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

SAP Approve Date: June 04, 2018

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# STATISTICAL ANALYSIS PLAN

## STUDY NUMBER: Vedolizumab-1015

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

## PHASE 1b

Version**:** Final v1.0

Date**:** June 04, 2018

**Prepared by:**

PPD

Based on:

Protocol Version: 2.0

Protocol Date: December 22, 2016

## 1.1 Approval Signatures

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

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

## 2.0 TABLE OF CONTENTS

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## LIST OF IN-TEXT FIGURES

## 3.0 LIST OF ABBREVIATIONS

| Term | Definition |
|---|---|
| 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 + fludaradine |
| $C_{trough}$ | 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 |
| IBD | inflammatory bowel disease |
| IBMTR | International Bone Marrow Transplant Registry Database |

| Term | Definition |
|---|---|
| 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 |
| US | United States |
| WHO | World Health Organization |

# 4.0 OBJECTIVES

## 4.1 Primary Objectives

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.

## 4.2 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 (compiled from individual organ scores of gut, skin, or liver) at 100 days after allo-HSCT.
- To determine the distribution of maximum severity of acute GvHD throughout the 100-day period after allo-HSCT.

## 4.3 Exploratory Objectives

The exploratory objectives are:

CCI

CCI

[redacted]

## 4.4 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 graft-versus-host disease (GvHD) prophylaxis (tacrolimus plus short-term methotrexate) in adult patients (18—75 years old) 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.

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. Vedolizumab will be administered initially on Day –1 before allo-HSCT and then on Days +13 and +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 and has at least 1 PK sample collected.

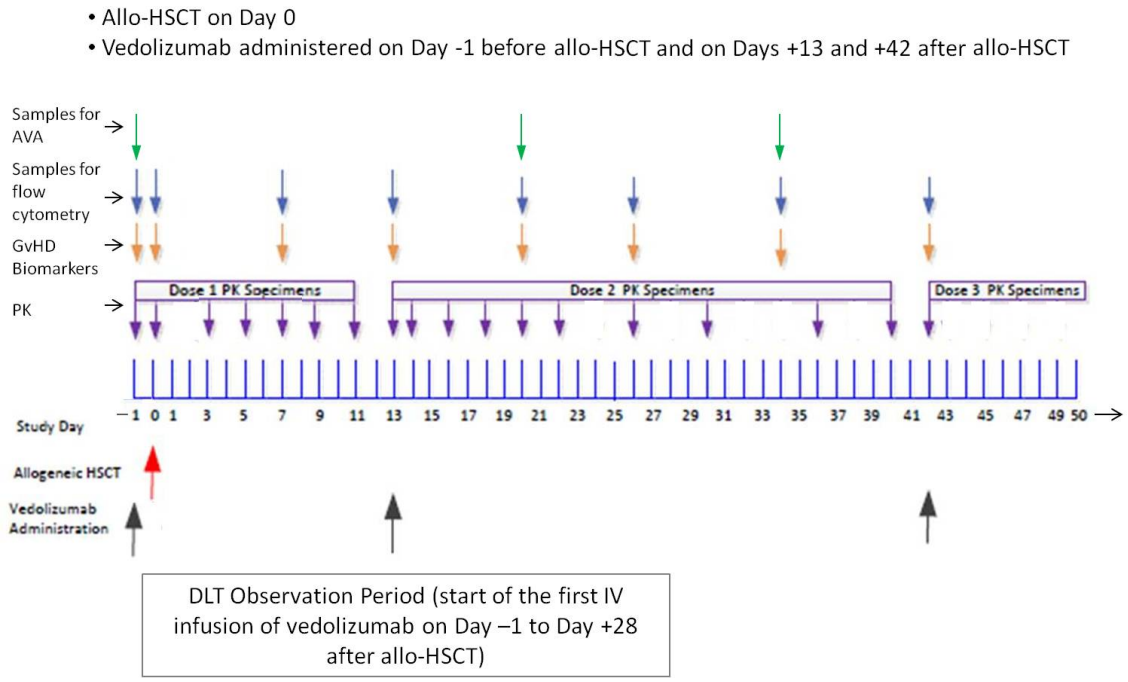
Patients will receive up to 3 doses of vedolizumab IV within the first 100 days after allo-HSCT. Patients who remain in remission will be followed for safety and development of acute and chronic GvHD for 1 year after allo-HSCT or until the patient's death or withdrawal of consent or termination of the 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 post treatment follow-up.

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 experience 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. DLT will be considered as a part of the PK/PD analysis and will be further outlined in the Clinical Pharmacology Analysis Plan (CPAP).

The graphical study design is presented on Figure 4.a.

**Figure 4.a Overview of Study Design (from day -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.

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 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.

# 5.0 ANALYSIS ENDPOINTS

## 5.1 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 are listed in Table 5.a:

**Table 5.a Description of the Primary Endpoints**

| Type of the Endpoints | Description of the Endpoints |
|---|---|
| Primary Safety Endpoints | 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. |
| Primary PK Endpoint | Mean serum concentrations of vedolizumab that will help inform the likelihood of α4β7 target saturation throughout the first 100 days following allo-HSCT. |

## 5.2 Secondary Endpoints

The secondary endpoints are listed in Table 5.b:

**Table 5.b Description of the Secondary Endpoints**

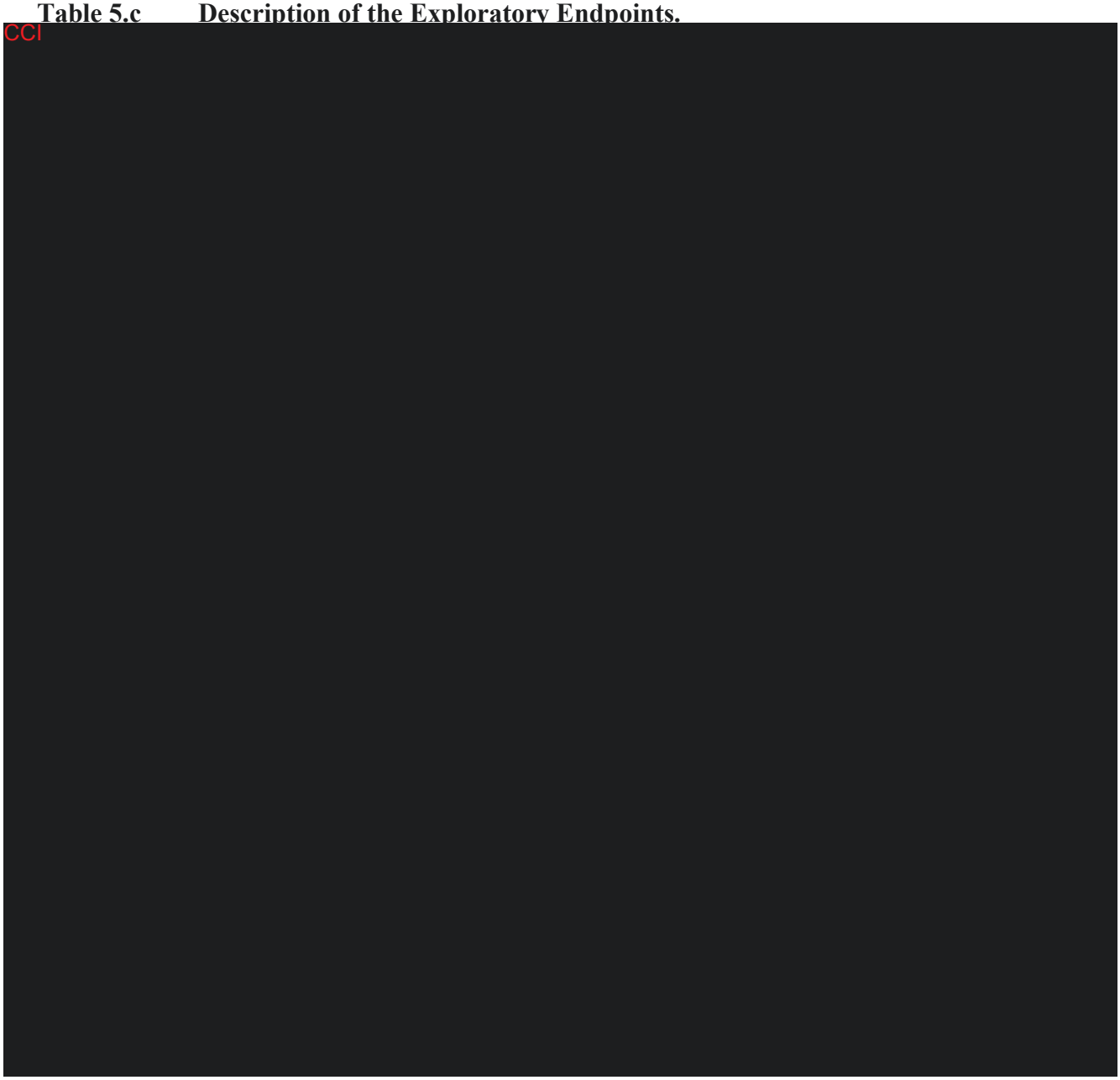
| Type of the Endpoints | Description of the Endpoints |
|---|---|
| Secondary Efficacy Endpoints | Time to neutrophil engraftment. |
| | Percentage of patients who have developed overall Grade 2 to 4 acute GvHD (compiled from individual organ scores of gut, skin, or liver) by 100 days after myeloablative allo-HSCT. |
| | The frequency of maximum severity of acute GvHD throughout the 100 day period after allo-HSCT(see GvHD assessment schedule in Appendix C), defined 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). |
| Secondary PK Endpoint | Mean serum concentrations of vedolizumab before dosing (Ctrough) on Days +13 and +42 after myeloablative allo-HSCT. |

## 5.3 Exploratory Endpoints

The exploratory endpoints are listed in Table 5.c:

**Table 5.c Description of the Exploratory Endpoints.**

CCI



## 6.0 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.

# 7.0 METHODS OF ANALYSIS AND PRESENTATION

## 7.1 General Principles

Statistical analysis plan (SAP) will be prepared and finalized prior to database freeze. After cleaning the data, the analyses of the primary, secondary and exploratory endpoints will be performed. Additional analysis will be performed after the 12-month follow-up data are locked and cleaned.

Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed.

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.

## 7.2 Study Definitions and Conventions

### 7.2.1 Study Terms

The definitions of the study terms are provided in the table below:

| Term | Definition |
|---|---|
| **Clinical Remission (for overall design and escalation phase entry)** | Defined by conventional WHO criteria: <5% blast cells, count recovery (although complete remission with incomplete platelet recovery [CRp] would be allowed), and no evidence of extramedullary disease. |
| **Clinical Remission (for expansion phase)** | Defined for patients with one of the following criteria:<br>a) Acute leukemia, chronic myelogenous leukemia, and myelodysplasia with no circulating blasts and <5% blasts in the bone marrow; OR<br>b) Chronic lymphocytic leukemia, small lymphocytic lymphoma, or other non-Hodgkin lymphoma with chemosensitive disease at time of transplantation; OR<br>c) Myelofibrosis and other myeloproliferative neoplasms with <5% blasts in the blood and bone marrow. |
| **Acute GvHD** | Defined as clinical evidence of acute GvHD per Glucksberg and IBMTR |
| **Chronic GvHD** | Defined as clinical evidence of chronic GvHD by the investigator per Seattle and NIH scale |
| **Neutrophil Engraftment Recovery** | Recovery of absolute neutrophil count [ANC], defined by an ANC >500/$mm^3$ for 3 consecutive days or >2000/$mm^3$ for 1 day. The first day of the 3-day period will be considered the day of neutrophil engraftment. |
| **Overall Survival (OS)** | Defined as the time from the date of enrollment to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. |
| **GRFS** | Defined as Grade 3—4 acute GvHD, chronic GvHD requiring systemic immunosuppression, disease relapse or progression, or death due to any cause. |

### 7.2.2 Definition of Study Days

Study Day 0 is defined as the date on which HSC infusion occurs (no sooner than 12 hours after completion of IV infusion of vedolizumab on Day –1). Other study days are defined relative to the Study Day 0 with Day +1 being the day after, and Day -1 being the day prior to Study Day 0.

### 7.2.3 Definition of Study Visit Windows

Baseline is defined as the last non-missing measurement prior to or on the date of the first dose of study drug (Study Day -1). All data will be categorized based on the scheduled and actual sampling time at which it was collected, allowing equally distanced windows (See Table 7.a) between the scheduled days when applicable. The visit windows should be used to summarize the endpoints that are defined to target the scheduled visit days.

**Table 7.a Visit Windows to be used for the summary of the efficacy endpoints.**

| Scheduled Visit Day | | Assessment of GvHD | Symptom-directed physical examination | Vital signs | Weight |
|---|---|---|---|---|---|
| Screening | | | | ≤ -2 | ≤ -2 |
| -1 | | | -1 | -1 [(b)] | |
| 0 | *Allo-HSCT (no sooner than 12 hours after IV vedolizumab infusion)* | | | | |
| +1 | *Blood sample collection (within 24 ±3 hours post-dose from Day 0)* | | | | |
| +7±2 | | +1 — +10 | +1 — +10 | +1 — +10 | +1 — +10 |
| +13±2 | | +11 — +16 | +11 — +16 | +11 — +16[(b)] | +11 — +16 |
| +20±2 | | +17 — +23 | +17 — +23 | +17 — +23 | +17 — +23 |
| +26±2 | | +24 — +30 | +24 — +30 | +24 — +30 | +24 — +30 |
| +34±2 | | +31 — +38 | +31 — +38 | +31 — +38 | +31 — +38 |
| +42±2 | | +39 — +71 | +39 — +71 | +39 — +71[(b)] | +39 — +71 |
| +100±7 | | +72 — +110 | +72 — +110 | +72 — +110 | +72 — +110 |
| 4 month[(a)] follow up | | +111 — +135 | +111 — +135 | +111 — +135 | +111 — +135 |
| 5 month[(a)] follow up | | +136 — +165 | +136 — +165 | +136 — +165 | +136 — +165 |
| 6 month[(a)] follow up | | +166 — +225 | +166 — +225 | +166 — +225 | +166 — +225 |
| 9 month[(a)] follow up | | +226 — +315 | +226 — +315 | +226 — +315 | +226 — +315 |
| 12 month[(a)] follow up | | ≥ +316 | ≥ +316 | ≥ +316 | ≥ +316 |

(a) One month here is considered to be 30 days. (b) Vital signs will be obtained before and within 60 minutes of completion of IV infusion of vedolizumab.

**Table 7.b Visit Windows to be used for the summary of the PD and biomarker endpoints.**

| Scheduled Visit Day | Flow Cytometry | Biomarkers |
|---|---|---|
| Screening | | |
| -1 | ≤ -1 | ≤ -1 |
| 0 | *Allo-HSCT (no sooner than 12 hours after IV vedolizumab infusion)* | |
| +1 | +1 — +3 | +1 — +3 |
| +7±2 | +4 — +10 | +4 — +10 |
| +13±2 | +11 — +16 | +11 — +16 |
| +20±2 | +17 — +23 | +17 — +23 |
| +26±2 | +24 — +30 | +24 — +30 |
| +34±2 | +31 — +38 | +31 — +38 |
| +42±2 | +39 — +111 | +39 — +71 |
| +100±7 | NA | ≥ +72 |
| 6 month[(a)] follow up | +112 — +270 | NA |
| 12 month[(a)] follow up | ≥ +271 | NA |

(a) One month here is considered to be 30 days.

The monitoring of concomitant medications and procedures, as well as the adverse event reporting is recorded from first dose of study drug (or from signing of the informed consent in case of SAE) through 18 weeks after the last dose of study drug, and should be summarized based on the reported dates (not following windows).

Subjects disposition tables should be based on the reported dates (not following visit windows).

### 7.2.4 Conventions for Missing Adverse Event Dates

Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

For AEs or SAEs, a missing or incomplete onset date will be imputed according to the following conventions:

1) If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):
    - First study medication date
    - Consent date (for SAEs only)
2) If an onset date is incomplete, the derived onset date will be calculated following:

- Missing day, but month and year present: the day will be imputed as the 15th of the month. If the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date.
- Missing day and month, but year present: the day and month will be imputed as the 30th June of the year. If the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date.

For AEs or SAEs, a missing or incomplete end date will be imputed according to the following conventions:

1) If an end date is missing, the derived end date will be imputed the last assessment date.
2) If an end date is incomplete, the derived end date will be calculated following:
   - Missing day, but month and year present: the day will be imputed as the last date (for example February 2009 will be imputed as 28 February 2009) of the month.
   - Missing day and month, but year present: the day and month will be imputed as the 31st December of the year.

### 7.2.5 Conventions for Missing Concomitant Medication Dates

Start and stop dates for all concomitant medications are collected on the CRF. However, in case of missing or partial information in these dates, the following rules will be used:

If the start date is missing or partial:

- If the day is missing, the start day will be the first day of the month
- If the month is missing, the start month will be the month corresponding to 90 days prior to the first study medication date
- If the year is missing, the start year will be the year of the entry visit (or consent date, for those missing entry visit)
- If the entire date is missing, the start date will be the date of first study drug administration

If the stop date is missing, partial or "continuing:"

- If the day is missing, the stop day will be the last day of the month reported
- If the month is missing, the stop month will be the month during which the last dose of induction treatment was administered
- If the year or the entire date is missing or if the medication is "continuing", the stop year will be the year in which the last dose of induction treatment was administered.

### 7.2.6 Conventions for Clinical Stages and Grades of Graft-Versus-Host Disease

The clinical Stages and Grades of Graft-Versus-Host Disease will be defined 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).

The classification the following rules apply:

1) For every organ involvement (skin, liver, or intestinal) if the GvHD involvement is marked as "YES" for this organ involvement (skin, liver, or intestinal) on eCRF. and the stage of this organ involvement is ≥ 1, the subjects should to be counted as having GvHD involvement for this organ (skin, liver, or intestinal respectively).
2) If the involvement of an organ (Skin, Liver, or Intestinal) is marked as "YES" but the stage of involvement is = 0, then the subject should not be counted as having GvHD of that organ.
3) A subject should be counted as having overall GvHD if this subject has at least one organ involvement with stage ≥1.
4) To assess the grade level for Liver GvHD involvement, the maximal bilirubin level within the visit window should be used (See Table 7.a).

## 7.3 Populations for Analyses

The following populations will be used for analysis:

- **Safety population:** The population of patients evaluable for vedolizumab safety is defined as all patients who receive any amount of vedolizumab IV.
- **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.

Any additional analyses/sub-analyses for cohorts will be outlined in the CPAP, if deemed necessary.

## 7.4 Disposition of Subjects

Summary of the subject disposition will include the following:

- Study Information, including date first subject signed ICF, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint.

- Summary of Screen Failures.
- Number of subjects enrolled by site and treatment dose group.
- Number and percent of subjects completing 28 days
- Number and percent of subjects completing 100 days
- Number and percent of subjects completing 180 days
- Number and percent of subjects completing 1 year
- Number and percent of subjects receiving all 3 infusions
- Number and percent of subjects receiving 2 infusions
- Number and percent of subjects receiving 1 infusions
- Number and percent of subject receiving 0 infusions
- Number of patients in the Safety population.
- Number of patients in the PK population.
- Number of patients in the PD population.
- Disposition of subjects based on the reasons for discontinuation of treatment and for failing to complete the study.
- Significant protocol deviations, captured on the eCRF will be summarized descriptively.

## 7.5 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by dose level using safety analysis dataset (see Table 7.c). No baseline comparison will be performed.

*Categorical variables* (including prior treatment therapies) will be tabulated. No baseline lab values will be tabulated. The number and percentage of the observations for each category will be reported. Categories that contain zero observations will be reported as '0', not omitted. Missing and non-reported observation will be reported as such, not omitted.

*Continuous variables* should be summarized for each dosing cohort using the following:

- Number of observations (*n*),
- Mean,
- Standard deviation (SD),
- Range of values (Min, Max).

## Table 7.c. Summary of Patients' Baseline and Demographic Characteristics

| *Characteristic* | *Summarized as* | *Categories and measurement units* |
|---|---|---|
| Age | Continuous | 18—75 years |
| Age group | Ordinal Categorical | <35<br>>= 35 years |
| Gender | Categorical | Female/Male |
| Race | Categorical | White/Black/Asian/Native American/ Asian Pacific/Other |
| Ethnicity | Categorical | Hispanic or Latino<br>Not Hispanic or Latino<br>Not Reported |
| Weight | Continuous | Kg |
| Height | Continuous | cm |
| Baseline ECOG Status | Ordinal Categorical | 0, 1, 2, 3, 4 |
| Smoking status | Categorical | Current Smoker<br>Never Smoked<br>Former Smoker |
| Underlying disease diagnosis | Categorical | Myeloproliferative Neoplasm,<br>Myelodysplastic or Myelofroliferative Neoplasm,<br>Myelodysplastic syndrome,<br>Acute myeloid leukaemia or related precursor neoplasm,<br>Precursor lymphoid neoplasm,<br>Mature B-cell neoplasm,<br>Mature T-cell and NK-cell neoplasm |
| Underlying disease duration since diagnosis | Ordinal Categorical and Continuous | < 1 years<br>≥1 — <3 years<br>≥ 3 — <7 years<br>≥7 years |
| Conditioning Regimen | Categorical | Myeloablative Transplant,<br>Reduced-intensity Transplant |
| Donor-recipient Gender Match | Categorical | Female Subject-Female Donor<br>Female Subject-Male Donor<br>Male Subject-Female Donor<br>Male Subject-Male Donor |
| Donor Relationship to Subject | Categorical | Related/Not related |
| HLA Compatability | Categorical | Match/Mismatch |
| Cytomegalovirus IgG Antibody | Catgorical | Positive/Negative |
| Source of stem cells | Catgorical | Bone Marrow/Peripheral Blood |

## 7.6 Medication History and Concomitant Medications

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. Medical and Surgical History will be summarized by system organ class and preferred term.

In addition, concomitant medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the first dose of vedolizumab through 18 weeks after the last dose of vedolizumab.

Concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by standardized medication name in the safety analysis set. Concomitant medications are medications taken anytime between 30 days prior to the administration of the first dose of vedolizumab through the last dose of the vedolizumab. Medications taken prior to dosing and stopped more than 30 days prior to the administration of the first dose of vedolizumab will not be included in the summary table. All concomitant medications administered and concomitant procedures will be provided in data listings.

## 7.7 Study Drug Exposure and Compliance

Vedolizumab 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 vedolizumab receipt and dispensing. The number of doses will be summarized as both continuous and ordinal categorical variable.

Exposure to vedolizumab will be summarized and reasons for discontinuation will be tabulated by dose level, as following:

$$\%\,\text{Compliance} = 100 * \text{Min}\left(\frac{\text{Actual Total Dose}}{\text{Expected Total Dose}}, 1\right)$$

## 7.8 Efficacy Analyses

Efficacy endpoints will be analyzed using the safety population.

### 7.8.1 Primary Efficacy Endpoint

{Not applicable}

### 7.8.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- Time to neutrophil engraftment (recovery of ANC). 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 of maximum severity of GvHD according to the modified Glucksberg criteria and BMT CTN-modified IBMTR index.

### 7.8.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are:

CCI

### 7.8.4 Descriptive Summary of Efficacy Endpoints

No formal statistical tests will be performed for this open-label study. The description of the statistical methods to analyze the endpoints is provided below. Additional exploratory analysis will be considered if confounding factors suspected.

Time-to-event (survival) endpoints will be summarized for each dosing cohort and will display:

- Number and percentage of events,
- Number and percentage of censored observations,
- Median time to event and 95% CI,
- $25^{th}$ percentile of the time to event and 95% CI,
- $75^{th}$ percentile of the time to event and 95% CI,
- Range (minimum and maximum time to event),
- Kaplan-Meier estimates of the event rates (percentage and *n*) at 6 months,
- Kaplan-Meier estimates of the event rates (percentage and *n*) at 12 months,
- Plots of the Kaplan-Meier estimated survival curves.

The proportion endpoints (percentage of subjects meeting endpoint criteria) will be summarized for each dosing cohort and will display:

- Number (*n*),
- Percentage and 95% CI.

Frequency of maximum severity of acute GvHD will be summarized for each dosing cohort throughout the 100 day period after allo-HSCT and will display:

- Number (*n*) of the acute GvHD cases for each severity category,
- Percentage and 95% CI for each severity category,
- Plot of the frequencies for each acute GvHD severity categories.

Unless otherwise noticed, all efficacy endpoints that are defined using GvHD grading scale, will be summarized twice: based on the modified Glucksberg criteria, and based on the IBMTR criteria, respectively. The appropriate grading scale should be explicitly listed on all related summary tables, reports and figures, e.g. *"Grade 2—4 acute GvHD-free survival at 6 months (using modified Glucksberg criteria)"*.

## 7.9 Pharmacokinetic/Pharmacodynamic 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. Details of the non-compartmental analysis (NCA) for the PK parameters will be provided in a

separate Clinical Pharmacology Analysis Plan (CPAP) and the results of the analysis will be reported in the Clinical Study Report.

### 7.9.1 Pharmacokinetic Analysis

The PK analysis set will be used for all PK analyses. Treatment groups will be presented as defined in Section 7.2. Missing PK data will not be imputed. More details on the PK analysis will be described in a separate document, i.e., CPAP.

Measured serum concentrations of vedolizumab will be summarized using descriptive statistics by treatment group and visit/time separately.

The mean serum concentration-time profile of vedolizumab will be plotted by treatment group and/or visit/time separately. Individual plot will be also presented.

The PK parameters (ex AUC, Cmax) will be summarized by treatment group and treatment period (day -1, day +13 and day +42 after allo-HSCT) separately using descriptive statistics (non-missing values, mean, SD, SE, %CV, geometric mean, geometric mean %CV, median, minimum and maximum) as appropriate.

Serum concentration data and PK parameters will also be listed.

### 7.9.2 Pharmacodynamic Analysis

CCI

Summary of pharmacodynamics results and change from baseline will be summarized descriptively by visit.

### 7.9.3 Other Outcomes

Immunogenicity (anti-vedolizumab antibodies, AVA) will be descriptively summarized. The AVA status will be summarized descriptively, using AVA positive, AVA negative, and Neutralizing AVA positive subgroups. AVA positive subgroup will be summarized descriptively by transient positive, persistently positive, and any neutralizing AVA positive subgroups. Summary of Anti-vedolizumab Antibody (AVA) Frequency will be summarized by study visit and study dose (75mg and 300 mg).

The effect of anti-vedolizumab antibodies on PK (ex, exclude ADA positive patients), safety and efficacy will be explored.

AVA positive and negative sample will be defined as follows:

- Negative AVA: defined as a sample that is evaluated as negative in the AVA screening assay. Samples that are determined to be positive in the AVA screening assay but the result is not confirmed in the AVA confirmatory assay are considered negative.

- Positive AVA: defined as a sample that was evaluated as positive in both the AVA screening and confirmatory assays.
  - Transiently positive: defined as patients with confirmed positive AVA in 1 sample.
  - Persistently positive: defined as patients with confirmed positive AVA in 2 or more consecutive positive AVA samples.
- Positive neutralizing AVA: defined as a sample that was evaluated as positive in the neutralizing AVA assay.

Patient AVA positive at baseline is defined as a positive AVA sample prior to Day -1 dose.

## 7.10 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.

Hematology results, chemistry results, and urinalysis results (including the appropriate changes from baseline) will be summarized by study day.

Vita sign analysis and urine laboratory tests will be summarized by study day.

Shifts in laboratory test results for hematology between low, normal and high levels will be summarized for each dose and the total by study visit.

### 7.10.1 Adverse Events

Unless specified otherwise, the 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 (i.e., those events reported by ≥10% of all patients) by system organ class and preferred term.
- SAEs by system organ class and preferred term.
- Serious Drug-Related TEAEs by system organ class and preferred term.

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

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.

### 7.10.2 Clinical Laboratory Evaluations

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. Key parameters are: Liver function tests (ALT, AST, Total Bilirubin, Alkaline phosphatase), WBC, Hemoglobin, Platelets, Eos, Mono, Lymph, Neut, Basophils, calculated ANC.

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

### 7.10.3 Vital Signs

Vital signs, including heart rate, respiratory rate, systolic and diastolic blood pressure, and temperature, will be recorded at the visits specified in the Schedule of Events (Appendix B), and summarized using descriptive statistics. On dosing days, vital signs will be obtained before the infusion. 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.

## 7.11 Interim Analysis

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.

## 7.12 Changes in the Statistical Analysis Plan

Not applicable.

## 8.0 REFERENCES

[1] 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.

# 9.0 APPENDIXES

## Appendix 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.

## Appendix B. 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[b] | | | | | X | | | X [b] | | | | X |
| ECOG performance status | X | | | | | | | | | | | | | |
| HCT-CI (dose-finding phase only) | | | | | | | | | | | | | | |
| Tuberculosis screening | X[d] | | | | | | | | | | | | | |
| 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 | | | | | | | | | | | | |
| | **Serious adverse events** (e) will be reported from signing of the informed consent form through 18 weeks after the last dose of study drug. | | | | | | | | | | | | | |
| Vedolizumab IV administration [f] | | X | | | | | | | | X | | | | |
| Allo-HSCT [g] | | | X | | | | | | | | | | | |
| **Samples/Laboratory Assessments** | | | | | | | | | | | | | | |
| Pregnancy test [h] | X1 | X1 | | | | | | | | | | | | |
| Hematology/chemistry | X1 | X1[b] | | | | | X1 | | | X1 [b] | | | | X1 |
| Urinalysis | X1 | X1[b] | | | | | | | | | | | | |
| Blood sample for flow cytometry [i,j,k] | | X1[b] | | X1 | | | X1 | | | X1 [b] | | | | X1 |
| Blood sample for serum biomarkers [j,l] | | X1[b] | | X1 | | | X1 | | | X1 [b] | | | | X1 |
| Blood sample for anti-vedolizumab antibodies [j] | | X1[b] | | | | | | | | | | | | X1 |

Allo-HSCT=allogeneic hematopoietic stem cell transplantation, ECOG= Eastern Cooperative Oncology Group, GvHD=graft-verus-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) QuantiFERON® test or tuberculin skin test only.
(e) Including serious pretreatment events.
(f) 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.
(g) Details on the HSC infusion including cell counts and donor CMV status will be recorded on the eCRF.
(h) 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.
(i) Additional specimens may be collected from any patient who experiences an infusion reaction.
(j) An additional sample may be collected from any patient who develops GvHD.
(k) Includes immunophenotyping and MAdCAM-1 (immunophenotyping includes the cell markers of GvDH).
(l) To be collected 24 hours (±3 hours) postdose from the preceding day.
(m) Time points for blood samples for PK analysis will be collected as specified in Appendix A.

## Appendix C. 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 (c) | | | | | | | |
| Follow-up phone calls | | | | | | | | | | | | | | Q3mo (d) |
| 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 | | | | | | | | | | | | | |
| | **Serious adverse events** (e) will be reported from signing of the informed consent form through 18 weeks after the last dose of study drug. | | | | | | | | | | | | | |
| Vedolizumab IV administration (f) | | | | | | | X | | | | | | | |
| **Samples/Laboratory Assessments** | | | | | | | | | | | | | | |
| Hematology/chemistry (g) | | X1 | | X1 | | | X1 (c) | X1 | X1 | X1 | X1 | X1 | X1 | |
| Urinalysis | | | | | | | | | | | | | | |
| Blood sample for chimerism analysis | | | X1 | | | | | | | | | | | |
| Blood sample for flow cytometry (h) | | X1 | | X1 | | | X1 (c) | | | | X1 | | X1 | |
| Blood sample for serum biomarkers (i) | | X1 | | X1 | | | X1 (c) | X1 | | | | | | |
| Blood sample for anti-vedolizumab antibodies (h) | | | | X1 | | | | X1 | | | | | | |
| Blood sample for PK (j) | See Appendix A.**Error! Reference source not found.** | | | | | | | | | | | | | |

Complete remission with incomplete platelet recovery=CRp, EOS=end-of-study, ET=early termination, GvHD=graft-verus-host disease, IV=intravenous, OS=overall survival, PK=pharmacokinetic(s), World Health Organization=WHO.
(a) Patients will attend a Day +100 visit (±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) Assessment/sample collection should be performed pre-dose.
(d) 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.
(e) Including serious pretreatment events; see Section 11.2.
(f) If engraftment is confirmed, vedolizumab will be administered via a 30-minute intravenous (IV) infusion on Day +42 after myeloablative allo-HSCT.
(g) Hepatitis and HIV testing are to be performed only at the Screening visit.
(h) Additional specimens may be collected from any patient who experiences an infusion reaction.
(i) An additional sample may be collected from any patient who develops GvHD.
(j) Time points for blood samples for PK analysis will be collected as specified in Appendix A.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (± 2 days, except where otherwise specified) with permission of the medical monitor for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.

## Appendix D. Clinical Stages and Grades of Graft-Versus-Host Disease

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

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

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

| | Skin | | | Liver | | | Intestinal tract | |
|---|---|---|---|---|---|---|---|---|
| **Index** | **Stage (max)** | **Extent of Rash** | | **Stage (max)** | **Total Bilirubin (µmol/L)** | | **Stage (max)** | **Volume of Diarrhea (mL/day)** |
| **A** | 1 | <25% | *and* | 0 | <34 | *and* | 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. [1]

**Clinical Stages for Skin, Liver, and Intestinal tract of GvHD.**

| Stage | Skin | Liver<br>Bilirubin: SI units<br>(standard units) | Intestinal tract<br>Diarrhea/day |
|---|---|---|---|
| 1 | Maculopapular rash <25% of body surface (a) | 34-50 µmol/L<br>(2-3 mg/dL) | >500 mL diarrhea/day |
| 2 | Maculopapular rash 25%-50% of body surface | 51-102 µmol/L<br>(3.1-6 mg/dL) | >1000 mL diarrhea/day |
| 3 | Rash >50% of body surface | 103-225 µmol/L<br>(6.1-15 mg/dL) | >1500 mL diarrhea/day |
| 4 | Generalized erythroderma with bullous formation | >255 µmol/L<br>(>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.

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| PPD | Biostatistics Approval | 06-Jun-2018 18:56 UTC |
| | Biostatistics Approval | 06-Jun-2018 18:59 UTC |
| | Clinical Science Approval | 07-Jun-2018 19:19 UTC |
| | Clinical Pharmacology Approval | 08-Jun-2018 02:19 UTC |
| | Pharmacovigilance Approval | 18-Jun-2018 19:43 UTC |