26 January 2023
EMA/3254/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Entyvio

vedolizumab

Procedure no: EMEA/H/C/002782/P46/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On November2023, the MAH submitted a paediatric study for Entyvio, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The study was interrupted (no for safety reasons) and the development of the drug for this indication interrupted for adults and paediatric patients.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study n° Vedolizumab-3035 "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" is part of a clinical development program.

The MAH submits a clinical study report (early termination) in accordance to Article 46 of the Paediatric Regulation (EC) No1901/2006, as amended, for study vedolizumab-3035.

Study Vedolizumab-3035 was included in Paediatric Investigation Plan (PIP) EMEA-000645-PIP03-18. The age entry criteria for this study included subjects aged ≥12 years and weighing ≥30 kg at the time of randomization. While the PIP stipulated this study (planned for adults) to have enrollment open to adolescents, it did not specify a minimum number for this age group.

Out of the 343 enrolled subjects, only 1 was aged <18 years at entry (placebo subject), and no subgroup analyses were conducted for subjects aged ≥12 to <18 years.

Enrollment was terminated early, and the study completed on 09 May 2022, primarily due to low subject recruitment and enrollment during the COVID-19 pandemic (since February 2020). The decision was influenced by multiple factors, none of which were related to safety concerns regarding the use of vedolizumab in this patient population.

The MAH decided to discontinue development of vedolizumab for use in this condition, in both adults and paediatrics.

Following early termination of enrollment into Study Vedolizumab-3035, a notification of PIP discontinuation was submitted to the Agency, on 01 June 2022, to withdraw PIP EMEA-000645-PIP03-18. The measures that had been agreed as part of this PIP are listed in Table 1.a

Table 1.a Vedolizumab PIP EMEA-000645-PIP03-18 Measures in Prevention of Intestinal aGvHD (Children Aged 2 to <18 Years)

Area	Description	Status
Quality	Development of an age-appropriated presentation of powder for concentrate for solution for infusion (dilution procedure and respective instructions for preparation).	Deferred; not started
Clinical	Double-blind, randomised, placebo-controlled study to evaluate efficacy and safety of vedolizumab as add-on to best standard of care as prophylaxis for intestinal aGvHD in adolescents from 12 to less than 18 years of age (and adults) planned to undergo allo-HSCT.	Completed (early termination of enrollment)
Clinical	Open-label, uncontrolled study to evaluate pharmacokinetics, immunogenicity, efficacy, safety and tolerability of vedolizumab as add-on to best standard of care as prophylaxis for intestinal aGvHD in children from 28 days to less than 18 years of age planned to undergo allo-HSCT.	Deferred; not started
Extrapolation, modeling, and simulation studies	Modelling and simulation study to evaluate the use of vedolizumab as prophylaxis for intestinal aGvHD in children from 28 days to less than 18 years of age undergoing allo-HSCT.	Deferred; not started
Extrapolation, modeling, and simulation studies	Extrapolation study to evaluate the use of vedolizumab as prophylaxis for intestinal aGvHD in children from 28 days to less than 18 years of age undergoing allo-HSCT.	Deferred; not started

aGvHD: acute graft-versus-host disease; allo-HSCT: allogeneic haematopoietic stem cell transplantation.

There were no new safety signals or concerns emerging from this study and there are no regulatory consequences identified by the Marketing Authorisation Holder with no changes to the currently approved Entyvio Summary of Product Characteristics proposed and no variation is planned to update the Product information with regards to the use of vedolizumab in the paediatric population as a result of this study.

2.2. Information on the pharmaceutical formulation used in the study

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. It has been granted marketing approval in several regions, including the United States and European Union. Vedolizumab IV is approved for the treatment of adults with moderately to severely active ulcerative colitis (UC) and Crohn's disease (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.

Vedolizumab IV has also been developed for the treatment of adult patients with pouchitis who have undergone proctocolectomy and ileal pouch-anal anastomosis (IPAA) for UC and have had an inadequate response, lost response, or are intolerant to antibiotic therapy, with marketing approval granted in several countries. As of 19 May 2022, approximately 7094 subjects (healthy or patients with UC or CD, pouchitis, melanoma, or undergoing allo-HSCT or with aGvHD involving the intestinal tract) have received at least 1 dose of vedolizumab across all studies in the clinical development program, and global cumulative postmarketing patient exposure to vedolizumab IV is estimated to be approximately 1,009,238 patient years. Overall, vedolizumab has been well tolerated in clinical studies.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study n° Vedolizumab-3035 "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".

Clinical study 3035

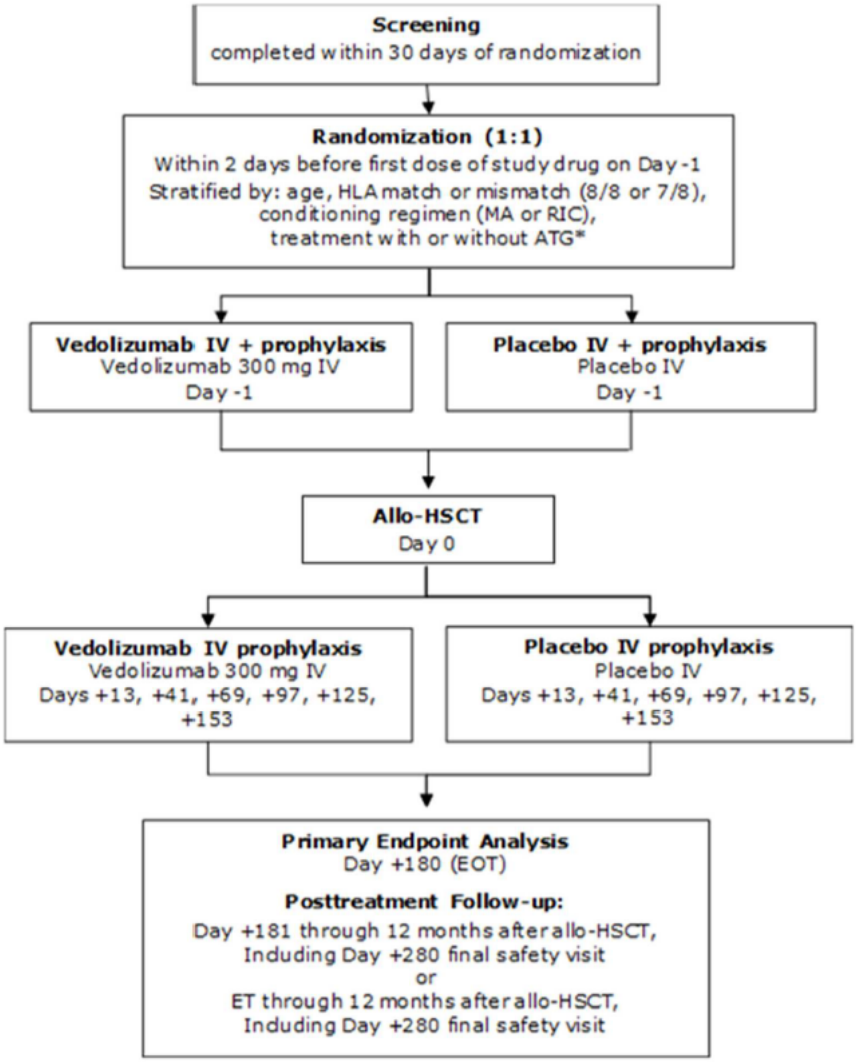
Description

This was 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 for intestinal aGvHD in subjects undergoing allo-HSCT.

The subject population consisted of subjects with hematologic malignancies or myeloproliferative disorders for whom allo-HSCT from an unrelated donor was planned, using either peripheral blood or bone marrow as the stem cell source.

The study consisted 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 that were completed by 12 months after allo-HSCT.

Figure 9.a Study Design for Study Vedolizumab-3035



Source: Appendix 16.1.1, Protocol Amendment 7.

allo-HSCT: allogeneic hematopoietic stem cell transplantation; ATG: antithymocyte globulin; EOT: end of treatment; ET: early termination; HLA: human leukocyte antigen; IV: intravenous; MA: myeloablative; RIC: reduced intensity conditioning.

* ATG was either ATG-Fresenius or thymoglobulin.

Dose Subjects received 7 doses of IV study drug, beginning on Day -1 before allo-HSCT and then on Days +13, +41, +69, +97, +125, and +153 after allo-HSCT. The end-of-treatment visit was conducted on Day +180 after allo-HSCT. Subjects who discontinued study drug treatment completed an early termination (ET) visit upon discontinuation and a final visit 12 months after allo-HSCT.

Subjects then participated in posttreatment follow-up that began after the Day +180 visit or after ET, included a Day +280 final safety visit (or 18 weeks after the last dose of study drug), and concluded 12 months after allo-HSCT (final visit/end of study [EOS]).

In addition, upon study completion or ET, all subjects or their parents/legally acceptable representative were administered the long-term follow-up (LTFU) safety questionnaire by telephone 6 months after their last dose of study drug. For all subjects receiving study drug, the investigator completed the EOS electronic case report form (eCRF) 12 months after allo-HSCT.

Subjects were 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.

Methods

Study participants

The population was chosen because it represents a high-risk, vulnerable population for development of intestinal aGvHD, which is widely recognized as a driver for poor outcomes, mortality, and for whom 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 (Jagasia et al. 2012) and 33% for matched related donor recipients, 51% in 8/8 HLA-MUD recipients, and 53% in 7/8 HLA-MUD recipients, with OS (45%) lowest in the 7/8 HLA-MUD recipients (Saber et al. 2012). Among pediatric subjects with allo-HSCT from unrelated donors, up to 56% develop Grade 2 to 4 aGvHD and 29% develop Grade 3 to 4 aGvHD (Davies et al. 2009; Rocha et al. 2001). The intestinal tract is often involved in Grade 3 to 4 aGvHD, and when the intestinal tract is involved in pediatric patients, NRM increases (Goussetis et al. 2011).

Main inclusion Criteria

1. Male or female subjects ≥18 years of age and adolescents aged ≥12 years and weighing ≥30 kg at the time of randomization.

2. DNA-based HLA matching 8/8 or 7/8 unrelated hematopoietic stem cell transplantation (HSCT) from either peripheral blood or bone marrow stem cells for a hematologic malignancy or myeloproliferative disorder.

3. Primary disease as follows: acute leukemia or chronic myelogenous leukemia, myelodysplasia,

Chronic lymphocytic leukemia/small lymphocytic lymphoma and other non-Hodgkin or Hodgkin lymphoma, myelofibrosis and other myeloproliferative disorders

4. Elegibility for myeloablative conditioning or reduced intensity conditioning.

5. Allo-HSCT eligible (met institutional criteria) subjects planned medical care included aGvHD prophylaxis with a combination of CNI (CYS or TAC) and MTX or CNI and MMF all other therapies, approved or investigational, for GvHD prophylaxis were excluded with the exception of ATG.

6. 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.

Main exclusion Criteria

Subjects meeting any of the following exclusion criteria were not 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 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. Prior or current therapy with α4 and/or β7 integrin inhibitors (including, but not limited to natalizumab, etrolizumab, AMG-181), MAdCAM-1-antibodies, or anti-CD11a mAb (eg, efalizumab) within 60 days or 5 half-lives, whichever was longer from randomization or5.prior known exposure of the transplant recipient to vedolizumab.

6. Any unstable or uncontrolled neurological/cerebral, psychiatric and meningeal diseases, or cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, coagulation, immunological, endocrine/metabolic or other medical disorder not related to the subject's primary disease that, in the opinion of the investigator, would have confounded the study results or compromised subject safety.

7. Clinically active systemic infection during screening.

8. Clinically active cytomegalovirus (CMV), active Clostridium difficile infection colitis or other intestinal pathogens during screening.

Study Sites

Subjects were enrolled into this study drug at 95 sites in 25 countries worldwide (19 sites in North America, 45 in Europe/Israel, 24 in Asia/Australia, and 7 in South America). For additional site-and region-specific randomization information, see Table 15.1.4.

Data Monitoring and Adjudication Committees

A data monitoring committee (DMC) was utilized in the study for safeguarding the interest of study participants, and assessed the safety and efficacy of the interventions during the study while maintaining the integrity of the study. The DMC conducted periodic scheduled reviews of safety, including a protocol-defined interim analysis (IA).

An Independent Adjudication Committee (IAC) was identified as part of the Risk Minimization Action Plan for PML (RAMP) program to review new neurological signs and symptoms potentially consistent with progressive multifocal leukoencephalopathy (PML). The IAC provided input regarding subject evaluation and management per the IAC PML project instructions.

Objectives

Primary Objective

The primary objective was 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 received allo-HSCT as treatment for a hematologic malignancy or myeloproliferative disorder.

Safety Objective

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

Secondary Objectives

The secondary objectives were to evaluate efficacy of vedolizumab using a range of clinical responses a day +180 (details are reported in the endpoints section).

A pletora of exploratory objectives are aimed at providing additional information on efficacy. (details on endpoints section)

Endpoints

Primary Endpoint intestinal aGvHD-free survival by Day +180 after allo-HSCT.

Intestinal aGvHD was defined as Stage 1-4 intestinal involvement per aGvHD clinical stage criteria.

The secondary endpoints were:

- 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.

The exploratory endpoints were:

- Chronic GvHD by Day +180 and 12 months after allo-HSCT.
- GvHD- and relapse-free (of the underlying malignancy) survival by Day +180 and 12 months after allo-HSCT.
- Intestinal aGvHD-free survival by 12 months after allo-HSCT.
- Stage 2-4 intestinal aGvHD-free survival by Day +180 and 12 months after allo-HSCT.
- Grade B-D aGvHD-free (any organ involvement) survival by 12 months after allo-HSCT.
- Grade C-D aGvHD-free (any organ involvement) survival by 12 months after allo-HSCT.
- OS by 12 months after allo-HSCT.
- NRM by 12 months after allo-HSCT.
- Relapse-free (of underlying malignancy) survival by Day +180 and 12 months after allo-HSCT.
- Frequency of aGvHD by maximum severity and organ involvement by Day +180 and 12 months after allo-HSCT.
- aGvHD outcomes by MAGIC criteria.
- Relapse by Day +180 and 12 months after allo-HSCT.
- Incidence and duration of systemic immunosuppression for GvHD treatment.
- FACT-BMT.
- EQ-5D scores.
- Health care utilization (eg, length of stay and re-hospitalization). Note that analyses were not performed for this exploratory endpoint; see Section 9.8.4 for details.
- Vedolizumab serum trough concentration on Day +180.
- The percentage of subjects with positive AVA and neutralizing AVA.

Sample size

Assuming the event rate for the intestinal aGvHD-free survival by Day +180 after allo-HSCT was 34.1% for the placebo group and 21.8% for the vedolizumab IV group, and the rate of loss-to-follow-up was 10% for both groups, a sample size of 279 subjects per group (558 subjects total) was expected to generate 148 events for the intestinal aGvHD-free survival, and hence provide 90% power at the at alpha of 0.05 for a 2-sided hypothesis based on log-rank test. Assuming the event rate for

the intestinal aGvHD-free and relapse-free survival was 39.5% for the placebo group and 27.1% for the vedolizumab IV group, this sample size was expected to generate 177 events for the intestinal aGvHD-free and relapse-free survival and hence provide approximately 86% power at alpha of 0.05 for a 2-sided hypothesis.

The study closed with a total of 343 subjects enrolled (with 71 primary efficacy events) of the 558 subjects originally planned (with an estimated 148 primary efficacy events anticipated).

IA An IA for futility and sample size re-estimation was conducted after 31% of the targeted primary endpoint events (specifically, 46 intestinal aGvHD/death events by Day +180 after allo-HSCT) were accrued. The analysis was performed by an independent statistical center (ie, an external vendor) in a manner that maintained blinding for the sponsor study team, investigators, and subjects. IA results were reviewed by the DMC, but not the sponsor.

The futility stopping was considered non binding.
At the time of the IA, 256 subjects had been randomized (130 to vedolizumab IV, 126 to placebo). This analysis included the primary endpoint: intestinal aGvHD-free survival by Day +180 after allo-HSCT. There were 17 events (13%) of intestinal aGvHD or death (any cause) in the vedolizumab IV group and 29 events (23%) in the placebo group. The Kaplan Meier estimates by Day +180 were 85.04% in the vedolizumab IV group and 74.76% in the placebo group. The HR (vedolizumab IV vs placebo) was 0.52, and the conditional power was 0.989.
Based on the review of IA data, the DMC recommended to continue the trial without modification.

Treatments

Treatments Administered

Vedolizumab and placebo

Table 9.a Identity of Study Drug

Study Drugs	Product Dose Strength and Form	Study Dosage	Mode of Administration	Drug Product Lot Numbers
Vedolizumab	300 mg/vial reconstituted with sterile water for injection to 60 mg/mL	300 mg on Days -1 and +13, and then Q4W through Day +153	IV	457023 458435 225910 222466
Matching placebo	250 mL of 0.9% sodium chloride	NA	IV	NA (Greece: 18E25G60, 19B08G60) [a]

IV: intravenous; NA: not applicable; Q4W: every 4 weeks.
[a] Takeda provided matching placebo to study sites in Greece; drug product lot numbers are provided. For all other study sites, placebo was supplied by the respective site.
Study drug manufacturer is listed in Appendix 16.1.4.4.

Selection of Vedolizumab Dose in the Study

The vedolizumab IV dose selected, 300 mg, was based on safety, efficacy, and PK data from Study Vedolizumab-1015 and the IBD program. This dosing regimen was estimated to provide serum concentrations above 10 µg/mL for 180 days.

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

The same vedolizumab dose regimen administered to adults (aged ≥18 years) who underwent allo-HSCT for prophylaxis of intestinal aGvHD was considered appropriate for administration to adolescents aged ≥12 years 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 treatment-emergent adverse events (TEAEs) and a similar safety profile in adults receiving vedolizumab IV every 8 weeks or every 4 weeks. 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 is not a clinically meaningful covariate. 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.

Background GvHD prophylaxis Additionally, all subjects received a combination of CNI (CYS or TAC) and MTX or MMF (Choi et al. 2014; Reshef 2012; Ruutu et al. 2012), which is commonly prescribed as prophylaxis of GvHD for subjects undergoing allo-HSCT. ATG (ATG-F or thymoglobulin) may have been used at the discretion of the treating physician; however, the proportion of subjects receiving ATG did not comprise more than approximately 25% of the total number of subjects enrolled into this study.

Prior and Concomitant Therapy

Excluded Medications and Treatments

The following is a list of medications and treatments that were prohibited during the 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. If 1 of the GvHD prophylaxis agents specified in the inclusion criteria had been discontinued due to toxicity and an alternative agent was started, the subject was 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 were instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Randomisation and blinding (masking)

Randomization and stratification: Subjects who met all eligibility criteria and provided written informed consent were randomized in a 1:1 fashion to 2 treatment arms (vedolizumab IV or placebo IV) no more than 2 days before the first dose of study drug on Day -1.

Randomization was stratified by age (≥18 years or adolescents aged 12 to <18 years), human leukocyte antigen (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).

There were inconsistencies in the information regarding one or more stratification factors for 22 subjects collected at the time of randomization (per the IRT) versus information collected after

randomization. The original IRT data (collected at randomization) were used for the main efficacy analyses.

Method of Assigning Subjects to Treatment

The investigator or the investigator's designee utilized the IRT to randomize the subject into the study. The medication ID number of the study drug dispensed was then provided by the IRT by email notification to the unblinded site pharmacist/nurse. To maintain the blind, the IRT ensured that the investigator or designee was unaware of the medication ID assigned to the subject.

Blinding The investigational drug blind was maintained using the IRT.

Statistical Methods

The end of treatment (EOT) analysis (ie, primary analysis) for efficacy and safety data was originally planned at the EOT, when all subjects completed Day +180 or withdrew from the study, or when the planned number of primary endpoint events as determined by the sample size adaptation rule in the IA were accrued. However, the sponsor decided to terminate study enrollment early due to the COVID-19 pandemic that resulted in a shift in standard of care for transplant practice Subsequently, the EOT analysis was not performed as planned and the SAP was amended to reflect this change. The EOS Analysis (ie, final analysis) was performed after the final database lock at the end of study.

All statistical testing was 2-sided, performed at an alpha level of 0.05. All Cis reported were 2-sided 95%, unless stated otherwise. P-values were rounded to 4 decimal places before assessment of statistical significance.

Table 9.e details how dates and/or censoring were reported for intestinal aGvHD events for the primary endpoint.

Table 9.e Date of Event/Censor for Primary Endpoint by Day +180 After Allo-HSCT

Reported Intestinal aGvHD Event?	Death?	Consider as Primary Efficacy Event?	Date of Primary Efficacy Event	Date of censoring
Yes	No	Yes	Date of reported intestinal aGvHD	
Yes	Yes	Yes	Date of first reported event, ie, intestinal aGvHD	
No	Yes	Yes	Date of death	
No	No	No. Censored		Date of last observation, or last contact, EOS visit, Day +180, or interim data cut date, whichever occurred first

Source: Appendix 16.1.9.1, SAP v3.0.

aGvHD: acute graft-versus-host disease; allo-HSCT: allogeneic hematopoietic stem cell transplantation; EOS: end of study.

Event or death that occurred after Day +180 was censored at Day +180.

In the case that liver or skin aGvHD occurred but neither intestinal aGvHD nor death occurred, subjects were censored.

Handling of Dropouts or Missing Data

Missing Efficacy Data

Through the end of the double-blind period, missing dichotomous efficacy data (eg, intestinal aGvHD event as dichotomous endpoint) were to be handled using the nonresponder imputation method, ie,

any subject with missing information for determination of endpoint status was considered as having an undesirable outcome in the analysis.

Missing data for continuous endpoints were imputed using the LOCF method. For subjects without any nonmissing postbaseline measurement, the missing data were to be imputed using the baseline observation carried forward method. Other missing data imputation methods (eg, multiple imputations or repeated measure mixed effects model) may have been explored.

Missing data for time to event endpoints were not to be imputed.

Analysis Sets

Analysis sets included the following:

Randomized set: All subjects who were randomized.

Safety analysis set (SAF): All subjects who received at least 1 dose of study drug. Subjects in this set were analyzed according to the treatment actually received. This population was used for safety analysis.

Full analysis set (FAS): Following the intent-to-treat principle, the FAS included all subjects who were randomized, received at least 1 dose of study drug, and underwent allo-HSCT. The analysis was based on the treatment to which subjects were randomized. This population was used for efficacy analysis.

PK population set: Subjects from the SAF with at least 1 posttreatment PK sample collected.

Efficacy Analysis

Efficacy data were analyzed using the FAS.

Efficacy endpoints and the associated supporting data were planned to be descriptively summarized by age groups. However, since only 1 subject was aged ≤18 years, results were descriptively summarized in the overall population.

Unless stated otherwise, all statistical comparisons were also conducted in the overall population.

All statistical testing was 2-sided and performed at an alpha level of 0.05. To control the overall type I error rate for the comparison between vedolizumab and placebo groups for the primary and key secondary efficacy endpoints in the overall population, a fixed-sequence testing approach was used. Specifically, the statistical testing of the intestinal aGvHD-free and relapse-free survival was only to be performed if the treatment difference for the primary efficacy endpoint was statistically significant (ie, $p < 0.05$). The next secondary efficacy endpoint was only to be tested if the treatment difference for the first secondary efficacy endpoint was significant (ie, $p < 0.05$), and so on for each subsequent secondary efficacy endpoint.

The order of the statistical testing for the primary and key secondary endpoints were as follows:

1. Intestinal aGvHD-free survival by Day +180 after allo-HSCT.

2. Intestinal aGvHD-free and relapse-free survival by Day +180.

3. Grade C-D aGvHD-free (any organ involvement) survival by Day +180.

4. NRM by Day +180.

5. OS by Day +180.

6. Grade B-D aGvHD-free (any organ involvement) survival by Day +180.

Testing of the additional efficacy endpoints were not multiplicity adjusted. Nominal p-values are presented.

Per the SAP, sensitivity analyses were performed for the primary and key secondary efficacy endpoints using corrected stratification information that was collected after randomization and recorded in the EDC.

Additionally, HLA compatibility also captured HLA matching (7/8, 8/8) between the study subject and an HLA-compatible donor. The source of these data was the donor page. HLA compatibility differed slightly from both sets of data for HLA match (collected at randomization and recorded in the IRT vs corrected stratification information collected after randomization and recorded in the EDC).

Primary Efficacy Analyses

The null (H0) and alternative (HA) hypotheses for the primary efficacy endpoint, intestinal aGvHD-free survival by Day +180 after allo-HSCT, were as follows:

H0: Intestinal aGvHD-free Survival by Day +180 Vedolizumab = Intestinal aGvHD-free Survival by Day +180 Placebo

HA: Intestinal aGvHD-free Survival by Day +180 Vedolizumab $\neq$ Intestinal aGvHD-free Survival by Day +180 Placebo

The primary endpoint was analyzed using the log-rank test, with Kaplan-Meier estimates presented. Subjects without documented intestinal aGvHD events or death before reaching Day +180 after allo-HSCT were censored at the date of last assessment/visit/contact or Day +180, whichever occurred first. Randomized subjects who did not receive any of their assigned study drug were censored at Day -1. The statistical significance of treatment effect was tested against a 2-sided alpha level of 0.05.

The primary efficacy endpoint was also analyzed using a Cox proportional hazards model with treatment group, stratified by randomization strata. Point estimate of hazard ratio (HR) and the

corresponding 95% CI are presented herein. The randomization strata are as follows:

- Age ($\geq$18, $\geq$12 and <18). Note: Only 1 subject was aged $\geq$12 and <18 years; therefore, age was not used as a stratification factor.
- HLA match (7/8, 8/8).
- Conditioning regimen (myeloablative, reduced intensity conditioning).
- ATG (with, without).

In addition, summary statistics and Kaplan-Meier estimates by treatment group are provided.

Secondary Efficacy Endpoints

The secondary efficacy endpoints are reported in the endpoints section.

All time-to-event endpoints were analyzed in a similar way as the primary efficacy endpoint, using log-rank test in the FAS. Cox proportional hazards model was fitted with treatment group and stratified by the randomization strata. Point estimate of HR and the corresponding 95% CI are presented.

Additional Efficacy Endpoints are reported in the endpoints section.

All time-to-event endpoints were analyzed in a similar way as the primary efficacy endpoint, using log-rank test in the FAS, with Kaplan-Meier estimates presented. Nominal p-values are provided.

Dichotomous efficacy endpoints were summarized by treatment group using descriptive statistics (count, percentage). The nominal p-value and point estimate of treatment difference based on the

Cochran-Mantel-Haenszel (CMH) method adjusted for randomization stratification factors along with 95% Cis are presented. All subjects with missing data for determination of status of dichotomous efficacy endpoints were considered treatment failures or as having an undesirable event in the analysis.

Duration of systemic immunosuppression for GvHD treatment by 12 months after allo-HSCT, was summarized descriptively (n, mean, SD, median, minimum, maximum), and tested using Wilcoxon rank-sum test between treatment groups.

The following **sensitivity analyses** were performed:

- To accommodate the events of interest that occurred within the protocol-defined +/- 7-day window, the primary and secondary efficacy endpoints were analyzed by Day +187 after allo-HSCT. Subjects who did not have an event by Day +187 after allo-HSCT were censored at last contact or Day +187 after allo-HSCT, whichever occurred first.
- Primary and secondary efficacy endpoints were analyzed using stratified log-rank test using the FAS, stratified by randomization stratification factors.
- Primary and secondary endpoints (with the exception of OS) were explored using competing risk analysis to accommodate the competing nature of multiple causes to the same event.

Due to inconsistency(ies) in stratification information collected in the IRT versus the EDC, sensitivity analysis for inconsistency(ies) among them were performed for the primary and secondary study endpoints using the corrected stratification information from the EDC.

Subgroup Analysis applied to the primary and key secondary efficacy endpoints.

Table 9.f List of Subgroups of Interest

Subgroup of Interest	Subgroup Categories
Gender	Male, female
Race	White, non-white
Geographic region	North America, South America, Western/Northern Europe, Central Europe, Eastern Europe, Asia/Australia
HLA antigen match	7/8, 8/8
Conditioning regimen	Myeloablative, reduced intensity conditioning
ATG	With, without
Primary disease	Acute leukemia, chronic myelogenous leukemia, myelodysplasia, chronic lymphocytic leukemia, small lymphocytic lymphoma with chemosensitive disease, other non-Hodgkin or Hodgkin lymphoma, myelofibrosis and other myeloproliferative disorders
GvHD prophylaxis therapies	CNI +MTX+ATG, CNI +MTX-ATG, CNI + MMF+ATG, and CNI + MMF-ATG
CNI	Tacrolimus vs cyclosporine
Stem cell source	Bone marrow, peripheral blood mononuclear cell

Source: Appendix 16.1.9.1, SAP v3.0.
ATG: antithymocyte globulin; CNI: calcineurin inhibitor; GvHD: graft-versus-host disease; MMF: mycophenolate mofetil; HLA: human leukocyte antigen; MTX: methotrexate; SAP: statistical analysis plan.

Exploratory analyses summarized the treatment effects across subpopulations. The treatment effect in vedolizumab and placebo and associated 95% Cis are provided for each subgroup.

Changes in the Conduct of the Study or Planned Analyses

The COVID-19 pandemic disrupted various aspects of the study conduct, including onsite visits for subjects and auditors; no other changes in conduct occurred during the study. Ultimately, enrolment was terminated early and the study completed on 09 May 2022, primarily due to low subject recruitment and enrollment during the COVID-19 pandemic (since February 2020). The decision was

influenced by multiple factors, none of which were related to safety concerns regarding the use of vedolizumab in this patient population. Reasons for reduced enrollment varied among sites, eg, an increased number of excluded donor sources (haploid transplants), excluded medications (post-transplantation cyclophosphamide), and increased use of ATG, for which a 25% cap had been met. Additionally, there was continued competition for hospital and study resources, minimization of hospital visits by patients to those considered strictly necessary, and voluntary discontinuations from the study due to concerns of participants during the COVID-19 pandemic.

The COVID-19 pandemic affected the following aspects of the planned study conduct:

- For sites that were not able to conduct onsite visits due to the COVID-19 pandemic, telehealth visits were conducted as an acceptable alternative to remotely assess subject safety and overall clinical status per the schedule of study procedures. Telehealth visits were done by delegated site staff speaking directly with the subject by telephone or other medium (eg, a computer-based video communication).
- A total of 8 investigator site audits were planned for the study; however, 3 site audits were not conducted due to an inability to physically visit sites related to COVID-19 restrictions.

Furthermore, European regulations did not allow remote access to subject data. The study completed before the investigator site audits could be rescheduled for when COVID-19 restrictions allowed.

Protocol Changes

A total of 7 amendments to the initial protocol (13 June 2018) were issued. Two of the amendments were global and 5 were local (France, Sweden, UK, Norway, and Germany).

Both global protocol amendments were considered substantial, and all local amendments were non-substantial. Although approved, no subjects were enrolled under the local Protocol Amendment 05 in Germany. Study subjects were enrolled under all other global and local protocols/protocol amendments.

Table 9.g Summary of Protocol and Protocol Amendments by Type and Region

Protocol 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/UK
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

Source: Appendix 16.1.1, Protocol Amendment 7.
UK: United Kingdom.

[…]

Protocol Amendment 6 (Dated 10 June 2019) – Global

The primary purpose of this substantial, global protocol amendment was to consolidate all of the preceding local amendments (France, Sweden, UK, Norway, and Germany) into a single global amendment that included (1) the addition of specified methods and time frame of highly effective contraception, (2) addition of PML or tuberculosis as examples of withdrawal criteria, (3) unblinding without sponsor permission in case of medical emergency, and (4) notification of the competent regulatory authorities upon study termination or suspension along with other local regulations. The following is a summary of the changes made in the amendment:

- Consolidation of the previous local amendments to meet local regulations into a single global amendment.
- Addition of final results from the completed Study Vedolizumab-1015.
    - Clarification of the screening window and that subjects may be rescreened.
    - Clarification that randomization may occur within 2 days of the first dose of study drug on Day -1.
    - Clarification of the inclusion and exclusion criteria.
    - Clarification of the excluded and permitted concomitant medications.
    - Addition of a criterion for withdrawal of a subject from the study for lack of efficacy.
    - Clarification of the management of clinical events.
    - Clarification regarding unscheduled PK sample collection.
    - Clarification regarding AEs: management of clinical events, specification of AESIs, and reporting periods for collection of AEs and SAEs.
    - Clarification of the timing of the primary analysis for efficacy and safety.
    - Clarifications to the footnotes of the schedule of events to align with updates to text.

Protocol Amendment 7 (Dated 18 September 2019) – Global

The primary purpose of this substantial, global protocol amendment was to open enrollment to adolescent subjects aged ≥12 years and weighing ≥30 kg, which was a required condition of the European Medicines Agency's Paediatric Committee–endorsed paediatric investigational plan for vedolizumab as prophylaxis of aGvHD after allo-HSCT. The following is a summary of the changes made in the amendment:

• Clarification of the description of the disease to be treated in adolescent subjects.

• Addition of results from nonclinical studies related to inclusion of adolescent subjects.

• Updated human experience as reported in the 9th development safety update report.

• Updated the study rationale and benefit:risk profile to support the inclusion of adolescent subjects.

• Addition of data supporting the dose regimen in adolescent subjects.

• Update to the inclusion criteria impacted by the addition of adolescent subjects.

• Updated the permitted medications to include use of topical anesthetic in adolescent subjects.

• Clarification to the procedures that were to be conducted after discontinuation or withdrawal of a subject.

• Addition of height assessment to be collected at the EOS visit.

• Updated the pregnancy testing and contraception requirements to include female adolescent subjects aged ≥12 years.

• Addition of necessary age-appropriate documentation that was to be completed for adolescent subjects.

• Addition of blood collection volumes for adolescent and adult subjects.

• Updated the version of Common Terminology Criteria for Adverse Events to be used for the grading of AEs.

• Updated stratification to include age group and data assessments in adolescent subjects.

• Updated the appendices regarding methotrexate treatment to support the inclusion of adolescent subjects, and to include age-appropriate assessments of aGvHD clinical stage and MAGIC severity index for aGvHD.

SAP Changes

A total of 2 amendments to the original SAP were issued.

The initial SAP and all revisions can be found in Appendix 16.1.9.1.

Table 9.h Summary of SAP Revisions

Version	Date	Description of Revisions
1.0	16 October 2019	Not applicable
2.0	27 August 2020	• Added COVID-19–related analyses to assess the impact of COVID-19. • Removed "by treatment group" from immunogenicity analysis. • Modified the classification of shift tables to present low, normal, and high values relative to normal range instead of NCI CTCAE grade. • Modified prespecified cutoff value for futility assessment for IA. • Updated the definition of aGvHD to include the criteria for adolescent subjects.
3.0	22 October 2021	• Clarified the determination of intestinal aGvHD event. • Clarified the relationship between study day per protocol versus analysis day in ADaM. • Removed PPS and sensitivity analysis based on PPS. • Removed subgroup analysis by age. • Added references of EQ-5D and FACT-BMT scoring. • Removed the EOT analysis.

Source: Appendix 16.1.9.1, SAP v3.0.

ADaM: analysis data model; aGvHD: acute graft-versus-host disease; COVID-19: coronavirus disease 2019; FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale; GvHD: graft-versus-host disease; IA: interim analysis; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; EOT: end of treatment; EQ-5D: EuroQOL-5 Dimension; PPS: per protocol set.

Results

Participant flow

Table 10.b Disposition of Subjects – Randomized Set

	Number of Subjects (%)		
	Placebo (N = 169)	**Vedolizumab (N = 174)**	**Total (N = 343)**
Randomized but not treated [a]	4 (2.4)	5 (2.9)	9 (2.6)
Completed study drug [a,b]	84 (49.7)	103 (59.2)	187 (54.5)
Discontinued study drug [a]	81 (47.9)	66 (37.9)	147 (42.9)
Reason for discontinuation of study drug [c]			
AE	21 (25.9)	23 (34.8)	44 (29.9)
AE (COVID-19–related)	0	0	0
Protocol deviation	5 (6.2)	2 (3.0)	7 (4.8)
Lost to follow-up	0	0	0
Withdrawal by subject	9 (11.1)	8 (12.1)	17 (11.6)
Pregnancy	0	0	0
Study termination	0	0	0
Relapse of primary malignancy	0	0	0
GvHD	0	0	0
Unsatisfactory therapeutic response	22 (27.2)	11 (16.7)	33 (22.4)
Death	19 (23.5)	16 (24.2)	35 (23.8)
Death (COVID-19–related)	0	0	0
Other	4 (4.9)	4 (6.1)	8 (5.4)
Other (COVID-19–related)	1 (1.2)	2 (3.0)	3 (2.0)
Completed Day +180 visit [a]	133 (78.7)	149 (85.6)	282 (82.2)
Completed study [a,d]	98 (58.0)	117 (67.2)	215 (62.7)
Discontinued study [a]	71 (42.0)	57 (32.8)	128 (37.3)
Reason for discontinuation of study [c]			
AE	5 (7.0)	6 (10.5)	11 (8.6)
AE (COVID-19–related)	0	0	0
Protocol deviation	3 (4.2)	0	3 (2.3)
Lost to follow-up	0	0	0
Withdrawal by subject	18 (25.4)	16 (28.1)	34 (26.6)

Table 10.b Disposition of Subjects – Randomized Set

	Number of Subjects (%)		
	Placebo (N = 169)	Vedolizumab (N = 174)	Total (N = 343)
Pregnancy	0	0	0
Study termination	1 (1.4)	0	1 (0.8)
Relapse of primary malignancy	0	0	0
GvHD	0	0	0
Unsatisfactory therapeutic response (lack of efficacy)	5 (7.0)	3 (5.3)	8 (6.3)
Death	33 (46.5)	26 (45.6)	59 (46.1)
Death (COVID-19–related)	1 (1.4)	0	1 (0.8)
Other	5 (7.0)	5 (8.8)	10 (7.8)
Other (COVID-19–related)	0	1 (1.8)	1 (0.8)
Completed all planned study visits [a]	118 (69.8)	134 (77.0)	252 (73.5)
Screening	165 (97.6)	169 (97.1)	334 (97.4)
Visit Day -1	165 (97.6)	169 (97.1)	334 (97.4)
Visit Day 0	165 (97.6)	169 (97.1)	334 (97.4)
Visit 1 / Day +6	165 (97.6)	169 (97.1)	334 (97.4)
Visit 2 / Day +13	165 (97.6)	169 (97.1)	334 (97.4)
Visit 3 / Day +20	162 (95.9)	169 (97.1)	331 (96.5)
Visit 4 / Day +27	160 (94.7)	168 (96.6)	328 (95.6)
Visit 5 / Day +34	159 (94.1)	166 (95.4)	325 (94.8)
Visit 6 / Day +41	155 (91.7)	164 (94.3)	319 (93.0)
Visit 7 / Day +69	151 (89.3)	163 (93.7)	314 (91.5)
Visit 8 / Day +97	150 (88.8)	158 (90.8)	308 (89.8)
Visit 9 / Day +125	146 (86.4)	157 (90.2)	303 (88.3)
Visit 10 / Day +153	141 (83.4)	156 (89.7)	297 (86.6)
Visit 11 / Day +180	133 (78.7)	149 (85.6)	282 (82.2)
Visit 12 / Day +280	129 (76.3)	148 (85.1)	277 (80.8)
Visit 13 / Day +365	118 (69.8)	134 (77.0)	252 (73.5)
Did not complete all planned study visits [a]	51 (30.2)	40 (23.0)	91 (26.5)

Source: Table 15.1.5.

AE: adverse event; COVID-19: coronavirus disease 2019; CRF: case report form; GvHD: graft-versus-host disease; LTFU: long-term follow-up.

The designation of visits was based on the actual day of evaluation relative to the start date of the study rather than the nominal visit recorded in the CRF.

[a] Percentages are based on the number of subjects eligible for randomization.

[b] Subjects completed study treatment if they received 7 doses of study drug and completed the Day +180 visit.

[c] Percentages are based on the number of subjects who discontinued study drug or discontinued the study.

[d] Study completion refers to the 180-day treatment period and the LTFU, 6 months after the last dose of study drug.

The blind was broken for a total of 6 subjects (3 subjects in each treatment group): 3 were accidentally unblinded on site (2 in the vedolizumab IV group and 1 in the placebo group), and 3 were unblinded per protocol due to a medical emergency related to GvHD progression (1 in the vedolizumab IV group and 2 in the placebo group).

Protocol Deviations

Significant Protocol Deviations

Table 10.d Significant Protocol Deviations – Randomized Set

	Number of Subjects (%)		
	Placebo (N = 169)	Vedolizumab (N = 174)	Total (N = 343)
Subjects with at least 1 significant protocol deviation	76 (45.0)	76 (43.7)	152 (44.3)
Entry – inclusion/exclusion	25 (14.8)	18 (10.3)	43 (12.5)
Entry – informed consent	7 (4.1)	11 (6.3)	18 (5.2)
Concomitant medication	12 (7.1)	6 (3.4)	18 (5.2)
Procedure not per protocol	45 (26.6)	46 (26.4)	91 (26.5)
Visit missed	3 (1.8)	5 (2.9)	8 (2.3)
Study medication	3 (1.8)	10 (5.7)	13 (3.8)
Other	1 (0.6)	4 (2.3)	5 (1.5)

Source: Table 15.1.6.1.

Subjects may appear in more than 1 category.

Significant COVID-19–Related Protocol Deviations

Table 10.e Summary of COVID-19 Impact – SAF

	Number of Subjects (%)		
	Placebo (N = 165)	Vedolizumab (N = 169)	Total (N = 343)
Number of missed visits [a]			
n	2	3	5
Mean (SD)	2.0 (1.41)	1.3 (0.58)	1.6 (0.89)
Median	2.0	1.0	1.0
Minimum, maximum	1, 3	1, 2	1, 3
Number of visits with missed assessments [a]			
n	23	13	36
Mean (SD)	2.5 (2.63)	2.3 (2.25)	2.4 (2.47)
Median	1.0	1.0	1.0
Minimum, maximum	1, 11	1, 9	1, 11
Number of visits with alternative method of contact [a]			
n	11	21	32
Mean (SD)	1.4 (0.50)	1.2 (0.51)	1.3 (0.51)
Median	1.0	1.0	1.0
Minimum, maximum	1, 2	1, 3	1, 3
Number of subjects with at least 1 missed visit	2 (1.2)	3 (1.8)	5 (1.5)

Source: Table 15.1.13.

COVID-19: coronavirus disease 2019; SAF: safety analysis set.

Missed visit, visit with missed assessments, and visit with alternative method of contact were due to COVID-19.

[a] Subjects may have had more than 1 missed visit: visit with missed assessments or visit with alternative method of contact, respectively.

Baseline data Demographic and Baseline Characteristics

Table 11.c Demographic and Baseline Characteristics – FAS

	Placebo (N = 165)	Vedolizumab (N = 168)	Total (N = 333)
Asian	36 (21.8)	29 (17.3)	65 (19.5)
Asian Indian	1 (2.8)	0	1 (1.5)
Chinese	1 (2.8)	2 (6.9)	3 (4.6)
Japanese	17 (47.2)	18 (62.1)	35 (53.8)
Korean	14 (38.9)	7 (24.1)	21 (32.3)
Not Reported	3 (8.3)	2 (6.9)	5 (7.7)
Black or African American	2 (1.2)	3 (1.8)	5 (1.5)
Native Hawaiian or Other Pacific Islander	0	0	0
White	114 (69.1)	121 (72.0)	235 (70.6)
Arab	0	2 (1.7)	2 (0.9)
European	54 (47.4)	77 (63.6)	131 (55.7)
Middle Eastern	3 (2.6)	2 (1.7)	5 (2.1)
North African	0	0	0
Not reported	57 (50.0)	40 (33.1)	97 (41.3)
Not reported	13 (7.9)	15 (8.9)	28 (8.4)
Height (cm)			
n	165	168	333
Mean (SD)	171.65 (10.325)	170.72 (10.476)	171.18 (10.396)
Median	171.00	170.05	171.00
Minimum, maximum	148.0, 198.0	131.2, 198.0	131.2, 198.0
Weight (kg)			
n	165	168	333
Mean (SD)	80.06 (20.649)	77.00 (17.404)	78.52 (19.114)
Median	76.40	75.00	75.80
Minimum, maximum	42.3, 157.4	39.3, 128.5	39.3, 157.4
BMI (kg/m^2) [a]			
n	165	168	333
Mean (SD)	27.03 (6.078)	26.29 (4.817)	26.66 (5.483)
Median	26.47	25.69	26.01
Minimum, maximum	15.8, 52.7	17.2, 38.4	15.8, 52.7
Geographic region (n [%])			
North America	60 (36.4)	46 (27.4)	106 (31.8)
South America	5 (3.0)	4 (2.4)	9 (2.7)
Western/Northern Europe	49 (29.7)	62 (36.9)	111 (33.3)
Central Europe	6 (3.6)	8 (4.8)	14 (4.2)
Eastern Europe	6 (3.6)	8 (4.8)	14 (4.2)
Asia/Australia	39 (23.6)	40 (23.8)	79 (23.7)

Table 11.c Demographic and Baseline Characteristics – FAS

| | Placebo (N = 165) | Vedolizumab (N = 168) | Total (N = 333) |

Source: Table 15.1.8.
BMI: body mass index; FAS: full analysis set.
Percentage is based on the number of subjects who provided nonmissing responses to the categorical variable.
Baseline was defined as the last nonmissing measurement before or on the date of the first dose of study drug (ie, Study Day -1). Recorded age was the age (in years) at informed consent.
[a] BMI = weight (kg) / (height [m])^2.

Medical History and Concurrent Medical Conditions

Medical History

All 334 study subjects (100% overall) reported medical history. The most commonly reported (≥25.0% of subjects overall) medical history terms by SOC were neoplasms benign, malignant and unspecified (incl cysts and polyps) (100%), vascular disorders (35.9%), metabolism and nutrition disorders (34.7%), gastrointestinal disorders (33.5%), surgical and medical procedures (31.7%),

musculoskeletal and connective tissue disorders (27.5%), psychiatric disorders (26.6%), and infections and infestations (26.0%).

The most commonly reported (≥10.0% of subjects overall) medical history terms by PT were acute myeloid leukemia (AML) (43.7%), hypertension (29.3%), myelodysplastic syndrome (21.9%), acute lymphocytic leukemia (15.9%), anemia (14.7%), and depression (10.8%).

Concurrent Medical Conditions

The most commonly reported concurrent condition terms by SOC were vascular disorders (32.3%), metabolism and nutrition disorders (31.1%), gastrointestinal disorders (25.1%), psychiatric disorders (24.0%), blood and lymphatic system disorders (21.0%), and musculoskeletal and connective tissue disorders (21.0%). The most commonly reported concurrent condition terms by PT were hypertension (27.5%), anemia (14.4%), nausea (9.6%), depression (9.6%), anxiety (9.0%), and hyperlipidemia (7.2%).

Baseline Disease Characteristics

Demographic and baseline disease characteristics for the FAS are summarized in Table 11.d.

Overall, baseline disease characteristics were generally well balanced between the vedolizumab and placebo treatment groups. Additionally, the study population (patients undergoing allo-HSCT) was also generally well balanced within the subgroups of conditioning regimen and ATG use and for other factors influencing the risk of intestinal aGVHD development.

Per protocol, the total number of subjects receiving ATG was not to comprise more than approximately 25% of the total number of subjects enrolled into the study. However, as enrollment terminated early (see Section 9.8), the overall percentage of subjects with ATG at baseline was higher: 41.1% (137 subjects) with ATG, and 58.9% (196 subjects) without ATG per IRT data collected at randomization.

Table 11.d Baseline Disease Characteristics – FAS

	Placebo (N = 165)	Vedolizumab (N = 168)	Total (N = 333)
Baseline ECOG status (n [%]) [a]			
0	65 (39.6)	64 (38.1)	129 (38.9)
1	86 (52.4)	89 (53.0)	175 (52.7)
2	13 (7.9)	14 (8.3)	27 (8.1)
3	0	1 (0.6)	1 (0.3)
4	0	0	0
HLA match (n [%]) [b]			
7/8	19 (11.5)	22 (13.1)	41 (12.3)
8/8	146 (88.5)	146 (86.9)	292 (87.7)
Conditioning regimen (n [%]) [b]			
Myeloablative	89 (53.9)	88 (52.4)	177 (53.2)
Reduced intensity conditioning	76 (46.1)	80 (47.6)	156 (46.8)
ATG (n [%]) [b]			
With	66 (40.0)	71 (42.3)	137 (41.1)
Without	99 (60.0)	97 (57.7)	196 (58.9)
Locus of mismatch (n [%])			
HLA-A gene	4 (6.3)	4 (5.4)	8 (5.8)
HLA-B gene	3 (4.7)	3 (4.1)	6 (4.3)
HLA-C gene	1 (1.6)	1 (1.4)	2 (1.4)
HLA-DRB1 gene	3 (4.7)	4 (5.4)	7 (5.1)
Other gene	53 (82.8)	62 (83.8)	115 (83.3)
Primary disease (n [%])			
Acute myeloid leukaemia	72 (43.6)	73 (43.5)	145 (43.5)

Table 11.d Baseline Disease Characteristics – FAS

	Placebo (N = 165)	Vedolizumab (N = 168)	Total (N = 333)
Acute lymphoid leukaemia	24 (14.5)	29 (17.3)	53 (15.9)
Chronic myeloid leukaemia	5 (3.0)	6 (3.6)	11 (3.3)
Other myeloproliferative disorder	14 (8.5)	16 (9.5)	30 (9.0)
Myelodysplastic syndrome	36 (21.8)	34 (20.2)	70 (21.0)
Chronic lymphocytic leukaemia	0	1 (0.6)	1 (0.3)
Non-Hodgkin lymphoma	14 (8.5)	7 (4.2)	21 (6.3)
Hodgkin lymphoma	0	2 (1.2)	2 (0.6)
Donor/recipient CMV match (n [%])			
D-/R+	35 (22.0)	33 (19.8)	68 (20.9)
D+/R+	45 (28.3)	54 (32.3)	99 (30.4)
D+/R-	19 (11.9)	18 (10.8)	37 (11.3)
D-/R-	44 (27.7)	48 (28.7)	92 (28.2)
Cytogenetic results (for AML only) (n [%])			
Favorable	12 (18.5)	14 (20.6)	26 (19.5)
Intermediate	29 (44.6)	38 (55.9)	67 (50.4)
Unfavorable	24 (36.9)	16 (23.5)	40 (30.1)
Unknown	0	0	0
Cytogenetic results (for MDS only) (n [%])			
Low	4 (11.8)	6 (18.2)	10 (14.9)
Intermediate 1	6 (17.6)	9 (27.3)	15 (22.4)
Intermediate 2	11 (32.4)	6 (18.2)	17 (25.4)
High	13 (38.2)	12 (36.4)	25 (37.3)
Unknown	0	0	0
Prior exposure-disease status at time of HSCT (ALL and AML) (n [%])			
Complete remission 1	79 (84.0)	70 (71.4)	149 (77.6)
Complete remission >1	15 (16.0)	26 (26.5)	41 (21.4)
Other	0	2 (2.0)	2 (1.0)
Prior exposure-disease status at time of HSCT (CML only) (n [%])			
1st chronic phase	0	3 (50.0)	3 (27.3)
Failing TKI	0	0	0
Accelerated phase or >1st chronic phase	2 (40.0)	1 (16.7)	3 (27.3)
Blast crisis	1 (20.0)	2 (33.3)	3 (27.3)
Progression	2 (40.0)	0	2 (18.2)
Source of stem cells (n [%])			
Bone marrow	22 (13.4)	27 (16.1)	49 (14.8)
Peripheral blood	142 (86.6)	141 (83.9)	283 (85.2)

Medication History

All 334 study subjects (100% overall) reported medication history. The most commonly reported medications (>50% of subjects overall) in the medication history were ursodeoxycholic acid (84.1%), acyclovir (81.4%), paracetamol (80.2%), methotrexate (79.6%), sulfamethoxazole; trimethoprim (73.4%), ondansetron (67.4%), furosemide (67.4%), fluconazole (60.5%), tacrolimus (57.5%), and magnesium sulfate (55.1%). As immunosuppressants, methotrexate and tacrolimus were part of the prophylaxis regimen for this study.

Concomitant Medications

A total of 181 subjects (54.2% overall) reported medications that started and stopped before baseline. The most commonly reported medications by therapeutic classification were antineoplastic agents (28.7%), antiemetics and antinauseants (24.9%), and corticosteroids for systemic use (15.9%).

Concomitant Medications That Were Ongoing or Started After Baseline

A total of 333 subjects (99.7% overall) reported medications that were ongoing at baseline or those that started after baseline. The most commonly reported (≥60% overall) ongoing/newly started concomitant medications by therapeutic classification were antivirals for systemic use (96.1%),

antibacterials for systemic use (95.2%), antimycotics for systemic use (94.0%), drugs for acid related disorders (90.4%), analgesics (85.9%), antiemetics and antinauseants (83.2%), bile and liver therapy (79.0%), blood substitutes and perfusion solutions (75.1%), antihistamines for systemic use (73.4%), corticosteroids for systemic use (67.7%), psycholeptics (65.9%), mineral supplements (62.6%), stomatological preparations (62.0%), and drugs for functional gastrointestinal disorders (60.8%).

Number analysed

Data Sets Analyzed

Analysis sets were the randomized set, safety analysis set (SAF), full analysis set (FAS), and PK population set. The analysis sets are defined in Section 9.7.1.2 and summarized in Table 11.a. Subjects excluded from the analysis set are included in Listing 16.2.3.1.

A total of 343 subjects were randomized to study treatment: 174 subjects to the 300 mg vedolizumab IV group and 169 subjects to the placebo IV group. Overall, 97.1% (169 of 174) and 97.6% (165 of 169) of subjects in the vedolizumab IV and placebo groups, respectively, were included in the SAF (Table 11.a). In the FAS, 96.6% (168 of 174) and 97.6% (165 of 169) of subjects in the vedolizumab IV and placebo groups, respectively, were included. One subject was randomized to treatment and received at least 1 dose of study drug but did not receive allo-HSCT per protocol; this subject was included in the SAF but not the FAS. The PK population set included 97.1% (169 of 174) of subjects in the vedolizumab IV group.

Table 11.a Analysis Sets – Randomized Set

	Number of Subjects (%)		
Analysis Set	Placebo (N = 169)	Vedolizumab (N = 174)	Total (N = 343)
Randomized set	169 (100.0)	174 (100.0)	343 (100.0)
SAF	165 (97.6)	169 (97.1)	334 (97.4)
FAS	165 (97.6)	168 (96.6)	333 (97.1)
PK population set	0	169 (97.1)	169 (49.3)

Source: Table 15.1.7.

FAS: full analysis set; PK: pharmacokinetic; SAF: safety analysis set.

Efficacy results

Primary Efficacy Endpoint

Intestinal aGvHD-free survival by Day +180 after allo-HSCT

Definition: Intestinal aGvHD was defined as Stages 1 through 4 intestinal involvement per aGvHD clinical stage criteria.

There was a statistically significant difference between the vedolizumab IV group and the placebo group in intestinal aGvHD-free survival by Day +180 after allo-HSCT ($p < 0.001$). The risk of an intestinal aGvHD event or death in subjects was 55% less in the vedolizumab IV group compared with the placebo group (HR, 0.45; 95% CI of HR, 0.27-0.73).

In the vedolizumab IV group, there were 24 subjects (14.3%) with an observed event of intestinal aGvHD or death (any cause), whichever occurred first, by Day +180 after allo-HSCT; in the placebo group, there were 47 subjects (28.5%) with an observed event (Table 11.h). Of those subjects, 12 (7.1%) from the vedolizumab IV group and 31 (28.8%) from the placebo group had an intestinal aGvHD event, and 12 subjects (7.1%) from the vedolizumab IV group and 16 subjects (9.7%) from the placebo group died.

Table 11.h Summary and Analysis of Intestinal aGvHD-Free Survival by Day +180 - FAS

	Placebo (N = 165)	Vedolizumab (N = 168)
Status (n [%])		
Events observed	47 (28.5)	24 (14.3)
Intestinal aGvHD	31 (18.8)	12 (7.1)
Death	16 (9.7)	12 (7.1)
Censored	118 (71.5)	144 (85.7)
Intestinal aGvHD-free survival (days) Percentile (95% CI) [a]		
25%	141.0 (61.0, NE)	NE
Median	NE	NE
75%	NE	NE
Range (minimum, maximum)	14, 182 [b]	2, 182 [b]
Kaplan-Meier estimate (95% CI)		
By Day +180	70.85 (63.16, 77.22)	85.52 (79.17, 90.05)
P-value (vedolizumab vs placebo) [c]		<0.001
Estimated hazard ratio (95% CI) Vedolizumab vs placebo [d]		0.45 (0.27, 0.73)

Source: Table 15.2.2.1.1.
aGvHD: acute graft-versus-host disease; allo-HSCT: allogeneic hematopoietic stem cell transplantation; FAS: full analysis set; HSCT: hematopoietic stem cell transplantation; NE: not evaluable.

Intestinal aGvHD-free survival was the time from the date of first study drug administration (Day -1) to intestinal aGvHD event/death, whichever occurred first, where an event was defined as death due to any cause or Stage 1-4 intestinal involvement per aGvHD clinical stage criteria.

[a] Kaplan-Meier estimate.

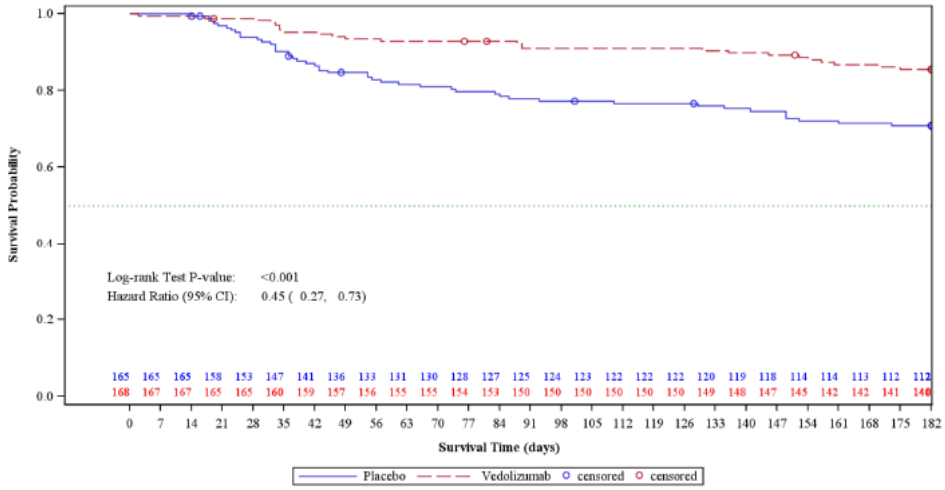
[b] Represents the censored valued. It was censored for subjects who did not have the intestinal aGvHD event or died or had the event after prespecified timing, eg, last contact or Day +180 after allo-HSCT, whichever occurred first. If a subject had an intestinal aGvHD event and died due to any cause including intestinal aGvHD, time to event was derived as time to first qualifying event, ie, intestinal aGvHD event.

[c] Obtained via log-rank test.

[d] Obtained via Cox proportional hazard model with treatment group, stratified by randomization strata: HLA match (7/8, 8/8), conditioning regimen (myeloablative, reduced intensity conditioning), ATG (with, without).

The Kaplan-Meier estimate for intestinal aGvHD-free survival by Day +180 was 85.52% (95% CI, 79.17-90.05) for the vedolizumab IV group and 70.85% (95% CI, 63.16-77.22) for the placebo group. Figure 11.a presents Kaplan-Meier survival curves for the primary endpoint.

Figure 11.a Kaplan-Meier Estimated Survival Curves for Intestinal aGvHD-Free Survival by Day +180 – FAS

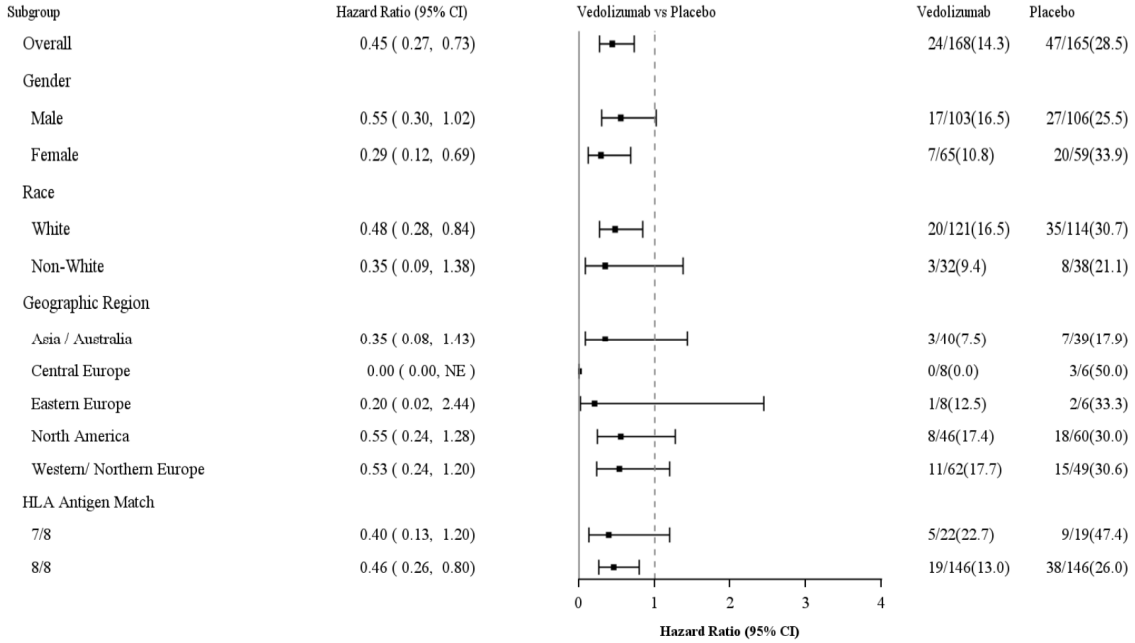


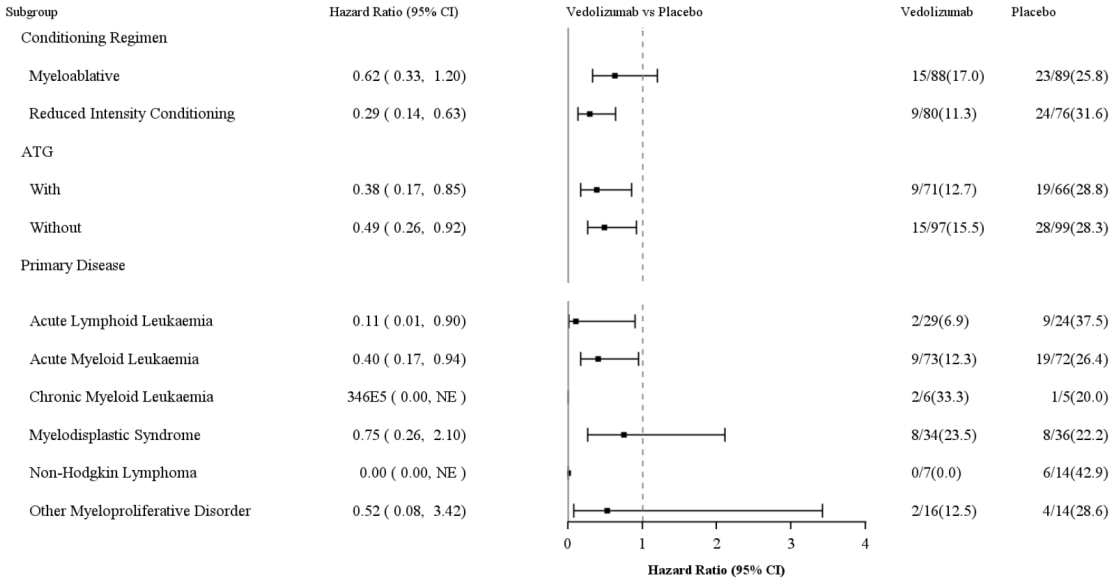
Source: Figure 15.2.1.1.
aGvHD: acute graft-versus-host disease; allo-HSCT: allogeneic hematopoietic stem cell transplantation; FAS: full analysis set.
Intestinal aGvHD-free survival was the time from the date of first study drug administration (Day -1) to intestinal aGvHD event/death, whichever occurred first, where an event was defined as death due to any cause or Stage 1-4 intestinal involvement per aGvHD clinical stage criteria. It was censored for subjects who did not have the intestinal aGvHD event or died, or had the event after prespecified timing, eg, last contact or Day +180 after allo-HSCT, whichever occurred first. If a subject had intestinal aGvHD event and died due to any cause, including intestinal aGvHD, time to event was derived as time to first qualifying event, ie, intestinal aGvHD event.
Hazard ratio was obtained via Cox proportional hazard model with treatment group, stratified by randomization strata: HLA match (7/8, 8/8), conditioning regimen (myeloablative, reduced intensity conditioning), ATG (with, without), and p-value from a log-rank test.

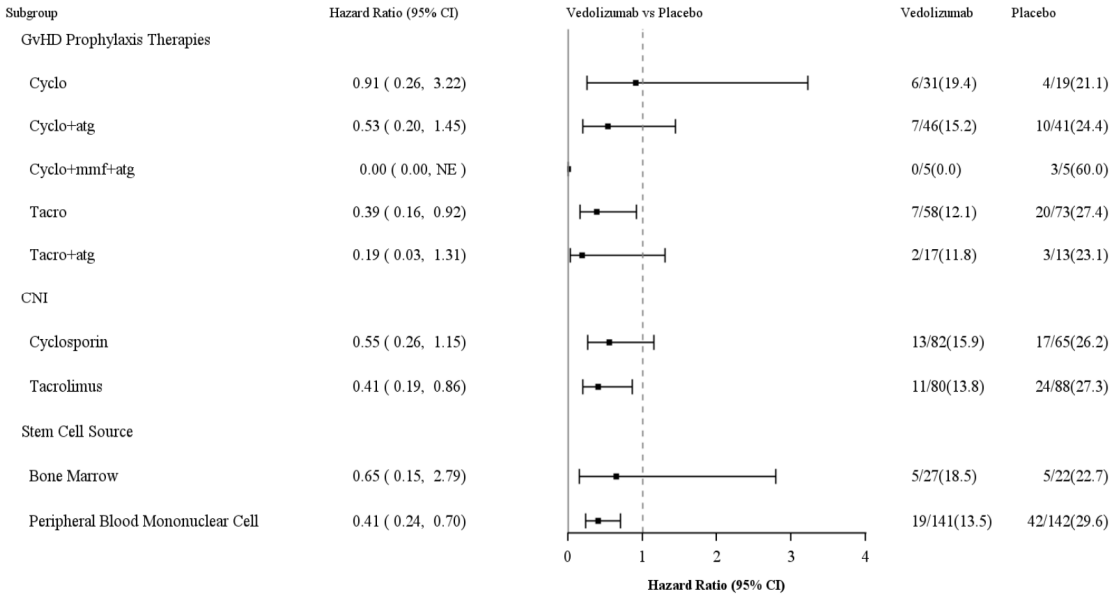
Consistent results were observed for the **sensitivity analyses** of the primary efficacy endpoint, which included the use of the Day +187 window, stratified log-rank test, competing risk analysis, and corrected stratification information.

A forest plot of **subgroup analyses** for intestinal aGvHD-free survival by Day +180 for the FAS is presented in Figure 11.b. These subgroup analyses provide further support for the benefit of vedolizumab IV in reducing the risk of intestinal aGvHD and mortality up to Day +180. In particular, HRs favoring vedolizumab IV were observed in subjects with a 8/8 HLA antigen match with a favorable trend in the 7/8 ones (not statistically relevant). Similarly, a favourable effect could be seen in patients conditioned with the RIC regimen while only a trend is recognizable with the myeloablative one. A positive effect was observed throughout the population regardless the ATG use (with or without), or stem cell source (peripheral blood or bone marrow). Overall, although in some cases a positive effect of Vedolizumab was recognized in the subgroup analysis, the reduced numbers of enrolled patients and, consequently, the small numbers of each subgroup could have impaired the strength of this analysis.

Figure 11.b


Subgroup
Hazard Ratio (95% CI)
Vedolizumab vs Placebo
Vedolizumab
Placebo
Overall 0.45 (0.27, 0.73) 24/168(14.3) 47/165(28.5)
Gender
Male 0.55 (0.30, 1.02) 17/103(16.5) 27/106(25.5)
Female 0.29 (0.12, 0.69) 7/65(10.8) 20/59(33.9)
Race
White 0.48 (0.28, 0.84) 20/121(16.5) 35/114(30.7)
Non-White 0.35 (0.09, 1.38) 3/32(9.4) 8/38(21.1)
Geographic Region
Asia / Australia 0.35 (0.08, 1.43) 3/40(7.5) 7/39(17.9)
Central Europe 0.00 (0.00, NE) 0/8(0.0) 3/6(50.0)
Eastern Europe 0.20 (0.02, 2.44) 1/8(12.5) 2/6(33.3)
North America 0.55 (0.24, 1.28) 8/46(17.4) 18/60(30.0)
Western/ Northern Europe 0.53 (0.24, 1.20) 11/62(17.7) 15/49(30.6)
HLA Antigen Match
7/8 0.40 (0.13, 1.20) 5/22(22.7) 9/19(47.4)
8/8 0.46 (0.26, 0.80) 19/146(13.0) 38/146(26.0)
0
1
2
3
4
Hazard Ratio (95% CI)


Subgroup
Hazard Ratio (95% CI)
Vedolizumab vs Placebo
Vedolizumab
Placebo
Conditioning Regimen
Myeloablative 0.62 (0.33, 1.20) 15/88(17.0) 23/89(25.8)
Reduced Intensity Conditioning 0.29 (0.14, 0.63) 9/80(11.3) 24/76(31.6)
ATG
With 0.38 (0.17, 0.85) 9/71(12.7) 19/66(28.8)
Without 0.49 (0.26, 0.92) 15/97(15.5) 28/99(28.3)
Primary Disease
Acute Lymphoid Leukaemia 0.11 (0.01, 0.90) 2/29(6.9) 9/24(37.5)
Acute Myeloid Leukaemia 0.40 (0.17, 0.94) 9/73(12.3) 19/72(26.4)
Chronic Myeloid Leukaemia 346E5 (0.00, NE) 2/6(33.3) 1/5(20.0)
Myelodisplastic Syndrome 0.75 (0.26, 2.10) 8/34(23.5) 8/36(22.2)
Non-Hodgkin Lymphoma 0.00 (0.00, NE) 0/7(0.0) 6/14(42.9)
Other Myeloproliferative Disorder 0.52 (0.08, 3.42) 2/16(12.5) 4/14(28.6)
0
1
2
3
4
Hazard Ratio (95% CI)



Secondary Endpoints

Intestinal aGvHD-free and relapse-free (of the underlying malignancy) survival by day +180

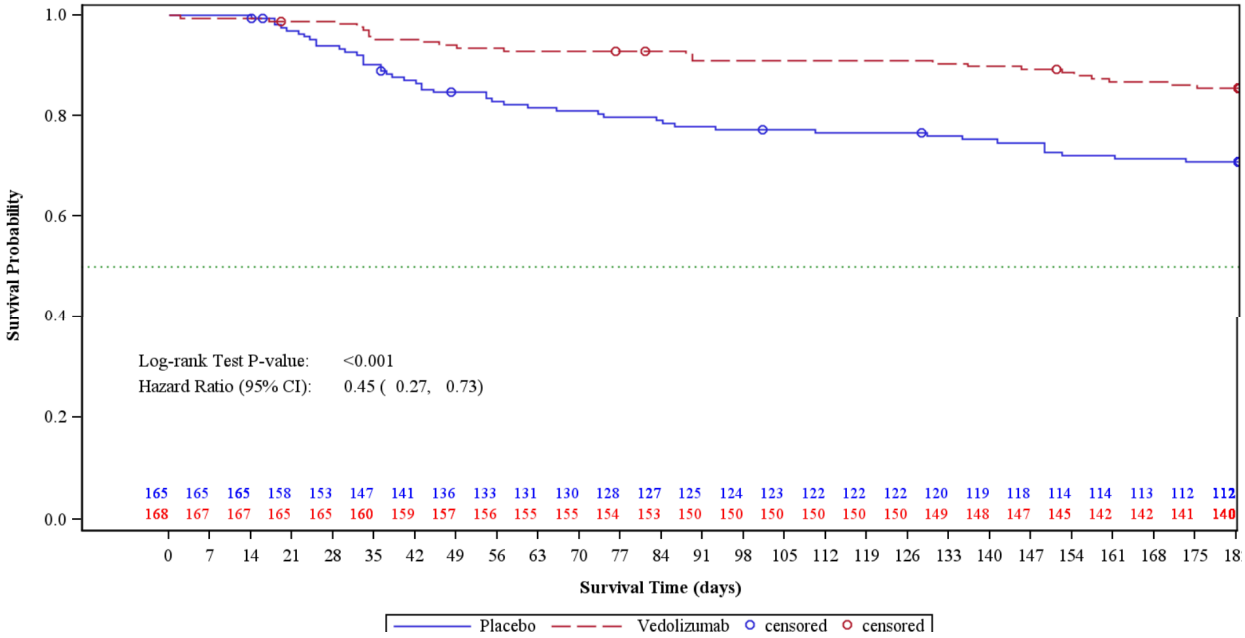
Definition: Risk of an intestinal aGvHD event, relapse, or death, whichever occurred first by day 180.

There was a statistically significant difference between the vedolizumab IV group and the placebo group in the intestinal aGvHD-free and relapse-free (of the underlying malignancy) survival by Day +180 ($p = 0.0043$). The risk of an event in subjects was 44% less in the vedolizumab IV group compared with the placebo group (HR, 0.56; 95% CI of HR, 0.37-0.86).

Although the number of subjects who relapsed was greater in the vedolizumab IV group (18 subjects) compared with placebo (13 subjects), the total number of subjects who relapsed during this study through Day +180 was similar between treatment groups (18 subjects in the vedolizumab IV group vs 17 subjects in the placebo group).

The Kaplan-Meier estimate for intestinal aGvHD-free and relapse-free survival by Day +180 was 78.87% (95% CI, 71.83-84.35) for the vedolizumab IV group and 65.35% (95% CI, 57.46-72.13).

Kaplan-Meier Estimated Survival Curves for Intestinal aGvHD-Free Survival by Day +180 - FAS



The subgroup analysis confirms what previously seen in the primary endpoint for the benefit of vedolizumab IV in reducing the risk of intestinal aGvHD and mortality up to Day +180. In particular, HRs favoring vedolizumab were observed in subjects with HLA antigen match of 8/8, RIC conditioning regimen and with peripheral stem cell source of graft. For the ATG use, patients treated with ATG presented a favorable HR. The same concerns raised about the small numbers of patients included in each subgroups and, consequently, about the strength of these evidences are valid.

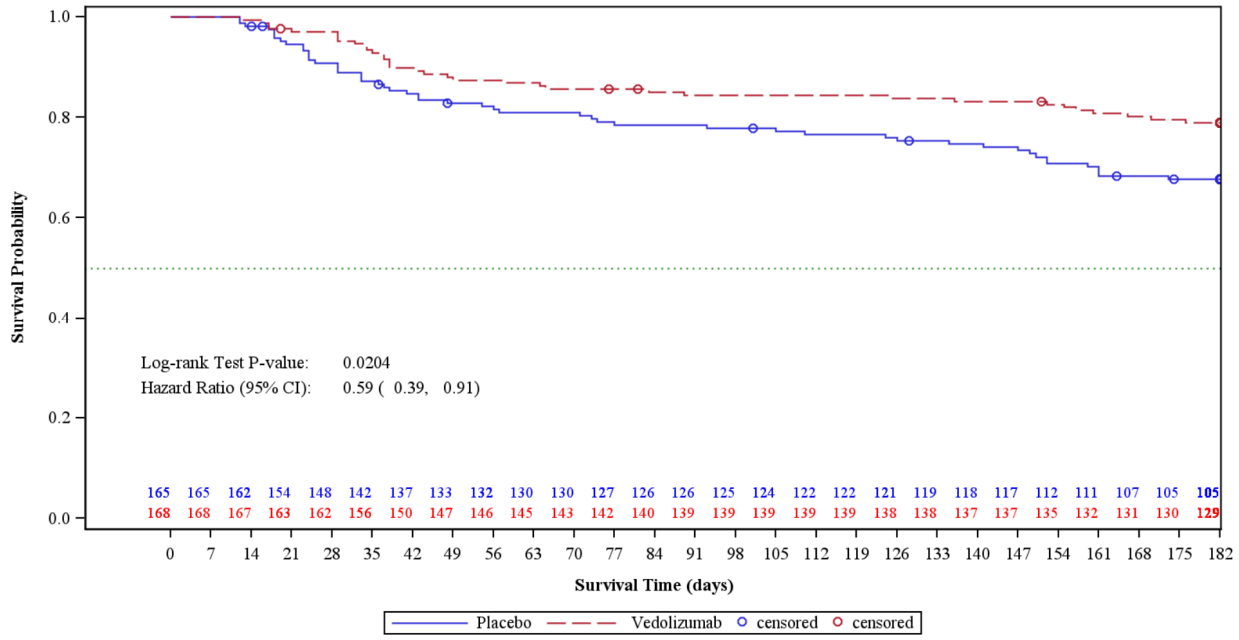
Grade C-D aGvHD-free survival by Day +180).

Definition: GVHD grade C-D in any organ involvement based on IBMDR Index by Day +180.

There was a statistically significant difference between the vedolizumab IV group and the placebo group; the risk of a Grade C-D aGvHD event or death, whichever occurred first, in subjects was 41% less in the vedolizumab IV group compared with the placebo group (HR, 0.59; 95% CI of HR, 0.39-0.91).

In the vedolizumab IV group, there were 35 subjects (20.8%) with an observed event of Grade C-D aGvHD or death, whichever occurred first, by Day +180; in the placebo group, there were 52 subjects (31.5%) with an observed event (Table 11.k). Of those subjects, 22 (13.1%) from the vedolizumab IV group and 35 (21.2%) from the placebo group had an observed Grade C-D aGvHD event, and 13 subjects (7.7%) from the vedolizumab IV group and 17 subjects (10.3%) from the placebo group died.

Kaplan-Meier Estimated Survival Curves for Grade C-D aGvHD-Free (Based on IBMTR Index for Any Organ Involvement) Survival by Day +180- FAS



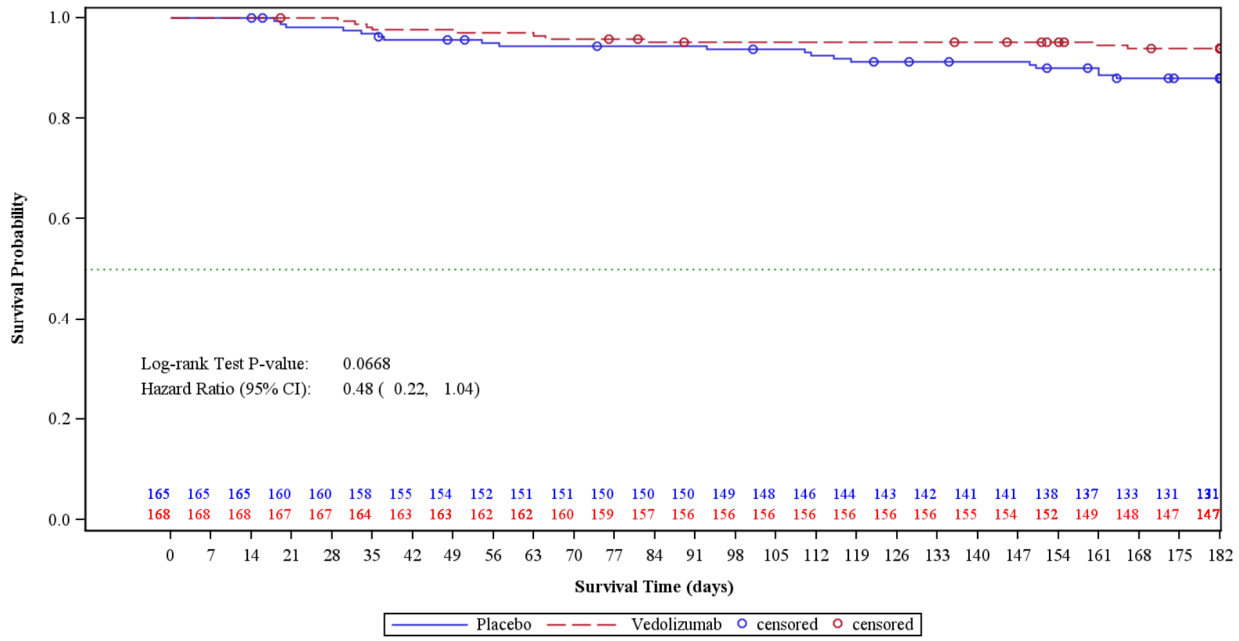
Although the numbers for each of the subgroup analyses related to standard GvHD prophylaxis therapies were small, the results were statistically consistent, suggesting a benefit with the addition vedolizumab IV therapy. The same consideration regarding the limits of analysis performed with small numbers of patients are valid also for the subgroup analysis of this endpoint.

Nor Relapse Mortality by Day +180

Definition: Effect of vedolizumab compared to placebo on NRM in subjects by Day +180

There was no statistically significant difference between the vedolizumab IV group and the placebo group in the endpoint of NRM by Day +180 (p = 0.0668). The marginal effect in NRM was observed in favor of the vedolizumab IV group compared with the placebo group (HR, 0.48; 95% CI of HR, 0.22-1.04). In the vedolizumab IV group, there were 10 subjects with an observed event of death without relapse by Day +180 (6.0% of subjects); in the placebo group, there were 19 subjects with an observed event (11.5% of subjects). The Kaplan-Meier estimate for NRM by Day +180 was 93.93% (95% CI, 89.01-96.69) for the vedolizumab IV group and 88.02% (95% CI, 81.85-92.19) for the placebo group.

Kaplan-Meier survival curves for NRM by Day +180 for the FAS



Overall Survival by day +180

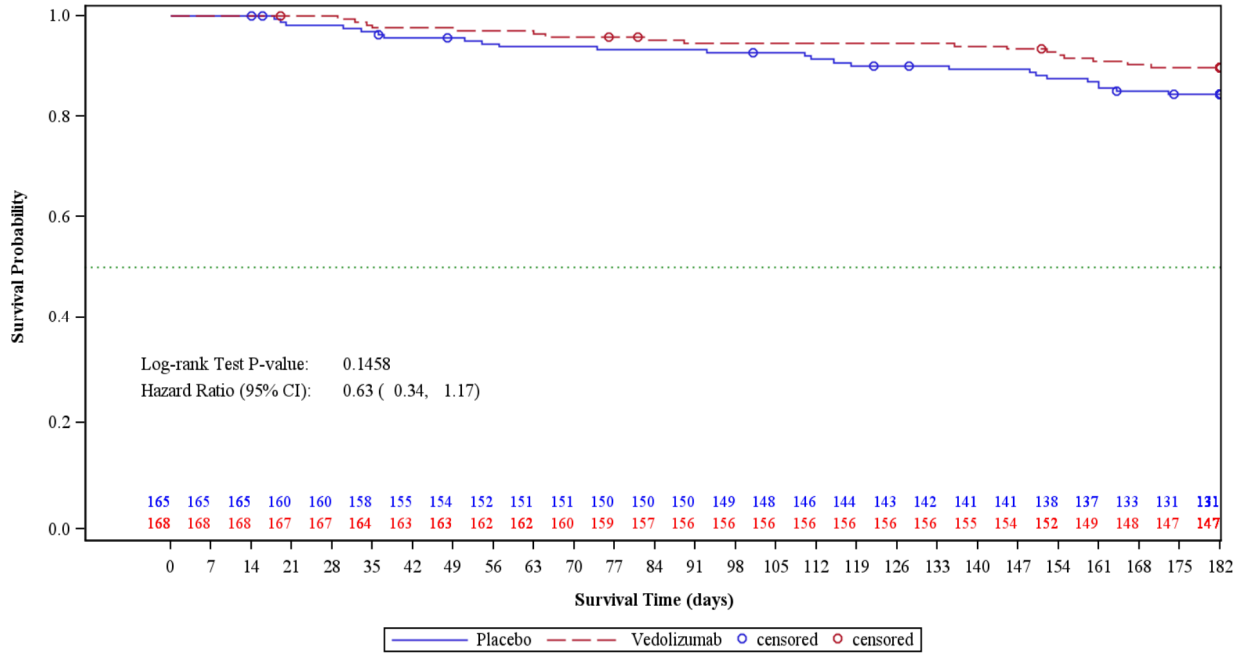
Definition: the effect of vedolizumab compared to placebo on OS by Day +180

Per the fixed-sequence hierarchical testing procedure following a prespecified order of primary and key secondary efficacy endpoints, the statistical testing of the fourth key secondary efficacy endpoint of OS was not performed given that the statistical significance of the preceding key secondary efficacy endpoint (ie, NRM) was not demonstrated (ie, p >0.05). By Day +180, 17 subjects (10.1%) from the vedolizumab IV group and 25 subjects (15.2%) from the placebo group had died.

Additionally, the nominal p-value for OS by Day +180 between the vedolizumab IV group and the placebo group was 0.1458.

The Kaplan-Meier estimate for OS by Day +180 was 89.72% (95% CI, 83.98-93.48) for the vedolizumab IV group and 84.38% (95% CI, 77.76-89.16) for the placebo group.

Kaplan-Meier survival curves for OS by Day +180 for the FAS.

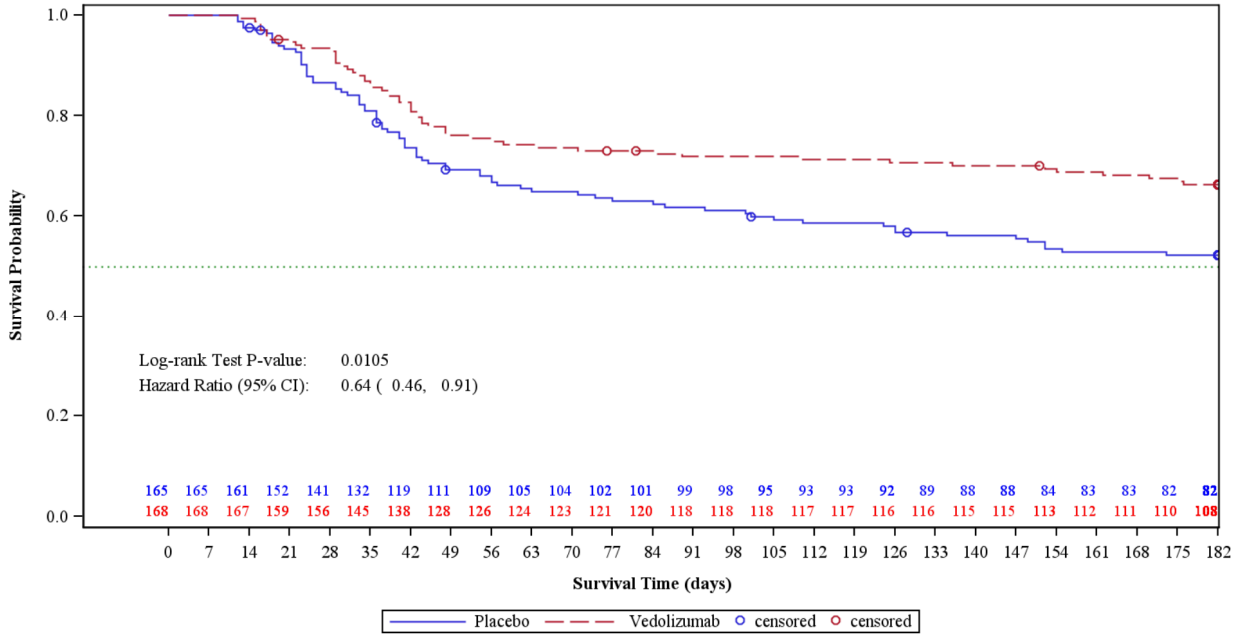


Grade B-D aGvHD-free survival, all by Day +180

Definition: GVHD grade B-D in any organ involvement based on IBMDR Index by Day +180

Per the fixed-sequence hierarchical testing procedure the fifth key secondary efficacy endpoint of Grade B-D aGvHD-free survival was not tested. Nominal p-value is provided instead. The nominal p-value for Grade B-D aGvHD-free survival by Day +180 between the vedolizumab IV group and the placebo group was 0.0105. The risk of a Grade B-D aGvHD event or death, whichever occurred first, was 36% less in the vedolizumab IV group compared with the placebo group (HR, 0.64; 95% CI of HR, 0.46-0.91). In the vedolizumab IV group, there were 56 subjects (33.3%) with an observed event of Grade B-D aGvHD or death, whichever occurred first, by Day +180; in the placebo group, there were 77 subjects (46.7%) with an observed event (Table 11.n). Of those subjects, 47 (28.0%) from the vedolizumab IV group and 64 (38.8%) from the placebo group had an observed Grade B-D aGvHD event, and 9 subjects (5.4%) from the vedolizumab IV group and 13 subjects (7.9%) from the placebo group died.

Kaplan-Meier Estimated Survival Curves for Grade B-D aGvHD-Free (for Any Organ Involvement) Survival by Day +180 - FAS



Exploratory Endpoints

An overview of the exploratory efficacy results by Day +180 and Day +365 is presented above.

Exploratory endpoints by Day +365 are similar to the primary and secondary efficacy endpoints (at Day +180) for this study:

- **Intestinal aGvHD-free survival by Day +365**

  A total of 21.4% of subjects in the vedolizumab IV group and 33.9% of subjects in the placebo group had an observed event of intestinal aGvHD or death (any cause), whichever occurred first, by Day +365 (nominal p = 0.0041; HR, 0.53 [95% CI of HR, 0.35-0.81]). At Day +180, there were 14.3% and 28.5% of subjects with an observed event in the vedolizumab IV and placebo groups, respectively (p <0.001).

- **Intestinal aGvHD-free and relapse-free (of the underlying malignancy) survival by Day +365**

  A total of 33.3% of subjects in the vedolizumab IV group and 38.8% of subjects in the placebo group had an observed event of intestinal aGvHD, relapse, or death, whichever occurred first, by Day +365 (nominal p = 0.1676; HR, 0.78 [95% CI of HR, 0.54-1.12]). At Day +180, there were 20.8% and 33.9% of subjects with an observed event in the vedolizumab IV and placebo groups, respectively (p = 0.0043).

- **Grade C-D aGvHD-free (based on IBMTR index for any organ involvement) survival by Day +365**

  A total of 28.0% of subjects in the vedolizumab IV group and 35.8% of subjects in the placebo group had an observed event of Grade C-D aGvHD or death, whichever occurred first, by Day +365 (nominal p = 0.0709; HR, 0.68 [95% CI of HR, 0.46-1.00]). At Day +180, there were 20.8% and 31.5% of subjects with an observed event in the vedolizumab IV and placebo groups, respectively (p = 0.0204).

- **NRM by Day +365**

  A total of 8.9% of subjects in the vedolizumab IV group and 15.2% of subjects in the placebo group had an observed event of death without relapse by Day +365 (nominal p = 0.0670; HR,

0.49 [95% CI of HR, 0.25-0.95]). At Day +180, there were 6.0% and 11.5% of subjects with an observed event in the vedolizumab IV and placebo groups, respectively (nominal p = 0.0668).

- **OS by Day +365**

  A total of 16.7% of subjects in the vedolizumab IV group and 21.8% of subjects in the placebo group died by Day +365 (nominal p = 0.1741; HR, 0.67 [95% CI of HR, 0.41-1.11]). At Day +180, 10.1% and 15.2% of subjects had died in the vedolizumab IV and placebo groups, respectively (nominal p = 0.1458).

- **Grade B-D aGvHD-free (any organ involvement) survival by Day +365**

  A total of 41.1% of subjects in the vedolizumab IV group and 49.7% of subjects in the placebo group had an observed event of Grade B-D aGvHD or death, whichever occurred first, by Day +365 (nominal p = 0.0534; HR, 0.71 [95% CI of HR, 0.52-0.99]). At Day +180, there were 33.3% and 46.7% of subjects with an observed event in the vedolizumab IV and placebo groups, respectively (nominal p = 0.0105).

Of additional interest was Stage 2-4 intestinal aGvHD-free survival at Day +180 compared with Day +365. At Day +180, 11.3% of subjects in the vedolizumab IV group and 20.0% of subjects in the placebo group had an observed event of Stage 2-4 intestinal aGvHD or death, whichever occurred first (nominal p = 0.0222). At Day +365, 19.0% of subjects in the vedolizumab IV group and 25.5% of subjects in the placebo group had an observed event of Stage 2-4 intestinal aGvHD or death, whichever occurred first (nominal p = 0.0981)

Global numbers of events increase during the follow up, from the day +180 to 365; this is consistent both with the follow up trend but also with the late onset of aGVHD. The reduced enrolment presented an effect in this subset analyses, considering that each analysis was conducted on small numbers of patients. Patient's distribution between the treatment groups were well balanced, with the exception of relapse of the underlying malignancy by Day +365 (19.6% of subjects with non-missing data in the vedolizumab IV group vs 13.3% in the placebo group).

For subjects with GvHD requiring immunosuppression, the mean number of days that immunosuppression was required was numerically less in the vedolizumab IV group compared with the placebo group through Day +180 (nominal p = 0.0151) but the effect was lost through Day +365 (nominal p = 0.4882), suggesting a time limited efficacy of Vedolizumab in reducing the need of immunosuppression treatments.

Table 11. and 11.q summarized an overview of the exploratory efficacy data at Day +180 and +365, respectively

Table 11.p Overview of Exploratory Efficacy Analyses by Day +180 After Allo-HSCT – FAS

Exploratory Endpoint Events Observed, n (%) [a]	Placebo (N = 165)	Vedolizumab (N = 168)	HR (95% CI) [b]	P-value [c]
Summary of analysis of time to chronic GvHD requiring systemic immunosuppression by Day +180 after allo-HSCT Chronic GvHD requiring systemic immunosuppression, or death	29 (17.6)	19 (11.3)	0.61 (0.34, 1.08)	0.0859
Summary and analysis of GvHD and relapse-free (of underlying malignancy) survival by Day +180 after allo-HSCT GvHD, relapse, or death	49 (29.7)	33 (19.6)	0.61 (0.39, 0.96)	0.0243
Summary and analysis of Stage 2-4 intestinal aGvHD-free survival Stage 2-4 intestinal aGvHD, or death	33 (20.0)	19 (11.3)	0.52 (0.29, 0.91)	0.0222
Summary and analysis of relapse-free survival (of underlying malignancy) by Day +180 after allo-HSCT Relapse or death	36 (21.8)	28 (16.7)	0.75 (0.46, 1.23)	0.2313
Summary and analysis of Grade 2-4 aGvHD-free survival by Day +180 after allo-HSCT per MAGIC criteria Grade 2-4 aGvHD per MAGIC criteria, or death	59 (35.8)	43 (25.6)	0.67 (0.45, 0.99)	0.0421
Summary and analysis of Grade 3-4 aGvHD-free survival by Day +180 after allo-HSCT per MAGIC criteria Grade 3-4 aGvHD per MAGIC criteria, or death	32 (19.4)	19 (11.3)	0.53 (0.30, 0.93)	0.0304
Summary of analysis of time to systemic immunosuppression for GvHD by Day +180 after allo-HSCT GvHD systemic immunosuppression, or death	33 (20.0)	23 (13.7)	0.64 (0.38, 1.10)	0.0982

Source: Table 15.2.8.2, 15.2.9.1, 15.2.10.1, 15.2.11.1, 15.2.14.1, 15.2.15.1, and 15.2.17.2.

allo-HSCT: allogeneic hematopoietic stem cell transplantation; aGvHD: acute graft-versus-host disease; ATG: antithymocyte globulin; GvHD: graft-versus-host disease; FAS: full analysis set; HLA: human leukocyte antigen; MAGIC: Mount Sinai Acute GvHD International Consortium.

[a] n is the number (%) of subjects with an observed event/relapse/death (as-applicable), whichever occurred first, from the date of first study drug administration (Day -1) through Day +180.

[b] Obtained via Cox proportional hazards model with treatment group, stratified by randomization strata: HLA match (7/8, 8/8), conditioning regimen (myeloablative, reduced intensity conditioning), ATG (with, without).

[c] Obtained via log-rank test.

Table 11.q Overview of Exploratory Efficacy Analyses by Day +365 After Allo-HSCT– FAS

Exploratory Endpoint Events Observed, n (%) [a]	Placebo (N = 165)	Vedolizumab (N = 168)	HR (95% CI) [b]	P-value [c]
Summary and analysis of intestinal aGvHD-free survival by Day +365 [d] Intestinal aGvHD (Stage 1-4 per aGvHD clinical stage criteria) or death	56 (33.9)	36 (21.4)	0.53 (0.35, 0.81)	0.0041
Summary and analysis of GvHD and relapse-free (of underlying malignancy) survival by Day +365 [d] GvHD, relapse, or death	64 (38.8)	56 (33.3)	0.78 (0.54, 1.12)	0.1676
Summary and analysis of Grade C-D aGvHD-free (based on IBMTR index for any organ involvement) survival by Day +365 [d] Grade C-D aGvHD (any organ involvement), or death	59 (35.8)	47 (28.0)	0.68 (0.46, 1.00)	0.0709
Summary and analysis of NRM by Day +365 [d] Death without relapse	25 (15.2)	15 (8.9)	0.49 (0.25, 0.95)	0.0670
Summary and analysis of OS by Day +365 [d] Death (any cause)	36 (21.8)	28 (16.7)	0.67 (0.41, 1.11)	0.1741
Summary and analysis of Grade B-D aGvHD-free (any organ involvement) survival by Day +365 [d] Grade B-D aGvHD (any organ involvement), or death	82 (49.7)	69 (41.1)	0.71 (0.52, 0.99)	0.0534
Summary of chronic GvHD requiring systemic immunosuppression by Day +365 Chronic GvHD requiring systemic immunosuppression, or death	45 (27.3)	34 (20.2)	0.66 (0.42, 1.03)	0.0866
Summary and analysis of Stage 2-4 intestinal aGvHD-free survival by Day +365 Stage 2-4 intestinal aGvHD, or death	42 (25.5)	32 (19.0)	0.64 (0.40, 1.03)	0.0981
Summary and analysis of relapse-free (of underlying malignancy) survival by Day +365 Relapse or death	47 (28.5)	48 (28.6)	0.95 (0.63, 1.42)	0.8490
Summary and analysis of Grade 2-4 aGvHD-free survival by Day +365 per MAGIC criteria Grade 2-4 aGvHD (MAGIC criteria), or death	68 (41.2)	54 (32.1)	0.70 (0.49, 1.00)	0.0582
Summary and analysis of Grade 3-4 aGvHD-free survival by Day +365 per MAGIC criteria Grade 3-4 aGvHD (MAGIC criteria), or death	42 (25.5)	29 (17.3)	0.57 (0.35, 0.92)	0.0405
Summary of analysis of time to systemic immunosuppression for GvHD by Day +365 GvHD requiring systemic immunosuppression, or death	49 (29.7)	38 (22.6)	0.68 (0.44, 1.04)	0.0915

Table 11.s Duration of Systemic Immunosuppression for GvHD by Days +180 and +365 After Allo-HSCT – FAS

Summary of Duration of Systemic Immunosuppression for GvHD		Placebo (N = 165)	Vedolizumab (N = 168)	P-value [b]
By Day +180	n [a]	11	10	0.0151
	Mean (SD)	31.3 (23.70)	12.0 (6.86)	
	Median	27.0	12.0	
	Min, Max	5, 90	1, 23	
By Day +365	n [a]	18	17	0.4882
	Mean (SD)	76.1 (62.32)	59.6 (54.11)	
	Median	67.0	53.0	
	Min, Max	1, 213	1, 193	

Source: Table 15.2.17.1 and 15.2.34.1.

allo-HSCT: allogeneic hematopoietic stem cell transplantation; GvHD: graft-versus-host disease; FAS: full analysis set; HSCT: hematopoietic stem cell transplantation.

[a] n is the number (%) of subjects with observed nonmissing data, from the date of first study drug administration (Day -1) through Day +180 or +365.

[b] P-value for comparison between vedolizumab and placebo was obtained from Wilcoxon rank-sum test.

Quality of life results

Results from the FACT-BMT at the Day +97, +180, and +365 visits were similar between treatment groups for FACT-G (general) and the BMT-specific subscales of physical well-being, social/family well-being, emotional well-being, functional well-being, bone marrow transplant subscale, and trial outcome index. A noted exception was the Day +97 subscale of social/family well-being that had a nominal p-value of 0.0203 between treatment groups (least-squares [LS] mean difference, -0.98; 95% CI, -1.81 to -0.15). The change from baseline in FACT total scores between the vedolizumab IV group and the placebo group (LS mean difference [95% CI]) was not statistically significant at any time point assessed (p = 0.1420, Day +97; p = 0.7754, Day +180; p = 0.4237, Day +365). A summary of the FACT-BMT and change from baseline by visit for the FAS can be found in Table 15.2.38.1.1.

A numerical benefit was observed in the change from baseline in the EQ visual analog scale (VAS) at Day +180 (LS mean difference, 3.93; 95% CI, 0.08-7.77) in favor of the vedolizumab IV group (minimal p-value = 0.0452); however, results were not statistically significant at the Day +97 (p = 0.3786) or Day +365 (p = 0.3570) visits. Additionally, results from the EQ-5D scores at the Day +97, +180, and +365 visits were not statistically different between treatment groups for the subscales of mobility, self-care, usual activities, pain/discomfort, or anxiety/depression at any time point assessed. Similarly, the change from baseline in the index scores (US) between the vedolizumab IV and placebo groups was not statistically significant at any time point (p = 0.5089, Day +97; p = 0.3646, Day +180; p = 0.7315, Day +365).

Safety results

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0, and summarized by System Organ Class (SOC), High-Level Term (HLT), and Preferred Term (PT). AEs were also summarized by severity and by relationship to study drug.

A TEAE was defined as any AE newly occurring or worsening from the first dose and 18 weeks after the last dose of study drug. A serious TEAE was defined as any SAE newly occurring or worsening from the first dose up to 18 weeks after the last dose of study drug, regardless of relationship to study drug. SAEs were also collected from 18 weeks after the last dose of study drug until the EOS.

Extent of Exposure

The mean duration of exposure was similar between the vedolizumab IV group and the placebo group (241.7 and 230.0 days, respectively).

The mean number of doses received was also similar between treatment groups (5.4 doses [SD, 2.05] for the vedolizumab IV group and 5.1 doses [SD, 2.25] for the placebo group). Most subjects received

7 doses of study drug per protocol (52.7% of subjects in the vedolizumab IV group and 50.9% of subjects in the placebo group).

Table 12.a Study Drug Exposure – SAF

	Number of Subjects (%)		
	Placebo (N = 165)	Vedolizumab (N = 169)	Total (N = 334)
Duration of exposure (days) [a]			
n	165	169	334
Mean (SD)	230.0 (61.46)	241.7 (56.30)	235.9 (59.11)
Median	278.0	280.0	279.0
Minimum, maximum	127, 296	127, 295	127, 296
Number of doses received			
n	165	169	334
Mean (SD)	5.1 (2.25)	5.4 (2.05)	5.3 (2.15)
Median	7.0	7.0	7.0
Minimum, maximum	1, 7	1, 7	1, 7
Number of doses received			
1	12 (7.3)	10 (5.9)	22 (6.6)
2	26 (15.8)	15 (8.9)	41 (12.3)
3	13 (7.9)	14 (8.3)	27 (8.1)
4	9 (5.5)	10 (5.9)	19 (5.7)
5	12 (7.3)	10 (5.9)	22 (6.6)
6	9 (5.5)	21 (12.4)	30 (9.0)
7	84 (50.9)	89 (52.7)	173 (51.8)
>7	0	0	0

Source: Table 15.1.12.

SAF: safety analysis set.

[a] Duration of exposure was defined as (date of last dose – date of first dose + 127 days). If last dose date was missing, then 127 days were imputed as duration of exposure.

Adverse Events

An overview of TEAEs (including TEAEs by grade, TEAEs leading to study drug discontinuation, serious TEAEs, and TEAEs resulting in death) is presented in the table below.

Table 12.c Overview of TEAEs – SAF

	Placebo (N = 165)		Vedolizumab (N = 169)		Total (N = 334)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
TEAEs	**4036**	**165 (100.0)**	**4287**	**169 (100.0)**	**8323**	**334 (100.0)**
Related	93	41 (24.8)	86	48 (28.4)	179	89 (26.6)
Not related	3943	124 (75.2)	4201	121 (71.6)	8144	245 (73.4)
Grade						
1	1849	3 (1.8)	1937	1 (0.6)	3786	4 (1.2)
2	1304	15 (9.1)	1477	12 (7.1)	2781	27 (8.1)
3	642	50 (30.3)	659	53 (31.4)	1301	103 (30.8)
4	213	70 (42.4)	193	82 (48.5)	406	152 (45.5)
5	28	27 (16.4)	21	21 (12.4)	49	48 (14.4)
Grade 3 or higher	**883**	**147 (89.1)**	**873**	**156 (92.3)**	**1756**	**303 (90.7)**
Grade 3 or higher, drug-related	**27**	**19 (11.5)**	**25**	**18 (10.7)**	**52**	**37 (11.1)**
Leading to discontinuation	**53**	**51 (30.9)**	**45**	**44 (26.0)**	**98**	**95 (28.4)**
Serious TEAEs	**271**	**114 (69.1)**	**294**	**120 (71.0)**	**565**	**234 (70.1)**
Drug-related	15	14 (8.5)	13	11 (6.5)	28	25 (7.5)
Not related	256	100 (60.6)	281	109 (64.5)	537	209 (62.6)
Leading to discontinuation	39	38 (23.0)	40	39 (23.1)	79	77 (23.1)
Deaths	**28** [a]	**27 (16.4)**	**21**	**21 (12.4)**	**49**	**48 (14.4)**

Source: Table 15.3.1.1 and Listing 16.2.7.1.

AE: adverse event; aGvHD: acute graft-versus-host disease; MedDRA: Medical Dictionary for Regulatory Activities; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Subjects with 1 or more AE within a level of MedDRA term were counted only once in that level. MedDRA Dictionary (version 24.0) was used for coding AEs. TEAE was defined as any AE that started or worsened after administration of the first dose of study drug and up through 18 weeks after the last dose of study drug.

[a] One subject in the placebo group had 2 TEAEs that were coded as resulting in death. Both events (aGvHD and sepsis) were included in the total number for the placebo group.

TEAEs

The most commonly reported (≥30% of subjects in any treatment group) TEAEs are summarized by PT (in descending order) in Table 12.d.

Table 12.e Greatest Exposure-Adjusted Rates of TEAEs (Incidence ≥25 Events/100 Subject Years in Any Treatment Group) by SOC and PT – SAF

SOC PT	Number of Subjects (Incidence Per 100 Subject Years) Placebo (N = 165)	 Vedolizumab (N = 169)	 Total (N = 334)
Subjects with any TEAE	**165 (158.8)**	**169 (151.1)**	**334 (154.8)**
Subject Years	**104**	**112**	**216**
Blood and lymphatic system disorders	**121 (116.4)**	**132 (118.0)**	**253 (117.3)**
Anaemia	75 (72.2)	68 (60.8)	143 (66.3)
Febrile neutropenia	62 (59.7)	72 (64.4)	134 (62.1)
Neutropenia	32 (30.8)	40 (35.8)	72 (33.4)
Thrombocytopenia	32 (30.8)	43 (38.4)	75 (34.8)
Cardiac disorders	**33 (31.8)**	**36 (32.2)**	**69 (32.0)**
Eye disorders	**43 (41.4)**	**51 (45.6)**	**94 (43.6)**
Dry eye	21 (20.2)	34 (30.4)	55 (25.5)
Gastrointestinal disorders	**160 (154.0)**	**150 (134.1)**	**310 (143.7)**
Diarrhoea	104 (100.1)	97 (86.7)	201 (93.2)
Abdominal pain	36 (34.6)	36 (32.2)	72 (33.4)

Table 12.e Greatest Exposure-Adjusted Rates of TEAEs (Incidence ≥25 Events/100 Subject Years in Any Treatment Group) by SOC and PT – SAF

SOC PT	Number of Subjects (Incidence Per 100 Subject Years) Placebo (N = 165)	 Vedolizumab (N = 169)	 Total (N = 334)
Constipation	47 (45.2)	43 (38.4)	90 (41.7)
Nausea	84 (80.8)	86 (76.9)	170 (78.8)
Vomiting	56 (53.9)	45 (40.2)	101 (46.8)
Dry mouth	28 (26.9)	27 (24.1)	55 (25.5)
Stomatitis	93 (89.5)	92 (82.3)	185 (85.7)
General disorders and administration site conditions	**124 (119.3)**	**130 (116.2)**	**254 (117.7)**
Fatigue	50 (48.1)	39 (34.9)	89 (41.2)
Pyrexia	69 (66.4)	83 (74.2)	152 (70.4)
Oedema peripheral	35 (33.7)	29 (25.9)	64 (29.7)
Hepatobiliary disorders	**26 (25.0)**	**33 (29.5)**	**59 (27.3)**
Immune system disorders	**106 (102.0)**	**98 (87.6)**	**204 (94.5)**
Acute graft versus host disease in skin	67 (64.5)	69 (61.7)	136 (63.0)
Acute graft versus host disease in intestine	29 (27.9)	15 (13.4)	44 (20.4)
Infections and infestations	**111 (106.8)**	**125 (111.8)**	**236 (109.4)**
Cytomegalovirus infection reactivation	30 (28.9)	40 (35.8)	70 (32.4)
Injury, poisoning and procedural complications	**34 (32.7)**	**45 (40.2)**	**79 (36.6)**
Investigations	**104 (100.1)**	**103 (92.1)**	**207 (95.9)**
Alanine aminotransferase increased	29 (27.9)	42 (37.6)	71 (32.9)
Aspartate aminotransferase increased	26 (25.0)	32 (28.6)	58 (26.9)
Blood bilirubin increased	27 (26.0)	22 (19.7)	49 (22.7)
Platelet count decreased	47 (45.2)	38 (34.0)	85 (39.4)
Blood creatinine increased	35 (33.7)	24 (21.5)	59 (27.3)
Metabolism and nutrition disorders	**130 (125.1)**	**130 (116.2)**	**260 (120.5)**
Decreased appetite	40 (38.5)	45 (40.2)	85 (39.4)
Hypomagnesaemia	52 (50.0)	60 (53.6)	112 (51.9)
Hypokalaemia	54 (52.0)	47 (42.0)	101 (46.8)
Musculoskeletal and connective tissue disorders	**64 (61.6)**	**77 (68.8)**	**141 (65.3)**
Back pain	20 (19.2)	36 (32.2)	56 (26.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**26 (25.0)**	**29 (25.9)**	**55 (25.5)**
Nervous system disorders	**95 (91.4)**	**93 (83.1)**	**188 (87.1)**
Headache	58 (55.8)	58 (51.9)	116 (53.8)
Psychiatric disorders	**57 (54.9)**	**65 (58.1)**	**122 (56.5)**
Insomnia	32 (30.8)	35 (31.3)	67 (31.1)
Renal and urinary disorders	**58 (55.8)**	**59 (52.7)**	**117 (54.2)**
Acute kidney injury	26 (25.0)	24 (21.5)	50 (23.2)
Respiratory, thoracic and mediastinal disorders	**90 (86.6)**	**85 (76.0)**	**175 (81.1)**
Skin and subcutaneous tissue disorders	**107 (103.0)**	**116 (103.7)**	**223 (103.4)**
Pruritus	33 (31.8)	28 (25.0)	61 (28.3)

Table 12.e Greatest Exposure-Adjusted Rates of TEAEs (Incidence ≥25 Events/100 Subject Years in Any Treatment Group) by SOC and PT – SAF

SOC PT	Number of Subjects (Incidence Per 100 Subject Years) Placebo (N = 165)	 Vedolizumab (N = 169)	 Total (N = 334)
Rash	36 (34.6)	43 (38.4)	79 (36.6)
Vascular disorders	**80 (77.0)**	**82 (73.3)**	**162 (75.1)**
Hypertension	54 (52.0)	55 (49.2)	109 (50.5)

Source: Table 15.3.1.3.

AE: adverse event; PT: Preferred Term; SAF: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

TEAE was defined as any AE that started or worsened after administration of the first dose of study drug and up through 18 weeks after the last dose of study drug. SOCs were sorted using alphabetical order and PTs were sorted in decreasing frequency based on the total number of subjects. The exposure-adjusted incidence rate was defined as the number of subjects experiencing the AE divided by the total exposure-time among subjects. The extent of exposure was calculated as (date of last dose of study drug - date of first dose of study drug +127) /365.25 for each subject.

Table 12.f The Most Commonly Reported (≥1% of Subjects in Any Treatment Group) Drug-Related TEAEs by SOC and PT – SAF

SOC PT	Number (%) of Subjects Placebo (N = 165)	 Vedolizumab (N = 169)	 Total (N = 334)
Subjects with any drug-related TEAE	**41 (24.8)**	**48 (28.4)**	**89 (26.6)**
Blood and lymphatic system disorders	**4 (2.4)**	**6 (3.6)**	**10 (3.0)**
Febrile neutropenia	2 (1.2)	1 (0.6)	3 (0.9)
Thrombocytopenia	0	2 (1.2)	2 (0.6)
Gastrointestinal disorders	**11 (6.7)**	**4 (2.4)**	**15 (4.5)**
Diarrhoea	2 (1.2)	0	2 (0.6)
Abdominal pain	3 (1.8)	3 (1.8)	6 (1.8)
Enterocolitis	2 (1.2)	0	2 (0.6)
Nausea	2 (1.2)	0	2 (0.6)
General disorders and administration site conditions	**4 (2.4)**	**4 (2.4)**	**8 (2.4)**
Pyrexia	1 (0.6)	3 (1.8)	4 (1.2)
Hepatobiliary disorders	**3 (1.8)**	**4 (2.4)**	**7 (2.1)**
Hyperbilirubinaemia	0	3 (1.8)	3 (0.9)
Hepatic function abnormal	3 (1.8)	1 (0.6)	4 (1.2)
Immune system disorders	**9 (5.5)**	**5 (3.0)**	**14 (4.2)**
Acute graft versus host disease in intestine	3 (1.8)	1 (0.6)	4 (1.2)
Acute graft versus host disease in skin	2 (1.2)	0	2 (0.6)
Chronic graft versus host disease in liver	0	2 (1.2)	2 (0.6)
Infections and infestations	**6 (3.6)**	**11 (6.5)**	**17 (5.1)**
Cytomegalovirus infection reactivation	1 (0.6)	2 (1.2)	3 (0.9)
Pneumonia	1 (0.6)	2 (1.2)	3 (0.9)

Drug related TEAEs

Table 12.f The Most Commonly Reported (≥1% of Subjects in Any Treatment Group) Drug-Related TEAEs by SOC and PT – SAF

SOC PT	Number (%) of Subjects Placebo (N = 165)	 Vedolizumab (N = 169)	 Total (N = 334)
Injury, poisoning and procedural complications	**0**	**2 (1.2)**	**2 (0.6)**
Investigations	**13 (7.9)**	**10 (5.9)**	**23 (6.9)**
Alanine aminotransferase increased	5 (3.0)	4 (2.4)	9 (2.7)
Aspartate aminotransferase increased	3 (1.8)	5 (3.0)	8 (2.4)
Blood bilirubin increased	1 (0.6)	2 (1.2)	3 (0.9)
Blood alkaline phosphatase increased	0	2 (1.2)	2 (0.6)
T-lymphocyte count decreased	2 (1.2)	0	2 (0.6)
Musculoskeletal and connective tissue disorders	**1 (0.6)**	**3 (1.8)**	**4 (1.2)**
Nervous system disorders	**2 (1.2)**	**3 (1.8)**	**5 (1.5)**
Headache	0	2 (1.2)	2 (0.6)
Reproductive system and breast disorders	**2 (1.2)**	**2 (1.2)**	**4 (1.2)**
Respiratory, thoracic and mediastinal disorders	**0**	**2 (1.2)**	**2 (0.6)**
Skin and subcutaneous tissue disorders	**4 (2.4)**	**6 (3.6)**	**10 (3.0)**
Rash	2 (1.2)	2 (1.2)	4 (1.2)

Source: Table 15.3.1.4.

AE: adverse event; HLT: High-Level Term; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAF: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

Subjects with 1 or more AE within a level of MedDRA term were counted only once in that level. MedDRA Dictionary (version 24.0) was used for coding AEs. TEAE was defined as any AE that started or worsened after administration of the first dose of study drug and up through 18 weeks after the last dose of study drug. SOC and HLTs were sorted using alphabetical order, and PTs were sorted in decreasing frequency based on the total number of subjects.

Drug related TEAEs-grade 3 or higher

Table 12.g The Most Commonly Reported (≥1% of Subjects in Any Treatment Group) Grade 3 or Higher Drug-Related TEAEs by SOC and PT – SAF

SOC PT	Number (%) of Subjects Placebo (N = 165)	 Vedolizumab (N = 169)	 Total (N = 334)
Subjects with at least 1 Grade 3 or higher drug-related TEAE	**19 (11.5)**	**18 (10.7)**	**37 (11.1)**
Blood and lymphatic system disorders	**4 (2.4)**	**5 (3.0)**	**9 (2.7)**
Febrile neutropenia	2 (1.2)	0	2 (0.6)
Thrombocytopenia	0	2 (1.2)	2 (0.6)
Immune system disorders	**5 (3.0)**	**1 (0.6)**	**6 (1.8)**
Acute graft versus host disease in intestine	2 (1.2)	1 (0.6)	3 (0.9)
Infections and infestations	**4 (2.4)**	**5 (3.0)**	**9 (2.7)**
Injury, poisoning and procedural complications	**0**	**2 (1.2)**	**2 (0.6)**
Investigations	**6 (3.6)**	**2 (1.2)**	**8 (2.4)**
Alanine aminotransferase increased	2 (1.2)	1 (0.6)	3 (0.9)
Musculoskeletal and connective tissue disorders	**0**	**2 (1.2)**	**2 (0.6)**

Source: Table 15.3.1.15.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAF: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

Subjects with 1 or more AE within a level of MedDRA term were counted only once in that level. MedDRA Dictionary (version 24.0) was used for coding AEs. TEAE was defined as any AE that started or worsened after administration of the first dose of study drug and up through 18 weeks after the last dose of study drug.

Study Drug-Related TEAEs

Overall, 26.6% (89 of 334) of subjects had a TEAE considered by the investigator to be related to study drug (48 of 169 subjects [28.4%] in the vedolizumab IV group and 41 of 165 subjects [24.8%] in the placebo group) (Table 12.c). Study drug-related TEAEs were similar between the vedolizumab IV and placebo groups.

The most frequently reported study drug-related TEAEs, by SOC, were investigations (5.9% in the vedolizumab IV group, 7.9% in the placebo group), infections and infestations (6.5% in the

vedolizumab IV group, 3.6% in the placebo group), gastrointestinal disorders (2.4% in the vedolizumab IV group, 6.7% in the placebo group), immune system disorders (3.0% in the vedolizumab IV group, 5.5% in the placebo group), blood and lymphatic system disorders (3.6% in the vedolizumab IV group, 2.4% in the placebo group), and skin and subcutaneous tissue disorders (3.6% in the vedolizumab IV group, 2.4% in the placebo group) (Table 12.f).

AEs by Intensity

Overall, 1756 TEAEs in 303 subjects were Grade 3 or higher in intensity (Table 12.c above); 156 subjects (92.3%) in the vedolizumab IV group had 873 Grade 3 or higher events, and 147 subjects (89.1%) in the placebo group had 883 such events.

Grade 3 or higher TEAEs were similar between the vedolizumab IV group and the placebo group. The most commonly reported Grade 3 or higher TEAEs, by SOC, were blood and lymphatic system disorders (62.1% in the vedolizumab IV group, 64.2% in the placebo group), gastrointestinal disorders (40.2% in the vedolizumab IV group, 44.8% in the placebo group), investigations (37.9% in the vedolizumab IV group, 40.0% in the placebo group), infections and infestations (35.5% in the vedolizumab IV group, 37.0% in the placebo group), and metabolism and nutrition disorders (21.9% in the vedolizumab IV group, 23.0% in the placebo group).

The most commonly reported Grade 3 or higher TEAEs, by PT, were anaemia (29.6% in the vedolizumab IV group, 31.5% in the placebo group), febrile neutropenia (31.4% in the vedolizumab IV group, 29.7% in the placebo group), stomatitis (27.2% in the vedolizumab IV group, 26.7% in the placebo group), platelet count decreased (21.9% in the vedolizumab IV group, 24.8% in the placebo group), neutropenia (17.2% in the vedolizumab IV group, 17.0% in the placebo group), and thrombocytopenia (17.8% in the vedolizumab IV group, 16.4% in the placebo group) (Table 15.3.1.14). All other Grade 3 or higher TEAEs were each reported for 29 subjects or fewer in the vedolizumab IV group.

No clinically meaningful difference in Grade 3 or higher TEAEs were found between the vedolizumab IV group and the placebo group.

Treatment-Emergent AESIs

Overall, 321 subjects (96.1%) reported a total of 1635 treatment-emergent AESIs; 161 subjects [95.3%] in the vedolizumab IV group reported 857 treatment-emergent AESIs, and 160 subjects [97.0%] in the placebo group reported 778 treatment-emergent AESIs. The treatment-emergent AESI data suggest comparable safety profiles between the vedolizumab IV group and the placebo group.

Table 12.h Overview of Treatment-Emergent AESIs – SAF

	Placebo (N = 165)		Vedolizumab (N = 169)		Total (N = 334)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Subjects with any AESI	778	160 (97.0)	857	161 (95.3)	1635	321 (96.1)
Serious infections	297	111 (67.3)	336	125 (74.0)	633	236 (70.7)
PML	2	2 (1.2)	3	3 (1.8)	5	5 (1.5)
Malignancy	36	26 (15.8)	35	29 (17.2)	71	55 (16.5)
Liver injuries	124	69 (41.8)	168	68 (40.2)	292	137 (41.0)
Hypersensitivity reactions including IRRs and injection site reactions	315	136 (82.4)	303	134 (79.3)	618	270 (80.8)
Leukopenia or lymphopenia	7	7 (4.2)	19	14 (8.3)	26	21 (6.3)
CMV colitis	2	1 (0.6)	1	1 (0.6)	3	2 (0.6)
CMV reactivation	54	38 (23.0)	61	45 (26.6)	115	83 (24.9)

Source: Table 15.3.1.20.

AESI: adverse event of special interest; CMV: cytomegalovirus; IRR: infusion-related reaction; MedDRA: Medical Dictionary for Regulatory Activities; PML: progressive multifocal leukoencephalopathy; SAF: safety analysis set.
Subjects with 1 or more adverse events within a level of MedDRA term are counted only once in that level.
The treatment-emergent period is defined as the period from administration of the first dose of study drug and up through 18 weeks after the last dose of study medication.
MedDRA Dictionary (Version 24.0) was used for coding adverse events.

Serious Infections

A total of 633 treatment-emergent AESIs of serious infection were reported for 236 subjects (70.7%) overall, with a numerically higher incidence in the vedolizumab IV group (125 subjects [74.0%]) compared with the placebo group (111 subjects [67.3%]).

The most commonly reported treatment-emergent serious infections, by PT, were CMV infection reactivation (23.7% in the vedolizumab IV group, 18.2% in the placebo group), pneumonia (7.7% in the vedolizumab IV group, 8.5% in the placebo group), sepsis (5.3% in the vedolizumab IV group, 7.3% in the placebo group), Candida infection (4.7% in the vedolizumab IV group, 4.2% in the placebo group), urinary tract infection (3.6% in the vedolizumab IV group, 4.8% in the placebo group), Epstein-Barr virus infection reactivation (4.1% in the vedolizumab IV group, 3.6% in the placebo group), nasopharyngitis (5.3% in the vedolizumab IV group, 2.4% in the placebo group), Clostridium difficile infection (5.9% in the vedolizumab IV group, 1.2% in the placebo group), and conjunctivitis (3.6% in each treatment group).

Seven subjects in the vedolizumab IV group had at least 1 SAE of pneumonia (including PTs of Pneumocystis jiroveci pneumonia, pneumonia pseudomonal, pneumonia bacterial, organising pneumonia, and pneumonia pneumococcal); 3 subjects had 2 SAEs of pneumonia, and 1 subject had 3 events. Ten events resolved or were resolving at study completion, and 1 subject died. Two of the SAEs of pneumonia were considered related to study drug; for both events, study drug was withdrawn. No other SAEs of pneumonia were related to study drug.

Seven subjects in the vedolizumab IV group had at least 1 SAE of sepsis (including PTs of staphylococcal sepsis and Klebsiella sepsis) (Listing 16.2.7.3). Six events resolved or were resolving at study completion, and 1 event did not resolve. None of the events were related to study drug.

One subject in the vedolizumab IV group had an SAE of urinary tract infection. The event resolved and was not considered related to study drug.

PML

A total of 3 subjects (1.8%) in the vedolizumab IV group and 2 subjects (1.2%) in the placebo group were listed as having "PML" in the clinical trial database (Table 12.h). In none of these cases was PML

listed as a PT; however, all were identified because they were reported to have had a TEAE (by PT) of Human polyomavirus infection. This PT was included as an event under the definition of an AESI, possibly suggestive of PML. An additional subject was confirmed as having PML. This subject had an AML status posttransplant and received a total of 6 doses of vedolizumab IV. Approximately 6 months after the last dose of vedolizumab IV, the subject developed AML relapse and aGvHD, for which the subject received intense immunosuppressive therapy with IV steroids, tacrolimus, and azacytidine. Approximately 1 month later, the subject developed the SAE of PML, with a fatal outcome. The investigator and the IAC deemed that the event of PML was due to acute GvHD and "heavy" immunosuppression treatment that was unrelated to vedolizumab IV. This case is not listed as a TEAE of PML (by PT) in the clinical trial database because the event of PML occurred more than 18 weeks after the last dose of study drug. The subject died after completing the study.

Malignancy

Malignancies, including relapse of the primary disease, were captured as AESIs and presented by SOC, HLT, and PT.

A total of 71 treatment-emergent AESIs of malignancy were reported for 55 subjects (16.5%) overall (29 subjects [17.2%] in the vedolizumab IV group and 26 subjects [15.8%] in the placebo group) (Table 12.h). Treatment-emergent AESIs of malignancy were similar between the vedolizumab IV group and the placebo group and consistent with a population of subjects undergoing allo-HSCT.

The most common treatment-emergent AESIs of malignancy, by PT, were acute myeloid leukaemia recurrent (5.9% in the vedolizumab IV group, 5.5% in the placebo group), myelodysplastic syndrome (3.0% in the vedolizumab IV group, 1.8% in the placebo group), acute lymphocytic leukaemia recurrent (1.8% in the vedolizumab IV group, 0.6% in the placebo group), chronic myeloid leukaemia recurrent (1.8% in the vedolizumab IV group 0.6% in the placebo group), and posttransplant lymphoproliferative disorder (none in the vedolizumab IV group, 1.8% in the placebo group).

Liver Injuries

A total of 292 treatment-emergent AESIs of liver injury were reported for 137 subjects (41.0%) overall (68 subjects [40.2%] in the vedolizumab IV group and 69 subjects [41.8%] in the placebo group) (Table 12.h). Treatment-emergent liver injuries, by SOC, included investigations (33.7% in the vedolizumab IV group, 33.3% in the placebo group), hepatobiliary disorders (10.1% in the vedolizumab IV group, 8.5% in the placebo group), and gastrointestinal disorders (0.6% in the vedolizumab IV group, 2.4% in the placebo group). The most common treatment-emergent AESIs of liver injury, by PT, were alanine aminotransferase increased (24.9% in the vedolizumab IV group, 17.6% in the placebo group), aspartate aminotransferase increased (18.9% in the vedolizumab IV group, 15.8% in the placebo group), blood bilirubin increased (13.0% in the vedolizumab IV group, 16.4% in the placebo group), hepatic function abnormal (4.1% in the vedolizumab IV group, 6.7% in the placebo group), gamma-glutamyltransferase increased (4.1% in the vedolizumab IV group, 2.4% in the placebo group), and hyperbilirubinaemia (5.3% in the vedolizumab IV group, none in the placebo group).

Hypersensitivity Reactions Including IRRs and Injection Site Reactions

A total of 618 treatment-emergent AESIs of hypersensitivity reactions including IRRs and injection site reactions were reported for 270 subjects (80.8%) overall (134 subjects [79.3%] in the vedolizumab IV group and 136 subjects [82.4%] in the placebo group) (Table 12.h). The high incidence of hypersensitivity reactions is confounded by the background/conditioning regimen that was administered 1 day before study drug dosing.

The most common treatment-emergent AESIs of hypersensitivity reactions including IRRs and injection site reactions, by SOC, were gastrointestinal disorders (55.0% in the vedolizumab IV group, 57.6% in the placebo group); skin and subcutaneous tissue disorders (27.8% in the vedolizumab IV group, 30.9% in the placebo group); general disorders and administration site conditions (26.6% in the vedolizumab IV group, 31.5% in the placebo group); renal and urinary disorders (16.0% in the vedolizumab IV group, 18.8% in the placebo group); and respiratory, thoracic and mediastinal disorders (8.9% in the vedolizumab IV group, 7.3% in the placebo group).

The most common treatment-emergent AESIs of hypersensitivity reactions including IRRs and injection site reactions, by PT, were stomatitis (54.4% in the vedolizumab IV group, 56.4% in the placebo group), oedema peripheral (17.2% in the vedolizumab IV group, 21.1% in the placebo group), pruritus (16.6% in the vedolizumab IV group, 20.0% in the placebo group), acute kidney injury (14.2% in the vedolizumab IV group, 15.8% in the placebo group), and erythema (13.6% in the vedolizumab IV group, 7.9% in the placebo group).

Leukopenia or Lymphopenia

A total of 26 treatment-emergent AESIs of leukopenia and lymphopenia were reported for 21 subjects (6.3%) overall, which is consistent with the patient population (subjects undergoing allo-HSCT and taking concomitant immunosuppressants). There were 14 subjects (8.3%) in the vedolizumab IV group and 7 subjects (4.2%) in the placebo group with an AESI of leukopenia or lymphopenia (Table 12.h).

Nine subjects (5.3%) in the vedolizumab IV group and 6 subjects (3.6%) in the placebo group had a treatment-emergent AESI of leukopenia. Five subjects (3.0%) in the vedolizumab IV group and 1 subject (0.6%) in the placebo group had a treatment-emergent AESI of lymphopenia (Table 15.3.1.26). Although the incidence of leukopenia and lymphopenia were numerically higher in the vedolizumab IV group compared with the placebo group, no clinically meaningful difference was observed between treatment groups given the small number of subjects with at least 1 event of leukopenia or lymphopenia.

CMV Reactivation

A total of 115 treatment-emergent AESIs of CMV reactivation were reported for 83 subjects (24.9%) overall (45 subjects [26.6%] in the vedolizumab IV group and 38 subjects [23.0%] in the placebo group) (Table 12.h). Forty subjects (23.7%) in the vedolizumab IV group and 30 subjects (18.2%) in the placebo group had CMV infection reactivation; 3 subjects (1.8%) in each treatment group had CMV infection, 1 subject (0.6%) in the vedolizumab IV group and 3 subjects (1.8%) in the placebo group had CMV viraemia, and 1 subject (0.6%) in the vedolizumab IV group and 3 subjects (1.8%) in the placebo group had CMV test positive. In the vedolizumab IV group, 7 subjects had 9 SAEs of CMV reactivation or active CMV infection (verbatim terms) that required or prolonged hospitalization. In the placebo group, 2 subjects each had 1 SAE of CMV reactivation. All 9 SAEs in the vedolizumab IV group resolved or were resolving at study completion, and no event led to study drug interruption. None of the events were related to study drug.

Deaths

A total of 65 subjects (19.5% of the SAF) who participated in this study died. A total of 48 subjects had a TEAE resulting in death (21 subjects [12.4%] in the vedolizumab IV group and 27 subjects [16.4%] in the placebo group) (Table 12.i). The treatment-emergent period (for TEAEs) was defined as the period from administration of the first dose of study drug through 18 weeks after the last dose of study drug. The leading causes of death included multiple organ dysfunction syndrome (3.0% in the vedolizumab IV group, 1.8% in the placebo group), acute myeloid leukaemia recurrent (0.6% in the vedolizumab IV group, 2.4% in the placebo group), respiratory failure (1.8% in the vedolizumab IV group, 1.2% in the placebo group), pneumonia (1.2% each in both treatment groups), and sepsis (no

subjects in the vedolizumab IV group, 1.8% in the placebo group). All other causes of death occurred in 2 subjects (0.6%) or fewer overall. None of the TEAEs resulting in death in the vedolizumab IV group were considered by the investigator to be related to study drug (Listing 16.2.7.5).

An additional 17 subjects (5.1%) died after the 6-month treatment-emergent period (ie, 18+ weeks after the last dose of study drug): 8 subjects (4.7%) in the vedolizumab IV group and 9 subjects (5.5%) in the placebo group.

Table 12.i TEAEs Resulting in Death by PT – SAF

	Number (%) of Subjects		
PT	Placebo (N = 165)	Vedolizumab (N = 169)	Total (N = 334)
Deaths during the treatment-emergent period	**27 (16.4)**	**21 (12.4)**	**48 (14.4)**
Multiple organ dysfunction syndrome	3 (1.8)	5 (3.0)	8 (2.4)
Acute myeloid leukaemia recurrent	4 (2.4)	1 (0.6)	5 (1.5)
Respiratory failure	2 (1.2)	3 (1.8)	5 (1.5)
Pneumonia	2 (1.2)	2 (1.2)	4 (1.2)
Sepsis	3 (1.8)	0	3 (0.9)
Acute graft versus host disease in intestine	2 (1.2)	0	2 (0.6)
Acute graft versus host disease in liver	1 (0.6)	1 (0.6)	2 (0.6)
Myelodysplastic syndrome	1 (0.6)	1 (0.6)	2 (0.6)
T-cell lymphoma recurrent	2 (1.2)	0	2 (0.6)
Acute graft versus host disease	0	1 (0.6)	1 (0.3)
Acute lymphocytic leukaemia recurrent	1 (0.6)	0	1 (0.3)
Acute respiratory distress syndrome	0	1 (0.6)	1 (0.3)
Cardiac arrest	0	1 (0.6)	1 (0.3)
Cardiac failure	0	1 (0.6)	1 (0.3)
Cardiopulmonary failure	1 (0.6)	0	1 (0.3)
Chronic myeloid leukaemia recurrent	0	1 (0.6)	1 (0.3)
Escherichia sepsis	1 (0.6)	0	1 (0.3)
Febrile neutropenia	0	1 (0.6)	1 (0.3)
Hepatic failure	1 (0.6)	0	1 (0.3)
Interstitial lung disease	1 (0.6)	0	1 (0.3)
Ischaemic stroke	0	1 (0.6)	1 (0.3)
Pneumonitis	1 (0.6)	0	1 (0.3)
Post transplant lymphoproliferative disorder	1 (0.6)	0	1 (0.3)
Respiratory tract infection	1 (0.6)	0	1 (0.3)
Septic encephalopathy	0	1 (0.6)	1 (0.3)

Source: Tables 15.3.1.18 and 15.3.1.19.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Subjects with 1 or more AEs within a level of MedDRA term were counted only once in that level. MedDRA Dictionary (version 24.0) was used for coding AEs. The treatment-emergent period was defined as the period from administration of the first dose of study drug through 18 weeks after the last dose of study drug. PTs are sorted in decreasing frequency based on the total number of subjects.

Other SAEs

Table 12.j Most Frequent Serious TEAEs (≥5% in Any Treatment Group) by PT – SAF

PT	Number (%) of Subjects		
	Placebo (N = 165)	Vedolizumab (N = 169)	Total (N = 334)
Subjects with at least 1 serious TEAE	**114 (69.1)**	**120 (71.0)**	**234 (70.1)**
Pyrexia	13 (7.9)	13 (7.7)	26 (7.8)
Acute graft versus host disease in intestine	16 (9.7)	6 (3.6)	22 (6.6)
Acute myeloid leukaemia recurrent	9 (5.5)	9 (5.3)	18 (5.4)
Alanine aminotransferase increased	4 (2.4)	9 (5.3)	13 (3.9)
Sepsis	9 (5.5)	4 (2.4)	13 (3.9)

Source: Table 15.3.1.5.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAF: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

Subjects with 1 or more AEs within a level of MedDRA term were counted only once in that level. MedDRA Dictionary (version 24.0) was used for coding AEs. TEAE was defined as any AE newly occurring or worsening after administration of the first dose of study drug through 18 weeks after the last dose of study drug. SOCs were sorted using alphabetical order, and PTs were sorted in decreasing frequency based on the total number of subjects.

Serious drug-related TEAE

Table 12.k Serious Drug-Related TEAEs by SOC and PT – SAF

SOC PT	Number (%) of Subjects		
	Placebo (N = 165)	Vedolizumab (N = 169)	Total (N = 334)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (0.6)**	**1 (0.3)**
Chronic myeloid leukaemia recurrent	0	1 (0.6)	1 (0.3)
Skin and subcutaneous tissue disorders	**1 (0.6)**	**0**	**1 (0.3)**
Rash macular	1 (0.6)	0	1 (0.3)

Source: Table 15.3.1.9.

AE: adverse event; incl: including; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAF: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

Subjects with 1 or more AEs within a level of MedDRA term were counted only once in that level. MedDRA Dictionary (version 24.0) was used for coding AEs. SOCs were sorted using alphabetical order and PTs were sorted in decreasing frequency based on the total number of subjects.

A total of 62 subjects (18.6%) had at least 1 SAE beyond the treatment-emergent period (ie, 18 weeks after the last dose of study drug): 36 subjects (21.3%) in the vedolizumab IV group and 26 subjects (15.8%) in the placebo group.

Reported SAEs beyond the treatment-emergent period were similar between treatment groups; most events occurred in only 1 subject per treatment group at the PT level.

Serious COVID-19–Related TEAEs

Overall, 2 subjects (0.6%) had at least 1 serious COVID-19–related TEAE; 1 subject in each treatment group. No clinically meaningful difference in COVID-19–related TEAEs was observed between treatment groups.

TEAEs Leading to Study Drug Discontinuation

Overall, 95 subjects (28.4%) had at least 1 TEAE leading to study drug discontinuation; 44 subjects (26.0%) in the vedolizumab IV group and 51 subjects (30.9%) in the placebo group.

The most frequently reported TEAEs leading to study drug discontinuation, by SOC, were immune system disorders (5.3% in the vedolizumab IV group, 12.1% in the placebo group); neoplasms benign, malignant and unspecified (incl cysts and polyps) (7.1% in the vedolizumab IV group, 6.7% in the placebo group); investigations (3.6% in the vedolizumab IV group, 2.4% in the placebo group);

infections and infestations (2.4% in the vedolizumab IV group, 3.0% in the placebo group); and respiratory, thoracic and mediastinal disorders (1.8% in each treatment group).

The most frequently reported TEAEs leading to study drug discontinuation, by PT, were acute graft versus host disease in intestine (1.2% in the vedolizumab IV group, 7.3% in the placebo group), acute myeloid leukaemia recurrent (2.4% in the vedolizumab IV group, 3.0% in the placebo group), alanine aminotransferase increased (3.6% in the vedolizumab IV group, 0.6% in the placebo group), and acute graft versus host disease (1.8% in the vedolizumab IV group and 1.2% in the placebo group) (Table 12.l). All other events were reported for 4 subjects or fewer overall.

Clinical Laboratory Evaluations

Serum Chemistry

Liver injury has been reported among AESI.

Kidney: a total of 50 subjects (15.0%) overall had at least 1 AESI of acute kidney injury: 24 subjects (14.2%) in the vedolizumab IV group and 26 subjects (15.8%) in the placebo group. Twenty-three subjects (13.6%) in the vedolizumab IV group had markedly abnormal creatinine values throughout the study compared with 22 subjects (13.3%) in the placebo group.

Hematology

In general, markedly abnormal hematology results were similar between treatment groups throughout the study.

Failure to engraft by Day +28 was considered as primary graft failure and was reported as an SAE. Most study subjects (97.3% overall) had a successful engraftment. Three subjects in the vedolizumab IV group and none in the placebo group had a life-threatening SAE of engraftment. For 2 of the 3 subjects, the event occurred in the treatment-emergent period; study drug was therefore withdrawn. None of the events were considered by the investigator to be related to study drug, and all subjects recovered.

Neutrophil engraftment, defined as absolute neutrophil count >500/mm3 for 3 consecutive days or >2000/mm3 for 1 day, occurred in 97.3% of all subjects (165 subjects [97.6%] in the vedolizumab IV group and 160 subjects [97.0%] in the placebo group) (Table 15.3.2.9). Overall, 5 subjects (1.5%) did not recover (2 in the vedolizumab IV group and 3 in the placebo group), and 3 subjects (0.9%) were not applicable for analysis. The overall mean (SD) number of days to engraftment was 16.8 (4.6) days, which was similar between treatment groups (17.1 [4.58] days for the vedolizumab IV group and 16.5 [4.60] days for the placebo group).

Platelet engraftment, defined as a platelet count >20,000 cells/mm3 without transfusion, occurred in 91.9% of all subjects (159 subjects [94.1%] in the vedolizumab IV group and 148 subjects [89.7%] in the placebo group). Four and 12 subjects did not recover in the vedolizumab IV and placebo groups, respectively, and 4 subjects from each treatment group were not applicable for analysis. The overall mean (SD) number of days to platelet recovery was 21.4 (20.02) days, which was similar between treatment groups (22.0 [17.51] days for the vedolizumab IV group and 20.9 [22.41] days for the placebo group). Additionally, markedly abnormal platelets (109/L) were similar between treatment groups throughout the study; a total of 158 subjects (93.5%) in the vedolizumab IV group and 155 subjects (93.9%) had low platelet values during the study, with the majority of subjects reporting low values at the Day +1 (76.0% overall) and Day +20 (61.% overall) visits.

Vital Signs

Overall, no clinically meaningful differences in mean changes from baseline for vital signs were observed

Pregnancy

No pregnancies were reported during this study.

Immunogenicity

A summary of AVA status is presented in Table 11.w.

Table 11.w Summary of AVA Status – FAS

	Number of Subjects (%)
	Vedolizumab (N = 168)
Number of subjects with at least 1 nonmissing AVA sample	168
AVA negative (%)	164 (97.6)
AVA positive (%)	4 (2.4)
Transient positive (%) [a]	3 (1.8)
Persistently positive (%) [a]	1 (0.6)
AVA positive neutralizing [a]	2 (1.2)

Source: Table 15.2.37.1.
AVA: antivedolizumab antibody; FAS: full analysis set.
Negative AVA was defined as a sample that was evaluated as negative in the AVA screening assay or samples that were determined to be positive in the AVA screening assay, but the result was not confirmed in the AVA confirmatory assay.
Positive AVA was defined as a sample that was evaluated as positive in both the AVA screening and confirmatory assays. Transiently positive was defined as patients with a confirmed positive AVA in at least 1 sample, but not consecutive samples. Persistently positive was defined as patients with confirmed positive AVA in 2 or more consecutive samples. Positive neutralizing AVA was defined as a sample that was evaluated as positive in the neutralizing AVA assay. AVA positive at baseline was defined as a positive AVA sample before the first dose of study drug administration.
[a] Percentage was calculated using the number of subjects with at least one nonmissing AVA sample as the denominator.

The overall positive AVA rate in subjects who were treated with vedolizumab via IV infusion was 2.4% (4 of 168 subjects). In the vedolizumab IV group, only 1 of the 168 AVA positive subjects was persistently positive (0.6%), and 2 of the 168 subjects developed neutralizing antibodies (1.2%).

PK Related to AVA Status The development of persistent AVA was associated with a decrease in vedolizumab serum trough concentrations.

Safety Related to AVA Status There was no relationship between AVA status and investigator defined infusion-related eactions.

Efficacy Related to AVA Status

There was no relationship between AVA-positive status and efficacy of vedolizumab IV.

Discussion on clinical aspects

Study Vedolizumab-3035 was included in Paediatric Investigation Plan (PIP) EMEA-000645-PIP03-18. The age entry criteria for this study included subjects aged ≥12 years and weighing ≥30 kg at the time of randomization.

Enrollment was terminated early (343 subjects had been enrolled (of the estimated target 558 subjects) with a total of 71 primary endpoint events accrued (of the anticipated 148 events), and the study completed on 09 May 2022, primarily due to low subject recruitment and enrollment during the COVID-19 pandemic (since February 2020). The decision was influenced by multiple factors, none of which were related to safety concerns regarding the use of vedolizumab in this patient population. All enrolled subjects were allowed to complete the study as per the protocol.

The reduced number of enrolled patients has affected the strength and reproducibility of the results, especially for subgroup analyses. Moreover, the absence (only 1 subject in the Placebo arm) of paediatric population did not allow to make any conclusion for the paediatric setting.

The MAH decided to discontinue development of vedolizumab for use in this condition, in both adults and paediatrics.

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

The study consisted 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 that were completed by 12 months after allo-HSCT. The study design is considered appropriate.

Randomization followed a 1:1 fashion to 2 treatment and was stratified by age (≥18 years or adolescents aged 12 to <18 years), human leukocyte antigen (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 were enrolled in 25 countries worldwide (19 sites in North America, 45 in Europe/Israel, 24 in Asia/Australia, and 7 in South America), with a good representation of EU sites.

Dose The vedolizumab dose and regimen in this phase 3 study was 300 mg on Day -1 before allo-HSCT and Days +13, +41, +69, +97, +125, and +153 after allo-HSCT. The end-of-treatment visit was conducted on Day +180 after allo-HSCT. The selected dose was based on as based on results from Study 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. The duration of vedolizumab prophylaxis in this study design was intended to provide coverage during the posttransplant period, when subjects are at risk of developing classic and late aGvHD.

The same vedolizumab dose regimen administered to adults (aged ≥18 years) who underwent allo-HSCT for prophylaxis of intestinal aGvHD was considered appropriate for administration to adolescents aged ≥12 years and weighing ≥30 kg.

Supportive data on the use of the same dose of adults in adolescents are from: i) the phase 3 studies in adults with IBD, body weights ranged from 28.7 to 170 kg, there was no difference in the safety profile in adults receiving vedolizumab IV every 8 weeks or every 4 weeks; ii) a population PK model in adults with UC or CD indicated that weight-based dosing is not required and that age is not a clinically meaningful covariate.

Background GvHD prophylaxis consisting of a combination of CNI (CYS or TAC) and MTX or MMF, ATG (ATG-F or thymoglobulin) was permissible in prophylaxis therapy per institutional practice is acceptable.

Study population

A substantial protocol amendment 7 (Dated 18 September 2019) was made to open enrollment to adolescent subjects aged ≥12 years and weighing ≥30 kg.

The selection criteria of the study resulted appropriate and included patients with a high risk of development of intestinal aGVHD, related to poor outcomes, mortality. The inclusion criteria respected the common standard clinical practice in stem cell transplantation; similarly, the allowed medical care for prophylaxis of aGVHD is in line with current international guidelines. In the exclusion criteria, the most important causes of infections that could mimic intestinal aGVHD were excluded (CMV and Clostridium Difficile infection), ensuring a reduction of interpretation bias.

Notably, the underlying primary haematologic diseases included in this trial are more frequent in the adult setting than in the paediatric one (except for acute lymphoblastic leukaemia or some types of lymphomas).

A sample size of 279 subjects per group (558 subjects total) was expected to generate 148 events for the intestinal aGvHD-free survival, and provide 90% power at the alpha of 0.05 for a 2-sided hypothesis based on log-rank test. For the primary and key secondary endpoints a hierarchy of the statistical testing was established and testing of the additional efficacy endpoints were not multiplicity adjusted.

Disposition of Subjects A total of 343 subjects were randomized to study drug. 187 (54.5% of total) completed 7 doses of IV study drug. The primary reasons for discontinuation from study drug were AEs (34.8% in the vedolizumab IV group, 25.9% in the placebo group), death (24.2% in the vedolizumab IV group, 23.5% in the placebo group) unsatisfactory therapeutic response (lack of efficacy) (16.7% in the vedolizumab IV group, 27.2% in the placebo group), and withdrawal by subjects (12.1% in the vedolizumab IV group, 11.1% in the placebo group).

A total of 282 subjects (82.2%) completed the Day +180 visit (ie, through the end of the treatment period). The majority of subjects who discontinued study drug (42.9%) also discontinued the study. The reasons for discontinuation of the study and of drug treatment were similar for each treatment group.

Seventy-six subjects from each treatment group had at least 1 significant protocol deviation (152 subjects overall [44.3%]); the most common significant protocol deviations, not related to the COVID-19 pandemic, were related to procedures not performed per protocol, which occurred in 91 subjects overall (26.5%) similarly distributed between vedolizumab and placebo groups.

Reasons for significant protocol deviation as a result of the COVID-19 pandemic included procedures not per protocol (10 subjects, 2.9%), a missed visit (5 subjects, 1.5%), informed consent (3 subjects, 0.9%), and study inclusion/exclusion criteria (1 subject, 0.3%). The overall number of significant deviations appear high potentially impacting the quality of the study.

Overall, demographic data were well balanced between the vedolizumab IV group and the placebo group; with the exception of gender, (more male than female subjects, 62.8% vs 37.2%), and ethnicity (majority of subjects were white,70.6%, and non-Hispanic or Latino, 79.9%). Regarding.

Baseline demographic and disease characteristics

Demographic data resulted well balanced between the vedolizumab and the placebo group, with the exception of gender and ethnicity. It is important to highlight that gender is not recognized, per se, as a risk factor for aGVHD, but the specific gender discrepancy between female donor-male recipient is associated with an increased risk of GVHD. Overall, this specific population (female donor/male recipient) has been well balanced between the two treatment arms, so that gender discrepancy does not affect the results.

Regarding the prevalence of the Caucasian ethnicity, this datum could be a consequence of the ethnicity bias associated with the search of matched stem cell donor: it is widely known that patients of Caucasian ethnicities have a higher probability of matching a suitable donor as a direct consequence of the higher number of Caucasian donors in the IBMDR registry.

The median age, it was of 55.0 years overall (16-74), with only one patient aged < 18 years enrolled in the placebo group: this limitation did not allow to perform any evaluation about the possible role of vedolizumab in the adolescent setting. All the other age group were well represented and balanced between the two treatments groups.

Overall, there were a good balance of the possible risk factors for the development of intestinal aGVHD (HLA match 7/8, Myeloablative Conditioning, absence of ATG prophylaxis) between vedolizumab and placebo groups, as well as for the main risk factors for disease relapse (adverse cytogenetic, disease status at ASCT).

The medication history, the concomitant medications, and the frequency of choice of stem cell source were in line with the common medical practice. Regarding the use of ATG in prophylaxis, its use was well balanced between the two groups, although the total number of subjects receiving ATG was higher in respect to what defined at baseline. It reasonable to assume that this datum could not have influenced the results between the two treatment arms.

Efficacy data

The primary endpoint (intestinal aGvHD-free survival by Day +180 after allo-HSCT) showed a statistically significant difference between the vedolizumab IV group and the placebo group in intestinal aGvHD-free survival by Day +180 after allo-HSCT (p <0.001). The risk of an intestinal aGvHD event or death in subjects was 55% less in the vedolizumab IV group compared with the placebo group (HR, 0.45; 95% CI of HR, 0.27-0.73). In the vedolizumab IV group, there were 24 subjects (14.3%) with an observed event of intestinal aGvHD or death (any cause), whichever occurred first, by Day +180 after allo-HSCT; in the placebo group, there were 47 subjects (28.5%) with an observed event. Of those subjects, 12 (7.1%) from the vedolizumab IV group and 31 (28.8%) from the placebo group had an intestinal aGvHD event, and 12 subjects (7.1%) from the vedolizumab IV group and 16 subjects (9.7%) from the placebo group died.

A consistent figure is shown by day +365 (exploratory endpoint, nominal p = 0.0041; HR, 0.53 [95% CI of HR, 0.35-0.81]).

A a statistically significant difference between the vedolizumab IV group and the placebo group is shown by the first key secondary endpoint (intestinal aGvHD-free and relapse-free, of the underlying malignancy, survival by day +180) (p = 0.0043). The risk of an event in subjects was 44% less in the vedolizumab IV group compared with the placebo group (HR, 0.56; 95% CI of HR, 0.37-0.86).

At Day +365 the HR was 0.78 [95% CI of HR, 0.54-1.12]), nominal p = 0.1676.

Grade C-D aGvHD-free survival by Day +180 was 41% less in the vedolizumab IV group compared with the placebo group (HR, 0.59; 95% CI of HR, 0.39-0.91). Similar results obtained by Day +365.

A positive trend in favour of vedolizumab was shown for the **Grade B-D aGvHD-free survival**, all by Day +180 although per the fixed-sequence hierarchical testing this endpoint was not tested. The nominal p-value was 0.0105. The risk of a Grade B-D aGvHD event or death, whichever occurred first, was 36% less in the vedolizumab IV group compared with the placebo group (HR, 0.64; 95% CI of HR, 0.46-0.91).

Analyzing other key secondary endpoints related to survival (**Nor Relapse Mortality by Day +180 and Overall Survival by day +180)** no statistically significant difference between the vedolizumab IV group and the placebo group were observed: for the endpoint of NRM by Day +180 (p = 0.0668; HR, 0.48; 95% CI of HR, 0.22-1.04); for Day +180 overall survival nominal p-value 0.1458). Similar results have been obtained by day +365.

Therefore, a statistic significance was reached favouring vedolizumab over the placebo group in terms of intestinal aGVHD free survival and relapse free survival, which was maintained through Day +365. Consistent results were observed for the sensitivity and subgroup analyses, although the reduced size impairs the strength of results. From these results seem that the favourable outcome with vedolizumab over placebo was not affected by ATG treatment; moreover, Vedolizumab effect in intestinal aGVHD prevention seemed clearer in a specific setting of patients with lower risk of aGVHD development (patients treated with RIC regimen instead of MAC and full 8/8 instead of 7/8 HLA match).

The benefit observed for the key primary and for the secondary efficacy endpoints of combined aGVHD/relapse free survival with vedolizumab at Day +180 was maintained through Day +365 and was more apparent with regard to aGvHD (intestinal or any organ involvement) than death (NRM and OS); this finding was consistent regardless of the assessment used for GvHD staging and grading (eg, clinical stage criteria, IBMTR severity index, MAGIC criteria) and probably it could be explained by the specific intestinal target of the drug.

For subjects with GvHD requiring immunosuppression, the mean number of days that immunosuppression was required was numerically less in the vedolizumab group compared with the placebo group through Day +180 but the effect was lost through Day +365, suggesting a time limited effect in reducing the need of immunosuppression.

SAFETY

Safety analysis was performed using the SAF with the actual treatment received. The mean duration of exposure was similar between the vedolizumab IV group and the placebo group (241.7 and 230.0 days, respectively).

The mean number of doses received was also similar between treatment groups (5.4 doses [SD, 2.05] for the vedolizumab IV group and 5.1 doses [SD, 2.25] for the placebo group). Most subjects received 7 doses of study drug per protocol (52.7% of subjects in the vedolizumab IV group and 50.9% of subjects in the placebo group).

All subjects (100.0%; 334 of 334 subjects) reported at least 1 TEAE, with a total of 8323 TEAEs overall: 4287 events in the vedolizumab IV group and 4036 events in the placebo group.

92.3% (156 of 169) of subjects in the vedolizumab IV group and 89.1% (147 of 165) of subjects in the placebo group had a Grade 3 or higher TEAE.

TEAEs were serious (120 subjects [71.0%] in the vedolizumab IV group and 114 subjects [69.1%] in the placebo group), and 79 serious TEAEs led to study drug discontinuation (39 subjects [23.1%] in the vedolizumab IV group and 38 subjects [23.0%] in the placebo group).

Forty-eight subjects (14.4% of total) died due to a TEAE during the study; 21 subjects (12.4%) in the vedolizumab IV group and 27 subjects (16.4%) in the placebo group.

The most frequently reported TEAEs, by PT, were diarrhoea (57.4% in the vedolizumab IV group, 63.0% in the placebo group), stomatitis (54.4% in the vedolizumab IV group, 56.4% in the placebo group), nausea (50.9% each in both treatment groups), pyrexia (49.1% in the vedolizumab IV group, 41.8% in the placebo group), anaemia (40.2% in the vedolizumab IV group, 45.5% in the placebo group), acute GvHD in skin (40.8% in the vedolizumab IV group, 40.6% in the placebo group), and febrile neutropenia (42.6% in the vedolizumab IV group, 37.6% in the placebo group).
No clinically meaningful difference in TEAEs or exposure-adjusted incidence rates were found between the vedolizumab IV and placebo groups.

Study Drug-Related TEAEs Overall, 26.6% (89 of 334) of subjects had a TEAE considered by the investigator to be related to study drug (48 of 169 subjects [28.4%] in the vedolizumab IV group and 41 of 165 subjects [24.8%] in the placebo group) (Table 12.c). Study drug-related TEAEs were similar between the vedolizumab IV and placebo groups. infections and infestations (6.5% in the vedolizumab IV group, 3.6% in the placebo group).

Deaths A total of 65 subjects (19.5% of the SAF) who participated in this study died.

A total of 48 subjects had a TEAE resulting in death (21 subjects [12.4%] in the vedolizumab IV group and 27 subjects [16.4%] in the placebo group).

AESI

– Serious infections a numerically higher incidence in the vedolizumab IV group (125 subjects [74.0%]) compared with the placebo group (111 subjects [67.3%]) was reported. The most commonly reported treatment-emergent serious infections, by PT, were CMV infection reactivation (23.7% in the vedolizumab IV group, 18.2% in the placebo group).

– PML A total of 3 subjects (1.8%) in the vedolizumab IV group and 2 subjects (1.2%) in the placebo group were listed as having "PML" in the clinical trial database. An additional subject was confirmed as having PML. the SAE of PML, with a fatal outcome. The investigator and the IAC deemed that the event of PML was due to acute GvHD and "heavy" immunosuppression treatment that was unrelated to vedolizumab IV.

– Malignancy A total of 71 treatment-emergent AESIs of malignancy were reported for 55 subjects (16.5%) overall (29 subjects [17.2%] in the vedolizumab IV group and 26 subjects [15.8%] in the placebo group). Treatment-emergent AESIs of malignancy were similar between the vedolizumab IV group and the placebo group and consistent with a population of subjects undergoing allo-HSCT. The most common treatment-emergent AESIs of malignancy, by PT, were acute myeloid leukaemia recurrent (5.9% in the vedolizumab IV group, 5.5% in the placebo group)

– Liver injury A total of 292 treatment-emergent AESIs of liver injury were reported for 137 subjects (41.0%) overall (68 subjects [40.2%] in the vedolizumab IV group and 69 subjects [41.8%] in the placebo group). The most common treatment-emergent AESIs of liver injury, by PT, were alanine aminotransferase increased (24.9% in the vedolizumab IV group, 17.6% in the placebo group).

– Hypersensitivity reactions including IRRs and IRRs of AEs. A total of 618 treatment-emergent AESIs of hypersensitivity reactions including IRRs and injection site reactions were reported for 270 subjects (80.8%) overall (134 subjects [79.3%] in the vedolizumab IV group and 136 subjects [82.4%] in the placebo group). The most common treatment-emergent AESIs of hypersensitivity reactions including IRRs and injection site reactions, by PT, were stomatitis (54.4% in the vedolizumab IV group, 56.4% in the placebo group).

– Leukopenia or lymphopenia. A total of 26 treatment-emergent AESIs of leukopenia and lymphopenia were reported for 21 subjects (6.3%) overall, which is consistent with the patient population (subjects undergoing allo-HSCT and taking concomitant immunosuppressants). There were 14 subjects (8.3%) in the vedolizumab IV group and 7 subjects (4.2%) in the placebo group with an AESI of leukopenia or lymphopenia. , no clinically meaningful difference was observed between treatment groups given the small number of subjects with at least 1 event of leukopenia or lymphopenia.

– CMV colitis. CMV colitis: 0.6% of subjects in the vedolizumab IV group and the placebo group each had an AESI of CMV colitis.

– CMV reactivation. A total of 115 treatment-emergent AESIs of CMV reactivation were reported for 83 subjects (24.9%) overall (45 subjects [26.6%] in the vedolizumab IV group and 38 subjects [23.0%] in the placebo group) (Table 12.h). Although treatment-emergent AESIs of CMV reactivation were reported in a numerically higher number of subjects in vedolizumab IV group compared with the placebo group, there was no clinically meaningful difference.

Laboratory findings similar trends between treatment groups in serum chemistry, hematology, vital signs, or physical examination findings were reported.

In conclusion, the observed safety profile was comparable between treatment groups no meaningful differences have been identified. A specific evaluation of the paediatric subset could not be made.

Overall, vedolizumab IV at a dose of 300 mg was well tolerated when added to standard GvHD prophylaxis (tacrolimus plus short-term methotrexate) in patients undergoing allo-HSCT. No new safety signals were identified. The safety profile reported for the indication should account for the known risk of undergoing allo-HSCT and taking concomitant immunosuppressants. with the known risk in the patient population undergoing allo-HSCT and taking concomitant immunosuppressants.

3. Rapporteur's CHMP overall conclusion and recommendation

Study n° Vedolizumab-3035 "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 was terminated early primarily due to low subject recruitment and not related to safety concerns regarding the use of vedolizumab in this patient population. Entyvio is not authorized in this indication.

There were no new safety signals or concerns emerging from this study and no changes to the currently approved Entyvio Summary of Product Characteristics are considered needed as a result of this study.

☒ Fulfilled:

No regulatory action required

Annex

Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Active substance: Vedolizumab

Study title	Study number	Date of completion	Date of submission of final study report
Vedolizumab in the Prophylaxis of Intestinal Acute Graft vs Host Disease in Subjects Undergoing Allogeneic Hematopoietic Stem Cell Transplantation	Vedolizumab 3035	09 May 2022	04 November 2022

Table 1.b Vedolizumab PIP EMEA-000645-PIP03-18 Measures in Prevention of Intestinal aGvHD (Children Aged 2 to <18 Years)

Area	Description	Status
Quality	Development of an age-appropriated presentation of powder for concentrate for solution for infusion (dilution procedure and respective instructions for preparation).	Deferred; not started
Clinical	Double-blind, randomised, placebo-controlled study to evaluate efficacy and safety of vedolizumab as add-on to best standard of care as prophylaxis for intestinal aGvHD in adolescents from 12 to less than 18 years of age (and adults) planned to undergo allo-HSCT.	Completed (early termination of enrollment)
Clinical	Open-label, uncontrolled study to evaluate pharmacokinetics, immunogenicity, efficacy, safety and tolerability of vedolizumab as add-on to best standard of care as prophylaxis for intestinal aGvHD in children from 28 days to less than 18 years of age planned to undergo allo-HSCT.	Deferred; not started
Extrapolation, modeling, and simulation studies	Modelling and simulation study to evaluate the use of vedolizumab as prophylaxis for intestinal aGvHD in children from 28 days to less than 18 years of age undergoing allo-HSCT.	Deferred; not started
Extrapolation, modeling, and simulation studies	Extrapolation study to evaluate the use of vedolizumab as prophylaxis for intestinal aGvHD in children from 28 days to less than 18 years of age undergoing allo-HSCT.	Deferred; not started

aGvHD: acute graft-versus-host disease; allo-HSCT: allogeneic haematopoietic stem cell transplantation.