myeloablative transplant for the treatment of hematologic malignancies and who are ≤60 years of age will be enrolled. After a recommended phase 2 dose has been identified, the cohort at that dose level may be expanded to include additional patients receiving myeloablative conditioning or RIC (≤75 years of age) who are undergoing either related or unrelated allogeneic HSCT for the treatment of hematologic malignancies or myeloproliferative neoplasms.	
<b>Main Criteria for Exclusion:</b> Patients will be excluded from the study who have received prior allogeneic transplants or who are planned to undergo umbilical cord blood transplant, receive ex vivo T-cell-depleted hematopoietic stem cells (HSCs), receive any in vivo T-cell depleting antibodies, or RIC (in the dose-finding portion only). Patients with active cerebral/meningeal disease, active cytomegalovirus (CMV) colitis, or signs and symptoms of progressive multifocal leukoencephalopathy (PML) or any history of PML will also be excluded. In addition, patients with nonmalignant hematological disorders (eg, aplastic anemia, sickle cell anemia, thalassemias, Fanconi anemia) will be excluded in the both portions of the study.	
<b>Main Criteria for Evaluation and Analyses:</b> The primary endpoint of this study is to determine the recommended phase 2 dose of vedolizumab IV administered for GvHD prophylaxis along with standard GvHD prophylaxis therapy as assessed by the frequency of DLTs and the number and percentage of patients who experience treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) from administration of the first dose of vedolizumab IV through 18 weeks after administration of the last dose of vedolizumab IV. In addition, mean serum concentrations of vedolizumab will help inform the likelihood of α4β7 target saturation throughout the first 100 days following allo-HSCT.	
<b>Statistical Considerations:</b> Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed. A formal statistical analysis plan will be developed and finalized before database lock.	

**Sample Size Justification:**

Approximately 18 evaluable patients will be enrolled to identify a tolerable vedolizumab dose level with acceptable PK. After the dose level has been identified, the cohort at that dose level may be expanded to include approximately 18 additional patients receiving myeloablative conditioning or RIC who are undergoing either related or unrelated allo-HSCT for the treatment of hematologic malignancies or myeloproliferative neoplasms. This group of patients will allow the further assessment of the tolerability and clinical activity of vedolizumab IV. The sample size estimates are based on the primary objective of determining a recommended phase 2 dose and to describe the initial tolerability and safety of vedolizumab IV administered along with standard GvHD prophylaxis.

### **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**

<b>Term</b>	<b>Definition</b>
AE	adverse event
ALL	acute lymphoblastic leukemia
allo-HSCT	allogeneic hematopoietic stem cell transplantation
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APC	antigen-presenting cell
AUC	area under the serum concentration-time curve
AVA	anti-vedolizumab antibody
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
BuFlu	busulfan + fludarabine
CD	Crohn's disease
C <sub>trough</sub>	serum concentration before dosing
CMV	cytomegalovirus
CRF	case report form
CRO	contract research organization
CRp	complete remission with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
CyTBI	cyclophosphamide + total body irradiation
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EU	European Union
FDA	Food and Drug Administration
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GCSF	granulocyte-colony stimulating factor
GI	gastrointestinal(ly)
GRFS	GvHD-free, relapse-free survival
GvHD	graft-versus-host disease
HBV	hepatitis B virus surface antigen
HCT-CI	Hematopoietic Cell Transplantation-Specific Comorbidity Index
HCV	hepatitis C virus antigen
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplantation
IAC	Independent Adjudication Committee
IB	Investigator's Brochure

<b>Term</b>	<b>Definition</b>
IBD	inflammatory bowel disease
IBMTR	International Bone Marrow Transplant Registry Database
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL-6	interleukin-6
IL-17	interleukin-17
IPS	idiopathic pneumonia syndrome
IRB	institutional review board
IV	intravenous(ly)
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PTE	pretreatment event
PVC	polyvinyl chloride
Q4W	once every 4 weeks
Q8W	once every 8 weeks
RAMP	Risk Assessment and Minimization of PML
RIC	reduced-intensity conditioning
SAE	serious adverse event
SAP	statistical analysis plan
ST2	suppressor of tumorigenicity 2
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF- $\alpha$	tumor necrosis factor-alpha
UC	ulcerative colitis
US	United States
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	Millenium 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 hematological malignant disorders and hematological genetic diseases, but its use is limited by the major complication of graft-versus-host disease (GvHD) [1]. The common complication of GvHD following an 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]. In patients receiving hematopoietic stem cells from an unrelated donor source after myeloablative conditioning, the risk of Grade 2 to 4 acute GvHD is approximately 40% to 50% [2,3]. The reduction of GvHD without causing significant systemic immunosuppression may improve overall outcomes following allo-HSCT [2,5].

GvHD results from an activation of alloreactive donor lymphocytes by histocompatibility antigens on host antigen-presenting cells (APCs) [6,7]. It has been postulated that intestinal microflora and endotoxin exert a crucial step in APC activation, and that this process occurs in the gut-associated lymphoid tissues (GALT). Clinically, GvHD can be reduced through the use of T-cell depletion strategies and gut decontamination, highlighting the respective roles of both T cells and gastrointestinal (GI) microflora on the development of GvHD. In clinical HSCT, the human lymphocyte integrin  $\alpha_4\beta_7$  has been shown to be significantly increased on naïve and memory T cells in patients who subsequently developed intestinal acute GvHD compared with patients who developed skin acute GvHD or no GvHD [8]. Studies in murine models of acute GvHD suggest that prevention of T-cell trafficking to GALT via interruption of the interaction between  $\alpha_4\beta_7$  and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) may prevent GvHD [9-11].

#### 4.1.2 Vedolizumab IV

Vedolizumab (also called MLN0002) is a humanized immunoglobulin (Ig) G1 mAb directed against the human lymphocyte integrin  $\alpha_4\beta_7$ . The  $\alpha_4\beta_7$  integrin mediates lymphocyte trafficking to GI mucosa and GALT through adhesive interaction with MAdCAM-1, which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [12-15]. Vedolizumab binds the  $\alpha_4\beta_7$  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 [16]. 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 which after appropriate reconstitution and dilution is intended for intravenous (IV) infusion that has been granted marketing approval in several regions, including the United States (US) and European Union (EU). 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- $\alpha$ ) blocker or immunomodulator; or had an inadequate response with, were

intolerant to, or demonstrated dependence on corticosteroids. The approved dosing and administration regimen consists of 300 mg vedolizumab infused intravenously 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, pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity of vedolizumab.

#### 4.1.2.1 *Nonclinical*

Several key nonclinical studies have been published that support the use of vedolizumab for the prevention of GvHD (see Section 4.1.1). 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 [16].

#### 4.1.2.2 *Human Experience*

To date, more than 3400 subjects have received at least 1 dose of vedolizumab across all studies in the clinical development program (see current version of Investigator's Brochure [IB]). Phase 3 placebo-controlled studies enrolled 2427 subjects with UC or CD, of whom 1434 subjects 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, 1786 subjects in clinical studies have been exposed to vedolizumab for  $\geq 12$  months, 1379 subjects for  $\geq 24$  months, 977 subjects for  $\geq 36$  months, 724 subjects for  $\geq 48$  months, and 344 subjects for  $\geq 60$  months. Since approval in May 2014, the patient exposure of vedolizumab in the postmarketing setting as of May 2015 is estimated to be approximately 11,943 patient-years on the basis of drug shipment data.

In subjects with moderately to severely active CD (Study C13007), including subjects who had failed treatment with 1 or more therapies including TNF- $\alpha$  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 to 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 (CDAI-100) 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, as well as important secondary endpoints, including enhanced clinical response at Week 52 and corticosteroid-free clinical remission at Week 52 [18].

In 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- $\alpha$  antagonists. The primary endpoint of clinical remission at Week 6 in the TNF- $\alpha$  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- $\alpha$  antagonist naïve [19].

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  $\mu\text{g/mL}$  with a serum terminal elimination half-life ( $t_{1/2z}$ ) 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 ( $\geq 5\%$  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 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.

CCI

Overall, vedolizumab was well tolerated in clinical studies.

#### 4.2 Rationale for the Proposed Study

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 undergoing allo-HSCT because of the specific mechanism of action of vedolizumab. Prophylactic administration of vedolizumab to patients undergoing allo-HSCT may prevent trafficking of alloreactive T-cells to GALT and GI mucosa, thereby preventing the development of acute GvHD.

##### Dose and Schedule

The starting dose and schedule of vedolizumab IV administration is 75 mg on Day –1 before allo-HSCT and on Days +13 and +42 after allo-HSCT. The first dose will be on Day –1 and the allo-HSCT will occur on Day 0, no sooner than 12 hours after completion of the IV infusion of vedolizumab to ensure distribution of vedolizumab and to minimize the likelihood of occurrence of infusion-related reactions at the time of HSC infusion. If none of the patients receiving vedolizumab IV at 75 mg experience dose-limiting toxicities (DLTs), dose escalation will continue to 300 mg on Day –1 before allo-HSCT and on Days +13 and +42 after allo-HSCT. A dose of 300 mg on Day –1 before allo-HSCT and on Days +13 and +42 is identical to the induction dose and schedule of vedolizumab approved for the treatment of UC or CD.

The no-observed-adverse-effect level (NOAEL) in both pharmacologically responsive species (monkeys and rabbits) was 100 mg/kg vedolizumab IV. Collectively, nonclinical studies show that doses up to 100 mg/kg vedolizumab IV were well tolerated. This dose was associated with an exposure 26 times (rabbits) and 18 times (cynomolgus monkeys) higher than the geometric mean clinical area under the serum concentration-time curve [AUC] after a single dose of 300 mg vedolizumab IV by 30-minute infusion.

In addition, extensive clinical data exists in healthy volunteers and patients with IBD. Vedolizumab IV has been administered as both weight-adjusted doses (0.15-10.0 mg/kg) and fixed doses (180-750 mg). The PK of vedolizumab in healthy subjects and patients with UC or CD is described by a 2-compartment model with parallel linear and nonlinear elimination. Elimination of vedolizumab is linear at serum concentrations higher than 1 to 10 µg/mL, but nonlinear at lower serum concentrations [20,21]. The linear elimination kinetics suggest that the  $\alpha_4\beta_7$  target is saturated at serum concentrations greater than 10 µg/mL, but not saturated at lower serum concentrations in healthy subjects and patients with either UC or CD. In addition, serum concentrations of vedolizumab needed to provide efficacy in both UC and CD are greater than serum concentrations for full receptor occupancy [21]. Based on the 300 mg dose of vedolizumab IV administered once every 8 weeks in patients with UC or CD, the serum concentration of vedolizumab is expected to maintain >90%  $\alpha_4\beta_7$  receptor saturation over the dosing interval in >90% of subjects.

Unlike healthy subjects and subjects with UC or CD, subjects undergoing a myeloablative conditioning regimen [22] followed by allo-HSCT are expected to have markedly changing T-cell

populations with variable  $\alpha_4\beta_7$  integrin expression during the posttransplant period. The rule-based dose-finding strategy with PK guidance will ensure that the dose and schedule of vedolizumab selected for this patient population are well tolerated and effectively saturate the  $\alpha_4\beta_7$  target.

The mechanistic hypothesis for the prevention of GvHD requires sustained  $\alpha_4\beta_7$ -blockade at the time of hematopoietic stem cell infusion. Given the safety profile for the range of exposure for vedolizumab as noted previously, a dose of 300 mg would achieve sustained receptor saturation. The kinetics of vedolizumab established in patients with IBD suggest that the intended dosing schedule of vedolizumab will result in target saturation throughout the first 100 days following HSCT, which is the time period where the vast majority of acute GvHD occurs.



## 5.0 STUDY OBJECTIVES

### 5.1 Primary Objective

The primary objective is:

- To describe the initial tolerability and safety and identify a recommended phase 2 dose of vedolizumab IV administered for GvHD prophylaxis along with standard GvHD prophylaxis therapy (tacrolimus plus short-term methotrexate) in patients undergoing allo-HSCT.

### 5.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK of vedolizumab in patients on Days -1, +13 and +42 after allo-HSCT.
- To determine the cumulative incidence and severity of acute GvHD at 100 days after allo-HSCT.
- To determine the distribution of maximum severity of acute GvHD throughout the 100-day period after allo-HSCT.

### 5.3 Exploratory Objectives

The exploratory objectives are:

CCI



## 6.0 STUDY ENDPOINTS

### 6.1 Primary Endpoints

The primary endpoints to identify the recommended phase 2 dose of vedolizumab IV administered for GvHD prophylaxis along with standard GvHD prophylaxis therapy include:

- Frequency of DLTs from the start of the first IV infusion of vedolizumab on Day –1 until Day +28 (the DLT observation period).
- 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 serious adverse events (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 that will help inform the likelihood of  $\alpha 4\beta 7$  target saturation throughout the first 100 days following allo-HSCT.

### 6.2 Secondary Endpoints

The secondary endpoints are:

- Mean time to neutrophil engraftment (recovery of absolute neutrophil count [ANC]) defined by an ANC  $>500/\text{mm}^3$  for 3 consecutive days or  $>2000/\text{mm}^3$  for 1 day. The first day of the 3-day period will be considered the day of neutrophil engraftment.
- Percentage of patients who have developed overall Grade 2 to 4 acute GvHD (compiled from individual organ scores of gut, skin, or liver) by 100 days after myeloablative allo-HSCT.
- The frequency by maximum severity of acute GvHD according to the modified Glucksberg criteria and Blood and Marrow Transplant Clinical Trials Network (BMT CTN)-modified International Bone Marrow Transplant Registry Database (IBMTR) index (See [Appendix D](#)).
- Mean serum concentrations of vedolizumab before dosing ( $C_{\text{trough}}$ ) on Days +13 and +42 after myeloablative allo-HSCT.

### 6.3 Exploratory Endpoints

The exploratory endpoints are:

CCI

CCI



CONFIDENTIAL

## 7.0 STUDY DESIGN

### 7.1 Overview of Study Design

This is a phase 1b, open-label, dose-finding study designed to evaluate the safety, tolerability, and clinical activity of adding vedolizumab to standard GvHD prophylaxis (tacrolimus plus short-term methotrexate) in adult patients undergoing allo-HSCT. Vedolizumab dose finding will be cohort based and follow a rule-based dose-finding study design with PK guidance. After a tolerated dose with acceptable PK has been identified, the cohort at that dose level may be expanded to further assess the tolerability and effectiveness of 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. Study drug will be administered initially on Day –1 before allo-HSCT and then on Day +13 and Day +42 after allo-HSCT.

Approximately 36 evaluable patients will be enrolled in this study. For PK endpoints, an evaluable patient is one who receives vedolizumab IV and has at least 1 PK sample collected.

Patients who remain in remission will be followed for safety and development of acute and chronic GvHD for 1 year after allo-HSCT or until the patient's death or withdrawal of consent or termination of the study by the sponsor. Remission will be defined by conventional World Health Organization (WHO) criteria: <5% blast cells, count recovery (although complete remission with incomplete platelet recovery [CRp] would be allowed), and no evidence of extramedullary disease. All patients will be followed for OS 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. Patients will attend a Day +100 visit ( $\pm 7$  days) at which time they will enter posttreatment follow-up. 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.

Dose escalation will start with a low-dose cohort receiving vedolizumab at 75 mg IV on Day –1 before allo-HSCT and on Days +13 and +42 after allo-HSCT. HSC infusion should occur on Day 0 no sooner than 12 hours after completion of IV infusion of vedolizumab on Day –1. The first patient in each dosing cohort will then be monitored for DLTs from the start of the first IV infusion of vedolizumab on Day –1 until Day +28 (the DLT observation period) including assessment for neutrophil recovery by Day +28. If the first patient in the first cohort tolerates vedolizumab IV at 75 mg and engraftment occurs, then 2 more patients will be enrolled in the first cohort. If none of the first 3 patients experience DLTs, the next cohort will receive vedolizumab 300 mg IV on Day –1 before allo-HSCT and on Days +13 and +42 after allo-HSCT. If the first patient in this cohort tolerates vedolizumab IV at 300 mg and engraftment occurs, then 2 more patients will be enrolled in the second cohort. If the first 3 patients at 300 mg tolerate the treatment without experiencing DLTs, then the decision on whether to increase the vedolizumab IV dose in the next cohort will be guided by the PK results. If 1 of the first 3 patients in the cohort experiences a DLT, then 3 additional patients will be enrolled at the same dose level and monitored for DLTs from Day –1 until Day +28. If none of the additional patients experiences a DLT, then the decision

on whether to increase the vedolizumab IV dose in the next cohort will be guided by the PK results. If 2 or more patients in a cohort of either 3 or 6 patients experience a DLT, then the dose of vedolizumab IV for the next cohort of 3 patients will be reduced. These patients will be monitored for DLTs in the same manner that patients in the previous cohort were monitored.

After a tolerated dose level with acceptable PK has been identified in patients who are undergoing unrelated-donor myeloablative transplant for the treatment of hematologic malignancies, the cohort at that dose level may be expanded to include approximately 18 additional patients undergoing myeloablative conditioning or reduced-intensity conditioning (RIC) [22] and are receiving either related or unrelated allo-HSCT for the treatment of hematologic malignancies or myeloproliferative neoplasms. This group of patients will allow the further assessment of the tolerability and clinical activity of vedolizumab IV.

Vital signs, physical and neurological examinations, adverse event (AE) assessments, and laboratory values (chemistry, hematology, and urinalysis as specified in Section 10.3.13) will be obtained to evaluate the safety and tolerability of vedolizumab IV, as described in the [Schedule of Events](#). To exclude patients with progressive multifocal leukoencephalopathy (PML), a Risk Assessment and Minimization for PML (RAMP) questionnaire will be administered at Screening and before vedolizumab IV administration on Days -1 before allo-HSCT and on Days +13 and +42 after allo-HSCT.

Serial blood samples for the evaluation of PK of vedolizumab will be obtained at prespecified time points as described in the [Schedule of Events](#). PK of vedolizumab will be analyzed for each of the first 3 patients at each dose level. It is expected that the concentration-time profile of vedolizumab will be influenced by the level of  $\alpha_4\beta_7$  target saturation. If  $\alpha_4\beta_7$  is saturated, then vedolizumab clearance would be linear; if  $\alpha_4\beta_7$  is not saturated, then clearance would be nonlinear indicating rapid elimination. If the clearance of vedolizumab is nonlinear at the 300 mg dose, then subsequent dosing for all patients will be increased in approximately 150 mg increments (up to a maximum of 600 mg) until linear PK clearance is achieved.

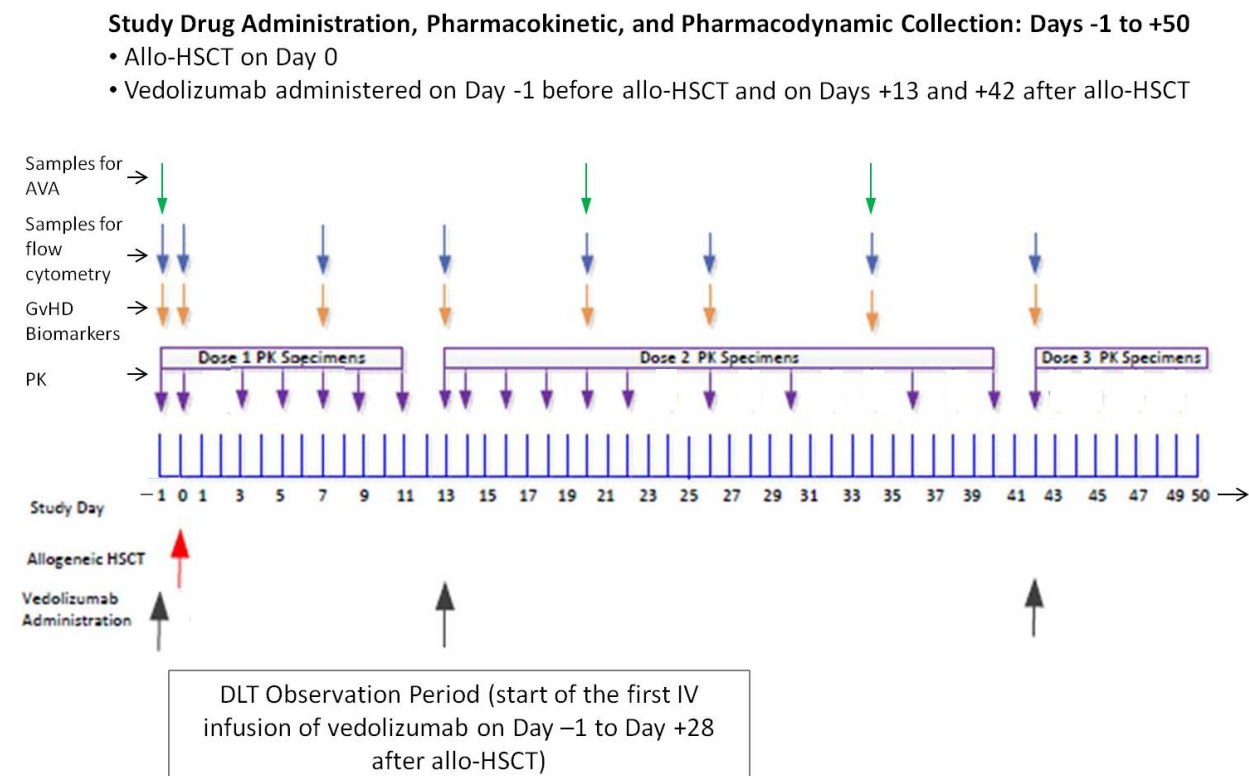
CCI



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 [24]. DLTs are defined in Section 9.2.

See [Figure 7.a](#) for an overview of the study design from Days -1 to +50.

**Figure 7.a Overview of Study Design From Days –1 to +50**



Allo-HSCT=allogeneic hematopoietic stem cell transplantation, AVA=anti-vedolizumab antibodies, DLT=dose-limiting toxicity, GvHD=graft-versus-host disease, IV=intravenous, PK=pharmacokinetic. PK sampling for patients who have been discharged from the hospital will be aligned to clinic visits, and therefore may not be as frequent as represented in this figure.

## 7.2 Number of Patients

Approximately 36 evaluable patients will be enrolled in this study from approximately 3 to 4 study centers in the United States. Enrollment is defined as when the written informed consent has been obtained and the patient's eligibility has been confirmed per the inclusion and exclusion criteria.

Patients in the dose-finding cohort who are withdrawn from treatment for reasons other than DLT during the DLT observation period will be replaced.

## 7.3 Duration of Study

Patients who remain in remission will be followed for safety and development of acute and chronic GvHD for 1 year after allo-HSCT 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 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.

It is anticipated that this study will last for approximately 2 to 3 years.

## 8.0 STUDY POPULATION

### 8.1 Inclusion Criteria

#### 8.1.1 Dose-Finding Phase

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

1. Male or female patients between 18 and 60 years, inclusive.
2. Candidates for human leukocyte antigen (HLA)-matched unrelated donor or 1-locus (antigen or allele) HLA-mismatched unrelated donor allo-HSCT, using either peripheral blood stem cells or bone marrow as the cell source, for the treatment of acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML).
3. Disease must be in remission at the time of allo-HSCT. Remission of ALL and AML will be defined by conventional WHO criteria: <5% blast cells, count recovery (although CRp would be allowed), and no evidence of extramedullary disease.
4. Patients for whom a myeloablative conditioning regimen (such as cyclophosphamide + total body irradiation [CyTBI], busulfan + cyclophosphamide, or busulfan + fludaradine [BuFlu]) is planned. For definitions of myeloablative conditioning versus RIC regimens refer to Bacigalupa et al, 2009 [22].
5. Patients who are planned to receive standard GvHD prophylaxis of tacrolimus + short-term methotrexate by the investigator (refer to [Appendix E](#)).
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (refer to [Appendix F](#)).
7. Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) score of  $\leq 4$  (refer to [Appendix G](#)).
8. Sufficient cognitive ability to reliably complete the RAMP questionnaire 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 2 effective methods of contraception, 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] and withdrawal are not acceptable methods of contraception.)

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 for the female partner] and withdrawal are not acceptable methods of contraception.)
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 pharmacodynamic sampling. Patients with a planned central venous access device will be allowed.

### 8.1.2 Expansion Phase

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

1. Male or female adult patients for whom a myeloablative conditioning (between 18 and 60 years of age, inclusive) or RIC regimen (between 18 and 75 years of age, inclusive) is planned [22].
2. Candidates for HLA-matched or 1-locus (antigen or allele) mismatched unrelated or related donor allo-HSCT, using either peripheral blood stem cells or bone marrow as the cell source, for the treatment of hematologic malignancy or myeloproliferative neoplasm.
3. Disease must be in remission at the time of allo-HSCT. Remission is defined as one of the following:
  - Patients with acute leukemia, chronic myelogenous leukemia, and myelodysplasia with no circulating blasts and <5% blasts in the bone marrow.
  - Patients with chronic lymphocytic leukemia, small lymphocytic lymphoma, or other non-Hodgkin lymphoma with chemosensitive disease at time of transplantation.
  - Patients with myelofibrosis and other myeloproliferative neoplasms with <5% blasts in the blood and bone marrow.
4. Patients who are planned to receive standard GvHD prophylaxis of tacrolimus + short-term methotrexate by the investigator (refer to [Appendix E](#)).
5. ECOG performance status of 0 to 2 (refer to [Appendix F](#)).
6. Sufficient cognitive ability to reliably complete the RAMP questionnaire at baseline.
7. 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 2 effective methods of contraception, 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] and withdrawal are not acceptable methods of contraception.)

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 for the female partner] and withdrawal are not acceptable methods of contraception.)
8. 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.
9. Suitable venous access for the study-required blood sampling, including PK and pharmacodynamic sampling. Patients with a planned central venous access device will be allowed.

## 8.2 Exclusion Criteria

### 8.2.1 Dose-Finding Phase

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

1. The patient has a positive PML subjective checklist before the administration of study drug.
2. The patient has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
3. Patients with active cytomegalovirus (CMV) colitis.
4. The patient has active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following:
  - History of TB.
  - A diagnostic TB test performed during screening that is positive, as defined by:
    - A positive QuantiFERON<sup>®</sup> test or 2 successive indeterminate QuantiFERON tests, OR
    - A tuberculin skin test reaction  $\geq 10$  mm ( $\geq 5$  mm in patients receiving the equivalent of  $>15$  mg/day prednisone).
5. The patient has chronic hepatitis B (HBV) or hepatitis C (HCV) infection.

6. The patient has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
7. The patient has evidence of active *C. difficile* infection or other intestinal pathogens during Screening.
8. The patient has evidence of an active systemic infection during Screening.
9. Female patients who are breastfeeding or have a positive serum or urine pregnancy test during the Screening period or on Day –1 before first dose of study drug.
10. Any serious medical or psychiatric condition that could, in the investigator or medical monitor's opinion, potentially interfere with the completion of treatment according to this protocol.
11. Patients who have received a prior allogeneic transplant.
12. Patients planned to undergo umbilical cord blood transplant or to receive in vivo or ex vivo T-cell-depleted HSCs.
13. Patients planned for RIC regimen or non-myeloablative regimen [22].
14. Single antigen mismatched patients who have donor-specific antibodies.
15. Prior exposure to vedolizumab, natalizumab, efalizumab, adalimumab, or rituximab, and anti-TNF- $\alpha$  or anti-TNF- $\alpha$  receptor antibodies, such as etanercept, lenercept, and infliximab.
16. Prior known exposure of either the donor or transplant recipient to vedolizumab.
17. The patient has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurologic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety.
18. The patient has a history of hypersensitivity or allergies to vedolizumab or its components.
19. Treatment with anti-T-cell antibody (eg, alemtuzumab, anti-thymocyte globulin) within 4 months before the first dose of vedolizumab.
20. Treatment with any live vaccinations within 30 days prior to enrollment.
21. 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.
22. If male, the patient intends to donate sperm during the course of this study or for 18 weeks thereafter.

### 8.2.2 Expansion Phase

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

1. The patient has a positive PML subjective checklist before the administration of study drug.

2. The patient has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
3. Patients with active CMV colitis.
4. The patient has active or latent TB, regardless of treatment history, as evidenced by any of the following:
  - History of TB.
  - A diagnostic TB test performed during screening that is positive, as defined by:
    - A positive QuantiFERON<sup>®</sup> test or 2 successive indeterminate QuantiFERON tests, OR
    - A tuberculin skin test reaction  $\geq 10$  mm ( $\geq 5$  mm in patients receiving the equivalent of  $>15$  mg/day prednisone).
5. The patient has chronic HBV or HCV infection.
6. The patient has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, HIV infection, organ transplantation).
7. The patient has evidence of active *C. difficile* infection or other intestinal pathogens during Screening.
8. The patient has evidence of an active systemic infection during Screening.
9. Female patients who are breastfeeding or have a positive serum or urine pregnancy test during the Screening period or on Day –1 before first dose of study drug.
10. Any serious medical or psychiatric condition that could, in the investigator or medical monitor's opinion, potentially interfere with the completion of treatment according to this protocol.
11. Patients who have received a prior allogeneic transplant.
12. Patients planned to undergo umbilical cord blood transplant or to receive in vivo or ex vivo T-cell-depleted HSCs.
13. Patients undergoing HSCT for the treatment of nonmalignant hematological disorders (eg, aplastic anemia, sickle cell anemia, thalassemias, Fanconi anemia).
14. Single antigen mismatched patients who have donor-specific antibodies.
15. Prior exposure to vedolizumab, natalizumab, efalizumab, adalimumab, or rituximab, and anti-TNF- $\alpha$  or anti-TNF- $\alpha$  receptor antibodies, such as etanercept, lenercept, and infliximab.
16. Prior known exposure of either the donor or transplant recipient to vedolizumab.
17. The patient has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurologic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety.

18. The patient has a history of hypersensitivity or allergies to vedolizumab or its components.
19. Treatment with anti-T-cell antibody (eg, alemtuzumab, anti-thymocyte globulin) within 4 months before the first dose of vedolizumab.
20. Treatment with any live vaccinations within 30 days prior to enrollment.
21. 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.
22. If male, the patient intends to donate sperm during the course of this study or for 18 weeks thereafter.

## 9.0 STUDY DRUG

### 9.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to 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 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.

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

### 9.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010 [24]. These criteria are provided in the Study Manual.

The DLT observation period in the proposed phase 1b study is defined as the start of the first IV infusion of vedolizumab on Day -1 to Day +28 after allo-HSCT.

A DLT will be any Grade 3 or higher toxicity assessed by the investigator as related to vedolizumab treatment. Hypersensitivity reactions and other infusion-related reactions will not be considered a DLT. Any patient who discontinues the study due to an infusion-related reaction will be replaced in the study.

Grade 4 or higher regimen-related organ toxicities (see [Appendix H](#)) will be considered as potential DLTs and reviewed as described in Section 12.0 before moving to the next dose level.

Grade 4 laboratory abnormalities that are not considered clinically significant by the investigator will not be considered DLTs.

Engraftment will be defined as ANC  $>500/\text{mm}^3$  for 3 consecutive days or  $>2000/\text{mm}^3$  for 1 day. Failure to engraft by Day +28 will be considered a DLT. In the event of engraftment failure, the third dose of vedolizumab should be withheld.

### 9.3 Dose Escalation Rules

The starting dose and schedule of vedolizumab IV administration is 75 mg on Day -1 before allo-HSCT and on Days +13 and +42 after allo-HSCT. If none of the patients receiving vedolizumab IV at 75 mg experience DLTs, dose escalation will continue to 300 mg on Day -1 before allo-HSCT and on Days +13 and +42 after allo-HSCT. A dose of 300 mg on Day -1 before

allo-HSCT and on Days +13 and +42 is identical to the induction dose and schedule of vedolizumab approved for the treatment of UC or CD.

The first patient enrolled will be monitored for engraftment before the second patient is enrolled. The dose escalation will start with sentinel dosing for the first cohort, whereby the first patient will receive 75 mg vedolizumab IV administration along with standard-of-care tacrolimus and short-term methotrexate prophylaxis. The patient will then be monitored for DLTs from the start of the first IV infusion of vedolizumab on Day -1 to Day +28 after allo-HSCT (the DLT observation period) including assessment for engraftment by Day +28. If the first patient in the first cohort tolerates vedolizumab IV at 75 mg and engraftment occurs, then 2 more patients will be enrolled in the first cohort. If at any time during the study it appears that vedolizumab might lead to unacceptable engraftment delay or failure, then the study design might be revised so that vedolizumab prophylaxis is initiated approximately 1 week after hematopoietic stem cell infusion.

If none of the first 3 patients experience DLTs, the next cohort will receive vedolizumab 300 mg IV on Day -1 before allo-HSCT and on Days +13 and +42 after allo-HSCT. If the first patient in this cohort tolerates vedolizumab IV at 300 mg and engraftment occurs, then 2 more patients will be enrolled in the second cohort. If the first 3 patients at 300 mg tolerate the treatment without experiencing DLTs, then the decision on whether to increase the vedolizumab IV dose in the next cohort will be guided by the PK results. If 1 of the first 3 patients in the cohort experiences a DLT, then 3 additional patients will be enrolled at the same dose level and monitored for DLTs from Day -1 until Day +28. If none of the additional patients experiences a DLT, then the decision on whether to increase the vedolizumab IV dose in the next cohort will be guided by the PK results.

Serial blood samples for the evaluation of PK of vedolizumab will be obtained at prespecified time points as described in the [Schedule of Events](#). PK of vedolizumab will be analyzed for each of the first 3 patients at each dose level. It is expected that the concentration-time profile of vedolizumab will be influenced by the level of  $\alpha_4\beta_7$  target saturation in depots outside of the peripheral blood compartment. If  $\alpha_4\beta_7$  is saturated, then vedolizumab clearance will be linear; if  $\alpha_4\beta_7$  is not saturated, then clearance will be nonlinear, indicating rapid elimination. If the clearance of vedolizumab is nonlinear at the 300 mg dose, then subsequent dosing for all patients will be increased in approximately 150 mg increments (up to a maximum of 600 mg) until linear PK clearance is achieved. Any dose escalation of vedolizumab IV will be cohort based. Inpatient dose escalation of vedolizumab IV will not be permitted.

If 2 or more patients in a cohort of either 3 or 6 patients experience a DLT, then the dose of vedolizumab for the next cohort of 3 patients will be reduced to the dose level in the previous cohort or to an interim dose level. These patients will be monitored for DLTs in the same manner that patients in the first cohort were monitored.

After a tolerated dose with acceptable PK has been identified, the cohort at that dose level may be expanded to include approximately 18 additional patients undergoing myeloablative conditioning or RIC and are receiving either related or unrelated allo-HSCT for the treatment of hematologic malignancies or myeloproliferative neoplasms. This group of patients will allow the further assessment of the tolerability and clinical activity of vedolizumab.

#### 9.4 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 case report form (CRF). 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.
- All live vaccines during study treatment and for at least 6 months after the last dose of study drug.
- Either 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) or agents required for treatment of GvHD (and after consultation with the medical monitor).

#### 9.5 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 electronic case report form (eCRF).

#### 9.6 Precautions and Restrictions

##### 9.6.1 HSC Source

A back-up plan for the event of primary graft failure must be identified for all patients in the study (ie, an alternate stem cell source) before performing the allo-HSCT.

##### 9.6.2 Criteria for Dosing on Days +13 and +42 After Allo-HSCT

After a patient has received the first dose of vedolizumab IV on Day –1 before allo-HSCT, patients may not receive the second and/or third dose on Days +13 and +42 after allo-HSCT 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 CMV colitis.
3. The patient has evidence of uncontrolled *C. difficile* colitis.
4. The patient experienced an anaphylactic reaction to vedolizumab.
5. If female, the patient is pregnant.

### 9.6.3 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 of 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 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] and withdrawal are not acceptable methods of contraception.)

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 for the female partner] and withdrawal are not acceptable methods of contraception.)

## 9.7 Management of Clinical Events

### 9.7.1 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 prior to any study drug administration. Corticosteroids, if given as a premedication, should be limited to the day of 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 measure 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 project clinician.

### **9.7.2 Leukopenia or Lymphopenia**

Leukocyte and lymphocyte counts will be monitored for all patients with a hematological panel (see Section 10.3.13). If engraftment has not occurred by Day +21 (defined as ANC  $>500/\text{mm}^3$  for 3 consecutive days or  $>2000/\text{mm}^3$  for 1 day), the use of prophylactic myeloid growth factors (ie, granulocyte-colony stimulating factor [G-CSF]) must be started with the product, dose, and route of administration at the discretion of the treating institution.

### **9.7.3 Cytomegalovirus 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  $\geq 500$  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 suspected of having GvHD for whom the cause of transplantation-associated diarrhea and/or enterocolitis is unclear, the subject will require endoscopy and histologic analyses of intestinal biopsy specimens as clinically appropriate.

### **9.7.4 Malignancy**

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

### **9.7.5 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 10.3.8) prior to 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.

### **9.8 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 9.7 for management of vedolizumab dosing for specific clinical events. The medical monitor should be contacted prior to any dose modification in vedolizumab for any patient in the study.

### **9.9 Blinding and Unblinding**

Not applicable. This is an open-label study.

### **9.10 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.

### **9.11 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 starting dose, 300 mg (5.0 mL) will be removed from each vial 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 prior to administration, whenever solution and container permit.

### **9.12 Packaging and Labeling**

Vedolizumab IV will be supplied in a 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.

### **9.13 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 to 46°F). A daily temperature log of the drug storage area must be maintained every working day.

### **9.14 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.

## **10.0 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.

### **10.1 Study Personnel and Organizations**

The contact information for the Millennium project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country (where applicable), 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.

### **10.2 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).

### **10.3 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.

#### **10.3.1 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.

#### **10.3.2 Patient Demographics**

The date of birth, race, ethnicity, and sex of the patient are to be recorded during Screening.

#### **10.3.3 Medical History**

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section [10.3.10](#).

#### 10.3.4 Physical Examination

Complete physical examinations and symptom-directed physical examinations, as appropriate, will be completed per standard of care at the times specified in the [Schedule of Events](#).

#### 10.3.5 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](#). The neurological examination will be performed by the study neurologist. 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.

#### 10.3.6 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](#).

#### 10.3.7 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](#). On dosing days, vital signs will be obtained before and within 60 minutes of completion of infusion.

#### 10.3.8 Progressive Multifocal Leukoencephalopathy 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](#) 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 [11.6](#) for additional details regarding the RAMP program.

#### 10.3.9 Pregnancy Test

A serum or urine pregnancy test will be performed for women of childbearing potential at screening and within 4 days prior to 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.

#### 10.3.10 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the first dose of study drug through 18 weeks after the last dose of study

drug. See Section 9.4 and Section 9.5 for a list of medications and therapies that are prohibited and/or allowed during the study.

### 10.3.11 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the [Schedule of Events](#). Refer to Section 11.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

### 10.3.12 Enrollment

Enrollment is defined as when the written informed consent has been obtained and the patient's eligibility has been confirmed per the inclusion and exclusion criteria. Procedures for completion of the enrollment information are described in the Study Manual.

### 10.3.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment 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 10.a](#) and urine samples for analysis of the parameters shown in [Table 10.b](#) will be obtained as specified in the [Schedule of Events](#).

**Table 10.a Clinical Chemistry and Hematology Tests**

Hematology		Chemistry
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase (ALP)	Glucose
Leukocytes with differential	ALT	Lactate dehydrogenase (LDH)
Neutrophils ANC	AST	Magnesium
Platelets (count)	Bilirubin (total)	Phosphate
	Blood urea nitrogen (BUN)	Potassium
	Calcium	Sodium
	Carbon dioxide (CO <sub>2</sub> )	Uric acid
	Creatinine	

PCR monitoring for CMV reactivation will be performed on a weekly basis (see Section 9.7.2). Additionally, blood samples for measurement of anti-vedolizumab antibodies will be obtained as specified in the [Schedule of Events](#).

**Table 10.b Clinical Urinalysis Tests**

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

#### 10.3.14 Tuberculosis Screening

All patients will complete TB screening to determine eligibility. All patients must complete a diagnostic test during screening, either a QuantiFERON<sup>®</sup> test or a tuberculin skin test. Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history, as defined in Section 8.2.

#### 10.3.15 Chimerism Analysis

A peripheral blood sample will be collected for chimerism analysis per institutional standards according to time points specified in the [Schedule of Events](#)

#### 10.3.16 Disease Assessment

Acute GvHD will be assessed as specified in the [Schedule of Events](#) using the Glucksberg criteria and BMT CTN-modified IBMTR index for staging and grading acute GvHD (see [Appendix D](#)).

#### 10.3.17 Pharmacokinetic 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 schedule in 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 prior to the start of infusion and end of the infusion samples should be collected within 5 minutes from the end of infusion. The exact dates and times of administration of vedolizumab (start and end of infusion) and the exact date 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.

### 10.3.18 Pharmacodynamic Measurements

CCI

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

### 10.3.19 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](#).

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

## 10.4 Completion of Treatment

Patients will be considered to have completed study treatment if they discontinue study drug for any of the reasons outlined in Section [10.6](#).

## 10.5 Completion of Study

Patients will be considered to have completed the study if they withdraw from the study for any of the reasons outlined in Section [10.7](#).

## 10.6 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- Adverse event.
- Protocol violation.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the End of Treatment visit will be completed as specified in the [Schedule of Events](#). The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients in the dose-finding cohort who are withdrawn from treatment for reasons other than DLT during the DLT observation period will be replaced.



### 10.7 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.

### 10.8 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.

### 10.9 Posttreatment Follow-up Assessments

Patients will attend a Day +100 visit ( $\pm 7$  days) at which time patients will enter posttreatment follow-up. If subsequent anticancer therapy is required before 30 days after the last dose, the Day +100 visit should be conducted before the initiation of subsequent anticancer therapy.

Patients who remain in remission will be followed for development of acute and chronic GvHD and safety during clinic visits at 4, 5, 6, 9, and 12 months after allo-HSCT (Day 0) 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 until death, withdrawal of consent, termination of study by the sponsor, or for a maximum of 1 year after until the last patient is enrolled in the study. Survivor information may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieved from online or other databases (eg, social security indexes).

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 11.0 for details regarding definitions, documentation, and reporting of SAEs.

## 11.0 ADVERSE EVENTS

### 11.1 Definitions

#### 11.1.1 Pretreatment Event Definition

A pretreatment event 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.

#### 11.1.2 Adverse Event 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.

#### 11.1.3 Serious Adverse Event 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 11.2 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 [24]. 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<sup>3</sup> 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.

## 11.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

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 11.3 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 pretreatment events (as defined in Section 11.1) must be reported (see Section 11.3 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 pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information	
CCI	[REDACTED]

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 intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [24]. The criteria are provided in the Study Manual.

**Relationship** to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

### 11.3 Monitoring of Adverse Events 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 pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to 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).

### 11.4 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 11.2). 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 11.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

### 11.5 Procedures for Reporting Product Complaints

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 below:

Call center	Phone number	E-mail	Fax
PPD			

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 CCI (refer to Section 11.2).

### 11.6 Risk Minimization Action Plan for PML (RAMP Program)

Natalizumab (TYSABRI), another integrin receptor antagonist, has been associated with PML, a rare and often fatal opportunistic infection of the central nervous system. PML is caused by the John Cunningham virus (JCV) and typically only occurs in patients who are immunocompromised [25,26]. 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 VCAM-1 mediates trafficking to the central nervous system. Natalizumab is a pan- $\alpha_4$  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 [27,28]. In contrast, vedolizumab binds to the  $\alpha_4\beta_7$  integrin only [16] 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.

Patients undergoing HSCT are immunocompromised because of underlying disease, prior therapies, HSCT conditioning, and GvHD prophylaxis and treatment. The baseline risk of PML in the population of patients undergoing allo-HSCT for the treatment of malignancy can be estimated at 35.4 per 100,000 person-years (95% CI: 0.90, 197.29) compared with 0.2 per 100,000 patients with autoimmune diseases who did not have HIV or malignancy (including patients with IBD).[29,30] To address the theoretical 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. The complete description of the RAMP program, including materials and instructions for its implementation and monitoring, is included in the Study Manual.

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

To ensure success of the RAMP program, site personnel will be trained to recognize the features of PML, and patients will be trained to report specific neurological signs and symptoms without delay. Educational materials for teaching site personnel and patients about PML and the RAMP procedures will be distributed to all sites and are included in the Study Manual. Formal teaching and training will be performed for site personnel prior to the start of the study. Patients will receive training and educational materials prior to receiving treatment. The informed consent form will contain specific information on the hypothetical risk of PML. Any documented case of PML will be reported as an SAE, regardless of whether hospitalization occurs.

## **12.0 STUDY-SPECIFIC COMMITTEES**

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

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.

### **12.1 Dose Escalation and Cohort Expansion Plan**

End-of-Cohort Meetings will be held to review safety and PK data before moving to the next dose level in subsequent cohorts. The safety review will encompass the following: all available AEs for DLTs, appropriate dosing information and patient eligibility/evaluability, dose-toxicity relationships, and any other pertinent available safety and PK data. The review committee for the End-of-Cohort Meetings will include the sponsor study team, the study investigators, and an independent, third-party HSCT expert consultant. The study sponsor team will include, but will not be limited to, the following: the study clinician, safety lead, and other members as appropriate (biostatistics, clinical pharmacology, and translational medicine to interpret PK, PD, and biomarker data). During the dose escalation and expansion phases, review of safety data by the above listed parties will occur as needed on the basis of continuous monitoring of safety data, but at least quarterly by the study sponsor team, with consideration of the study stopping criteria (see Section [14.2](#)).

### 13.0 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.

#### 13.1 eCRFs

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.

#### 13.2 Record Retention

The investigator agrees to keep the records stipulated in Section 13.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last



approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the 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.

## **14.0 STATISTICAL METHODS**

### **14.1 Statistical and Analytical Plans**

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

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

#### **14.1.1 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.
- PK population: Defined as patients from the safety set with at least 1 PK sample collected.
- PD population: Defined as patients from the safety set with at least 1 PD sample collected.

For the primary endpoint, an evaluable patient is one who receives vedolizumab IV and is assessed for engraftment on or before Day +28.

#### **14.1.2 Procedures for Handling Missing, Unused, and Spurious Data**

All available safety, tolerability, efficacy, PK, and PD 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.

#### **14.1.3 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.

#### **14.1.4 Efficacy Analysis**

Secondary efficacy endpoints include:

- Percentage of patients who have developed overall Grade 2 to 4 acute GvHD (compiled from individual organ scores of gut, skin, or liver) by 100 days after myeloablative allo-HSCT.
- The frequency by maximum severity of GvHD according to the modified Glucksberg criteria and BMT CTN-modified IBMTR index.

CCI



#### 14.1.5 Pharmacokinetic 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.

#### 14.1.6 Pharmacodynamic Analysis

CCI



#### 14.1.7 Immunogenicity Analysis

Immunogenicity (anti-vedolizumab antibodies) will be descriptively summarized. The effect of anti-vedolizumab antibodies on safety and efficacy will be explored.

#### 14.1.8 Safety Analysis

For the primary endpoint, an evaluable patient is one who receives vedolizumab IV and is assessed for engraftment on or before Day +28.

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 system organ class, high-level terms, and preferred terms and will include the following categories:

- TEAEs.

- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs (ie, those events reported by  $\geq 10\%$  of all patients).
- 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.

#### **14.2 Interim Analysis and Criteria for Early Termination**

No interim analysis is planned. Toxicities will be continuously monitored during all phases of the study.

In addition to ongoing safety reviews of cumulative data, early termination of the study will occur if any of the following are observed during the expansion phase of the study:

- 3 cases of CMV colitis, or
- 3 cases of engraftment failure; however, if first 2 cases of engraftment failure are in patients who received myeloablative conditioning, the study will be stopped.

#### **14.3 Determination of Sample Size**

Approximately 18 evaluable patients will be enrolled to identify a tolerable vedolizumab dose level with acceptable PK. After the dose level has been identified, the cohort at that dose level may be expanded to include approximately 18 additional patients receiving myeloablative conditioning or RIC who are undergoing either related or unrelated allo-HSCT for the treatment of hematologic malignancies or myeloproliferative neoplasms. This group of patients will allow the further assessment of the tolerability and clinical activity of vedolizumab IV.

The sample size estimates are based on the primary objective of determining a recommended phase 2 dose and to describe the initial tolerability and safety of vedolizumab IV administered along with standard GvHD prophylaxis.

## **15.0 QUALITY CONTROL AND QUALITY ASSURANCE**

### **15.1 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 informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

### **15.2 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.

### **15.3 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 15.1.

## 16.0 ETHICAL ASPECTS OF THE STUDY

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

### 16.1 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 Investigator’s Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB’s or IEC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will {ship drug/notify site once} the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives [drug/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 informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator’s final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

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

## 16.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

### **16.3 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, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 16.2).

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 [e]CRF).

### **16.4 Publication, Disclosure, and Clinical Trial Registration Policy**

#### **16.4.1 Publication and Disclosure**

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

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



#### **16.4.2 Clinical Trial Registration**

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

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once 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.

#### **16.4.3 Clinical Trial Results Disclosure**

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

#### **16.5 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.

## 17.0 REFERENCES

1. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet* 2009;373(9674):1550-61.
2. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorrow ML, Boeckh M, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med* 2010;363(22):2091-101.
3. McDonald GB, Tabellini L, Storer BE, Lawler RL, Martin PJ, Hansen JA. Plasma biomarkers of acute GVHD and nonrelapse mortality: predictive value of measurements before GVHD onset and treatment. *Blood* 2015;126(1):113-20.
4. Murray S. Engraftment. In: Maziarz RT, Slater SS, editors. *Blood and Marrow Transplant Handbook*. 2nd ed: Springer; 2015; Chapter 14, p. 161-66.
5. Gratwohl A, Brand R, Frasson F, Rocha V, Niederwieser D, Reusser P, et al. Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time. *Bone Marrow Transplant* 2005;36(9):757-69.
6. Ferrara JL, Deeg HJ. Graft-versus-host disease. *N Engl J Med* 1991;324(10):667-74.
7. Welniak LA, Blazar BR, Murphy WJ. Immunobiology of allogeneic hematopoietic stem cell transplantation. *Annu Rev Immunol* 2007;25:139-70.
8. Chen YB, Kim HT, McDonough S, Odze RD, Yao X, Lazo-Kallanian S, et al. Up-Regulation of alpha4beta7 integrin on peripheral T cell subsets correlates with the development of acute intestinal graft-versus-host disease following allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2009;15(9):1066-76.
9. Murai M, Yoneyama H, Ezaki T, Suematsu M, Terashima Y, Harada A, et al. Peyer's patch is the essential site in initiating murine acute and lethal graft-versus-host reaction. *Nat Immunol* 2003;4(2):154-60.
10. Waldman E, Lu SX, Hubbard VM, Kochman AA, Eng JM, Terwey TH, et al. Absence of beta7 integrin results in less graft-versus-host disease because of decreased homing of alloreactive T cells to intestine. *Blood* 2006;107(4):1703-11.
11. Ueha S, Murai M, Yoneyama H, Kitabatake M, Imai T, Shimaoka T, et al. Intervention of MAdCAM-1 or fractalkine alleviates graft-versus-host reaction associated intestinal injury while preserving graft-versus-tumor effects. *J Leukoc Biol* 2007;81(1):176-85.
12. Butcher EC, Williams M, Youngman K, Rott L, Briskin M. Lymphocyte trafficking and regional immunity. *Adv Immunol* 1999;72:209-53.
13. Salmi M, Jalkanen S. Lymphocyte homing to the gut: attraction, adhesion, and commitment. *Immunol Rev* 2005;206:100-13.

14. Briskin M, Winsor-Hines D, Shyjan A, Cochran N, Bloom S, Wilson J, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol* 1997;151(1):97-110.
15. Erle DJ, Briskin MJ, Butcher EC, Garcia-Pardo A, Lazarovits AI, Tidswell M. Expression and function of the MAdCAM-1 receptor, integrin alpha 4 beta 7, on human leukocytes. *Immuno* 1994;153(2):517-28.
16. Soler D, Chapman T, Yang LL, Wyant T, Egan R, Fedyk ER. The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther* 2009;330(3):864-75.
17. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369(8):699-710.
18. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369(8):711-21.
19. Sands B, Feagan B, Rutgeerts P, Colombel J-F, Sandborn W, Sy R, et al. Vedolizumab induction therapy for patients with Crohn's disease and prior anti-tumour necrosis factor antagonist failure: a randomised, placebo-controlled, double-blind, multicentre trial. *Journal of Crohn's and Colitis* 2013;7(Suppl. 1):Pages S5–S6. 8th Congress of the European Crohn's and Colitis Organisation.
20. Parikh A, Leach T, Wyant T, Scholz C, Sankoh S, Mould DR, et al. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. *Inflamm Bowel Dis* 2012;18(8):1470-9.
21. Rosario M, Dirks NL, Gastonguay MR, Fasanmade AA, Wyant T, Parikh A, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther* 2015;42(2):188-202.
22. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant* 2009;15(12):1628-33.
23. Khandelwal P, Lane A, Chaturvedi V, Owsley E, Davies SM, Marmer D, et al. Peripheral Blood CD38 Bright CD8+ Effector Memory T Cells Predict Acute Graft-versus-Host Disease. *Biol Blood Marrow Transplant* 2015;21(7):1215-22.
24. Common Terminology Criteria for Adverse Events (CTCAE). National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services Series v4.03. June 14, 2010. Publication No. 09-5410.
25. Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. *Annu Rev Med* 2010;61:35-47.

26. Steiner I, Berger JR. Update on progressive multifocal leukoencephalopathy. *Curr Neurol Neurosci Rep* 2012;12(6):680-6.
27. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, et al. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005;353(18):1912-25.
28. TYSABRI (natalizumab) injection. Full Prescribing Information. Cambridge, MA: Biogen Idec Inc., Revised May 2015.
29. Bharat A, Xie F, Baddley JW, Beukelman T, Chen L, Calabrese L, et al. Incidence and risk factors for progressive multifocal leukoencephalopathy among patients with selected rheumatic diseases. *Arthritis care & research* 2012;64(4):612-5.
30. Amend KL, Turnbull B, Foskett N, Napalkov P, Kurth T, Seeger J. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. *Neurology* 2010;75(15):1326-32.
31. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 1995;15(6):825-8.
32. Rowlings PA, Przepiorka D, Klein JP, Gale RP, Passweg JR, Henslee-Downey PJ, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *Br J Haematol* 1997;97(4):855-64.
33. Mori T, Kato J, Shimizu T, Aisa Y, Nakazato T, Yamane A, et al. Effect of early posttransplantation tacrolimus concentration on the development of acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation from unrelated donors. *Biol Blood Marrow Transplant* 2012;18(2):229-34.
34. Ruutu T, Gratwohl A, de Witte T, Afanasyev B, Apperley J, Bacigalupo A, et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. *Bone Marrow Transplant* 2014;49(2):168-73.

## Appendix A Schedule of Events

### Schedule of Events (Screening through Day +20)

	Screening (a)	Day -1	Day 0	Day +1	Day +3	Day +5	Day +7	Day +9	Day +11	Day +13	Day +14	Day +16	Day +18	Day +20
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					X			X				X
Height	X													
Weight	X						X			X				X
Vital signs	X	X (d)					X			X (d)				X
ECOG performance status	X													
HCT-CI (dose-finding phase only)														
Tuberculosis screening	X (e)													
RAMP questionnaire	X	X (b)								X (b)				
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												
		<b>Serious adverse events</b> (f) will be reported from signing of the informed consent form through 18 weeks after the last dose of study drug.												
Vedolizumab IV administration (g)		X								X				
Allo-HSCT (h)			X											

Footnotes are on last table page.

**CONFIDENTIAL**

### Schedule of Events (Screening through Day +20) (continued)

	Screening (a)	Day -1	Day 0	Day +1	Day +3	Day +5	Day +7	Day +9	Day +11	Day +13	Day +14	Day +16	Day +18	Day +20
<b>Samples/Laboratory Assessments</b>														
Pregnancy test (i)	X1	X1												
Hematology/chemistry	X1	X1 (b)					X1			X1 (b)				X1
Urinalysis	X1	X1 (b)												
Blood sample for flow cytometry (j,k,l)		X1 (b)		X1			X1			X1 (b)				X1
<b>CCI</b>														
Blood sample for anti-vedolizumab antibodies (k)		X1 (b)												X1
Blood sample for PK (n)														See Table A

Allo-HSCT=allogeneic hematopoietic stem cell transplantation, ECOG= Eastern Cooperative Oncology Group, GvHD=graft-versus-host disease, HCT-CI=Hematopoietic Cell Transplantation-Specific Comorbidity Index, ICF=informed consent form, IV=intravenous, PK=pharmacokinetic(s), RAMP= Risk Assessment and Minimization for Progressive Multifocal Leukoencephalopathy (PML).

(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 prior to 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) QuantiFERON® test or tuberculin skin test only.

(f) Including serious pretreatment events; see Section 11.2.

(g) Vedolizumab will be administered via a 30-minute intravenous (IV) infusion on Day -1. HSC infusion should occur on Day 0 no sooner than 12 hours after completion of IV infusion of vedolizumab on Day -1. Vedolizumab will also be administered via a 30-minute IV infusion on Day +13 after myeloablative allo-HSCT.

(h) Details on the HSC infusion including cell counts and donor CMV status will be recorded on the eCRF.

(i) A serum beta-human chorionic gonadotropin (β-hCG) 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.

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

(k) **CCI**

(l) Includes immunophenotyping and MAdCAM-1 (immunophenotyping includes the cell markers of GvDH).

(m) **CCI**

CONFIDENTIAL

(n) Time points for blood samples for PK analysis will be collected as specified in [Table A](#).

Note: Tests and procedures should be performed on schedule, but occasional changes are allowable ( $\pm 2$  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.**

**Schedule of Events (Day +22 Through End of Study)**

	Day +22	Day +26	Day +30	Day +34	Day +36	Day +40	Day +42	Day +100 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)	12 month Follow-up/ EOS/ET Visit (b)	OS Follow- up
Symptom-directed physical examination		X		X			X	X	X	X	X	X	X	
Weight		X		X			X	X	X	X	X	X	X	
Vital signs		X		X			X (c)	X	X	X	X	X	X	
RAMP questionnaire							X (d)							
Follow-up phone calls														Q3mo (e)
Assessment of GvHD		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													
	<b>Serious adverse events</b> (f) will be reported from signing of the informed consent form through 18 weeks after the last dose of study drug.													
Vedolizumab IV administration (g)							X							
<b>Samples/Laboratory Assessments</b>														
Hematology/chemistry (h)		X1		X1			X1 (d)	X1	X1	X1	X1	X1	X1	
Urinalysis														
Blood sample for chimerism analysis			X1											
Blood sample for flow cytometry (i)		X1		X1			X1 (d)				X1		X1	
<b>CCI</b>														
Blood sample for anti-vedolizumab antibodies (i)				X1				X1						
Blood sample for PK(k)	See <a href="#">Table A</a>													

CONFIDENTIAL



Complete remission with incomplete platelet recovery=CRp, EOS=end-of-study, ET=early termination, GvHD=graft-versus-host disease, IV=intravenous, OS=overall survival, PK=pharmacokinetic(s), World Health Organization=WHO.

- (a) Patients will attend a Day +100 visit ( $\pm 7$  days) at which time patients will enter posttreatment follow-up. If subsequent anticancer therapy is required before 30 days after the last dose, the Day +100 visit should be conducted before the initiation of subsequent anticancer therapy.
- (b) Patients who remain in remission will be followed for development of acute and chronic GvHD and safety during clinic visits at 4, 5, 6, 9, and 12 months after allo-HSCT 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). Patients who have been discontinued will attend an ET visit 30 to 40 days after the last dose of study drug using all study procedures outlined for the 12-month follow-up visit.
- (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 pre-dose.
- (e) Patients will be followed for overall survival 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 11.2.
- (g) If engraftment is confirmed, vedolizumab will be administered via a 30-minute intravenous (IV) infusion on Day +42 after myeloablative allo-HSCT.
- (h) Hepatitis and HIV testing are to be performed only at the Screening visit.
- (i) Additional specimens may be collected from any patient who experiences an infusion reaction.
- (j) CCI [REDACTED].
- (k) Time points for blood samples for PK analysis will be collected as specified in Table A.

Note: Tests and procedures should be performed on schedule, but occasional changes are allowable ( $\pm 2$  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.**

**Table A Pharmacokinetic Sample Breakdown**

	Day																			
	-1	0	+3	+5	+7	+9	+11	+13	+14	+16	+18	+20	+22	+26	+30	+36	+40	+42	+100 (±7 days)	
	Serum																			
PK collection on non-dosing days (a)			X1	X1	X1	X1	X1			X1	X1	X1	X1	X1	X1	X1	X1		X1	
Predose	X1							X1										X1		
30 min postdose (±5 min)	X1							X1										X1		
1 hr postdose (±10 min)																		X1		
2 hrs postdose (±20 min)	X1							X1										X1		
12 hrs postdose (±30 min)	X1							X1												
24 hrs postdose (±60 min)		X1							X1											

(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.

CONFIDENTIAL

## **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, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/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 informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject’s personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject’s legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

## **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 Clinical Stages and Grades 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 [31].

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.

### Acute Graft-versus-Host Disease Grade (modified Glucksberg)

Grade	Skin	Liver	Intestinal tract
I	Stage 1-2	None	None
II	Stage 3 or →	Stage 1 or →	Stage 1
III	-	Stage 2-3 or →	Stage 2-4
IV	Stage 4 or →	Stage 4	-

From Przepiorka et al., 1995 [31].

ECOG PS=Eastern Cooperative Oncology Group performance status.

### Criteria for IBMTR Severity Index for Acute Graft-versus-Host Disease

Index	Skin			Liver			Intestinal tract	
	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 [32].

IBMTR=International Bone Marrow Transplant Registry Database.

## **Appendix E Recommended Tacrolimus + Short-Term Methotrexate Prophylaxis Regimen**

### Tacrolimus (Mori et al, 2012) [33]

- Tacrolimus treatment should start during conditioning.
- The goal of tacrolimus treatment should be to achieve a trough concentration of 5-10 ng/dL.
- Keep at therapeutic levels through Day +100, tapering off after Day +100 if no signs of GvHD are observed.
- The goal should be to discontinue tacrolimus treatment by Day +180 after allo-HSCT.

### Methotrexate (Ruutu et al, 2014) [34]

- Administer at 10 mg/m<sup>2</sup> IV on Days +1, +3, +6, and +11 after allo-HSCT per institutional standards.
- Doses may be modified or held based on toxicity.

---

**Appendix F 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, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.



## Appendix G Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) Scores

Comorbidity	Definitions of Comorbidities	HCT-CI Weighted Scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease (a), congestive heart failure, myocardial infarction, or ejection fraction $\leq 50\%$	1
IBD	CD or UC	1
Diabetes (b)	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance (b)	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild (b)	Chronic hepatitis, bilirubin $>ULN$ to $1.5 \times ULN$ , or AST/ALT $>ULN$ to $2.5 \times ULN$	1
Obesity (b)	Patients with a body mass index $>35 \text{ kg/m}^2$	1
Infection (b)	Requiring continuation of antimicrobial treatment after Day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal (b)	Serum creatinine $>2 \text{ mg/dL}$ , on dialysis, or prior renal transplantation	2
Moderate pulmonary (b)	$DL_{CO}$ and/or $FEV_1$ 66%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease (b)	Except mitral valve prolapse	3
Severe pulmonary (b)	$DL_{CO}$ and/or $FEV_1 \leq 65\%$ or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic (b)	Liver cirrhosis, bilirubin $>1.5 \times ULN$ , or AST/ALT $>2.5 \times ULN$	3

Source: Sorrow ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005;106(8):2912-9.

AST=aspartate transaminase, ALT=alanine transaminase, CD=Crohn's disease, CTD=connective tissue disease,  $DL_{CO}$ =diffusion capacity of carbon monoxide,  $FEV_1$ =volume that has been exhaled at the end of the first second of forced expiration, HCT-CI=Hematopoietic Cell Transplantation-Comorbidity Index, IBD=inflammatory bowel disease, RA=rheumatoid arthritis, SLE=systemic lupus erythematosus, UC=ulcerative colitis, ULN=upper limit of normal.

(a) One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.

(b) Comorbidity is currently active or patient required medical treatment.

## **Appendix H Grade 4 Regimen-Related Organ Toxicities**

Occurrence of the following Grade 4 regimen-related organ toxicities will be considered as a possible DLT. Review of any such regimen-related toxicities will occur at each End-of-Cohort Review meeting prior to any dose escalation.

- Cardiac toxicity: Cardiac rhythm disturbance with life-threatening consequences, hemodynamic compromise requiring urgent intervention, cardiac failure requiring continuous IV or mechanical hemodynamic support.
- Bladder toxicity: Hemorrhagic cystitis with life-threatening consequences, urgent radiologic or operative intervention indicated.
- Renal toxicity: Life-threatening consequences, dialysis required.
- Pulmonary toxicity: Diffuse alveolar hemorrhage or idiopathic pneumonia syndrome (IPS) with life-threatening consequences, intubation with ventilatory support indicated.
- Hepatic toxicity: Moderate to severe hepatic encephalopathy, coma, ascites requiring operative intervention, life-threatening consequences.
- CNS toxicity: Life-threatening, prolonged repetitive seizures or coma not explained by other medication, infection or bleeding.
- Mucositis: Life-threatening airway compromise, urgent intervention indicated (eg, tracheotomy or intubation).
- GI toxicity: Life-threatening hemorrhagic enterocolitis requiring urgent intervention, small bowel obstruction requiring surgical intervention.

## Appendix I Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 01.

### **Page 31, Section 8.1.2 Inclusion Criteria: Expansion Phase**

#### **Existing Text**

2. Candidates for HLA-matched or 1-locus (antigen or allele) mismatched unrelated or related donor allo-HSCT, using either peripheral blood stem cells or bone marrow as the cell source, for the treatment of *ALL*, *AML*, or myeloproliferative neoplasm.
3. Disease must be in remission at the time of allo-HSCT. Remission is defined as:
  - Patients with acute leukemia, chronic myelogenous leukemia, and myelodysplasia with no circulating blasts and <5% blasts in the bone marrow.
  - Patients with chronic lymphocytic leukemia, small lymphocytic lymphoma, or other non-Hodgkin lymphoma with chemosensitive disease at time of transplantation.
  - Patients with myelofibrosis and other myeloproliferative neoplasms with <5% blasts in the blood and bone marrow.

#### **Revised Text**

2. Candidates for HLA-matched or 1-locus (antigen or allele) mismatched unrelated or related donor allo-HSCT, using either peripheral blood stem cells or bone marrow as the cell source, for the treatment of **hematologic malignancy** or myeloproliferative neoplasm.
3. Disease must be in remission at the time of allo-HSCT. Remission is defined as **one of the following**:
  - Patients with acute leukemia, chronic myelogenous leukemia, and myelodysplasia with no circulating blasts and <5% blasts in the bone marrow.
  - Patients with chronic lymphocytic leukemia, small lymphocytic lymphoma, or other non-Hodgkin lymphoma with chemosensitive disease at time of transplantation.
  - Patients with myelofibrosis and other myeloproliferative neoplasms with <5% blasts in the blood and bone marrow.

#### **Rationale for Amendment**

As non-Hodgkin lymphoma is not classified as a myeloproliferative neoplasm, clarifications were made to the text to provide clarity based on the FDA communication received on 28 December 2015.

### **Page 36, Section 9.2 Definitions of Dose-Limiting Toxicity**

#### **Existing Text**

A DLT will be any Grade 3 or higher toxicity assessed by the investigator as *clearly* related to vedolizumab treatment. Hypersensitivity reactions and other infusion-related reactions will not be

considered a DLT. Any patient who discontinues the study due to an infusion-related reaction will be replaced in the study.

#### Revised Text

A DLT will be any Grade 3 or higher toxicity assessed by the investigator as related to vedolizumab treatment. Hypersensitivity reactions and other infusion-related reactions will not be considered a DLT. Any patient who discontinues the study due to an infusion-related reaction will be replaced in the study.

#### Rationale for Amendment

Regarding the DLT definition, a Grade 3 or higher toxicity assessed by the investigator as clearly related to vedolizumab treatment was not acceptable according to the FDA communication received on 28 December 2015; thus, this was removed from the protocol text.

#### Page 44, Section 10.3.7 Vital Signs

##### Existing Text

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](#). On dosing days, vital signs will be obtained before *the* infusion.

##### Revised Text

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](#). On dosing days, vital signs will be obtained before **and within 60 minutes of completion of** infusion.

##### Rationale for Amendment

The recording of vital signs after study drug infusion was added on the basis of the FDA communication received on 28 December 2015. The change also appears in the [Schedule of Events](#) on Days -1, +13, and +42.

#### Page 54, Section 12.1 Dose Escalation and Cohort Expansion Plan

##### Existing Text

End-of-Cohort Meetings will be held to review safety and PK data before moving to the next dose level in subsequent cohorts. The review committee for the End-of-Cohort Meetings will include the sponsor study team, the study investigators, and a third-party HSCT expert consultant. During the expansion *phase*, review of safety data will occur at least quarterly with consideration of the study stopping criteria (see Section [14.2](#)).

##### Revised Text

End-of-Cohort Meetings will be held to review safety and PK data before moving to the next dose level in subsequent cohorts. **The safety review will encompass the following: all available AEs for DLTs, appropriate dosing information and patient eligibility/evaluability, dose-toxicity relationships, and any other pertinent available safety and PK data.** The review committee for

the End-of-Cohort Meetings will include the sponsor study team, the study investigators, and **an independent**, third-party HSCT expert consultant. **The study sponsor team will include, but will not be limited to, the following: the study clinician, safety lead, and other members as appropriate (biostatistics, clinical pharmacology, and translational medicine to interpret PK, PD, and biomarker data).** During the **dose escalation and expansion phases**, review of safety data **by the above listed parties** will occur **as needed on the basis of continuous monitoring of safety data, but** at least quarterly **by the study sponsor team**, with consideration of the study stopping criteria (see Section [14.2](#)).

#### **Rationale for Amendment**

Language was added to clarify who is responsible for reviewing safety and PK data for the purposes of applying the dose escalation and early protocol stopping rules, and how often this review is to occur. These modifications were made on the basis of the FDA communication received on 28 December 2015.

Vedolizumab-1015 Protocol Amend 1

**ELECTRONIC SIGNATURES**

<b>Signed by</b>	<b>Meaning of Signature</b>	<b>Server Date</b> (dd-MMM-yyyy HH:mm)
PPD	Clinical Pharmacology Approval	14-Jan-2016 19:54
	Statistical Approval	14-Jan-2016 20:09
	Clinical Science Approval	14-Jan-2016 21:03
	Clinical VP Approval	14-Jan-2016 21:26