Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vedolizumab in the Prophylaxis of Intestinal Acute Graft-Versus-Host Disease in Subjects Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

NCT Number: NCT03657160

Protocol Approve Date: 18 September 2019

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

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vedolizumab in the Prophylaxis of Intestinal Acute Graft-Versus-Host Disease in Subjects Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Vedolizumab in the prophylaxis of intestinal acute graft vs host disease in subjects undergoing allogeneic hematopoietic stem cell transplantation.

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-3035

EudraCT Number: 2018-002141-11

Compound: Vedolizumab IV

Date: 18 September 2019 **Amendment Number:** 07

Amendment History:

Date	Amendment Number	Amendment Type	Region
13 June 2018	Initial Protocol	Not applicable	Global
13 November 2018	Amendment 01	Nonsubstantial	Local/France
07 November 2018	Amendment 02	Nonsubstantial	Local/Sweden
07 November 2018	Amendment 03	Nonsubstantial	Local/United Kingdom
12 November 2018	Amendment 04	Nonsubstantial	Local/Norway
06 December 2018	Amendment 05	Nonsubstantial	Local/Germany
10 June 2019	Amendment 06	Substantial	Global
18 September 2019	Amendment 07	Substantial	Global

1.0 ADMINISTRATIVE

1.1 Contacts

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

Serious adverse event and pregnancy reporting information is presented in Section 10.0.

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.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

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 Council for Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories can be found on the signature page.

Electronic Signatures are provided 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, prescribing information, 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 Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix C).

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment No. 07 Summary of Changes

This document describes the changes to the Protocol Incorporating Amendment No. 07. This amendment is considered a substantial amendment as the primary purpose of this amendment is to open enrollment to adolescent subjects aged 12 years and greater and weighing ≥30 kg, as a required condition of the European Medicines Agency's Paediatric Committee–endorsed paediatric investigational plan for vedolizumab as prophylaxis of acute graft versus host disease (aGvHD) after allogeneic hematopoietic stem cell transplantation. Other changes incorporated into this amendment are outlined below and are detailed in Appendix G.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific description of text changes and where the changes are located, see Appendix G.

Changes in Amendment 07:

1. Clarification of the description of the disease to be treated in adolescent subjects.
2. Addition of results from nonclinical studies related to inclusion of adolescent subjects.
3. Updated human experience as reported in the 9th development safety update report.
4. Update to the study rationale to support the inclusion of adolescent subjects.
5. Update to the benefit:risk profile to support the inclusion of adolescent subjects.
6. Addition of data supporting the dose regimen in adolescent subjects.
7. Update of the inclusion criteria impacted by inclusion of adolescent subjects.
8. Update to permitted medications to include use of topical anesthetic in adolescent subjects.
9. Clarification to the procedures to be conducted after discontinuation or withdrawal of a subject.
10. Added assessment of height to be collected at the end of study visit.
11. Updated the pregnancy testing and contraception requirements to include female adolescent subjects aged 12 years and greater.
12. Addition of necessary age-appropriate documentation that must be completed for adolescent subjects.
13. Addition of blood collection volumes for adolescent and adult subjects.
14. Update to the version of Common Terminology Criteria for Adverse Events to be used for the grading of adverse events.
15. Update to stratification to include age group and data assessments in adolescent subjects.
16. Updates to Appendix A, Schedule of Events footnotes, to align with updates in text.

17. Update to Appendix B regarding methotrexate treatment to support the inclusion of adolescent subjects.
18. Update to Appendix F to include age-appropriate assessments of aGvHD clinical stage and Mount Sinai Acute GVHD International Consortium severity index for aGvHD.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc.	**Compound:** Vedolizumab IV
Title of Protocol: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vedolizumab in the Prophylaxis of Intestinal Acute Graft-Versus-Host Disease in Subjects Undergoing Allogeneic Hematopoietic Stem Cell Transplantation	**EudraCT No.:** 2018-002141-11
Study Number: Vedolizumab-3035	**Phase:** 3

Study Design:

This is a phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of vedolizumab compared to placebo as prophylaxis for intestinal acute graft-versus-host disease (aGvHD) in subjects undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) for the treatment of hematological malignancies or myeloproliferative disorder.

Subjects will be randomized into 2 arms at 1:1 ratio, vedolizumab versus placebo. Randomization will be stratified by age (≥18 years or adolescents aged 12 to <18 years), human leukocyte antigen (HLA) match (8/8 or 7/8), conditioning regimen (myeloablative or reduced intensity conditioning), and with or without antithymocyte globulin (ATG) (antithymocyte globulin-Fresenius [ATG-F] or thymoglobulin). Subjects will subsequently be followed and evaluated for development of intestinal aGvHD for the first 180 days after allo-HSCT. The study day numbering convention will be based on the first day of cell infusion, which will be Day 0. Pretransplant procedure days are designated with negative numbers (eg, Day -1), whereas posttransplant procedure days are designated with positive numbers (eg, Day +13).

The study consists of a 30-day screening period, 155-day treatment period, and a follow-up period for safety assessments and survival for up to 12 months after allo-HSCT. Subjects randomized to the vedolizumab treatment arm will receive vedolizumab intravenously (IV) at a 300-mg dose at the start of the treatment period on Day -1 before allo-HSCT and then on Day +13, Day +41, Day +69, Day +97, Day +125, and Day +153. Subjects randomized in the placebo treatment arm will receive placebo IV on Day -1, Day +13, Day +41, Day +69, Day +97, Day +125, and Day +153.

The vedolizumab 300 mg dose has been evaluated in the previous graft-versus-host disease (GvHD) Vedolizumab-1015 phase 1b study, and the dose and schedule of vedolizumab in this study is similar to the approved dose and schedule of vedolizumab administered to subjects with ulcerative colitis or Crohn's disease.

All subjects will receive a background GvHD prophylaxis regimen consisting of a combination of a calcineurin inhibitor (CNI, cyclosporine [CYS] or tacrolimus [TAC]) with methotrexate (MTX) (Appendix B). ATG (ATG-F or thymoglobulin) may be included in prophylaxis therapy per institutional practice and mycophenolate mofetil (MMF) may be used in place of MTX at the discretion of the investigator. TAC and CYS will be administered IV or orally during conditioning and subsequent dosing should be adjusted according to whole blood concentration and toxicity, per institutional practice. The recommended targeted whole blood concentration for CNIs and tapering schedule is provided (Appendix B).

Assessment of Intestinal aGvHD

Subjects will be followed and evaluated for development of intestinal aGvHD according to the Bone Marrow Transplant Clinical Trials Network modified International Bone Marrow Transplant Registry index summarized in Appendix F.

Primary Objective:

To evaluate the efficacy of vedolizumab when added to background aGvHD prophylaxis regimen compared to placebo and background aGvHD prophylaxis regimen on intestinal aGvHD-free survival by Day +180 in subjects who receive allo-HSCT as treatment for hematologic malignancy or myeloproliferative disorder.

Secondary Objectives:

- To evaluate the effect of vedolizumab versus placebo on intestinal aGvHD-free, relapse-free (free of underlying malignancy) survival by Day +180.
- To evaluate the effect of vedolizumab compared to placebo on Grade C-D aGvHD-free (any organ involvement) survival by Day +180.
- To evaluate the effect of vedolizumab compared to placebo on nonrelapse mortality (NRM) in subjects by Day +180.
- To evaluate the effect of vedolizumab compared to placebo on overall survival by Day +180.
- To evaluate the effect of vedolizumab compared to placebo on Grade B-D aGvHD-free (any organ involvement) survival by Day +180.

Safety Objective:

To evaluate the safety of vedolizumab when added to background aGvHD prophylaxis regimen compared to placebo and background aGvHD prophylaxis regimen.

Subject Population: Subjects aged ≥18 years or adolescents aged 12 years and greater and weighing ≥30 kg at time of randomization, who are undergoing their first allo-HSCT from an unrelated donor for the treatment of hematologic malignancy or myeloproliferative disorder.

Number of Subjects:	**Number of Sites:**
Per treatment group (placebo/vedolizumab): 279 Estimated total: 558 subjects undergoing allo-HSCT for the treatment of hematologic malignancy or myeloproliferative disorder.	Approximately 150 sites in approximately 30 countries worldwide.
Dose Level(s): Vedolizumab IV, 300 mg	**Route of Administration:** IV
Duration of Treatment: Vedolizumab or placebo at Day -1, Day +13, Day +41, Day +69, Day +97, Day +125, and Day +153.	**Period of Evaluation:** This study includes a 30-day screening period, 155-day treatment period, and a posttreatment follow-up period to be completed by 12 months after allo-HSCT. Subjects will be followed for development of intestinal aGvHD for 12 months after allo-HSCT or until subject's death, withdrawal of consent, or termination of the study by the sponsor. Additionally, all subjects will be required to participate in a long-term follow-up safety survey completed 6 months after the last dose of study drug.

Main Criteria for Inclusion:

Male and female subjects aged ≥18 years and, in selected countries (where local requirements permit and based on feasibility), adolescents aged 12 years and greater and weighing ≥30 kg at time of randomization, with a diagnosis of hematologic malignancy or myeloproliferative disorder who are candidates for HLA-matched or mismatched (8/8 or 7/8) unrelated donor allo-HSCT (per institutional criteria) using either peripheral blood or bone marrow as the stem cell source.

Planned medical care for allo-HSCT-eligible subjects must include a background GvHD prophylaxis regimen with a

combination CNI (CYS or TAC) and MTX (MMF may be used in place of MTX at the discretion of the investigator). When considered part of standard prophylactic treatment for GvHD, ATG (ATG-F or thymoglobulin) may be used at the discretion of the treating physician; however, the proportion of subjects receiving ATG shall comprise no more than approximately 25% of the total number of subjects enrolled into the study.

At the time of allo-HSCT, eligible status of underlying disease stage (hematologic malignancy or myeloproliferative disorder), as defined on the basis of the specific malignancy, is as follows:

a. for subjects with acute leukemia or chronic myelogenous leukemia, no circulating blasts and <5% blasts in the bone marrow;
b. for subjects with myelodysplasia, no circulating blasts and <10% blasts in the bone marrow;
c. for subjects with chronic lymphocytic leukemia and small lymphocytic lymphoma, chemosensitive disease (partial response or complete response to last salvage therapy) at time of transplantation;
d. for subjects with other non-Hodgkin lymphoma or Hodgkin lymphoma, a response to last salvage therapy or chemo-sensitive disease per institutional guidelines; and
e. for subjects with myelofibrosis and other myeloproliferative disorders, <5% blasts in the blood and bone marrow.

Performance status must be assessed as ≤2 using Eastern Cooperative Oncology Group performance status for subjects aged ≥18 years at randomization or as ≥60% using the Karnofsky performance status for adolescent subjects aged ≥16 years at randomization and Lansky performance status for adolescent subjects aged ≥12 to <16 years at randomization.

Main Criteria for Exclusion:

Subjects who have received prior allogeneic transplants or who are planned to undergo umbilical cord blood transplant.

Subjects who are planned to receive ex vivo T cell-depleted hematopoietic stem cells, in vivo T cell-depleting antibodies (with the exception of ATG-F or thymoglobulin), or posttransplant cyclophosphamide.

Subjects with any active cerebral/meningeal disease (including central nervous system involvement of the primary disease) or signs and symptoms of progressive multifocal leukoencephalopathy (PML) or any history of PML.

Subjects who are planned to undergo allo-HSCT for a nonmalignant hematological disorder (eg, aplastic anemia, sickle cell anemia, thalassemias, Fanconi anemia or immunodeficiency).

Subjects with clinically active systemic infection during screening.

Excluded Concomitant Medications:

Any therapy for GvHD prophylaxis, including approved, investigational or T cell-depleting agents other than ATG (ATG-F or thymoglobulin), and other than that specified in the inclusion criteria.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is intestinal aGvHD-free survival by Day +180 in subjects after allo-HSCT for treatment of primary malignancy or myeloproliferative disorders. The study will also determine the number and percentage of subjects who experience treatment-emergent adverse events or serious adverse events from the administration of the first dose of study drug through 18 weeks after administration of the last dose of study drug.

Secondary endpoints for this study are to determine: intestinal aGvHD-free, relapse-free (of underlying malignancy) survival by Day +180; Grade C-D aGvHD-free (any organ involvement) survival by Day +180; NRM by Day +180; overall survival by Day +180; and Grade B-D aGvHD-free (any organ involvement) survival by Day +180.

Statistical Considerations:

All statistical testing will be performed at a 2-sided 0.05 level of significance. To control the overall Type I error rate for the comparison between vedolizumab and placebo groups for the primary and secondary efficacy endpoints, a gatekeeping procedure will be used. Specifically, the statistical testing of the first secondary efficacy endpoint will only be performed if the treatment difference for primary efficacy endpoint is statistically significant, the next secondary efficacy endpoint will only be tested if the treatment difference for the first secondary efficacy endpoint is significant and so on for each subsequent secondary efficacy endpoint.

All time-to-event endpoints will be analyzed using log-rank tests. Cox proportional hazards models, stratified by randomization strata will be fit with hazard ratios reported. All dichotomous efficacy endpoints will be analyzed using Cochran-Mantel-Haenszel tests for risk differences, stratified by randomization strata. Details of the data analyses will be specified in the statistical analysis plan.

Sample Size Justification: Assuming the rate for the primary endpoint is 34.1% for the placebo group and 21.8% for the vedolizumab group, a sample size of 279 subjects per group is expected to generate 148 primary endpoint events and provide 90% power at 2-sided 0.05 level of significance. Assuming the event rate for the first secondary endpoint is 39.5% for the placebo group and 27.1% for the vedolizumab group, this sample size is expected to generate 177 events for the first secondary endpoint and provide approximately 86% power at 2-sided 0.05 level of significance.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors 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, and 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

Acronym	Definition
AE	adverse event
AESI	adverse event of special interest
aGvHD	acute graft-versus-host disease
allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALT	alanine aminotransferase
ANSM	Agence nationale de sécurite du médicament et des produits de santé
APC	antigen-presenting cell
AST	aspartate aminotransferase
ATG	antithymocyte globulin
ATG-F	antithymocyte globulin-Fresenius
CCI	[redacted]
CD	Crohn's disease
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYS	cyclosporine
DLI	donor leukocyte infusion
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DSUR	development safety update report
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
EQ-5D	EuroQOL-5 Dimension
ET	early termination
EU	European Union
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GI	gastrointestinal

GvHD	graft-versus-host disease
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRQOL	health-related quality of life
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
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology system
IV	intravenous
LFT	liver function test
LTFU	long-term follow-up
MA	myeloablative
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MAGIC	Mount Sinai Acute GVHD International Consortium
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MLN0002	vedolizumab, also known as ENTYVIO, KYNTELES
MMF	mycophenolate mofetil
MPA	Medical Products Agency of Sweden
MTX	methotrexate
MUD	matched unrelated donor
NOMA	Norwegian Medicines Agency
NRM	nonrelapse mortality
OS	overall survival
PCR	polymerase chain reaction
PK	pharmacokinetic(s)

PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PML	progressive multifocal leukoencephalopathy
PTE	pretreatment event
Q4W	every 4 weeks
Q8W	every 8 weeks
RAMP	Risk Minimization Action Plan for PML
RIC	reduced intensity conditioning
SAE	serious adverse event
SAP	statistical analysis plan
SOE	schedule of events
TAC	tacrolimus
TB	tuberculosis
TEAE	treatment-emergent adverse event
UC	ulcerative colitis
ULN	upper limit of normal
US	United States

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease to be Treated

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important and potentially curative therapy for many hematologic malignancies, but its use is limited by the major complication of graft-versus-host disease (GvHD) [1,2]. GvHD is a common complication of allo-HSCT and a major cause of morbidity and mortality. Acute GvHD results from the activation of alloreactive donor lymphocytes by histocompatibility antigens on host antigen-presenting cells (APCs) [3,4]. The risk of GvHD and its severity depends on several factors including recipient age, cell source, donor characteristics, degree of histocompatibility between the donor and recipient, the conditioning regimen used, and the GvHD prophylaxis strategy used [1,5-7]. Despite GvHD prophylaxis, approximately 40% to 70% of all allo-HSCT recipients (inclusive of pediatric and adult subjects) develop Grade 2 to 4 acute GvHD (aGvHD) [5,6,8-11]. Approximately 45% to 56% of pediatric allo-HSCT (ranging from <1 to 20 years of age) from unrelated donors will develop Grade 2 to 4 aGvHD, and nonrelapse mortality (NRM) appears to be greater in those pediatric patients with intestinal involvement [12-14]. Classical aGvHD occurs around the time of engraftment (~10-21 days following HSCT infusion) up to Day 100 [15] and late aGvHD occurs greater than 100 days from allo-HSCT [16,17].

aGvHD most commonly involves the skin, liver, and gut and results from an activation of alloreactive donor lymphocytes by histocompatibility antigens on host APCs [3,4]. Immunocompetent donor T cells migrate to lymphoid tissues soon after infusion, recognize host alloantigens, and become activated upon interaction with host APCs [18]. Homing of these alloreactive donor T cells to the gastrointestinal (GI) tract, which is dependent on the expression of the integrin α4β7 molecule on the donor T cells, is fundamental to the pathogenesis of intestinal aGvHD [19-21]. Data from the Center for International Blood & Marrow Transplant Research showed that 76% of Grade II to IV aGvHD cases in 2006 to 2012 had intestinal involvement [22]. Intestinal aGvHD is the most serious form and may be less responsive than liver and skin GvHD to first-line corticosteroids, and corticosteroid resistance develops in 73% of subjects with severe intestinal GvHD (stage 3-4) [23,24].

Given the high level of immunosuppression, the risk of opportunistic infections is increased in subjects who develop intestinal aGvHD [25,26] and overall survival (OS) for stage 3 to 4 intestinal aGvHD has been reported as 25% in a study from the Fred Hutchinson Cancer Center [24].

GvHD prophylaxis is employed for all subjects undergoing allo-HSCT and routine prophylaxis commonly consists of calcineurin inhibitors (CNIs) in combination with a short course methotrexate (MTX) or mycophenolate mofetil (MMF) [6,8,9,11,27]. CNI (cyclosporine [CYS] or tacrolimus [TAC]) and MTX are typically administered during conditioning, with subsequent CNI doses adjusted according to whole blood concentration and toxicity. T cell-depleting agents, including antithymocyte globulins (ATG) (antithymocyte globulin-Fresenius [ATG-F] or thymoglobulin) or alemtuzumab, may be added to prophylaxis therapy; however, use of these

agents have raised concerns for delayed immune recovery and increased risk of infection and relapse [27].

Reducing the risk of developing aGvHD without systemic immunosuppression has the potential to improve overall outcomes in allo-HSCT and possibly extend and/or save lives from this rare disease.

4.1.2 Vedolizumab IV

Vedolizumab (also called MLN0002) is a humanized immunoglobulin (Ig) G1 monoclonal antibody (mAb) directed against the human lymphocyte integrin α4β7. The α4β7 integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue (GALT) through adhesive interaction with antimucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [28-31]. Vedolizumab specifically binds the α4β7 integrin, selectively 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 [32]. 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 (also known as ENTYVIO; KYNTELES; Vedolizumab for Injection, for Intravenous Use; Vedolizumab Powder for Concentrate for Solution for Infusion; or MLN0002 IV) 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 US and EU. Vedolizumab IV is approved for the treatment of adults 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 blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. The approved dosing and administration regimen for adults consists of 300 mg vedolizumab infused IV over approximately 30 minutes at Weeks 0, 2, and 6, then once every 8 weeks (Q8W) thereafter. Vedolizumab dosing every 4 weeks (Q4W) is also approved in most parts of the world. Previously conducted clinical studies in healthy subjects and subjects with UC and CD have characterized the efficacy, safety, tolerability, pharmacokinetic (PK), pharmacodynamic, and immunogenicity of vedolizumab.

The ongoing clinical development program of vedolizumab IV includes clinical studies in pediatric subjects (aged 2-17 years) with UC or CD that are summarized in the current edition of the investigator's brochure (IB).

4.1.2.1 Nonclinical

Several published key nonclinical studies support the use of vedolizumab for the prevention of GvHD. Nonclinical pharmacology studies in murine models of aGvHD suggest that the prevention of T cell trafficking to GALT, via interruption of the α4β7/MAdCAM-1 interaction, may prevent GvHD [33-35]. In a mouse model of GvHD, when using donor cells sorted and purified based on

the presence or absence of α4β7, the absence of α4β7+ cells greatly delayed and reduced the presence of GvHD [19]. Like these results, α4β7 expression on donor T cells has been shown to be important in the induction of GvHD [20]. By blocking the infiltration of cells into the intestines, vedolizumab may act to reduce the severity and intensity of intestinal GvHD. Extensive nonclinical evaluations of the cardiovascular, acute, local, subchronic, chronic, immunologic, and reproductive toxicity of vedolizumab in pharmacologically responsive species (New Zealand white rabbits and cynomolgus monkeys) have been conducted. Vedolizumab bound with similar affinity to rabbit, monkey, and human α4β7 integrin.

Results from a 13-week toxicity study in juvenile cynomolgus monkeys identified 100 mg/kg (human equivalent dose 1920 mg in a 60-kg human) as the no-observed-adverse-effect level. (NOAEL). Inclusion of sexually immature monkeys in the 3- and 6-month toxicity studies support administration of vedolizumab in clinical studies with adolescent subjects (aged 12 years and greater).

Nonclinical studies also show that vedolizumab does not antagonize 4β1 integrin [3].

4.1.2.2 Human Experience

As of 19 May 2019, approximately 6376 subjects (healthy or patients with UC or CD, pouchitis, melanoma, or undergoing allo-HSCT) have received at least 1 dose of vedolizumab across all studies in the clinical development program. As reported in the 9th development safety update report (DSUR, for the period 20 May 2018 to 19 May 2019), global cumulative postmarketing patient exposure to vedolizumab IV is estimated to be approximately 336,400 patient-years.

Vedolizumab has shown an acceptable and consistent safety profile in clinical studies and in postmarketing experience. Adverse reactions that have been reported following vedolizumab administration include: nasopharyngitis, bronchitis, upper respiratory tract infection, influenza, sinusitis, headache, oropharyngeal pain, cough, nausea, rash, pruritus, arthralgia, back pain, pain in extremities, pyrexia, fatigue, and injection site reactions. Risks associated with vedolizumab treatment have been identified and categorized. Important identified risks are hypersensitivity reactions, including infusion-related reactions (IRRs) and upper respiratory infections, including nasopharyngitis, sinusitis, bronchitis, and influenza. Most IRRs are mild/moderate in intensity and resolve with minimal or no intervention. Important potential risks are infections, including gastrointestinal infections and systemic infections against which the gut constitutes a defensive barrier; serious infections, including opportunistic infections such as progressive multifocal leukoencephalopathy (PML); malignancy; and liver injury. Reported serious infections include tuberculosis, sepsis, *Salmonella* sepsis, *Listeria* meningitis, and cytomegaloviral colitis.

Most serious adverse events (SAEs) were related to exacerbations or complications of the underlying UC or CD. Similar safety profiles for vedolizumab have been observed in subjects who received vedolizumab IV Q4W or Q8W and in subjects following long-term Q4W treatment for up to 8 years, and in subjects administered vedolizumab subcutaneously (SC). With the exception of injection site reactions, the safety profile for vedolizumab SC is consistent with that for vedolizumab IV.

In the phase 1b Study Vedolizumab-1015, conducted in 24 subjects who underwent allo-HSCT, vedolizumab (at 75 or 300 mg on Days -1, +13, and +42) was added to standard GvHD prophylaxis (TAC and MTX) therapy. All subjects engrafted and no new safety signals were reported. In clinical studies, no safety concerns were identified in subjects with aGvHD or undergoing allo-HSCT, and the events reported were consistent with known risks in these patient populations.

In addition, no new safety information that alters the benefit:risk balance of vedolizumab was identified in the IBD clinical development program, including ongoing studies in pediatric subjects with UC or CD (DSUR, for the period 20 May 2018 to 19 May 2019).

Overall, vedolizumab has been well tolerated in clinical studies. Further detail on the safety profile of vedolizumab can be found in the current edition of the IB.

4.2 Rationale for the Proposed Study

The objective of this proposed study is to evaluate the safety and efficacy of vedolizumab compared to placebo when added to a background aGvHD prophylaxis regimen in prophylaxis of intestinal aGvHD within the first 180 days after allo-HSCT from unrelated donors. Vedolizumab binds the α4β7 integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing leukocytes into GI mucosa, effectively acting as a gut-selective immunomodulator [32]. Vedolizumab (ENTYVIO) is approved for treatment of CD and UC and demonstrates efficacy in clinical remission in CD and UC. Inflammation and damage to the GI tract is a major mechanism for amplification of systemic aGvHD [36] and several key similarities exist with intestinal aGvHD and other immune-mediated diseases like inflammatory bowel disease (IBD). In IBD, the migration of T cells to the GI tract appears to play important role in induction and perpetuation of GI inflammation. Once in the GI tract, the interaction between effector T cells and APCs result in downstream uncontrolled production of inflammatory mediators as well as recruitment and activation of additional leukocytes resulting in chronic gut inflammation [37].

The migration of naive donor T cells to the GALT where they are activated and migration of activated donor T cells to the target tissues, especially the intestinal mucosa, are essential steps in aGvHD in both children and adults [4,38]. Intestinal aGvHD in children and adults is often involved in Grade 3 to 4 aGvHD and is a major cause of morbidity and mortality after allo-HSCT. Systemic immunosuppression for aGvHD prophylaxis increases the risk for infections and can affect the graft-versus-tumor effect. Therefore, using standard nonspecific systemic immunosuppressive therapies involves a fine balance of prevention of life-threatening aGvHD against life-threatening infection and recurrence of underlying malignant disease. Therapy that targets the trafficking of cells to the GI tract and reduces GI inflammation without adding to systemic immunosuppression could have profound effects on the morbidity and mortality of intestinal GvHD.

Results from Vedolizumab-1015, a phase 1b study that enrolled 24 subjects aged ≥18 years, demonstrated the safety and tolerability of adding vedolizumab on Day -1 (before allo-HSCT) and then on Days +13 and +42 after allo-HSCT to a background aGvHD prophylaxis regimen

(TAC+MTX) in subjects undergoing allo-HSCT. Vedolizumab dose finding was cohort-based and followed a rule-based dose-finding study design with PK guidance. After a tolerated dose with acceptable PK was identified, the cohort at that dose level was expanded to further assess the tolerability and effectiveness of vedolizumab. Dose escalation started with a low dose cohort of vedolizumab 75 mg IV. With no dose-limiting toxicities (DLTs) and no engraftment failures in the 75 mg dose cohort, the next cohort received vedolizumab 300 mg IV. A total of 3 subjects were enrolled in the 75 mg dose cohort and 21 subjects were enrolled in the 300 mg dose cohort. The 300-mg dose cohort consisted of adult subjects for whom a myeloablative conditioning or RIC regimen was planned and who were 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 treatment of hematologic malignancy or myeloproliferative neoplasm. No subject in either cohort experienced a DLT and all subjects engrafted (median time to neutrophil engraftment was 22 days in the vedolizumab 75 mg dose cohort and 14 days in the vedolizumab 300 mg dose cohort). The PK of 300 mg vedolizumab in this subject population was similar to that of subjects with IBD and provides serum concentrations above 10 µg/mL up to Day 100. The study results demonstrate less than expected intestinal aGvHD events and less than expected Grade 3-4 aGvHD events in the 300 mg dose cohort. By Day +100, 3 of 21 subjects who received vedolizumab 300 mg IV developed maximum stage 1 lower intestinal aGvHD and no subjects developed stage 2 or greater lower intestinal aGvHD. By 12 months, lower intestinal aGvHD developed in 3 of 21 subjects (2 subjects developed maximum stage 1 intestinal aGvHD and 1 subject developed maximum stage 2 intestinal aGvHD). In subjects who received vedolizumab 300 mg IV, Grade 2-4 aGvHD developed in 4 of 21 subjects by Day +100 and in 5 of 21 subjects by 12 months after allo-HSCT. Grade 3 aGvHD developed in 1 of 21 subjects by Day +100 and in 2 of 21 subjects by 12 months and no subject developed Grade 4 aGvHD by Day +100 and by 12 months. Overall survival and non-relapse mortality in the vedolizumab 300 mg cohort was 84.7% and 5.6% by 12-month follow-up, respectively. The results of this study support further evaluation of the vedolizumab 300 mg IV dose in subjects undergoing allo-HSCT.

The proposed vedolizumab dose and regimen in this phase 3 study is 300 mg on Days -1, +13, +41, +69, +97, +125, and +153. This is based on the results of Vedolizumab-1015 and, similarly, on the known safety profile of Q4W vedolizumab schedule evaluated in phase 3 studies and long-term follow-up (LTFU) of IBD subjects. The proposed duration of vedolizumab prophylaxis is intended to provide coverage during the posttransplant period, when subjects are at risk of developing classic and late aGvHD.

4.3 Benefit:Risk Profile

The proposed phase 3 study is designed to evaluate the efficacy and safety of vedolizumab compared to placebo when added to background aGvHD prophylaxis regimen as prophylaxis for intestinal aGvHD for subjects undergoing allo-HSCT. The mechanism of action of vedolizumab, results from nonclinical studies demonstrating the role of T cell trafficking in GvHD, and results of the phase 1b Study Vedolizumab-1015, all support further investigation of vedolizumab in this indication. Vedolizumab specifically targets the α4β7 integrin expressed on the surface of T

lymphocytes, thus preventing T cells from binding to MAdCAM-1 expressed on the endothelium, subsequently preventing T cells from homing to the intestinal tract. Nonclinical pharmacology studies in murine model demonstrate that inhibition of the α4β7/MAdCAM-1 pathway via neutralizing anti-MAdCAM-1 antibodies attenuated the development of the graft versus host reaction [33] and the absence of α4β7+ cells on donor cells greatly delayed and reduced the presence of GvHD [19]. Furthermore, in Study Vedolizumab-1015, a low incidence of intestinal aGvHD was observed in adults undergoing allo-HSCT for a hematologic malignancy or myeloproliferative disorder who received vedolizumab 300 mg IV in combination with standard GvHD prophylaxis. There remains an unmet medical need in patients undergoing allo-HSCT who, despite routine prophylaxis, remain at risk of developing intestinal aGvHD and its associated complications.

The available PK data, nonclinical toxicology data, and clinical data are supportive of the inclusion of adolescent subjects aged ≥12 years and weighing ≥30 kg in this phase 3 study. In phase 3 studies in adults with UC or CD, body weights ranged from 28.7 to 170 kg. Safety data from these studies showed that there was no difference in the incidence of treatment-emergent adverse events (TEAEs) based on weight or age (18-70 years). Furthermore, a similar safety profile has been observed in adults with UC or CD who received vedolizumab IV Q8W or Q4W. No additive risk of infection was identified among subjects who received a concomitant immunosuppressant. Results of population PK analyses in subjects with IBD indicate that a weight-based dosing regimen is not required and that a tiered flat-dose is appropriate for different weight groups. Age was not a clinically meaningful covariate. PK data from Study Vedolizumab-1015 indicates that the PK of vedolizumab in subjects undergoing an allo-HSCT who received 300 mg is similar to that of subjects with UC or CD. In addition, no new safety information that alters the benefit:risk balance of vedolizumab have been identified in the UC/CD clinical development program, including ongoing studies in pediatric subjects (aged 2-17 years). Therefore, the benefit:risk profile is expected to be similar in adults and adolescent subjects aged ≥12 years and weighing ≥30 kg.

All subjects will receive a standardized GvHD prophylaxis regimen consisting of a CNI (CYS or TAC) and MTX or MMF with or without the addition of ATG (ATG-F or thymoglobulin). The dosing of vedolizumab in combination with a CNI (TAC) and MTX was well tolerated in the phase 1b clinical study in this subject population. Similarly, vedolizumab in conjunction with systemic immunosuppressive therapy (such as MTX, 6-mercaptopurine, and prednisone) has been well tolerated in clinical studies in subjects with IBD.

The subject population was chosen because it represents a high-risk, vulnerable population for development of intestinal aGvHD, a driver for poor outcomes, mortality, and for whom a significant unmet medical need exists. The risks of this subject population include those that are associated with hematological transplantation. Specifically, allo-HSCT patients are at risk of infections (opportunistic, GI, and CNS infections); liver injury; infusion-related reactions (IRR) and hypersensitivity reactions, and relapse or new primary malignancy. The important identified risks specific for vedolizumab include IRRs and upper respiratory tract infections, including bronchitis, influenza, nasopharyngitis, and sinusitis. The important potential risks for vedolizumab

are: malignancies, liver injury; infections (GI infections and systemic infections [serious and nonserious]); and other serious infections, including opportunistic infections such as PML. Several risk mitigation strategies are incorporated in this phase 3 study including exclusion of subjects with ongoing or active infections (Section 7.2), criteria for discontinuation and withdrawal of subjects (Section 7.4), and instructions for managing these risks (Section 8.7). The mitigation strategies are adequate to monitor safety of the subjects participating in the study. In combination with the results from the phase 1b Study Vedolizumab-1015 and supported by the available nonclinical, clinical, and PK data, the benefit:risk profile is expected to be similar in adults and adolescent subjects aged 12 years and greater and weighing ≥30 kg, supporting further investigation of vedolizumab in the subject population with significant unmet medical need.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is:

- To evaluate the efficacy of vedolizumab when added to background aGvHD prophylaxis regimen compared to placebo and background aGvHD prophylaxis regimen on intestinal aGvHD-free survival by Day +180 in subjects who receive allo-HSCT as treatment for a hematologic malignancy or myeloproliferative disorder.

5.1.2 Safety Objective

The safety objective is to evaluate the safety of vedolizumab when added to background aGvHD prophylaxis regimen compared to placebo and background aGvHD prophylaxis regimen.

5.1.3 Secondary Objectives

The secondary objectives are:

- To evaluate the effect of vedolizumab compared to placebo on intestinal aGvHD-free, relapse-free (free of underlying malignancy) survival by Day +180.
- To evaluate the effect of vedolizumab compared to placebo on Grade C-D aGvHD-free (any organ involvement) survival by Day +180.
- To evaluate the effect of vedolizumab compared to placebo on NRM in subjects by Day +180.
- To evaluate the effect of vedolizumab compared to placebo on OS by Day +180.
- To evaluate the effect of vedolizumab compared to placebo on Grade B-D aGvHD-free (any organ involvement) survival by Day +180.

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5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is intestinal aGvHD-free survival by Day +180 after allo-HSCT. Intestinal aGvHD is defined as Stage 1-4 intestinal involvement per Acute Graft-versus-Host Disease Clinical Stage criteria (Appendix F).

5.2.2 Safety Endpoint

Safety as assessed by adverse events (AEs), adverse events of special interest (AESIs), SAEs, vital signs, results of standard laboratory test and procedures (eg, clinical chemistry, hematology, coagulation).

5.2.3 Secondary Endpoints

The secondary endpoints are:

- Intestinal aGvHD-free and relapse-free (of the underlying malignancy) survival by Day +180.
- Grade C-D aGvHD-free (any organ involvement) survival by Day +180.
- NRM by Day +180.
- OS by Day +180.
- Grade B-D aGvHD-free (any organ involvement) survival by Day +180.

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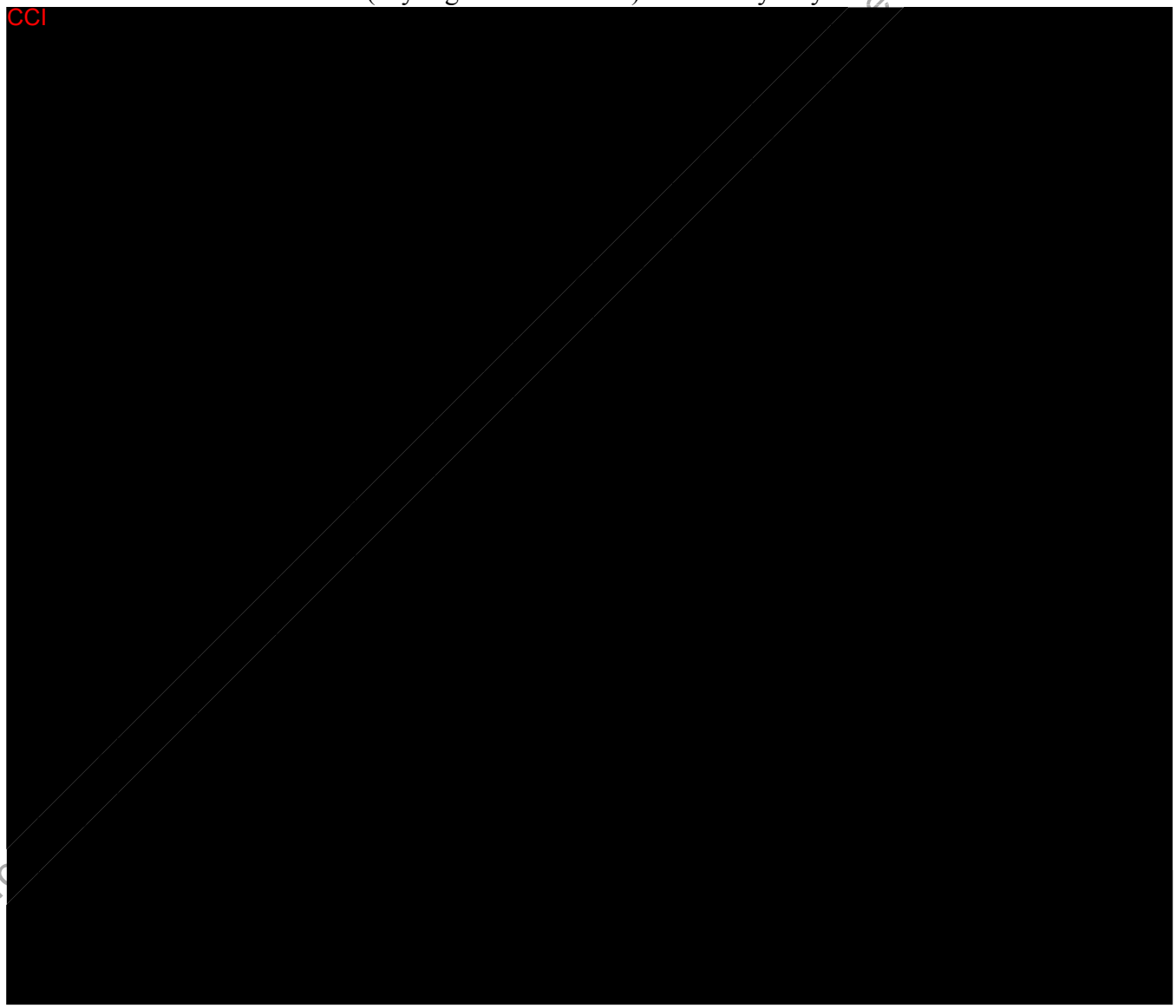

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6.0 STUDY DESIGN AND DESCRIPTION

6.1 Overview of Study Design

This is a phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vedolizumab when added to a background aGvHD prophylaxis regimen as prophylaxis for intestinal aGvHD in subjects undergoing allo-HSCT. The subject population will consist of subjects with hematologic malignancies or myeloproliferative disorders for whom allo-HSCT from an unrelated donor is planned, using either peripheral blood or bone marrow as the stem cell source.

Eligibility will be determined during the screening period, which may last for up to 30 days before Day -1 (designation of the day of the first IV infusion of study drug). Subjects who meet all eligibility criteria and provide written informed consent will be randomized into this study within 2 days of the first dose of study drug on Day -1. Approximately 558 subjects will be randomized in a 1:1 fashion to 2 treatment arms (vedolizumab IV or placebo IV). Randomization will be stratified by age (≥18 years or adolescents aged 12 to <18 years), HLA match or mismatch (8/8 or 7/8), conditioning regimen (myeloablative or reduced intensity conditioning), and treatment with or without ATG (ATG-F or thymoglobulin). Subjects randomized to the vedolizumab IV arm will receive 7 doses of vedolizumab IV, beginning on Day -1 before allo-HSCT and then on Days +13, +41, +69, +97, +125, and +153 after allo-HSCT. Subjects randomized to the placebo IV arm will receive 7 doses of placebo IV, beginning on Day -1 before allo-HSCT and then on Days +13, +41, +69, +97, +125, and +153 after allo-HSCT.

6.1.1 Schedule of Observations and Procedures

The study consists of a 30-day screening period, 155-day treatment period, a visit on Day +180 after allo-HSCT, and a posttreatment follow-up period for safety assessments and survival to be completed by 12 months after allo-HSCT. The study overview is depicted in Figure 6.a.

6.1.1.1 Screening

Subjects will be screened within 30 days before Day -1. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Sections 7.1 and 7.2. See Section 9.4 for procedures for documenting screening failures. Rescreening is permitted in consultation with the medical monitor.

Procedures to be completed at screening can be found in the Schedule of Events (SOE) (Appendix A).

6.1.1.2 Randomization

Randomization will take place within 2 days of the first dose of study drug on Day -1. If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria, the subject should be randomized using the interactive response technology system (IRT), as described in Section 8.2.

Subjects will be administered the first dose of study drug as described in Section 8.1.1. The procedure for documenting screening failures is provided in Section 9.4.

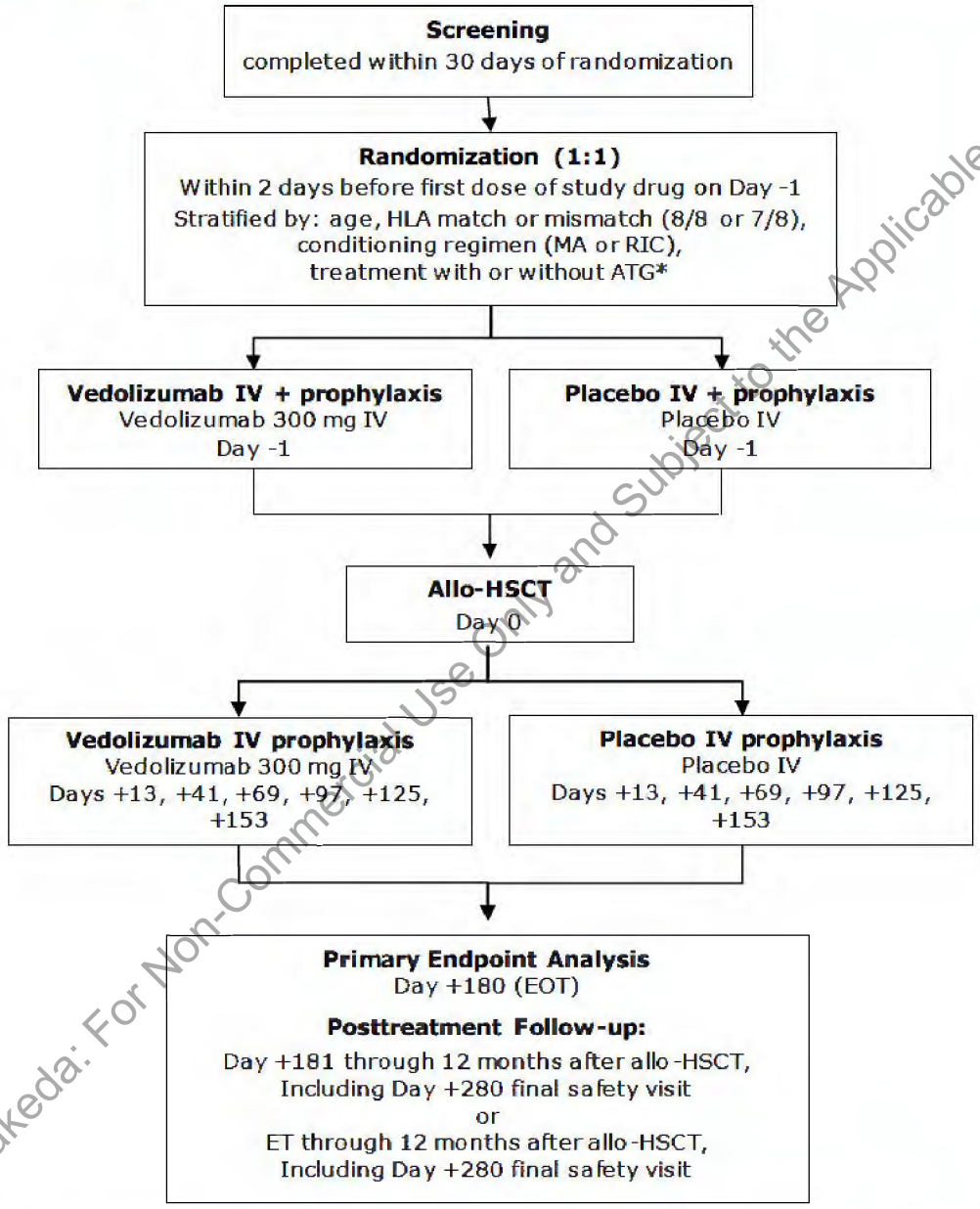
6.1.1.3 Final Visit or Early Termination

The final visit (end of study [EOS]) will be performed 12 months after allo-HSCT. Subjects who discontinue study drug treatment (refer to Section 7.4) will complete an early termination (ET) visit upon discontinuation and a final visit 12 months after allo-HSCT. The global study will end after the last subject has completed the final visit 12 months after allo-HSCT, or the subject has died, withdrawn consent, or been lost to follow-up.

6.1.1.4 Posttreatment Follow-up

The end-of-treatment visit will be conducted on Day +180 after allo-HSCT. All subjects will participate in posttreatment follow-up as outlined in the SOE (Appendix A) that will begin after the Day +180 visit or after ET, will include a Day +280 final safety visit (or 18 weeks after the last dose of study drug), and will conclude 12 months after allo-HSCT. In addition, upon completion or ET, all subjects or their parents/legally acceptable representative will be administered by telephone the LTFU safety questionnaire 6 months after their last dose of study drug. For all subjects receiving study drug, the investigator must complete the EOS electronic case report form (eCRF) 12 months after allo-HSCT.

Figure 6.a Study Design for Study Vedolizumab-3035



Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATG, antithymocyte globulin; EOT, end-of-treatment; ET, early termination; IV, intravenous; MA, myeloablative; RIC, reduced intensity conditioning.
* ATG may be either ATG-Fresenius (ATG-F) or thymoglobulin.

Subjects will be followed for safety, development of acute and chronic GvHD, and OS for 12 months after allo-HSCT or until the subject's death or withdrawal of consent/assent or termination of the study by the sponsor.

Vital signs, physical examinations, AE assessments, and laboratory values (chemistry, hematology, liver function tests [LFTs] as specified in Section 9.3.15) will be obtained as described in the SOE (Appendix A) to evaluate the safety and tolerability of the study drug. To exclude subjects with PML, the PML checklist will be administered at screening and before each administration of study drug beginning on Day -1 and thereafter as shown in the SOE (Appendix A).

Sparse blood samples for determination of the serum concentration of vedolizumab [redacted] will be collected pre- and postdose on study drug dosing days as shown in the SOE (Appendix A).

6.2 Justification for Study Design and Dose

6.2.1 Study Design

The subject population was chosen because it represents a high-risk, vulnerable population for development of intestinal aGvHD, a driver for poor outcomes, mortality, and for whom a significant unmet medical need exists with no currently approved medical therapy. The incidence of Grade B-D aGvHD has been reported to be 39% for HLA-matched sibling donors and 59% for HLA-matched unrelated donors (MUD) in 1 study [9] and 33% for matched related donor recipients, 51% in 8 of 8 HLA-MUD recipients, and 53% in 7/8 HLA-MUD recipients, with OS (45%) lowest in the 7 of 8 HLA-MUD recipients [39]. Among pediatric subjects with allo-HSCT from unrelated donors, up to 56% will develop Grade 2 to 4 aGvHD and 29% will develop Grade 3 to 4 aGvHD [13,14]. The intestinal tract is often involved in Grade 3 to 4 aGvHD, and when the intestinal tract is involved in pediatric patients, NRM increases [40]. All subjects will receive a background GvHD prophylaxis regimen consisting of a CNI (CYS or TAC) and MTX or MMF. When considered a part of standard prophylactic treatment for GvHD, ATG (ATG-F or thymoglobulin) may be used at the discretion of the treating physician; however, the proportion of subjects receiving ATG shall comprise no more than approximately 25% of the total number of subjects enrolled into the study. Subjects who have received or are receiving prophylactic agents other than those listed in the inclusion criteria, including approved or other investigational therapies, are excluded.

6.2.2 Dose Selection

All subjects will receive a combination of CNI (CYS or TAC) and MTX or MMF [41-43], which is commonly prescribed as prophylaxis of GvHD for subjects undergoing allo-HSCT. ATG (ATG-F or thymoglobulin) may be included as noted in Section 6.2.1.

The vedolizumab dose and schedule for this phase 3 study are 300 mg on Days -1, +13, +41, +69, +97, +125, and +153. This dose selection is based on safety, efficacy and PK data from Study Vedolizumab-1015 and the IBD program. The dosing regimen selected is estimated to provide serum concentrations above 10 µg/mL for 180 days. PK data from Study Vedolizumab-1015 indicates that the PK of vedolizumab in subjects with GvHD who received 300 mg is similar to that of subjects with IBD.

The 300 mg dose of vedolizumab was well tolerated in subjects in Study Vedolizumab-1015 without delay of engraftment (median 14 days for the vedolizumab 300 mg cohort) or new safety concerns. Repeated vedolizumab dosing during the 6 months after the allo-HSCT is proposed, during which time subjects are at the highest risk of developing intestinal aGvHD.

The same vedolizumab dose regimen to be administered to adults (aged ≥18 years) planned to undergo allo-HSCT for prophylaxis of intestinal aGvHD is considered appropriate for administration to adolescents aged 12 years and greater and weighing ≥30 kg. In phase 3 studies in adults with IBD, body weights ranged from 28.7 to 170 kg. Safety data from these studies showed no difference in the incidence of TEAEs and a similar safety profile in adults receiving vedolizumab IV Q8W or Q4W (Section 4.3). A population PK model was developed using pooled phase 1, 2, and 3 study data from the vedolizumab IV clinical program in adults with UC or CD to characterize the PK of vedolizumab and to assess the impact of patient demographic characteristics (eg, age and body weight) on PK. This model indicated that weight-based dosing is not required and that age was not a clinically meaningful covariate (Section 4.3). In addition, results from Study Vedolizumab-1015 indicated that the PK of vedolizumab (300 mg) in adults with aGvHD was similar to that in adults with UC or CD.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known benefit/risk profile for the product, such that the benefit/risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objective or compromises subject safety.
- The sponsor elects to terminate or suspend the study due to plans to modify, suspend, or discontinue development of the study drug.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an

investigational site, a study-specific procedure for ET or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension. The competent regulatory authority will be notified in case of study termination or suspension following local regulations.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

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

1. The subject or, when applicable, the subject's legally acceptable representative voluntarily signs and dates a written, informed consent form (ICF) and any required privacy authorization before performance of any study-related procedures not part of standard medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care. As applicable, a parent/both parents or legally acceptable representative must provide signature of informed consent, and there must be documentation of age-appropriate assent by the subject.
2. Male or female subjects ≥18 years of age and, in selected countries (where local requirements permit and based on feasibility), adolescents aged 12 years and greater and weighing ≥30 kg at time of randomization.
3. Subjects must undergo DNA-based HLA matching and be 8 of 8 or 7 of 8 HLA-matched (single allele or antigen mismatch at HLA-A, -B, and -C, and HLA-DRB1 is allowable) unrelated hematopoietic stem cell transplantation (HSCT) from either peripheral blood or bone marrow stem cells for a hematologic malignancy or myeloproliferative disorder. Subjects should follow local practice for additional HLA-match, for example France, 9/10 or 10/10 HLA match.
4. Subjects for whom a myeloablative conditioning or RIC is planned.
5. Allo-HSCT eligible (meeting institutional criteria)-subjects planned medical care should include aGvHD prophylaxis with a combination of CNI (CYS or TAC) and MTX or CNI and MMF. With the exception of ATG (ATG-F or thymoglobulin), all other therapies, approved or investigational, for GvHD prophylaxis are excluded.
6. Status of the primary disease as follows:
   a) Subjects with acute leukemia or chronic myelogenous leukemia: no circulating blasts and <5% blasts in the bone marrow.
   b) Subjects with myelodysplasia: no circulating blasts and <10% blasts in the bone marrow.
   c) Subjects with chronic lymphocytic leukemia or small lymphocytic lymphoma with chemosensitive disease at the time of transplantation (partial or complete response to last salvage therapy).
   d) Subjects with other nonHodgkin or Hodgkin lymphoma with a response to last salvage therapy or chemo-sensitive disease per institutional standards at the time of transplantation.
   e) For subjects with myelofibrosis and other myeloproliferative disorders: <5% blasts in the blood and bone marrow.

7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 for subjects aged ≥18 years at randomization or ≥60% using the Karnofsky performance status for adolescent subjects aged ≥16 years at randomization or the Lansky performance status for adolescent subjects aged 12 to <16 years at randomization (Appendix E).
8. Sufficient cognitive ability to reliably complete the PML checklist at baseline.
9. Female subjects who are:

    - Postmenopausal for at least 1 year before signing of the informed consent (specified in Section 9.3.19), OR
    - Surgically sterile, OR
    - If they are aged 12 years and greater and not postmenopausal (Section 9.3.19) or surgically sterilized must use a highly effective method of contraception (specified in Section 9.3.19) during the study and through 18 weeks after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

    - Agree to practice an acceptable effective barrier method of contraception (specified in Section 9.3.19) during the entire study treatment period and through 18 weeks after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

10. Suitable venous access for the study-required blood sampling, including PK sampling.

7.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Prior allo-HSCT.
2. Planned umbilical cord blood transplant or planned to receive posttransplant cyclophosphamide, in vivo or ex vivo T cell-depleted hematopoietic stem cells (HSCs) with the exception of ATG (ATG-F or thymoglobulin).
3. Planned allo-HSCT for nonmalignant hematological disorders (eg, aplastic anemia, sickle cell anemia, thalassemias, Fanconi anemia or immunodeficiency).

4. Known active cerebral/meningeal disease (including central nervous system involvement of the primary disease), or signs or symptoms of PML, any history of PML, or a positive PML subjective checklist before the administration of study drug on Day -1.
5. Evidence of encephalopathy at screening.
6. History of any major neurological disorder, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
7. Prior or current therapy with α_4 and/or β_7 integrin inhibitors (including, but not limited to natalizumab, etrolizumab, AMG-181), MAdCAM-1-antibodies, anti-CD11a mAb (eg, efalizumab) within 60 days or 5 half-lives, whichever is longer from randomization.
8. Prior known exposure of the transplant recipient to vedolizumab.
9. 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.
10. Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, coagulation, immunological, endocrine/metabolic, neurologic or other medical disorder not related to the subject's primary disease that, in the opinion of the investigator, would confound the study results or compromise subject safety.
11. Clinically active systemic infection during screening.
12. Clinically active cytomegalovirus (CMV) colitis during screening.
13. Clinically active *Clostridium difficile* infection or other intestinal pathogen during screening.
14. Active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following: history of TB, OR positive QuantiFERON test or T-spot or 2 successive indeterminate QuantiFERON or T-spot tests, OR a tuberculin skin test reaction ≥10 mm (≥5 mm in subjects receiving the equivalent of >15 mg/day prednisone).
15. Chronic hepatitis B (hepatitis B surface antigen [HBsAg] positive [$HBsAg^+$]) or hepatitis C infection (evident by active viral replication by polymerase chain reaction [PCR] if hepatitis C virus antibody positive). Hepatitis B core antibody (HBcAb) positive ($HBcAb^+$) and negative for hepatitis B surface antigen ($HBsAg^-$) may be enrolled if viral DNA is undetectable.
16. History of human immunodeficiency virus (HIV) positive test.
17. Treatment with anti-T cells antibody such as alemtuzumab (anti-CD52), excluding ATG (ATG-F or thymoglobulin), within 4 months before the first dose of study drug on Day -1.
18. Treatment with any live vaccinations within 30 days before randomization.
19. If female, the subject is pregnant, lactating or breastfeeding, or intending to become pregnant before, during, or within 18 weeks after participating in this study, or intending to donate ova during such time period.

20. Diagnosed or treated for another malignancy within 2 years before the first dose of study drug or previously diagnosed with another malignancy and have any evidence of residual disease. Subjects with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

7.3 Medications and Treatments

7.3.1 Excluded Concomitant Medications and Treatments While On-study

- Any investigational agent (other than vedolizumab), including agents other than corticosteroids for treatment of GvHD.
- Checkpoint inhibitors.
- Any therapy for aGvHD prophylaxis other than that specified in the inclusion criteria (Appendix B). Should 1 of the GvHD prophylaxis agents specified in the inclusion criteria be discontinued due to toxicity and an alternative agent started, the subject may be permitted to remain on study drug after consultation with the medical monitor.
- All live vaccines from 30 days before randomization to at least 6 months after the last dose of study drug.
- Either approved or investigational monoclonal antibody or equivalent biologics for the treatment of other conditions (eg, rheumatoid arthritis), other than localized injections (eg, intra-ocular injections for wet macular degeneration).

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

7.3.2 Permitted Medications and Treatments

Other medications considered necessary for the safety and well-being of the subject may be administered at the discretion of the investigator. Corticosteroids may be initiated for treatment of GvHD; however, if lower intestinal tract aGvHD occurs, study drug must be discontinued (Section 7.4). Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; hence, such premedication is unlikely to be necessary or beneficial. At the discretion of the investigator, however, subjects may be administered premedication before any study drug administration. Use of topical anesthetic (eg, lidocaine, tetracaine, prilocaine) is recommended for blood draws or IV insertions for the comfort of subjects aged 12 to <18 years. This use will *not* be recorded as a concomitant medication. Corticosteroids, if given as a premedication, should be limited to the day of administration.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories.

- The subject has experienced an AE that requires ET because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of that AE, such as:
  - PML or tuberculosis
  - LFT Abnormalities

    Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.3.15.3), if the following circumstances occur at any time during study medication treatment:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 8 times the upper limit of normal (ULN), or
    - ALT or AST more than 5 times the ULN and persists for more than 2 weeks, or
    - ALT or AST more than 3 times the ULN in conjunction with elevated total bilirubin more than 2 times the ULN or international normalized ratio (INR) more than 1.5 with no alternate etiology, or
    - ALT or AST more than 3 times the ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, with fever and rash.
- Significant protocol deviation. The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
- Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
- Voluntary withdrawal. The subject wishes to withdraw from the study, or the subject's parent/legally acceptable representative wishes to have the subject withdrawn from the study.

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

  Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.3.20.

- Lack of efficacy. Subjects who develop lower intestinal aGvHD (stage 1-4 per Table 1: aGvHD Clinical Stage, as defined in Appendix F) should discontinue study drug.
- Other. Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the ET visit, the final safety visit, and the 6-month LTFU safety survey. Discontinued or withdrawn subjects will not be replaced.

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

8.0 STUDY DRUG/CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding study medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol.

8.1 Study Medication

All protocol-specific criteria for administration of study drug must be met and documented before study drug administration. Study drug will be administered only to eligible subjects under the supervision of the investigator or identified subinvestigator(s). The drugs contained in the background GvHD prophylaxis regimen (Appendix B) will be obtained by the study sites.

8.1.1 Vedolizumab IV or Matching Placebo

The study sites will be supplied by the sponsor with the following medication in an open-label manner: vedolizumab IV 300 mg/vial, for single use, in 20 mL vials. The study 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. Sites provide all other materials for infusion.

The placebo infusion will be 250 mL of 0.9% sodium chloride and should be provided by the sites. For all infusions, the unblinded investigational pharmacist or designee will mask the IV bags after preparation to maintain the study blind.

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

8.1.2 Storage

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

Vedolizumab IV must be stored at 2ºC to 8ºC (36ºF to 46ºF), protected from light. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

The dosing regimen for all subjects is shown in Figure 8.a. All subjects will receive double-blind treatment of study drug by IV infusion per the designated schedule. The Vedolizumab IV dose is 300 mg on each dosing day.

All infusions will be administered IV over approximately 30 minutes. Longer infusion times of up to 60 minutes may be used based on study observations. Subjects should be observed for 2 hours after the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion in a room where appropriate treatment for IRRs is available (see Section 8.7.1). The subject should be considered clinically stable by the investigator or designee before discharge.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0, pretreatment events (PTEs) and AEs.

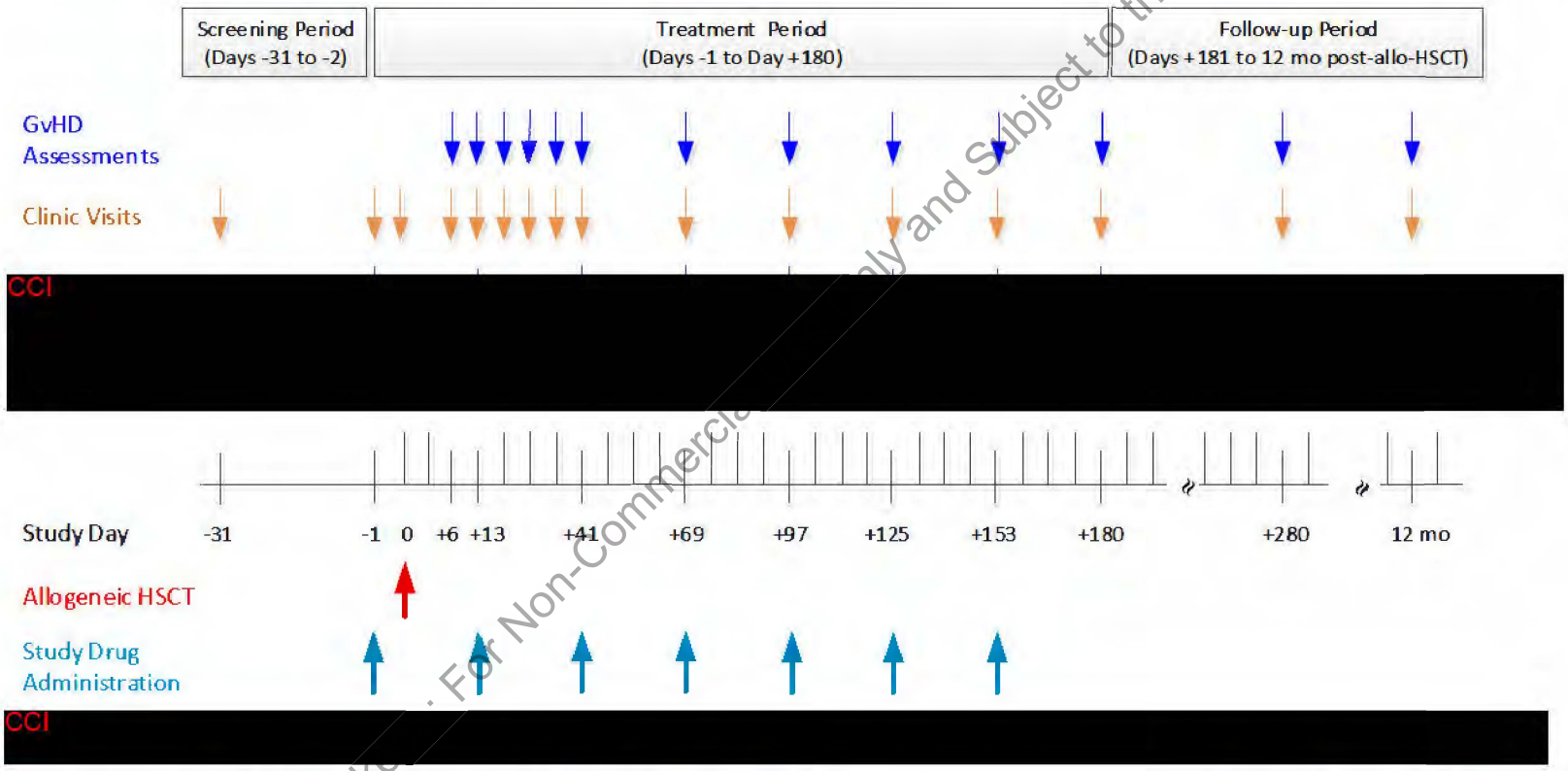
SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

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

Figure 8.a Dosing of Study Drug, CCI

Allogeneic HSCT on Day 0

Study drug is administered on Days -1, +13, +41, +69, +97, +125, and +153.



Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; CCI; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; CCI

8.2 Treatment Assignment and Dispensing Procedures

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization. Subjects will receive the treatment for the assigned treatment arm and according to the study schedule.

The investigator or investigator's designee will access the IRT at screening to obtain the subject study number. The investigator or the investigator's designee will utilize the IRT to randomize the subject into the study. The medication identification (ID) number of the investigational drug to be dispensed will then be provided by the IRT by email notification to the unblinded site pharmacist/nurse. To maintain the blind the IRT will ensure the investigator or designee is unaware of a medication ID assigned to the subject. If sponsor-supplied drug is lost or damaged, the unblinded site staff can request a replacement from IRT.

At subsequent drug-dispensing visits, the investigator or designee will again contact the IRT to request additional investigational drug for a subject. The medication ID number of the investigational drug to be dispensed will be provided by the IRT to the unblinded site staff only.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Additional information is provided in the study manual.

8.3 Investigation Blind Maintenance

The investigational drug blind will be maintained using the IRT. All subjects and study personnel except for those directly involved with study drug preparation will be blinded to study drug assignment for the entire study.

8.4 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, the investigational drug blind can be broken without permission from the sponsor, although the medical monitor should be contacted immediately. In non-urgent cases (ie, a non-medical emergency), the medical monitor must be contacted before the subject is unblinded.

For unblinding a subject, the investigational drug blind can be obtained by the investigator, by accessing the IRT. Additional information for unblinding a subject is provided in the study manual.

Subjects discontinuing study participation for any other reason will be kept blind.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

8.5 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed at the site. The site will maintain source documents in addition to entering data into the IRT.

The blinded investigator or blinded designee and the unblinded investigational pharmacist or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the unblinded investigational pharmacist or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the unblinded investigational pharmacist or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, the unblinded investigational pharmacist or designee should acknowledge the receipt of the shipment in the IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator must ensure that 100% accountability is maintained for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. The unblinded investigational pharmacist will maintain 100% accountability, including but not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the medication ID used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- Continuously monitoring expiration dates, if expiry date is provided.

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

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The unblinded investigational pharmacist or designee will acknowledge all sponsor-supplied drugs in the IRT and maintain the drug accountability logs as described in the unblinded pharmacy manual. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed, and the initials, seal, or signature of the person dispensing the drug.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction or destroyed at the site. Accountability

for clinical study material being destroyed at the site must be documented using a study accountability tracking document or equivalent document. In addition, a certificate of destruction document must be provided by the sites that can identify or allow traceability to the batches, and/or medication ID numbers involved, and actual quantities destroyed. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

8.6 Precautions and Restrictions

8.6.1 Study Drug Dosing

After a subject has received the first dose of study drug on Day -1 before allo-HSCT, if the clinical events described in Section 8.7 are observed, subjects may not receive subsequent study drug doses after allo-HSCT as indicated in the SOE (Appendix A).

8.6.2 Reproductive Effects

It is not known what effects vedolizumab has on human pregnancy or development of the embryo or fetus. Therefore, female subjects participating in this study should avoid becoming pregnant, and male subjects should avoid impregnating a female partner. Nonsterilized female subjects of reproductive age group and male subjects should use effective methods of contraception (specified in Section 9.3.19) through defined periods during and after study treatment as specified in the following.

Female subjects must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit (specified in Section 9.3.19), or
- Surgically sterile, or
- If they are aged 12 years and greater and are not postmenopausal (Section 9.3.19) or surgically sterilized, must use a highly effective method of contraception (specified in Section 9.3.19) during the study 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] and withdrawal are not acceptable methods of contraception.)

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

- Practice an acceptable effective barrier method of contraception (specified in Section 9.3.19) 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.)

In addition, using the approved product information for the medicinal products used as part of a subject's routine care, including the conditioning regimen, investigators should advise subjects on the appropriate duration for use of contraception after the last dose of such medicinal products.

8.7 Management of Clinical Events

8.7.1 Hypersensitivity Reactions

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; hence such premedications are unlikely to be necessary or beneficial. At the discretion of the investigator, however, subjects may be administered premedication before any study drug administration. Corticosteroids, if given as a premedication, should be limited to the day of administration. Study drug 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. Subjects should be observed during the infusion and until the infusion is complete.

Subjects, parents, or legally acceptable representatives should be instructed to report the development of rash, hives, pruritus, flushing, urticaria, etc. that may represent an IRR to study medication. If signs or symptoms of IRR are observed during the administration of study drug, it should be immediately discontinued and the subject treated as medically appropriate. In the case of a mild reaction, study drug administration may be reinitiated (with appropriate premedication) at the discretion of the investigator. Subjects with severe or serious IRRs (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 subjects with less severe IRRs should be discussed with the project clinician.

8.7.2 Leukopenia or Lymphopenia

Leukocyte and lymphocyte counts will be monitored for all subjects with a hematological panel (see Section 9.3.15.3) and the use of prophylactic myeloid growth factors (ie, granulocyte-colony stimulating factor) may be started with the product, dose, and route of administration at the discretion of the treating institution. If engraftment has not occurred by Day +21 (defined as absolute neutrophil count >500/mm^3 for 3 consecutive days or >2000/mm^3 for 1 day), it is recommended that prophylactic myeloid growth factors be started. Failure to engraft by Day +28 will be considered as primary graft failure and should be reported as an SAE, and study drug should be discontinued.

8.7.3 CMV Colitis

Regular assessments will include symptom-directed assessment for GI toxicity and monitoring for CMV reactivation per institutional standards. Preemptive CMV therapy will be initiated per institutional standards. Subjects with active CMV colitis during screening will be excluded from

the study. For subjects with suspected CMV colitis, it is recommended that an endoscopy be performed. Subjects with confirmed CMV colitis during the study will require dosing hold, and the medical monitor should be contacted before resuming study drug. In subjects suspected of having aGvHD for whom the cause of posttransplantation diarrhea and/or enterocolitis is unclear, the subject will require endoscopy and histologic analyses of intestinal biopsy specimens as clinically appropriate.

8.7.4 Malignancy

All cases of malignancies that are detected during the study, including relapse of primary disease will be reported as SAEs. Study drug should be discontinued, and subjects will continue to be followed as specified per the SOE (Appendix A).

8.7.5 Liver Injury

For subjects with normal baseline ALT/AST, a subject noted to have ALT or AST elevated more than 3 times the ULN for 2 consecutive weeks, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

For subjects who had elevated ALT or AST at baseline, if elevations of ALT or AST are more than 2 times the baseline value or ALT or AST is more than 5 times the ULN, the abnormality should be recorded as an AE and reported via the LFT Increases eCRF.

For both of these scenarios, study drug will be held until further discussion with the medical monitor. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A, B, or E, reactivation of hepatitis B, or acute liver GvHD or other acute liver disease or medical history/concurrent medical conditions before subsequent dosing. Follow-up laboratory tests as described in Section 9.3.15.3 must also be performed.

If a subject is noted to have ALT or AST more than 3 times the ULN and total bilirubin more than 2 times the ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2; treatment with study drug should be immediately held. The investigator must contact the medical monitor to discuss alternate etiologies. In addition, an LFT Increases eCRF must be completed.

In addition, an event meeting any of the criteria listed for LFT Abnormalities (Section 7.4) should be reported as an SAE.

8.7.6 Hepatitis B Reactivation

Subjects who are $HBcAb^{+}$ and $HBsAg^{-}$ with a detectable hepatitis B virus (HBV) DNA by PCR at screening should be excluded from the study. Only subjects with a negative PCR evident by undetectable HBV DNA may be enrolled in the study. Assessments for reactivation in such

subjects should be monitored periodically (at the minimum every 3 months) by determination of HBV serology and HBV DNA. All subjects who meet any of the following criteria will be immediately discontinued from study drug. All reactivation events should be reported as an SAE.

- Detectable HBV DNA.
- Reverse seroconversion from $HBsAg^-$ to $HBsAg^+$.
- Jaundice.

8.7.7 Other Clinical Events

8.7.7.1 Serious Infections

Subjects who, in the opinion of the investigator, have serious infections will be monitored during the study. Subjects with serious infections, including viral, fungal, and bacterial infections, will be treated as clinically indicated. Interventions may include antibiotic treatment, if appropriate and/or discontinuation of concomitant immunomodulators. Blood, sputum, urine, cerebrospinal fluid, and/or stool cultures should be obtained as appropriate for the detection and diagnosis of infection. Study drug should be withheld, and the medical monitor should be contacted before resuming study drug. Terminating study drug administration may be considered as described in Section 7.5.

8.7.7.2 PML

All subjects will be screened for new neurological signs and symptoms potentially consistent with PML using the PML subjective checklist (see Section 9.3.11) before dosing with study drug. Any subjects in whom signs or symptoms of PML are reported will undergo objective testing. If a subject demonstrates a neurologic deficit related to PML upon administration of the PML checklist, no further doses of study drug should be administered to that subject. The subject 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 Risk Minimization Action Plan for PML (RAMP) algorithm.

8.7.7.3 Donor Leukocyte Infusion

Planned donor leukocyte infusion (DLI) is not permitted.; however, for subjects who experience mixed chimerism, DLI may be permitted after consultation with the medical monitor. For subjects who require DLI for other reasons, such as disease relapse, study drug should be discontinued, and subjects will continue to be followed as specified in the SOE (Appendix A).

9.0 STUDY CONDUCT

This study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and International Council for Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the Takeda 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.

9.2 Randomization

Randomization will take place within 2 days of the first dose of study drug on Day -1 provided the subject has satisfied all of the inclusion criteria and none of the exclusion criteria. The subject should be randomized using the IRT as described in Section 8.2. The procedure for documenting screening failures is provided in Section 9.4. Rescreening is permitted in consultation with the medical monitor.

9.3 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Refer to the SOE (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.3.1 Informed Consent

The requirements of the informed consent/age-appropriate assent are described in Section 15.2.

Informed consent/age-appropriate assent must be obtained before the subject enters into the study, and before any protocol-directed procedures are performed.

Subjects reaching an age that is not covered by their signed assent must provide consent for their appropriate age group to remain in the study. Subjects who reach the age of consent must provide consent with a signed ICF to remain in the study.

9.3.2 Inclusion/Exclusion

The inclusion/exclusion criteria will be assessed during screening (within 30 days before the first dose of study drug on Day -1).

9.3.3 Demographics

Demographic information to be obtained may include (depending on local regulations) the date of birth or age, race, ethnicity, and sex of the subject and are to be recorded during screening.

9.3.4 Medical History

During the screening period, a complete medical history will be compiled for each subject. The history will emphasize the background and progress of the subject's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 9.3.13.

9.3.5 Physical Examination

A baseline physical examination (defined as the assessment before the first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) GI system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment before the first dose of study drug.

Any physical examination finding that is assessed by the investigator as a clinically significant change (worsening) compared to baseline value will be considered an AE and will be recorded and monitored as described in Section 10.2.

9.3.6 Weight and Height

A subject should have weight and height measured while wearing indoor clothing and without shoes, socks, or hats. The Takeda standard for collecting weight is kilograms (kg) with 1 decimal place.

Height should be recorded to the nearest tenth of a centimeter (if possible). Height may be measured using a wall-mounted stadiometer using replicated measurements (average of 3 measurements). Height will be measured during screening (within 30 days before the first dose of study drug on Day -1) and at EOS.

9.3.7 Vital Signs

Vital sign measurements include blood pressure, heart rate, respiration rate, and body temperature to be determined at the times specified in the SOE (Appendix A). On dosing days, vital signs are taken predose.

9.3.8 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at the time points specified in the SOE (Appendix A).

9.3.9 Performance Status

The type of performance status scale to be used is based on subject age at randomization. The ECOG performance status is used for subjects aged ≥18 years, the Karnofsky performance status

for adolescent subjects aged ≥16 years, and the Lansky performance status for adolescent subjects aged 12 to <16 years will be assessed at the time points specified in the SOE (Appendix A).

9.3.10 Assessment of GvHD

aGvHD will be staged according to the extent and severity of each organ involvement (Stages 0-4) on the basis of objective clinical criteria (Appendix F). These stages are then combined to generate an overall clinical grade, which are Grades 0 through IV in the modified Glucksberg system (Appendix F), MAGIC system, and Grades A through D in the International Bone Marrow Transplant Registry Database (IBMTR) system (Appendix F). Glucksberg and IBMTR performed similarly in explaining variability in OS by grade in aGvHD. aGvHD events will be recorded and staged according to aGvHD Clinical Stage criteria (Appendix F) and graded per the IBMTR system in this study unless otherwise noted.

In subjects suspected of having intestinal aGvHD, endoscopy with rectal biopsy is recommended, and infectious etiologies (eg, *C. difficile*, CMV colitis) should be evaluated.

9.3.11 PML Checklist

Clinic staff will administer the age-appropriate subjective PML checklist during screening to exclude subjects 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 SOE (Appendix A) to probe for symptoms suggestive of PML. The checklist must be administered by appropriate clinic staff as it is not designed to be completed by a subject, parent, or legally acceptable representative. If a new and persistent change(s) is reported per the subjective checklist, the corresponding objective test(s) must be completed, and the subject may be referred to a neurologist for a full evaluation as described in the RAMP algorithm. The PML checklist and the RAMP algorithm and tools are included in the Study Manual. See Section 10.7 for additional details regarding the RAMP program.

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9.3.13 Concomitant Medications and Procedures

Medications used by the subject and therapeutic procedures completed by the subject will be recorded in the eCRF from the first dose of study drug on Day -1 through 12 months after allo-HSCT. See Section 7.3.1 and Section 7.3.2 for a list of medications and therapies that are prohibited and/or allowed during the study.

9.3.14 AEs

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

9.3.15 Clinical Laboratory Evaluations

Clinical laboratory evaluations as specified in the SOE (Appendix A) will be performed by a central laboratory. Local laboratories may be used to conduct assessments needed more rapidly and for urgent medical management throughout the study per investigator's discretion. In adolescent subjects aged 12 years and greater and weighing ≥30 kg, the maximum volume of blood collected at any single visit (CCI [redacted]) is approximately 14 mL, and the approximate total volume of blood for the study is 144 mL. The maximum volume of blood collected from adult subjects is 29 mL and 300 mL, respectively. Clinical laboratory evaluations to be conducted during this study are summarized in Table 9.a.

9.3.15.1 TB Screening

All subjects will complete TB screening to determine eligibility. All subjects must complete a diagnostic test during screening, either a QuantiFERON test, T-Spot, 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 7.2.

9.3.15.2 Pregnancy Test

For female subjects aged 12 years and greater who are not postmenopausal (Section 9.3.19) or surgically sterilized, a serum pregnancy (choriogonadotropin beta) test will be completed at

screening before the first dose of study drug, and a urine pregnancy test will be completed predose on each study drug dosing day (and in the UK, on Day +180; and in Norway, on Day +180, Day +280 [or 18 weeks after the last dose of study drug], and at ET; and in Argentina, monthly from Day +153 up to 18 weeks after the last dose of study drug). The results from these tests must be available and negative before the study drug is administered. 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.

9.3.15.3 Clinical Hematology, Coagulation, Chemistry, and LFT

The clinical laboratory tests (clinical hematology, coagulation testing, blood chemistry, and LFTs) to be conducted during the study are summarized in Table 9.a. The central laboratory will perform these tests and return the results to the investigator, who is responsible for reviewing and filing them. Blood samples for these analyses will be obtained at the time points specified in the SOE (Appendix A).

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

(Please refer to Section 7.4 for discontinuation criteria, and Section 8.7.5 for the appropriate guidance on reporting of abnormal LFTs in relation to ALT or AST more than 3 times the ULN in conjunction with total bilirubin more than 2 times the ULN.)

If the ALT or AST remains elevated more than 3 times the ULN on these 2 consecutive weeks, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details, and possible alternative etiologies. The abnormality should be recorded as an AE (refer to Section 8.7.5 reporting of abnormal LFTs for reporting requirements).

Table 9.a Clinical Hematology, Coagulation, Chemistry, and LFTs

Hematology	**Serum Chemistry**	
Hematocrit	Albumin	Glucose
Hemoglobin	Bicarbonate (HCO_3)	Phosphate
Red blood cells (RBC)	Blood urea nitrogen (BUN)	Potassium
Leukocytes with differential including neutrophils, monocytes, and lymphocytes	Calcium	Sodium
	Creatinine	Urate
Platelets	Chloride	
Coagulation [a]	**Liver Functions**	
Prothrombin (PT)/INR	Alkaline phosphatase (ALP)	Bilirubin (total and direct)
Activated partial thromboplastin time (aPTT)	ALT	Lactate dehydrogenase (LDH)
	AST	
Other:		
HIV	beta hCG and urine pregnancy hCG (predose on dosing days) for female subjects of childbearing potential	
Hepatitis panel, including HBsAg, anti-HCV, and HCV PCR (as applicable)	FSH, if menopause is suspected	
QuantiFERON for TB		
CCI		

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI ; FSH, follicle-stimulating hormone; HBsAg, hepatitis B surface antigen; hCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; PCR, polymerase chain reaction; TB, tuberculosis.

[a] Performed in subjects as specified in the SOE (Appendix A).

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[redacted]

9.3.19 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, female subjects aged 12 years and greater who are not postmenopausal or surgically sterilized and who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (Section 8.6.2). In addition, they must be advised not to donate ova during this period.

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception considered effective in men (eg, condom with spermicidal cream or jelly) (Section 8.6.2). In addition, they must be advised not to donate sperm during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented) (Section 8.6.2).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate (Section 8.6.2).

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

- **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, including oral, intravaginal, and transdermal formulations.**
- **Progestogen-only hormonal contraception associated with inhibition of ovulation, including oral, injectable, and implantable formulations.**
- **Intrauterine device (IUD).**
- **Intrauterine hormone-releasing system (IUS).**
- **Bilateral tubal occlusion.**
- **Vasectomised partner.**
- **Sexual abstinence.**

Barrier methods (eg, male condom PLUS spermicide, cap [plus spermicidal cream or jelly] PLUS male condom and spermicide, diaphragm [plus spermicidal cream or jelly] PLUS male condom and spermicide) can be used each time the subject has intercourse in addition to methods listed in the table above to ensure acceptable protection level.

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

During the course of the study, urine hCG pregnancy tests will be performed (Section 8.6.2) for female subjects aged 12 years and greater who are not postmenopausal or surgically sterilized, and these subjects will receive continued guidance with respect to the avoidance of pregnancy and ova donation as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at screening, female subjects aged 12 years and greater who are not postmenopausal or surgically sterilized must have a negative urine hCG pregnancy test before receiving any dose of study drug, preferably on the same day.

Male subjects must be advised not to donate sperm from signing of informed consent through 18 weeks after the last dose of study medication.

Using the approved product information for the medicinal products used as a part of a subject's routine care, including the conditioning regimen, investigators should advise subjects on the appropriate duration for use of contraception after the last dose of such medicinal products.

9.3.20 Pregnancy

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

If the pregnancy occurs during administration of study drug, eg, after the first dose on Day -1 or through 18 weeks after the last dose of study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in the study manual.

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

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

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

9.4 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent/age-appropriate assent.

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

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

- An existing substantial AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other.

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

9.5 Completion of Study Treatment (for Individual Subjects)

Subjects will be considered to have completed study treatment if they receive 7 doses of study drug and completed the Day +180 study visit.

9.6 Study Compliance

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

If a subject is persistently noncompliant with the study medication, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.7 Post Study Care

Study drug is administered for defined duration in addition to background aGvHD prophylaxis as part of the prophylaxis regimen. Therefore, the study drug will not be supplied by the sponsor after the subject has completed the study. The subject should return to the care of a physician and standard therapies as required.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

An AE therefore can be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is considered related to the medicinal product. In addition, drug-device AEs related to quality or malfunction will be collected.

10.1.3 Additional Points to Consider for AEs

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation expected in this subject population). A laboratory retest and/or continued monitoring of an

abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

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

Preexisting conditions:

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

Worsening of AEs:

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

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 SAEs

SAE means any untoward medical occurrence that at any dose:

1. Results in **death.**
2. 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).
3. Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
4. 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).
5. Is a **congenital anomaly/birth defect**.
6. Is a **medically important event** that satisfies any of the following:
    - may require intervention to prevent one of the outcomes listed above (1-5).

- may expose the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.
- includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

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

10.1.5 AEs of Special Interest

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

The following will be reported AESIs:

- serious infections,
- PML,
- Malignancy, including relapse of the primary disease,
- Liver injury,
- Hypersensitivity reactions including IRRs and injection site reactions,
- Leukopenia or lymphopenia,

- CMV colitis, and
- CMV reactivation.

10.1.6 Severity of AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Grade descriptions are:

1. Mild: asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
2. Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3. Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
4. Life-threatening consequences; urgent intervention indicated.
5. Fatal AE: an event that results in the death of the subject.

10.1.7 Causality of AEs

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

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

10.1.8 Relationship to Study Procedures

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

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

10.1.9 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.10 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

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

10.1.12 Action Concerning Study Medication

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

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – AEs that are considered the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collecting and Reporting AEs

10.2.1.1 AE Collection Period

Nonserious AEs must be collected from the time of the first dose of study drug until 18 weeks after the last dose of study medication.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects, parents, or legally acceptable representatives may report AEs occurring at any other time during the study.

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

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

10.2.1.3 AESI Reporting

If AESIs occur during the study period or the posttreatment follow-up period and are considered clinically significant based on the criteria below, the AEs should be recorded in the AESI eCRF and an SAE Form, as applicable. The SAE form should be completed and reported within 24 hours to the SAE reporting contact number recorded in the study manual.

Injection Site Reactions and/or IRRs and Hypersensitivity

Refer to Section 8.7.1.

Serious Infections

Refer to Section 8.7.7.1. Withholding or terminating study drug administration may be considered as described in Section 7.4.

Malignancies

Refer to Section 8.7.4. All cases of malignancies that are detected during the study will be reported as SAEs.

Liver Injury

Refer to Section 8.7.5.

Other

Other AESIs include leukopenia or lymphopenia and PML and are discussed in Sections 8.7.2 and 10.7, respectively.

10.2.2 Collection and Reporting of SAEs

SAEs must be collected from the time the subject signs the informed consent/age-appropriate assent to participate in the study until the EOS or the subject discontinues study participation. SAEs should be reported according to the following procedure:

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

- A short description of the event and the reason why the event is categorized as serious.
- Subject ID number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

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

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

Reporting SAEs that occur before the first dose of study drug will follow the procedure described for SAEs.

10.3 Follow-Up of SAEs

Regardless of causality, SAEs must be reported (see Section 10.4 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile or email of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the study manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

10.4 Monitoring of AEs and Period of Observation

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

- AEs will be collected from the first dose of study drug through 18 weeks after administration of the last dose of study drug and recorded in the eCRFs.
- Only serious PTEs will be collected and reported to the Takeda Global Pharmacovigilance department or designee from the time of signing of the ICF up to the first dose of study drug and recorded in the eCRF.
- Related and unrelated SAEs will be collected and reported to the Takeda Global Pharmacovigilance department or designee from the signing of the informed consent through EOS and recorded in the eCRF.

10.5 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a female subject 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 sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male subject becomes pregnant during the male subject's participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

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

10.7 RAMP Program

Subjects who have undergone 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 subjects who have undergone 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 subjects with autoimmune diseases who did not have HIV or malignancy (including subjects with IBD) [46,47]. To minimize the risk of the development of PML in subjects treated with vedolizumab, the sponsor, with input from PML experts, has developed 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. Subjects are assessed for signs and symptoms of PML before the administration of each dose of study drug using an age-appropriate PML subjective symptom checklist. Subjects with a positive PML subjective symptom checklist at any time after enrollment in a vedolizumab clinical study will be evaluated according to a prespecified algorithm (the PML Case Evaluation Algorithm). The next dose of vedolizumab will be held until the evaluation is complete and results are available. Subsequent doses of vedolizumab 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 subject evaluation and management as defined in the IAC charter.

To ensure success of the RAMP program, site personnel will be trained to recognize the features of PML, and subjects/parents/legally acceptable representatives will be trained to report specific neurological signs and symptoms without delay. Educational materials for teaching site personnel and subjects/parents/legally acceptable representatives 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 before the start of the study. Subjects will receive age-appropriate training and educational materials before receiving treatment. The ICF 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.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 DMC

A DMC will be utilized in the study for safeguarding the interest of study participants, assessing the safety and efficacy of the interventions during the study while maintaining the integrity of the study. The DMC will conduct periodic scheduled reviews of safety and conduct an interim analysis. Further details of the interim analysis can be found in Section 13.2.

The composition of, working procedures for, and frequency of DMC meetings are defined in the DMC Charter and will be provided to the DMC members before their first meeting. The DMC Charter is not included in this protocol.

11.2 Adjudication Committee

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. Details of the adjudication procedure are captured in the RAMP program that is contained in the study manual.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, 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 Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF/assent.

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 designee) 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, contact information of the person making the correction, the date the correction was made, and the reason for the 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 designee) will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the ID log of all participating subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs/assents, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential

documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

The primary analysis for efficacy and safety data will be performed at the end of treatment (EOT), when all subjects have completed Day +180, withdrawn from the study, or ET, or when the planned number of primary endpoint events as determined by the sample size adaptation rule in the interim analysis are accrued.

To protect the integrity of the study and ensure the unbiased study conduct from EOT to EOS, a selected group of Takeda personnel will be identified to conduct the unblinded primary analysis. Study investigators, participating subjects, and sponsor personnel responsible for conduct of the remainder of the study will remain blinded. Details of unblinding for primary analysis will be provided in the SAP and/or data access management plan (DAMP). The EOS analysis will be performed after the final database lock at EOS.

A targeted data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods. Data may also be summarized descriptively by age group (aged ≥18 years and ≥12 years to <18 years).

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- Full analysis set (FAS): Following the intent-to-treat principle, the FAS will include all subjects who are randomized, receive at least 1 dose of the treatment, and undergo allo-HSCT. The analysis will be based on the treatment to which the subjects are randomized.
- Per-protocol population is defined to include all randomized subjects who received any amount of blinded study drug and have no significant protocol deviations. All decisions to exclude subjects from the per-protocol population dataset will be made before to the study is un-blinded. Analyses using the per-protocol population may be provided as a sensitivity analysis.
- Safety analysis set will include all subjects who receive at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment actually received.

CCI [redacted]

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information will be listed and summarized by treatment group and for the overall FAS. For continuous variables, the summary will consist of descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). For categorical variables, the summary will consist of number and percentage of subjects in each category.

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

13.1.3 Efficacy Analysis

All statistical testing will be performed at a 2-sided 0.05 level of significance. To control the overall Type I error rate for the comparison between vedolizumab and placebo groups for the primary and secondary efficacy endpoints, a gatekeeping procedure will be used. Specifically, the statistical testing of the first secondary efficacy endpoint will only be performed if the treatment difference for primary efficacy endpoint is statistically significant. The next secondary efficacy endpoint will only be tested if the treatment difference for the first secondary efficacy endpoint is significant, and so on for each subsequent secondary efficacy endpoint.

The order of the statistical testing for the key secondary endpoints is:

1. Intestinal aGvHD-free and relapse-free survival by Day +180.
2. Grade C-D aGvHD-free (any organ involvement) survival by Day +180.
3. NRM by Day +180.
4. OS by Day +180.
5. Grade B-D aGvHD-free (any organ involvement) survival by Day +180.

All time-to-event endpoints will be analyzed using log-rank tests. Cox proportional hazard models, stratified by randomization strata, will also be fit with hazard ratios reported. All dichotomous efficacy endpoints will be analyzed using Cochran-Mantel-Haenszel tests for risk differences, stratified by randomization strata; for dichotomous endpoints, subjects with a missing outcome will be included in the analysis based on nonresponder imputation, ie, treated as having the undesirable outcome.

CCI [redacted]

CCI

[redacted]

13.1.6 Safety Analysis

Safety analysis will be performed using the safety analysis set. No statistical inference will be made for safety analyses.

The number and percentage of subjects with treatment-emergent AEs (defined as any AEs newly occurring or worsening from the first dose and 18 weeks after last dose of study treatment, regardless of relationship to study drug), AESIs (ie, serious infections, PML, malignancies, liver injury, infusion reactions, injection site reactions), and SAEs that occur on or after the first dose date and through EOS will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term overall, by severity, and by relationship to study drug for each treatment group. Separate summaries will also be generated for treatment-related AEs overall and by severity. Change from baseline in clinical laboratory tests and vital signs will be summarized by treatment group.

13.2 Interim Analysis and Criteria for ET

One interim analysis for futility and sample size re-estimation is planned for this study, which will occur after approximately 30% of the targeted primary endpoint events (ie, approximately 44 events) have been accrued. The analysis will be performed by an independent statistical center in a manner that maintains the blinding to the study team, the investigators, and the subjects. The interim analysis results will be presented to the DMC but will not be shared with the sponsor. Specific criteria for DMC recommendations will be provided in the DMC charter. The futility stopping is considered nonbinding.

If 148 primary endpoint events are accrued before all subjects have completed Day +180 or dropped out, the primary analysis for efficacy may be performed at that time.

Details of Type I error control following sample size re-estimation will be provided in the SAP.

13.3 Determination of Sample Size

Assuming the event rate for the primary endpoint is 34.1% for the placebo group and 21.8% for the vedolizumab group and the rate of loss-to-follow-up is 10% for both groups, a sample size of 279 subjects per group (558 subjects total) is expected to generate 148 primary endpoint events and hence provide 90% power at 2-sided 0.05 level of significance. Assuming the event rate for the first secondary endpoint is 39.5% for the placebo group and 27.1% for the vedolizumab group, this sample size is expected to generate 177 events for the first secondary endpoint and hence provide approximately 86% power at 2-sided 0.05 level of significance.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized) including, but not limited to, the investigator's binder, study medication, subject medical records, informed consent/age-appropriate assent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs/age-appropriate assents), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

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

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

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and the protocol.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US Food and Drug Administration [FDA], the UK Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and

Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state, federal, and/or 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.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and where applicable, age-appropriate assent(s), and if applicable, subject recruitment materials, 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/age-appropriate assent 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 its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. 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 the competent authority to begin the study. 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 ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

The ICF/age-appropriate assent, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF/age-appropriate assent, 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. If the subject is not capable of rendering adequate written informed consent/age-appropriate assent, 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 to participate in the study. If the subject, or the subject's legally acceptable representative, determines that he or she will participate in the study, then the ICF/age-appropriate assent and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF/age-appropriate assent and subject authorization (if applicable) at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF/age-appropriate assent, 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/age-appropriate assent in the subject's medical record. Copies of the signed ICF/age-appropriate assent, the signed

subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs/age-appropriate assents 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/age-appropriate assent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF/age-appropriate assent.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will be linked to the sponsor's clinical study database or documentation only via a unique ID 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 ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA, Japan PMDA), 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/assent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed, eg, subject name, address, and other identifier fields not collected on the subject's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with

this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

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

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, clinicaltrialsregister.eu for studies conducted in the EU, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving subject care. Qualified independent researchers will be permitted to use data collected from subjects during the study to conduct additional scientific research, which may be unrelated to the study drug or the subject's disease. The data provided to external researchers will not include information that identifies subjects personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the clinical study site agreement regarding the sponsor's policy on subject compensation

and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Study Period:	Screening	Treatment														Posttreatment	
Days				(±3 d)										(±7 d)		(±7 d)	
	Screening [a]	Day −1	Day 0	+6	+13	+20	+27	+34	+41	+69	+97	+125	+153	Day +180 [b]	ET/ UnsV [c]	Day +280/ FSV [b, d]	12 mo/ final FU [e]
Informed consent/assent [f]	X	X															
Inclusion/exclusion criteria	X	X															
Demographics/medical history	X																
Complete PE [g]	X																
Height	X																X
Targeted PE [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate) [i]	X																
Performance status [j]	X	X			X		X		X	X	X	X	X	X	X	X	X
GvHD assessment [k]				X	X	X	X	X	X	X	X	X	X	X	X	X	X
PML checklist [l]	X	X			X				X	X	X	X	X				
PML wallet card	X																
HRQOL [m]		X									X			X	X		X
Healthcare resource utilization		Recorded from first dose of study drug through 12 months after allo-HSCT															
LTFU safety survey		All subjects, including those who withdraw from the study, will be required to complete a LTFU safety survey by phone 6 months after the last dose of study drug.															
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through 12 months after allo-HSCT															
AE reporting	AEs will be recorded from the first dose of study drug through 18 weeks after the last dose of study drug																
	SAEs will be recorded and reported from the signing of the ICF through the end of study																

Study Period:	Screening	Treatment														Posttreatment	
Days				(±3 d)									(±7 d)			(±7 d)	
	Screening [a]	Day −1	Day 0	+6	+13	+20	+27	+34	+41	+69	+97	+125	+153	Day +180 [b]	ET/ UnsV [c]	Day +280/ FSV [b, d]	12 mo/ final FU [e]
Laboratory Assessments																	
HIV, hepatitis panel [n]	X																
TB testing [n]	X																
Pregnancy [o]	X	X			X				X	X	X	X	X				
Hematology/chemistry [p]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Liver function	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Other Samples/Assessments																	
CCI [redacted]																	
Allo-HSCT [s]			X														
Study drug IV dosing [t]		X			X				X	X	X	X	X				

Abbreviations: AE, adverse event; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CCI [redacted]; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D, European Quality of Life 5-Dimension; ET, early termination; FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale; FSV, final safety visit; GI, gastrointestinal; GvHD, graft-versus-host disease; HIV, human immunodeficiency virus; HRQOL, health-related quality of life; HSC, hematopoietic stem cell; IBMTR, International Bone Marrow Transplant Registry; ICF, informed consent form; IV, intravenous; LTFU, long-term follow-up; PE, physical examination; CCI [redacted] PML, progressive multifocal leukoencephalopathy; SAE, serious adverse event; TB, tuberculosis; UnsV, unscheduled visit.

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

[a] Unless otherwise noted, the screening visit must occur within 30 days before the day of the first dose of study drug (Day -1). Randomization will take place within 2 days of the first dose of study drug on Day -1. Rescreening is permitted in consultation with the medical monitor.

[b] Visit should be performed on the scheduled day (as shown) but is allowed ±7 days.

[c] CCI [redacted]. HRQOL instruments are completed at ET and not at an unscheduled visit.

All subjects, including those who withdraw from the study, will be required to have an FSV 18 weeks (approximately 5 half-lives for vedolizumab) ±7 days after the last dose of

study drug.

[e] All subjects will be followed for overall survival up to EOS, 12 months after allo-HSCT.

[f] Subjects (or their parents/legally acceptable representative) must complete informed consent/age-appropriate assent before any study-related procedures are conducted. Subjects reaching an age that is not covered by their signed assent must provide consent for their appropriate age group to remain in the study. Subjects who reach the age of consent while participating in the study must provide updated consent with a signed ICF to remain in the study.

[g] Baseline PE (assessed before the first dose of study drug) consists of examination of the following body systems: eyes; ears, nose, throat; cardiovascular; respiratory; GI; dermatologic; extremities; musculoskeletal; nervous; lymph nodes; other; and weight. Targeted PE should assess clinically significant changes from the baseline assessment. Weight is also assessed at EOS.

[h] Measured vital signs to include blood pressure, heart rate, respiration rate, and body temperature. Vital signs will be obtained before and within 60 minutes of completion of IV infusion of study drug.

[i] Triplicate 12-lead ECGs will be performed at screening.

[j] Performance status is assessed based on subject's age at randomization using ECOG for subjects aged ≥18 years, Karnofsky for adolescent subjects aged ≥16 years, or Lansky for adolescent subjects aged 12 to <16 years. If a subject's age category changes during the study, the age-appropriate performance status should be used for subsequent assessments.

[k] GvHD assessment to evaluate the extent and severity of each organ involvement after allo-HSCT; refer to Appendix F.

[l] During scheduled clinic visits, trained site personnel will complete the age-appropriate PML checklist for each subject to assess for signs and symptoms of PML at screening and before the administration of each dose of study drug. Refer to Section 9.3.11 for further details. The PML checklists and the RAMP and other related information are age-appropriate and contained in the study manual.

[m] HRQOL instruments include FACT-BMT (administered to subjects aged 18 years and greater at randomization) and EQ-5D (administered to subjects aged ≥16 years at randomization).

[n] Immunodeficiency and hepatitis virus testing and TB testing are required to be performed only at the screening visit, unless satisfactory documentation of negative results of these tests within 30 days of randomization are available. If hepatitis B core antibody (HBcAb) positive (HBcAb+) and negative for hepatitis B surface antigen (HBsAG-), a viral DNA test must be performed and results undetectable.

[o] A serum choriogonadotropin beta pregnancy test will be performed during screening for female subjects aged 12 years and greater who are not postmenopausal (Section 9.3.19) or surgically sterilized. A urine choriogonadotropin beta pregnancy test will be performed for female subjects aged 12 years and greater who are not postmenopausal (Section 9.3.19) or surgically sterilized on each day before study drug dosing, and in the UK, on Day +180; and in Norway, on Day +180, Day +280 (or 18 weeks after the last dose of study drug), and at ET; and in Argentina, monthly from Day +153 up to 18 weeks after the last dose of study drug; FSH screening will be performed for postmenopausal subjects. The results must be negative before each dose of study drug is administered or as otherwise required by local regulations. 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.

[p] Blood samples collected on dosing days should be taken predose and according to process outlined in the laboratory manual.

[q] CCI

CCI

[s] HSC infusion should occur on Day 0 no sooner than 12 hours after the completion of the IV infusion of study drug on Day −1.

[t] Study drug will be administered via an approximately 30-minute IV infusion on Days −1, +13, +41, +69, +97, +125, and +153.

Appendix B Recommended Prophylaxis Treatment: A Combination of CNI (TAC or CYS) + MTX and ATG

The background aGvHD prophylaxis regimen described herein is recommended. Dose and regimen modification are allowed based on toxicity per investigator discretion, per institutional practice, and/or per local prescribing information.

CNI:

1. ***TAC***
   a. TAC treatment should start during conditioning, before infusion of the graft.
   b. The goal TAC treatment should be to achieve a trough concentration of 5 to 20 ng/mL.
   c. Recommended to keep at therapeutic levels through Day +100 or per institutional standard.
   d. Taper off after Day +100 if no signs of GvHD are observed.
   e. The goal should be to discontinue TAC treatment by Day +180 after allo-HSCT.
   f. Doses may be modified or held based on toxicity and institutional practice.
2. ***CYS***
   a. CYS should start during conditioning, before infusion of the graft.
   b. The goal CYS treatment should be to achieve 150 to 450 ng/mL
   c. Recommended to keep at therapeutic levels through Day +100 or per institutional standard.
   d. Taper off after Day +100 if no signs of GvHD are observed
   e. The goal should be to discontinue CYS treatment by Day +180 after allo-HSCT.
   f. Doses may be modified or held based on toxicity and institutional practice.

MTX[a]

a. Administer after allo-HSCT at 10 to 15 mg/m^2 IV on Day +1, and 10 mg/m^2 IV on Days +3 and +6 to all subjects, with a recommended fourth dose for subjects aged ≥18 years on Day +11.
b. Doses may be modified or held based on toxicity and institutional practice.
c. Leucovorin rescue may be administered per institutional practice.

ATG

1. ***ATG-F***
   a. Administer up to 10 mg/kg/day (up to a cumulative dose of 30 mg/kg in divided doses) and per institutional practice.

b. NOT to be administered on the same day as study drug (eg, Day -1).

2. Thymoglobulin

a. Administer up to 2.5 mg/kg/day (up to a cumulative dose of 7.5 mg/kg in divided doses) and per institutional practice.

b. NOT to be administered on the same day as study drug (eg, Day -1).

[a] MMF may be substituted for MTX at investigator's discretion.

Appendix C 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 investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH and local regulatory requirements.
7. 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.
8. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
9. Obtain valid informed consent/age-appropriate assent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. 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.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, 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.

The 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 the 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.

The 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 the investigator's own country.

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

Appendix E Performance Status Assessments

ECOG Scale for Performance Status for Adult Subjects (aged ≥18 years)

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.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
Source: Oken MM, 1982 [48].

Karnovsky/Lansky Performance Status for Adolescent Subjects (aged ≥12 to <18 years)

Karnovsky Scale (recipient age ≥16 years)		Lansky Scale (recipient age 12 to <16 years)	
Score	**Description**	**Score**	**Description**
	Able to carry on normal activity; no special care is needed		***Able to carry on normal activity; no special care is needed***
100	Normal, no complaints, no evidence of disease	100	Fully active
90	Able to carry on normal activity	90	Minor restriction in physically strenuous play
80	Normal activity with effort	80	Restricted in strenuous play, tires more easily, otherwise active
	Unable to work, able to live at home, cares for most personal needs, a varying amount of assistance is needed		***Mild to moderate restriction***
70	Cares for self, unable to carry on normal activity or to do active work	70	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	60	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	50	Considerable assistance required for any active play, fully able to engage in quiet play
	Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		***Moderate to severe restriction***
40	Disabled, requires special care and assistance	40	Able to initiate quiet activities
30	Severely disabled, hospitalization indicated, although death not imminent	30	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	20	Limited to very passive activity initiated by others (eg, TV)
10	Moribund, fatal process progressing rapidly	10	Completely disabled, not even passive play
0	Dead		

Source: CIBMTR.org (www.cibmtr.org/manuals/fim/1/en/topic/appendix-L-karnofsky-lansky-performance-status); accessed 12July2019.

Abbreviation: CIBMTR, Center for International Blood & Marrow Transplant Research.

Appendix F Clinical Stages and Grades of GvHD

Table F-1: aGvHD Clinical Stage

Stage	Skin	Liver Bilirubin: SI units (standard units)	Intestinal Tract [a] Diarrhea/day	
			Subjects ≥18 yrs or <18 yrs and ≥50 kg	*Subjects <18 yrs and <50 kg*
1	Maculopapular rash <25% of body surface [b]	34-50 µmol/L (2-3 mg/dL)	>500 mL diarrhea/day	10-19.9 mL/kg/d
2	Maculopapular rash 25%-50% of body surface	51-102 µmol/L (3.1-6 mg/dL)	>1000 mL diarrhea/day	20-30 mL/kg/d
3	Rash >50% of body surface	103-255 µmol/L (6.1-15 mg/dL)	>1500 mL diarrhea/day	>30 mL/kg/d
4	Generalized erythroderma with bullous formation	>255 µmol/L (>15 mg/dL)	Severe abdominal pain, with or without ileus	Severe abdominal pain, with or without ileus

Source: Przepiorka et al., 1995 [49].
Abbreviations: aGvHD, acute graft-versus-host disease; GvHD, graft-versus-host disease; SI, International System of Units.
[a] Staging of intestinal tract should be assessed based on subject's age and weight at the time of assessment.
[b] Use the "Rule of Nines" or burn chart to determine the extent of the rash.

Table F-2: Criteria for IBMTR Severity Index for aGvHD

	Skin		Liver		Intestinal Tract
Index	**Stage (max)**		**Stage (max)**		**Stage (max)**
A	1		0		0
B	2	*or*	1-2	*or*	1-2
C	3	*or*	3	*or*	3
D	4	*or*	4	*or*	4

Source: Adapted from Rowlings et al., 1997 [50].
Abbreviations: aGvHD, acute graft-versus-host disease; IBMTR, International Bone Marrow Transplant Registry Database.

Table F-3: aGvHD 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	-

Source: Przepiorka et al., 1995 [49].
Abbreviations: aGvHD, acute graft-versus-host disease.

Table F-4: Criteria for MAGIC Severity Index for aGvHD

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Intestinal Tract [a] (stool output/day)	
				Subjects ≥18 yrs or <18 yrs and ≥50 kg	*Subjects <18 yrs and <50 kg*
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting or anorexia	<500 mL/day or <3 episodes/day	<10 mL/kg/d or <4 episodes/day
1	Maculopapular rash <25% of body surface (a)	2-3 mg/dL	Persistent nausea, vomiting or anorexia	500-999 mL/day or 3-4 episodes/day	10-19.9 mL/kg/d or 4-6 episodes/day
2	Maculopapular rash 25%-50% of body surface	3.1-6 mg/dL	-	1000-1500 mL/day or 5-7 episodes/day	20-30 mL/kg/d or 7-10 episodes/day
3	Maculopapular rash >50% of body surface	6.1-15 mg/dL	-	>1500 mL/day or >7 episodes/day	>30 mL/kg/d or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% body surface	>15 mg/dL	-	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume)	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume)

Source: Harris et al, 2016 [51].
Abbreviations: aGvHD, acute graft-versus-host disease; BSA, body surface area; GI, gastrointestinal; GVHD, graft-versus-host disease; MAGIC, Mount Sinai Acute GVHD International Consortium.
Overall clinical grade (based upon most severe target organ involvement):

- Grade 0: No stage 1-4 of any organ
- Grade I: Stage 1-2 skin without liver, upper GI or lower GI involvement
- Grade II: Stage 3 rash and/or Stage 1 liver and/or Stage 1 upper GI and/or Stage 1 lower GI
- Grade III: Stage 2-3 liver and/or Stage 2-3 lower GI, with Stage 0-3 skin and/or Stage 0-1 upper GI
- Grade IV: Stage 4 skin, liver or lower GI involvement, with Stage 0-1 upper GI.

[a] Staging of intestinal tract should be assessed based on subject's age and weight at the time of assessment.

Appendix G Amendment 07 Detailed Summary of Changes

The primary sections of the protocol affected by the changes in Amendment 07 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Clarification of the description of the disease to be treated in adolescent subjects.

The primary change occurs in Section 4.1.1 Disease to be Treated:

Added text: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important and potentially curative therapy for many hematologic malignancies, but its use is limited by the major complication of graft-versus-host disease (GvHD) [1,2]. GvHD is a common complication of allo-HSCT and a major cause of morbidity and mortality. **Acute GvHD results from the activation of alloreactive donor lymphocytes by histocompatibility antigens on host antigen-presenting cells (APCs) [3,4]**. The risk of GvHD and its severity depends on several factors including recipient age, cell source, donor characteristics, degree of histocompatibility between the donor and recipient, the conditioning regimen used, and the GvHD prophylaxis strategy used **[1,5-7]**. Despite GvHD prophylaxis, approximately 40% to 70% of **all** allo-HSCT recipients **(inclusive of pediatric and adult subjects)** develop Grade 2 to 4 acute GvHD (aGvHD) **[5,6,8-11]**. **Approximately 45% to 56% of pediatric allo-HSCT (ranging from <1 to 20 years of age) from unrelated donors will develop Grade 2 to 4 aGvHD, and nonrelapse mortality (NRM) appears to be greater in those pediatric patients with intestinal involvement [12-14]**. Classical aGvHD occurs around the time of engraftment (~10-21 days following HSCT infusion) up to Day 100 **[15]** and late aGvHD occurs greater than 100 days from allo-HSCT **[16,17]**.

Rationale for Change: Clarified the presentation of aGvHD that occurs commonly in both adult and adolescent subjects.

Section 6.2.1 Study Design also contains this change.

Change 2: Addition of results from nonclinical studies related to inclusion of adolescent subjects.

The primary change occurs in Section 4.1.2.1 Nonclinical:

Initial wording:	Several published key nonclinical studies support the use of vedolizumab for the prevention of GvHD. Nonclinical pharmacology studies in murine models of aGvHD suggest that the prevention of T cell trafficking to GALT, via interruption of the α4β7/MAdCAM-1 interaction, may prevent GvHD [30-32]. In a mouse model of GvHD, when using donor cells sorted and purified based on the presence or absence of α4β7, the absence of α4β7+ cells greatly delayed and reduced the presence of GvHD [16]. Like these results, α4β7 expression on donor T cells has been shown to be important in the induction of GvHD [17]. By blocking the infiltration of cells into the intestines, vedolizumab may act to reduce the severity and intensity of intestinal GvHD. Extensive nonclinical evaluations of the cardiovascular, acute, local, subchronic, chronic, immunologic, and reproductive toxicity of vedolizumab in pharmacologically responsive species (New Zealand white rabbits and cynomolgus monkeys) have been conducted and support its clinical development. Nonclinical studies also show that vedolizumab does not antagonize 4β1 integrin [13].
Amended or new wording:	Several published key nonclinical studies support the use of vedolizumab for the prevention of GvHD. Nonclinical pharmacology studies in murine models of aGvHD suggest that the prevention of T cell trafficking to GALT, via interruption of the α4β7/MAdCAM-1 interaction, may prevent GvHD ~~[30-32]~~**[33-35]**. In a mouse model of GvHD, when using donor cells sorted and purified based on the presence or absence of α4β7, the absence of α4β7+ cells greatly delayed and reduced the presence of GvHD ~~[16]~~**[19]**. Like these results, α4β7 expression on donor T cells has been shown to be important in the induction of GvHD ~~[17]~~**[20]**. By blocking the infiltration of cells into the intestines, vedolizumab may act to reduce the severity and intensity of intestinal GvHD. Extensive nonclinical evaluations of the cardiovascular, acute, local, subchronic, chronic, immunologic, and reproductive toxicity of vedolizumab in pharmacologically responsive species (New Zealand white rabbits and cynomolgus monkeys) have been conducted ~~and support its clinical development~~. **Vedolizumab bound with similar affinity to rabbit, monkey, and human α4β7 integrin.** **Results from a 13-week toxicity study in juvenile cynomolgus monkeys identified 100 mg/kg (human equivalent dose 1920 mg in a 60-kg human) as the no-observed-adverse-effect level (NOAEL). Inclusion of sexually immature monkeys in the 3- and 6 month toxicity studies support administration of vedolizumab in clinical studies with adolescent subjects (aged 12 years and greater).** Nonclinical studies also show that vedolizumab does not antagonize 4β1 integrin ~~[13]~~**[3]**.

Rationale for Change: Addition of results from nonclinical studies related to inclusion of adolescent subjects.

Change 3: Updated human experience as reported in the 9th development safety update report.

The primary change occurs in Section 4.1.2.2 Human Experience:

Initial wording:	As of 19 Nov 2017, approximately 5224 subjects (healthy or patients with UC or CD, aGvHD, pouchitis, or melanoma) have received at least 1 dose of vedolizumab across all studies in the clinical development program. As reported in the development safety update report (dated 19 May 2017), cumulative patient exposure to vedolizumab, in more than 5100 patients and including approximately 3 years of *marketing* experience, was estimated at 114,071 patient-years. Vedolizumab has shown an acceptable and consistent safety profile in clinical studies and in postmarketing experience. Adverse reactions that have been reported following vedolizumab administration include: nasopharyngitis, bronchitis, upper respiratory tract infection, influenza, sinusitis, headache, oropharyngeal pain, cough, nausea, rash, pruritus, arthralgia, back pain, pain in extremities, and pyrexia. Risks associated with vedolizumab treatment have been identified and categorized. Important identified risks are infusion-related reactions (IRRs) and hypersensitivity reactions, and upper respiratory infections, including bronchitis, influenza, nasopharyngitis, and sinusitis. Important potential risks are GI infections and systemic infections against which the gut constitutes a defensive barrier; serious infections, including opportunistic infections such as progressive multifocal leukoencephalopathy (PML); malignancy; and liver injury. Most serious adverse events (SAEs) were related to exacerbations or complications of the underlying UC or CD. Similar safety profiles for vedolizumab have been observed in subjects who received vedolizumab IV Q4W or Q8W and in subjects following long-term Q4W treatment for up to 8 years. In the phase 1b Study Vedolizumab-1015, conducted in 24 subjects who underwent allo-HSCT, vedolizumab (at 75 or 300 mg on Days -1, +13, and +42) was added to standard GvHD prophylaxis (TAC and MTX) therapy. All subjects engrafted and no new safety signals were reported. Overall, vedolizumab has been well tolerated. Further detail on the safety profile of vedolizumab can be found in the current edition of the investigator's brochure (IB).

Amended or new wording:

As of 19 ~~Nov~~ **May** 201~~7~~**9**, approximately ~~5224~~ **6376** subjects (healthy or patients with UC or CD~~, aGvHD~~, pouchitis, ~~or~~ melanoma**, or undergoing allo-HSCT**) have received at least 1 dose of vedolizumab across all studies in the clinical development program. As reported in the **9th** development safety update report (~~dated~~**DSUR, for the period 20 May 2018 to** 19 May ~~2017~~**2019**), **global** cumulative **postmarketing** patient exposure to vedolizumab~~, in more than 5100 patients and including~~ **IV is estimated to be** approximately ~~3 years of *marketing* experience, was estimated at 114,071~~**336,400** patient-years.

Vedolizumab has shown an acceptable and consistent safety profile in clinical studies and in postmarketing experience. Adverse reactions that have been reported following vedolizumab administration include: nasopharyngitis, bronchitis, upper respiratory tract infection, influenza, sinusitis, headache, oropharyngeal pain, cough, nausea, rash, pruritus, arthralgia, back pain, pain in extremities, ~~and~~ pyrexia**, fatigue, and injection site reactions**. Risks associated with vedolizumab treatment have been identified and categorized. Important identified risks are **hypersensitivity reactions, including** infusion-related reactions (IRRs) and ~~hypersensitivity reactions, and~~ upper respiratory infections, including ~~bronchitis, influenza,~~ nasopharyngitis, ~~and~~ sinusitis**, bronchitis, and influenza. Most IRRs are mild/moderate in intensity and resolve with minimal or no intervention**. Important potential risks are ~~GI~~**infections, including gastrointestinal** infections and systemic infections against which the gut constitutes a defensive barrier; serious infections, including opportunistic infections such as progressive multifocal leukoencephalopathy (PML); malignancy; and liver injury. **Reported serious infections include tuberculosis, sepsis, *Salmonella* sepsis, *Listeria* meningitis, and cytomegaloviral colitis.**

Most serious adverse events (SAEs) were related to exacerbations or complications of the underlying UC or CD. Similar safety profiles for vedolizumab have been observed in subjects who received vedolizumab IV Q4W or Q8W and in subjects following long-term Q4W treatment for up to 8 years**, and in subjects administered vedolizumab subcutaneously (SC). With the exception of injection site reactions, the safety profile for vedolizumab SC is consistent with that for vedolizumab IV**.

In the phase 1b Study Vedolizumab-1015, conducted in 24 subjects who underwent allo-HSCT, vedolizumab (at 75 or 300 mg on Days -1, +13, and +42) was added to standard GvHD prophylaxis (TAC and MTX) therapy. All subjects engrafted and no new safety signals were reported. **In clinical studies, no safety concerns were identified in subjects with aGvHD or undergoing allo-HSCT, and the events reported were consistent with known risks in these patient populations.**

In addition, no new safety information that alters the benefit:risk balance of vedolizumab was identified in the IBD clinical development program, including ongoing studies in pediatric subjects with UC or CD (DSUR, for the period 20 May 2018 to 19 May 2019).

Overall, vedolizumab has been well tolerated **in clinical studies**. Further detail on the safety profile of vedolizumab can be found in the current edition of the ~~investigator's brochure (~~IB~~)~~.

Rationale for Change: Updated human experience as reported in the 9th DSUR.

Section 4.1.2 Vedolizumab IV also contains this change.

Change 4: Update to the study rationale to support the inclusion of adolescent subjects.

The primary change occurs in Section 4.2 Rationale for the Proposed Study:

Added text: The migration of naive donor T cells to the GALT where they are activated and migration of activated donor T cells to the target tissues, especially the intestinal mucosa, are essential steps in aGvHD **in both children and adults [52]**. **Intestinal aGvHD in children and adults is often involved in Grade 3 to 4 aGvHD and is a major cause of morbidity and mortality after allo-HSCT.** Systemic immunosuppression for aGvHD prophylaxis increases the risk for infections and can affect the graft-versus-tumor effect. Therefore, using standard nonspecific systemic immunosuppressive therapies involves a fine balance of prevention of life-threatening aGvHD against life-threatening infection and recurrence of underlying malignant disease. Therapy that targets the trafficking of cells to the GI tract and reduces GI inflammation without adding to systemic immunosuppression could have profound effects on the morbidity and mortality of intestinal GvHD.

Results from Vedolizumab-1015**,** ~~is~~ a phase 1b study ~~(~~**that enrolled** 24 subjects ~~enrolled) that~~ **aged ≥18 years,** demonstrated the safety and tolerability of adding vedolizumab on Day -1 (before allo-HSCT) and then on Days +13 and +42 after allo-HSCT to a background aGvHD prophylaxis regimen (TAC+MTX) in subjects undergoing allo-HSCT.

Rationale for Change: Update to the study rationale to support inclusion of adolescent subjects.

Change 5: Update to the benefit:risk profile to support the inclusion of adolescent subjects.

The primary change occurs in Section 4.3 Benefit:Risk Profile:

Added text: The proposed phase 3 study is designed to evaluate the efficacy and safety of vedolizumab compared to placebo when added to background aGvHD prophylaxis regimen as prophylaxis for intestinal aGvHD for subjects undergoing allo-HSCT. The mechanism of action of vedolizumab, results from nonclinical studies demonstrating the role of T cell trafficking in GvHD, and results of the phase 1b Study Vedolizumab-1015, all support further investigation of vedolizumab in this indication. Vedolizumab specifically targets the α4β7 integrin expressed on the surface of T lymphocytes, thus preventing T cells from binding to MAdCAM-1 expressed on the endothelium, subsequently preventing T cells from homing to the intestinal tract. Nonclinical pharmacology studies in murine model demonstrate that inhibition of the α4β7/MAdCAM-1 pathway via neutralizing anti-MAdCAM-1 antibodies attenuated the development of the graft versus host reaction ~~[30]~~**[33]** and the absence of α4β7+ cells on donor cells greatly delayed and reduced the presence of GvHD ~~[16]~~**[19]**. Furthermore, in Study Vedolizumab-1015, a low incidence of intestinal aGvHD was observed in adults undergoing allo-HSCT for a hematologic malignancy or myeloproliferative disorder who received vedolizumab 300 mg IV in combination with standard GvHD prophylaxis. **There remains an unmet medical need in patients undergoing allo-HSCT who, despite routine prophylaxis, remain at risk of developing intestinal aGvHD and its associated complications.**

The available PK data, nonclinical toxicology data, and clinical data, are supportive of the inclusion of adolescent subjects aged ≥12 years and weighing ≥30 kg in this phase 3 study. In phase 3 studies in adults with UC or CD, body weights ranged from 28.7 to 170 kg. Safety data from these studies showed that there was no difference in the incidence of treatment-emergent adverse events (TEAEs) based on weight or age (18-70 years). Furthermore, a similar safety profile has been observed in adults with UC or CD who received vedolizumab IV Q8W or Q4W. No additive risk of infection was identified among subjects who received a concomitant immunosuppressant. Results of population PK analyses in subjects with IBD indicate that a weight-based dosing regimen is not required and that a tiered flat-dose is appropriate for different weight groups. Age was not a clinically meaningful covariate. PK data from Study Vedolizumab-1015 indicates that the PK of vedolizumab in subjects undergoing an allo-HSCT who received 300 mg is similar to that of subjects with UC or CD. In addition, no new safety information that alters the benefit:risk balance of vedolizumab have been identified in the UC/CD clinical development program, including ongoing studies in pediatric subjects (aged 2-17 years). Therefore, the benefit:risk profile is expected to be similar in adults and adolescent subjects aged ≥12 years and weighing ≥30 kg.

....

The subject population was chosen because it represents a high-risk, vulnerable population for development of intestinal aGvHD, a driver for poor outcomes, mortality, and for whom a significant unmet medical need exists. The risks of this subject population include those that are associated with hematological transplantation. Specifically, allo-HSCT patients are at risk of infections (opportunistic, GI, and CNS infections); liver injury; infusion-related reactions (IRR) and hypersensitivity reactions, and relapse or new primary malignancy. The important identified risks specific for vedolizumab include IRRs and upper respiratory tract infections, including bronchitis, influenza, nasopharyngitis, and sinusitis. The important potential risks for vedolizumab are: malignancies, liver injury; infections (GI infections and systemic infections [serious and nonserious]); and other serious infections, including opportunistic infections such as PML. Several risk mitigation strategies are incorporated in this phase 3 study including exclusion of subjects with ongoing or active infections (Section 7.2), criteria for discontinuation and withdrawal of subjects (Section 7.4), and instructions for managing these risks (Section 8.7). The mitigation strategies are adequate to monitor safety of the subjects participating in the study. In combination with the results from the phase 1b Study Vedolizumab-1015~~,~~ **and supported by the available nonclinical, clinical, and PK data,** the benefit:risk profile ~~supports~~ **is expected to be similar in adults and adolescent subjects aged 12 years and greater and weighing ≥30 kg, supporting** further investigation of vedolizumab in the subject population with significant unmet medical need.

Rationale for Change: Update to the benefit:risk profile to support the inclusion of adolescent subjects.

Change 6: Addition of data supporting the dose regimen in adolescent subjects.

The primary change occurs in Section 6.2.2 Dose Selection:

Added text: The 300 mg dose of vedolizumab was well tolerated in subjects in Study Vedolizumab-1015 without delay of engraftment (median 14 days for the vedolizumab 300 mg cohort) or new safety concerns. Repeated vedolizumab dosing during the 6 months after the allo-HSCT is proposed, during which time subjects are at the highest risk of developing intestinal aGvHD.

The same vedolizumab dose regimen to be administered to adults (aged ≥18 years) planned to undergo allo-HSCT for prophylaxis of intestinal aGvHD is considered appropriate for administration to adolescents aged 12 years and greater and weighing ≥30 kg. In phase 3 studies in adults with IBD, body weights ranged from 28.7 to 170 kg. Safety data from these studies showed no difference in the incidence of TEAEs and a similar safety profile in adults receiving vedolizumab IV Q8W or Q4W (Section 4.3). A population PK model was developed using pooled phase 1, 2, and 3 study data from the vedolizumab IV clinical program in adults with UC or CD to characterize the PK of vedolizumab and to assess the impact of patient demographic characteristics (eg, age and body weight) on PK. This model indicated that weight-based dosing is not required and that age was not a clinically meaningful covariate (Section 4.3). In addition, results from Study Vedolizumab-1015 indicated that the PK of vedolizumab (300 mg) in adults with aGvHD was similar to that in adults with UC or CD.

Rationale for Change: Addition of data to support the dose regimen in adolescent subjects.

Change 7: Update of the inclusion criteria impacted by inclusion of adolescent subjects. These changes are detailed as Change 7a – Change 7c.

Change 7a: Clarification to informed consent/age-appropriate assent and who provides this.

The primary change occurs in Section 7.1 Inclusion Criteria, criterion #1:

Added text: 1. The subject or, when applicable, the subject's legally acceptable representative voluntarily signs and dates a written, informed consent form (ICF) and any required privacy authorization before performance of any study-related procedures not part of standard medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care. **As applicable, a parent/both parents or legally acceptable representative must provide signature of informed consent and there must be documentation of age-appropriate assent by the subject.**

Rationale for Change: Clarification to informed consent/age-appropriate assent and who provides this.

The following sections also contain this change:

- Section 6.1.1.4 Posttreatment Follow-up.
- Section 7.4 Criteria for Discontinuation or Withdrawal of a Subject.
- Section 8.7.1 Hypersensitivity Reactions.
- Section 9.3.1 Informed Consent.
- Section 9.3.11 PML Checklist.
- Section 9.4 Documentation of Screen Failure.
- Section 10.2.1.2 AE Reporting.
- Section 10.2.2 Collection and Reporting of SAEs.
- Section 10.7 RAMP Program.
- Section 12.1 eCRFs.
- Section 14.1 Study-Site Monitoring Visits.
- Section 15.1 IRB and/or IEC Approval
- Section 15.2 Subject Information, Informed Consent, and Subject Authorization.
- Appendix A Schedule of Events, footnote f.
- Appendix C Responsibilities of the Investigator, item 9.

Change 7b: Clarification regarding eligibility of adolescent subjects.

The primary change occurs in Section 7.1 Inclusion Criteria, criterion #2:

Added text: 2. Male or female subjects ≥18 years of age~~.~~ **and, in selected countries (where local requirements permit and based on feasibility), adolescents aged 12 years and greater and weighing ≥30 kg at time of randomization**.

Rationale for Change: Clarification to specify the eligibility of adolescent subjects.

Section 2.0 STUDY SUMMARY also contains this change:

Change 7c: Clarification regarding use of age-appropriate performance status scales.

The primary change occurs in Section 7.1 Inclusion Criteria, criterion #7:

Added text: 7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 **for subjects aged ≥18 years at randomization or ≥60% using the Karnofsky performance status for adolescent subjects aged ≥16 years at randomization or the Lansky performance status for adolescent subjects aged 12 to <16 years at randomization** (Appendix E).

Rationale for Change: Clarification regarding use of age-appropriate performance status scales.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 9.3.9 Performance Status.
- Section Appendix A Schedule of Events, footnote j.
- Appendix E Performance Status Assessments (new table added).

Change 8: Update to permitted medications to include use of topical anesthetic in adolescent subjects.

The primary change occurs in Section 7.3.2 Permitted Medications and Treatments:

Added text: Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; hence, such premedication is unlikely to be necessary or beneficial. At the discretion of the investigator, however, subjects may be administered premedication before any study drug administration. **Use of topical anesthetic (eg, lidocaine, tetracaine, prilocaine) is recommended for blood draws or IV insertions for the comfort of subjects aged 12 to <18 years. This use will *not* be recorded as a concomitant medication.** Corticosteroids, if given as a premedication, should be limited to the day of administration.

Rationale for Change: Clarification to include use of local anesthetic in adolescent subjects.

Change 9: Clarification to the procedures to be conducted after discontinuation or withdrawal of a subject.

The primary change occurs in Section 7.5 Procedures for Discontinuation or Withdrawal of a Subject:

Added text: The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the ET ~~V~~visit**, the final safety visit, and the 6-month LTFU safety survey**. Discontinued or withdrawn subjects will not be replaced.

Rationale for Change: Clarification to the procedures to be conducted after discontinuation or withdrawal of a subject.

Change 10: Added assessment of height to be collected at the end of study visit.

The primary change occurs in Section 9.3.6 Weight and Height:

Added text: Height should be recorded to the nearest tenth of a centimeter (if possible). Height may be measured using a wall-mounted stadiometer using replicated measurements (average of 3 measurements). Height will be measured only during screening (within 30 days before the first dose of study drug on Day -1) **and at EOS**.

Rationale for Change: Added assessment of height to be collected at the end of study visit.

Appendix A Schedule of Events, footnote g also contains this change.

Change 11: Updated the pregnancy testing and contraception requirements to include female adolescent subjects aged 12 years and greater. These changes are detailed as Change 11a and Change 11b.

Change 11a: Clarification to pregnancy testing to include female adolescent subjects aged 12 years and greater.

The primary change occurs in Section 9.3.15.2 Pregnancy Test:

Added text: For **female subjects aged 12 years and greater who are not postmenopausal (Section 9.3.19) or surgically sterilized**, a serum pregnancy (choriogonadotropin beta) test will be completed at screening before the first dose of study drug**,** and a urine pregnancy test **will be completed** predose on each study drug dosing day (and in the UK, on Day +180; and in Norway, on Day +180, Day +280 [or 18 weeks after the last dose of study drug], and at ET; and in Argentina, monthly from Day +153 up to 18 weeks after the last dose of study drug). The results from these tests must be available and negative before the study drug is administered. 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.

Rationale for Change: Clarification to pregnancy testing to include female adolescent subjects aged 12 years and greater.

Appendix A Schedule of Events, footnote o also contains this change.

Change 11b: Clarification to the requirements for contraception and pregnancy avoidance to include female adolescent subjects aged 12 years and greater.

The primary change occurs in Section 9.3.19 Contraception and Pregnancy Avoidance Procedure:

Initial wording:	From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (Section 8.6.2). In addition, they must be advised not to donate ova during this period. … During the course of the study, urine hCG pregnancy tests will be performed (Section 8.6.2) only for women of childbearing potential and female subjects will receive continued guidance with respect to the avoidance of pregnancy and ova donation as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at screening, women of childbearing potential must have a negative urine hCG pregnancy test before receiving any dose of study drug, preferably on the same day.
Amended or new wording:	From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, female subjects **aged 12 years and greater who are not postmenopausal (Section 9.3.19) or surgically sterilized and** ~~of childbearing potential*~~ who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (Section 8.6.2). In addition, they must be advised not to donate ova during this period. ... During the course of the study, urine hCG pregnancy tests will be performed (Section 8.6.2) ~~only~~ for **female subjects aged 12 years and greater who are not postmenopausal or surgically sterilized** ~~women of childbearing potential~~ and ~~female~~ **these** subjects will receive continued guidance with respect to the avoidance of pregnancy and ova donation as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at screening, **female subjects aged 12 years and greater who are not postmenopausal or surgically sterilized** ~~women of childbearing potential~~ must have a negative urine hCG pregnancy test before receiving any dose of study drug, preferably on the same day.

Rationale for Change: Clarification to the requirements for contraception and pregnancy avoidance to include female adolescent subjects aged 12 years and greater

Section 8.6.2 Reproductive Effects also contains this change.

Change 12: Addition of necessary age-appropriate documentation that must be completed for adolescent subjects. These changes are detailed as Change 12a – Change 12d.

Change 12a: Clarification regarding the informed consent/age-appropriate assent procedure for adolescent subjects.

The primary change occurs in Section 9.3.1 Informed Consent:

Added text: The requirements of the informed consent**/age-appropriate assent** are described in Section 15.2.

Informed consent**/age-appropriate assent** must be obtained before the subject enters into the study, and before any protocol-directed procedures are performed.

Subjects reaching an age that is not covered by their signed assent must provide consent for their appropriate age group to remain in the study. Subjects who reach the age of consent must provide consent with a signed ICF to remain in the study.

Rationale for Change: Clarification regarding the informed consent/age-appropriate assent procedure for adolescent subjects.

Appendix A Schedule of Events footnote f also contains this change.

Change 12b: Clarification regarding completion of PML checklists.

The primary change occurs in Section 9.3.11 PML Checklist:

Initial wording:	Clinic staff will administer the subjective PML checklist during screening to exclude subjects with positive responses from enrolling into the study. The subjective PML checklist will be administered (before dosing, if applicable) at the time points specified in the SOE (Appendix A) to probe for symptoms suggestive of PML. The checklist must be administered by appropriate clinic staff as it is not designed as a subject questionnaire. A subject who reports a new and persistent change(s) per the subjective checklist must have the corresponding objective test(s) and may be referred to a neurologist for a full evaluation, as described in the RAMP algorithm. The PML checklist and the RAMP algorithm and tools are included in the Study Manual. See Section 10.7 for additional details regarding the RAMP program.
Amended or new wording:	Clinic staff will administer the **age-appropriate** subjective PML checklist during screening to exclude subjects 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 SOE (Appendix A) to probe for symptoms suggestive of PML. The checklist must be administered by appropriate clinic staff as it is not designed ~~as a subject questionnaire. A subject who reports~~ **to be completed by a subject, parent, or legally acceptable representative. If** a new and persistent change(s) **is reported** per the subjective checklist**,** ~~must have~~ the corresponding objective test(s) ~~and~~ **must be completed, and the subject** may be referred to a neurologist for a full evaluation~~,~~ as described in the RAMP algorithm. The PML checklist and the RAMP algorithm and tools are included in the Study Manual. See Section 10.7 for additional details regarding the RAMP program.

Rationale for Change: Clarification regarding completion of PML checklists.

The following sections also contain this change:

- Section 8.7.7.2 PML.
- Appendix A Schedule of Events, footnote l.

Change 12c: Clarification of age-appropriate use of the FACT-BMT.

The primary change occurs in Section 9.3.12.1 FACT-BMT:

Initial wording:	The FACT-BMT instrument is a valid and reliable measure of QOL in bone marrow transplant subjects and combines the functional assessment of cancer therapy general tool with the bone marrow transplant subscale [40]. FACT-BMT is a 47-item tool that assesses responses on a Likert scale. This measure assesses across 5 domains: physical well-being, social/family well being, emotional well-being, functional well-being, and additional concerns.
Amended or new wording:	The FACT-BMT instrument **will be used for subjects aged ≥18 years at the time of randomization and** is a valid and reliable measure of **HR**QOL in bone marrow transplant ~~subjects and~~ **that** combines the functional assessment of a cancer therapy general tool with the bone marrow transplant subscale ~~[40]~~**[44]**. FACT-BMT is a 47-item tool that assesses responses on a Likert scale. This measure assesses across 5 domains: physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns.

Rationale for Change: Added the age-appropriate range for use of the FACT-BMT.

Appendix A Schedule of Events, footnote m also contains this change.

Change 12d: Clarification regarding completion of the EQ-5D in adolescent subjects.

The primary change occurs in Section 9.3.12.2 EQ-5D:

Added text: CCI [redacted]

Rationale for Change CCI [redacted]

Appendix A Schedule of Events, footnote m also contains this change.

Change 13: Addition of blood collection volumes for adolescent and adult subjects.

The primary change occurs in Section 9.3.15 Clinical Laboratory Evaluations:

Added text: Clinical laboratory evaluations as specified in the SOE (Appendix A) will be performed by a central laboratory. Local laboratories may be used to conduct assessments needed more rapidly and for urgent medical management throughout the study per investigator's discretion. **In adolescent subjects aged 12 years and greater and weighing ≥30 kg, the maximum volume of blood collected at any single visit** CCI [redacted] **is approximately 14 mL, and the approximate total volume of blood for the study is 144 mL. The maximum volume of blood collected from adult subjects is 29 mL and 300 mL, respectively.** Clinical laboratory evaluations to be conducted during this study are summarized in Table 9.a.

Rationale for Change: Added specifications regarding maximum blood collections from all subjects as required by European regulations regarding adolescent subjects.

Change 14: Update to the version of Common Terminology Criteria for Adverse Events to be used for the grading of adverse events.

The primary change occurs in Section 10.1.6 Severity of AEs:

Initial wording:	All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Grade descriptions are:
Amended or new wording:	All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version ~~4.03~~**5.0**. Grade descriptions are:

Rationale for Change: Update to the version of CTCAE to be used for the grading of adverse events.

Change 15: Update to stratification to include age group and data assessments in adolescent subjects. These changes are detailed as Change 15a and Change 15b.

Change 15a: Update to include stratification by age group.

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

Added text: Eligibility will be determined during the screening period, which may last for up to 30 days before Day -1 (designation of the day of the first IV infusion of study drug). Subjects who meet all eligibility criteria and provide written informed consent will be randomized into this study within 2 days of the first dose of study drug on Day -1. Approximately 558 subjects will be randomized in a 1:1 fashion to 2 treatment arms (vedolizumab IV or placebo IV). Randomization will be stratified by **age (≥18 years or adolescents aged 12 to <18 years),** HLA match or mismatch (8/8 or 7/8), conditioning regimen (myeloablative or reduced intensity conditioning), and treatment with or without ATG (ATG-F or thymoglobulin).

Rationale for Change: Update to include stratification by age group.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Figure 6.a Study Design for Study Vedolizumab-3035.

Change 15b: Update that data assessments may be summarized descriptively by age group.

The primary change occurs in Section 13.1 Statistical and Analytical Plans:

Added text: A targeted data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods. **Data may also be summarized descriptively by age group (aged ≥18 years and ≥12 years to <18 years)**.

Rationale for Change: Update that data assessments may be summarized descriptively by age group.

Change 16: Updates to Appendix A, Schedule of Events footnotes, to align with updates in text..

The primary change occurs in Appendix A Schedule of Events:

Added text: [redacted]. **HRQOL instruments are completed at ET and not at an unscheduled visit.**

…

[k] GvHD assessment to evaluate the extent and severity of each organ involvement after allo-HSCT**; refer to Appendix F**.

…

[n] Immunodeficiency and hepatitis virus testing and TB testing are required to be performed only at the screening visit, unless satisfactory documentation of negative results of these tests within 30 days of randomization are available. **If hepatitis B core antibody (HBcAb) positive ($HBcAb^+$) and negative for hepatitis B surface antigen ($HBsAG^-$), a viral DNA test must be performed and results undetectable.**

…

[p] Blood samples collected on dosing days should be taken predose **and according to process outlined in the laboratory manual.**

Rationale for Change: Updates to footnotes to align with associated protocol text.

Change 17: Update to Appendix B regarding methotrexate treatment to support the inclusion of adolescent subjects.

The primary change occurs in Appendix B Recommended Prophylaxis Treatment: A Combination of CNI (TAC or CYS) + MTX and ATG:

Initial wording:	***MTX***[a] a. Administer at 10 to 15 mg/m^2 IV on Day +1, and 10 mg/m^2 IV on Days +3 and +6, and recommended fourth dose on Day +11 after allo-HSCT.
Amended or new wording:	***MTX***[a] a. Administer **after allo-HSCT** at 10 to 15 mg/m^2 IV on Day +1, and 10 mg/m^2 IV on Days +3 and +6~~, and~~ **to all subjects, with a** recommended fourth dose **for subjects aged ≥18 years** on Day +11 ~~after allo-HSCT~~.

Rationale for Change: Updates to Appendix B regarding MTX treatment to support inclusion of adolescent subjects.

Change 18: Update to Appendix F to include age-appropriate assessments of aGvHD clinical stage and Mount Sinai Acute GVHD International Consortium severity index for aGvHD.

The primary change occurs in Appendix F Clinical Stages and Grades of GvHD:

Added text: Addition of age-appropriate columns for assessments in adolescent subjects to: Table F-1 (aGvHD Clinical Stage) and Table F-4 (Criteria for MAGIC Severity Index for aGvHD).

Addition of footnotes that the intestinal tract should be assessed based on the subject's age and weight at the time of assessment.

Rationale for Change: To include the age-appropriate assessments of aGvHD clinical stage and MAGIC severity index for aGvHD in adolescent subjects.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	19-Sep-2019 17:43 UTC
	Clinical Pharmacology Approval	19-Sep-2019 17:59 UTC
	Biostatistics Approval	19-Sep-2019 18:11 UTC
	Clinical Approval	19-Sep-2019 23:04 UTC