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Human Medicines Division

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

Orencia

abatacept

Procedure no: EMEA/H/C/000701/P46/067

Note

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

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1. Introduction

The MAH has submitted a completed paediatric study for ORENCIA (abatacept), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The final clinical study report (CSR) is for the company-sponsored observational study **IM101841**:

"Overall Survival in 7/8 HLA-matched Hematopoietic Stem Cell Transplantation Patients Treated with Abatacept Combined with a Calcineurin Inhibitor and Methotrexate - An Analysis of the Center for the International Blood and Marrow Transplant Research (CIBMTR) Database"

Study IM101841 was a retrospective observational study evaluating adult and pediatric patients (6 years of age or older) who received abatacept in addition to standard of care acute Graft Versus Host Disease (aGVHD) prophylaxis regimens in the context of an unrelated donor (URD) allogeneic hematopoietic stem cell transplant (HSCT). These patients were compared to matched controls. The primary objective of the study was to compare the overall survival (OS) 180 days post-HSCT in 7/8 HLA-matched patients between those treated with a calcineurin inhibitor (CNI) + methotrexate (MTX) + abatacept without antithymocyte globulin (ATG) to those treated with CNI + MTX without ATG.

This submission includes also a short clinical overview (dated 22092021).

The study IM101841 CSR was issued on 31 March 2021, which was considered the date of completion of this observational study for the due date of the Article 46 submission.

The study IM101841 is not part of a specific paediatric investigation plan. According to the MAH, the EU submission plan has not yet been decided and will be evaluated after the conclusion of FDA's assessment.

2. Scientific discussion

2.1. Information on the development program

In the US, initial discussions of possible registrational intent pathways began with the US Food and Drug Administration (FDA) in Jun-2017 with early data from a Phase 2 investigator-sponsored research study, ABA2 (IM1091311). The FDA granted orphan drug designation to abatacept for the prevention of graft versus host disease (GVHD) in Dec-2017 (DRU-2017-6141) and Breakthrough Therapy Designation in Oct-2019, based on the results of the ongoing study IM101311. Additional interactions on the subsequent development program occurred, including discussion on the FDA's Real-World Evidence (RWE) Program that focuses on exploring the potential of RWE to support regulatory decisions about product effectiveness. In support of the RWE program, the BMS-sponsored registry Study IM101841 was submitted to the FDA on 23 June 2021 as an efficacy supplement to the development program. Study IM101841 protocol and analytical plan were then prospectively discussed with the FDA under BTD, following consideration of the ABA2 study. Accordingly, these studies have been submitted to the FDA on 23 June 2021 and are currently under review for this indication.

The study IM101841 CSR was issued on 31 March 2021, which was considered the date of completion of this observational study for the due date of the Article 46 submission.
The supplemental Biologics License Application (BLA) is under FDA Priority Review with a feedback expected before 23-Dec-2021.

The study is not part of a specific pediatric investigation plan. Accordingly, the EU submission plan has not yet been decided and will be evaluated after the conclusion of the FDA assessment.

2.2. Information on the pharmaceutical formulation used in the study

Abatacept is a selective costimulation modulator and a soluble fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte (T cell)-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Intravenous (IV) abatacept is approved for the treatment of moderate to severe adult rheumatoid arthritis (RA) and psoriatic arthritis (PsA) in the European Union (EU), United States (US), Japan, Latin America, and other countries. A subcutaneous (SC) formulation of abatacept in a prefilled syringe and autoinjector has been approved for adult RA and PsA patients in the EU, US, and several other countries. IV abatacept is also approved for juvenile idiopathic arthritis (JIA) in patients aged 6 and above in the EU, US, and other countries, and SC abatacept is approved for JIA in patients aged 2 and above in the EU and US.

2.3. Clinical aspects

2.3.1. Introduction

Scientific Background

Overview of GVHD

Allogeneic HSCT is an effective treatment for aggressive leukemias and other hematological malignancies, often offering the only option for potential cure. However, some of its benefit, especially in the case of URD transplantation, is offset by a high rate of transplant-related mortality (TRM) stemming largely from severe acute GVHD and infection. Acute GVHD occurs when reconstituting donor T cells become activated against recipient tissues. This activation can result in severe immune-mediated tissue damage to the host, with the skin, liver and gastrointestinal (GI) tract being the most common targets. Acute GVHD-mediated damage to these vital organs has been associated with increased morbidity and death.

GVHD is the leading cause (20%) of non-relapse mortality in HSCT recipients. GVHD is divided into acute (aGVHD) and chronic (cGVHD) forms, and are both common complications of HSCT. aGVHD and cGVHD variants have been classically characterized by the time to onset, with aGVHD occurring within the first 100 days post-transplantation and cGVHD occurring thereafter. However, clinical findings, rather than a set time period, have increasingly been used to differentiate between the subtypes.

While T cell depletion of the allograft can successfully reduce rates of aGVHD, patients receiving T cell-depleted grafts exhibit profound defects in protective immunity and often die of infection or relapse of the primary disease. This has created an unmet clinical need for a strategy that more effectively prevents severe aGVHD, while preserving the transplant recipient's protective immune response.

Standard Treatments for GVHD Prophylaxis

There are no approved therapies for the prevention of aGVHD, which is a significant cause of morbidity and mortality following allogenic HSCT. Current transplant management focuses on prevention of aGVHD using prophylactic regimens aimed at either suppression of donor T cell function with immunomodulatory agents, or depletion of T cells from the donor graft. Using current therapeutic

protocols, a high number of allogeneic HSCT recipients ultimately fail standard CNI + MTX prophylaxis and develop aGVHD, which is the leading cause of non-relapse related death after URD HSCT. While the use of post-transplant cyclophosphamide (PT-Cy)-based GVHD prophylaxis is growing, CNI + MTX-based regimens remain the standard to which new strategies are compared, with ongoing studies actively comparing a variety of drug combinations (including PT-Cy) to CNI + MTX. Transplant recipients at high risk include those receiving HSCT from URDs with whom they are matched at only 7 of 8 human leukocyte antigen (HLA) loci ("7/8 *mis*matched" URD [MMUD] transplants); the incidence rate of severe (Grade [Gr] III-IV) aGVHD in this population is reported to be as high as 40% after HSCT,[17] and transplant associated mortality as high as 45%. Especially in certain ethnic groups, the ability to find a "fully matched" ("8/8 matched" URD [MUD] transplants) donor is greatly reduced, limiting access to this therapy due to the concern about the higher risk of morbid sequelae and fatal outcomes associated with mismatched transplants.

Role of Abatacept in the Prophylaxis of GVHD

The immune activation observed in aGVHD bears close resemblance to the immune activation that occurs during both organ rejection and autoimmunity. Studies in these diseases have led to the development of a new class of protein biologics called costimulation blockade agents, which specifically target T cells and interfere with their ability to become fully activated effector cells.

Abatacept, a fusion protein consisting of the extracellular domain of CTLA-4 fused to a modified Fc fragment of IgG1, is a selective costimulation modulator that inhibits full T cell activation. Abatacept binds to CD80 and CD86 on antigen presenting cells, thereby blocking the interaction with CD28 on T cells that provide a costimulatory signal necessary for full activation of T cells.[21] Abatacept has proven efficacy in RA, which is thought to be a systemic T cell-mediated autoimmune disease predominately affecting the joints. Similar to the pathophysiology of RA, T cells capable of contributing to the pathogenesis of GVHD become fully activated by, and then utilize the CD28:CD80/86 co-stimulatory signaling pathway to propagate the immune response. As such, studies in both murine and non-human primate models have shown CTLA4-Ig-mediated blockade of the CD28:CD80/86 costimulatory pathway can modulate the T cell activation that occurs during GVHD. Therefore, despite the differences between the 2 diseases, T cells are thought to play a critical role in the diverse clinical manifestations of each disease.

Study ABA2 (IM101311)

Study ABA2 was an investigator-sponsored study providing data that would help understand the role of abatacept for aGVHD prophylaxis. The results are submitted in a CSR within the references with the study identified as Study IM101311.

This *ongoing* Phase 2, investigator-sponsored study has a duration of up to Day 180 (primary endpoint), with 5 years of long-term follow-up. The study consists of 2 cohorts:

- **8/8 MUD cohort** - A randomized, double blind, placebo-controlled cohort for subjects who received a HSCT from 8/8 MUD
  - 146 enrolled subjects were randomized
  - 142 subjects were treated with study medication and transplanted (73 with Abatacept+CNI + MTX and 69 with Placebo+CNI+ MTX)
- **7/8 MMUD cohort** - A single arm cohort for subjects who received a HSCT from 7/8 MMUD.
  - Of the 46 subjects enrolled, 44 were eligible for treatment
  - 43 subjects were treated with Abatacept+CNI + MTX

In the 8/8 MUD cohort, the addition of abatacept to a CNI + MTX-based prophylactic regimen resulted in numerical improvement in severe graft vs. host disease-free survival (GFS), a numerically lower incidence rate of severe aGVHD, and numerically lower TRM rates compared to placebo. The OS and disease-free survival (DFS) rates in the abatacept treated subjects were also numerically higher compared to placebo.

In the 7/8 MMUD cohort, the addition of abatacept to a CNI + MTX-based prophylactic regimen resulted in a clinically significant improvement in GFS, a lower incidence rate of severe aGVHD, and lower TRM rates. The OS and DFS rates were also significantly higher in the abatacept treated subjects, compared to pre-specified matched registry controls.

The adverse events reported in this study were consistent with those expected in a population of patients with hematologic malignancies undergoing stem cell transplantation; review of those events did not identify any unexpected safety concerns among abatacept-treated patients. At Day 365, there were more cases of CMV invasive disease (9) and post-transplant lymphoproliferative disease (PTLD) (2) in the abatacept group compared to the placebo group (2 cases of CMV disease and no PTLD) in the 8/8 MUD cohort. Through Day 365, there were 2 cases of CMV invasive disease and 2 cases of PTLD in the 7/8 MMUD cohort. All evaluable cases of CMV disease and PTLD were successfully treated with standard therapies, with clinical resolution in all subjects.

Unmet Medical Need

While the risk of severe aGVHD is impacted by multiple factors, the degree of matching between recipient and donor HLA alleles is the single most important factor affecting the incidence and severity of this potentially life-threatening complication of HSCT. Thus, the transplants with the least risk are those performed between siblings who have complete HLA matching, whereas those between donor/recipient pairs that have 1 or more HLA mismatches carry a significantly higher risk of GVHD. While fully HLA-matched sibling-sibling transplants are preferable, only a minority of patients (< 20%) have access to such donors.[26] For the majority of patients, an alternative source of donor cells must be found. These include umbilical cord blood, and those from HLA-mismatched family members and URDs who have registered with the United States National Marrow Donor Program (NMDP). The NMDP has been a major source of donors for HSCT for the last 35 years. Prospective transplant recipients are matched with potential donors in this registry for 8 HLA (A, B, C and DRB1) alleles.

The likelihood of finding a suitable 8/8 MUD varies by ethnicity. Globally, the probability of finding a 8/8 match was 72% for white patients, 46% for Asian or Pacific Islander patients, and 30% for African patients. The probability of successful HSCT greatly increases when an 8/8 MUD is found compared to a 7/8 MMUD. As such, the development of treatment regimens that better prevent aGVHD represents a critical need for URD transplant recipients, particularly those (often non-white patients) receiving a 7/8 MMUD HSCT.

Clinical study number and title

The MAH has submitted the final CSR for the company-sponsored observational study IM101841 titled

"Overall Survival in 7/8 HLA-matched Hematopoietic Stem Cell Transplantation Patients Treated with Abatacept Combined with a Calcineurin Inhibitor and Methotrexate - An Analysis of the Center for the International Blood and Marrow Transplant Research (CIBMTR) Database"

Description

Study IM101841 was a retrospective observational study using routine data collected in the database of the Center for International Blood and Marrow Transplant Research (CIBMTR) on outcomes for URD

HSCT patients treated by transplant specialists. The CIBMTR collects data on all allogeneic (related and unrelated) HSCTs performed in the US and on all HSCTs done with products procured through the C. W. Bill Young Cell Transplantation Program, but performed outside of the US.

Methods

Study participants

The disposition for key study groups is found in Table 1.

Table 1 Disposition of Patients in IM101841

Group	N (%)
CNI + MTX + abatacept without ATG[a,b]	54 (7.6)
CNI + MTX without ATG[a]	162 (22.7)
CNI + MTX with ATG[b]	162 (22.7)
Tacrolimus + MTX + abatacept without ATG[c]	33 (4.6)
Tacrolimus + MTX without ATG[c]	99 (13.9)
CsA + MTX + abatacept without ATG[d]	21 (2.9)
CsA + MTX without ATG[d]	21 (2.9)
PT-Cy without ATG[e]	162 (22.7)

[a] These 2 groups make up the Primary Objective Cohort.

[b] OS in these 2 groups is the first secondary objective. Gr II-IV and Gr III-IV GFS in these 2 groups is an exploratory objective.

[c] OS in these 2 groups is the second secondary objective. Gr II-IV and Gr III-IV GFS in these 2 groups is an exploratory objective.

Eligible subjects were patients in the CIBMTR registry who were at least 6 years old at the time of transplant, who had a bone marrow (BM) or peripheral blood (PB) stem cell donor with whom they were matched at 7/8 HLA (A, B, C, DRB1) loci, and met other inclusion/exclusion criteria. For the primary objective, the study included 7/8-HLA-matched URD transplant recipients treated with CNI + MTX + abatacept without ATG or CNI + MTX without ATG from the CIBMTR database.

To adjust for possible confounding due to differences between the treatment groups based on known key prognostic factors, a propensity score, predicting probability of abatacept treatment was developed, and the inverse probability of treatment weighting (IPTW) was applied to estimate the average treatment effect if the entire cohort had been treated. The patients were weighted by the stabilized inverse probability of receiving the treatment they actually received. The comparison of OS within 180 days of follow-up post-HSCT between the treatment groups was based on a weighted log-rank test using a 2-sided alpha of 0.05. Supplemental analyses were conducted using a propensity score matching approach.

The analysis methods for the secondary and exploratory comparisons were similar to the primary comparison.

Inclusion Criteria

Patients in the CIBMTR database meeting the following criteria were included in the eligible patient population:

- Patients who underwent first allogenic transplant in the United States
- Patients with an unrelated donor who are HLA-matched at 7/8 loci (A, B, C, DRB1)
- Patients at least 6 years old with weight at least 20 kg
- Patients with a Karnofsky/Lansky performance score $\geq$ 80%
- Patients whose first allogeneic transplant occurred from 01-Jan-2011 to 31-Dec-2018
- Patients with any of the following diseases: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), myelodysplastic syndromes (MDS), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL)
- Patients with any of the following GVHD prophylaxis treatments:
- CNI + MTX (with or without ATG and with or without abatacept); or
- PT-Cy without ATG
- Patients treated with any of the following conditioning regiments: total body irradiation (TBI)/cyclophosphamide (Cy), busulfan (Bu)/Cy, Bu/fludarabine (flu), Flu/Melphalan (MEL)

Exclusion Criteria

Patients with the following characteristics were excluded from the eligible patient population:

- Patients with missing information on ATG (yes/no)
- Patients receiving alemtuzumab (Campath)
- Patients with cord blood grafts
- Patients with non-MDS myeloproliferative disorders (NOTE: Patients with chronic myelomonocytic leukemia [CMMoL] were included)
- Patients who did not consent to participate in research
- Patients treated at embargoed centers for research
- Patients treated with abatacept and ATG
- Among non-abatacept treated patients, patients transplanted at centers with abatacept trial patients
- Patients with any of the following missing propensity score variables:
  - Disease status at transplantation (early, intermediate, advanced HL and NHL- chemosensitive)
  - Age
  - Gender (male, female)
  - HSCT graft source (BM, PB)
  - Conditioning intensity (myeloablative, non-myeloablative / reduced intensity)
  - Karnofsky/Lansky Performance Score (80%, 90-100%)
  - CNI type (tacrolimus, CsA)

Treatments

Treatment was not administered in this observational study**.** The primary objective cohort comprised patients who were 7/8 HLA-matched and received either:

- CNI + MTX + abatacept without ATG
- CNI + MTX without ATG

Subgroups for secondary and exploratory objectives were also 7/8 HLA matched and received 1 of the following GVHD prophylaxis regimens:

- CNI + MTX + abatacept without ATG
- CNI + MTX with ATG
- Tacrolimus + MTX + abatacept without ATG
- Tacrolimus + MTX without ATG
- PT-Cy without ATG
- CsA + MTX + abatacept without ATG
- CsA + MTX without ATG

Duration of follow-up

OS data from first transplant up to and including 180 days after the transplant were analyzed. For the safety endpoints, data at 100 days and 180 days after transplant were analysed.

Concomitant Therapy

Study groups were based on GVHD prophylaxis treatments. Concomitant therapy for comorbid diseases or other reasons were not collected.

Criteria for evaluation

This clinical study report (CSR) includes results for the primary, secondary, and exploratory objectives in addition to the analyses requested by the Food and Drug Administration. The primary and secondary objective includes OS during 180 days of follow-up post-transplant. The event for this outcome was death by any cause. OS time was defined as the time between the date from allogeneic transplant to the documented date of death as reported by the treating physicians. All causes of death were reported under this outcome. Patients still alive were censored at 181 days after transplantation.

Objectives

Primary

- To compare the 180-day OS post-HSCT in 7/8 HLA-matched patients treated with CNI + MTX + abatacept without ATG to those treated with CNI + MTX without ATG

Secondary

- To compare the OS with 180 days of follow-up post-HSCT in patients treated with CNI + MTX + abatacept without ATG to those treated with CNI + MTX with ATG
- To assess the OS with 180 days of follow-up post-HSCT in patients treated with tacrolimus + MTX + abatacept without ATG and those treated with tacrolimus + MTX without ATG

Endpoints

- *Primary Endpoint*

Overall survival was the primary outcome and was evaluated during 180 days of follow-up post-transplant. The event for this outcome was death by any cause. OS time was defined as the time between the date from allogeneic transplant to the documented date of death as reported by treating physicians. All causes of death were reported under this outcome. Patients still alive were censored at 181 days after transplantation.

- *Secondary Endpoints*

The secondary endpoint was OS and was assessed in the manner described above, in the following subgroups:

- Patients treated with CNI + MTX + abatacept without ATG to those treated with CNI + MTX with ATG
- Patients treated with tacrolimus + MTX + abatacept without ATG and those treated with tacrolimus + MTX without ATG

Sample size

The sample size is not based on statistical assumptions, but on the availability of patients in the base. Approximate sample sizes for each of the exposure groups are provided in Table 2.

Table 2 Approximate Number of Eligible Patients by Treatment Group (Planned)

Abatacept Groups (including ABA2 patients):	CNI + MTX + abatacept without ATG			Tacrolimus + MTX + abatacept without ATG	CsA + MTX + abatacept without ATG
	~50			~30	~20
Comparator Groups:	**CNI + MTX without ATG**	**CNI + MTX with ATG**	**PT-Cy without ATG**	**Tacrolimus + MTX without ATG**	**CsA + MTX without ATG**
	~150	~150	~150	~141	~9

Abbreviations: ATG = anti-thymocyte globulin; CNI = calcineurin inhibitor; CsA = cyclosporine; MTX = methotrexate; PY-Cy = post-transplant cyclophosphamide.

Randomisation and blinding (masking)

N/A

Statistical Considerations

For the primary objective cohort, the weighted log-rank test was used to compare OS with 180 days of follow-up post-transplant in patients receiving GVHD prophylaxis with CNI + MTX + abatacept without ATG to standard GVHD prophylaxis with CNI + MTX without ATG, using the stabilized inverse of the propensity score as weights. Patients were censored at 181 days post-transplant or at time of last follow-up, whichever was earlier. The primary comparison was evaluated at a 2-sided alpha of 0.05.

The marginal hazards ratio (HR) for OS and the corresponding 2-sided 95% confidence intervals (CIs) were estimated in a weighted Cox proportional hazards model with treatment as the only covariate using a robust variance estimator that accounts for the sample weights.

In addition, the marginal HR for OS and the corresponding 2-sided 95% CI was estimated in a weighted Cox proportional hazards model with treatment and disease status (early, intermediate, advanced, chemo-sensitive, chemo-resistant) as covariates. The estimated survival probability over time was provided by weighted Kaplan-Meier curves up to 180 days after transplant.

A hierarchical testing procedure was applied for the secondary comparison of OS between CNI + MTX + abatacept without ATG and those treated with CNI + MTX with ATG. The secondary comparison test was performed if the primary comparison was statistically significant at alpha=0.05. The analysis methods to assess OS among patients treated with CNI + MTX + abatacept without ATG and those treated with CNI + MTX with ATG will be the same as for the primary analysis.

Formal log-rank tests were not conducted for the sub-group of patients treated with tacrolimus + MTX + abatacept without ATG and those treated with tacrolimus + MTX without ATG. However, the

marginal HR for OS (and the corresponding 2-sided 95% CI for OS) were estimated in a weighted Cox proportional hazards models using stabilized IPTW with treatment as the only covariate and with treatment and disease status as the covariates, and a robust variance estimator that accounted for the sample weights. The estimated survival probabilities over time were provided by weighted Kaplan-Meier curves up to 180 days after transplant.

Changes in Study Conduct and Planned Analysis

In response to comments from the US FDA, the study protocol was amended once to incorporate changes to the planned statistical analyses intended to better establish comparability between the comparison groups by accounting for unmeasured confounding factors:

- Inclusion Criteria were added to ensure comparability between patient populations and to more closely reflect patients under the regulatory authority of the FDA:
- Removed the exclusion criteria regarding conditioning regimens and reworded into an equivalent inclusion criterion to improve readability.
- Added relapse free-survival and post-transplant lymphoproliferative disease as outcomes to be reported.
- Clarified that the weighted long-rank test will use a two-sided alpha of 0.05.
- Exploratory objectives were added to evaluate patients enrolled in the ABA2 clinical trial and those who were not enrolled (off-label use setting) and for the evaluation of relapse-free survival and PTLD.
- The Patient Sampling section was added.
- Subgroups were added to include patients treated with CNI + MTX + abatacept without ATG in the ABA2 clinical trial and CNI + MTX + abatacept without ATG among patients who were not treated (off-label use setting).
- A list of comorbidities was added, along with an overall Hematopoietic Cell Transplant-Comorbidity Index.
- A stipulation was added for description of outcomes and independent variables of interest among those patients excluded due to missing data.
- The number of eligible patients was adjusted, and details were added describing the propensity score modeling.

Sensitivity analyses were also included to evaluate the patients with missing covariate or outcome data and to further analyse the relationship between covariates, treatment assignment, and outcome.

Ethics and Subject Rights

The study did not require review and approval by ethics committees or informed consent as it was a secondary data analysis of an existing registry, the CIBMTR database, that provided a subset of its data for this study. Research conducted by CIBMTR was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The rights, safety, and well- being of the study subjects were the most important consideration and prevailed over the interests of science and society. The study did not require review and approval by ethics committees or informed consent as these activities are covered under the consent process for the CIBMTR observational database.

Results

Participant flow

Disposition of each study group is presented in Table 3.

Table 3 Disposition of Patients in IM101841

Study Exposure Group	N (%)
CNI + MTX + abatacept without ATG[a,b]	54 (7.6)
CNI + MTX without ATG[a]	162 (22.7)
CNI + MTX with ATG[b]	162 (22.7)
Tacrolimus + MTX + abatacept without ATG[c]	33 (4.6)
Tacrolimus + MTX without ATG[c]	99 (13.9)
CsA + MTX + abatacept without ATG	21 (2.9)
CsA + MTX without ATG	21 (2.9)
PT-Cy without ATG	162 (22.7)

[a] These 2 groups make up the Primary Objective Cohort. [b] OS in these 2 groups is the first secondary objective. Gr II-IV and Gr III-IV GFS in these 2 groups is an exploratory objective. [c] OS in these 2 groups is the second secondary objective. Gr II-IV and Gr III-IV GFS in these 2 groups is an exploratory objective.

Numbers analysed

The population selected (N = 216) included patients with hematologic malignancies in the US who received allogenic transplant from an URD HLA-matched at 7/8 loci.

Demographic and Other Baseline Characteristic

In the primary analysis group, patients receiving CNI + MTX + abatacept without ATG were younger than patients receiving CNI + MTX without ATG based on mean age (Table 1.2.5-1). Two-thirds of patients in CNI + MTX + abatacept without ATG were male, whereas approximately one-half of patients in CNI + MTX without ATG were male. The majority of patients in both groups had Karnofsky/ Lansky Performance Scores between 90 and 100 and were white. Twenty-seven (27; 12.5%) patients were < 18 years of age.

Within the cohort used to meet the primary objective, in the weighted samples using stabilized IPTW with propensity scores (PS), the CNI + MTX + abatacept without ATG group and the CNI + MTX without ATG group had nearly the same mean age, with a much smaller difference between the groups compared to unweighted age. All other characteristics were similar between the unweighted and the weighted analyses, with smaller differences between the groups for the weighted variables. The weighted distribution of key demographics was similar between the 2 treatment groups.

The primary objective cohort demographics are presented in Table 4.

Table 4 Demographic Characteristics at Transplant - Primary Objective Cohort (unweighted)

	CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162	Total N = 216
AGE (YEARS)			
N	54	162	216
MEAN	35.9	47.9	44.9
SD	22.8	16.2	18.8
MEDIAN	36.5	51.0	49.0
MIN	6	10	6
MAX	76	74	76
GENDER (%)			
MALE	36 (66.7)	87 (53.7)	123 (56.9)
FEMALE	18 (33.3)	75 (46.3)	93 (43.1)
KARNOFSKY/LANSKY PERFORMANCE SCORE (%)			
70	2 (3.7)	0	2 (0.9)
80	13 (24.1)	53 (32.7)	66 (30.6)
90-100	39 (72.2)	109 (67.3)	148 (68.5)
KARNOFSKY/LANSKY PERFORMANCE SCORE, COLLAPSED (%)			
70 OR 80	15 (27.8)	53 (32.7)	68 (31.5)
90-100	39 (72.2)	109 (67.3)	148 (68.5)
RACE (%)			
WHITE	39 (72.2)	135 (83.3)	174 (80.6)
BLACK OR AFRICAN AMERICAN	9 (16.7)	6 (3.7)	15 (6.9)
ASIAN	3 (5.6)	6 (3.7)	9 (4.2)
NOT REPORTED	3 (5.6)	15 (9.3)	18 (8.3)
ETHNICITY (%)			
HISPANIC OR LATINO	9 (16.7)	25 (15.4)	34 (15.7)
NOT HISPANIC OR LATINO	44 (81.5)	135 (83.3)	179 (82.9)
NOT REPORTED	1 (1.9)	2 (1.2)	3 (1.4)

Source: Table 6.3.1-1 of IM101841 CSR

Clinical pharmacology results

N/A

Efficacy results

Study IM101841 found that use of abatacept + CNI + MTX results in a statistically significant improvement in OS (P-value = 0.0028; survival rate at Day 180: 98% vs 75%; HR: 0.07 [95% CI, 0.01, 0.30]) (Figure 1 and Table 5) and GFS (Gr II-IV survival rate at Day 180: 65% vs 35%, HR: 0.44 [95% CI, 0.19, 0.99]; Gr III-IV survival rate at Day 180: 100% vs 61%, HR 0.00 [95% CI, NA, no abatacept subjects reported events]) compared to CNI + MTX alone.

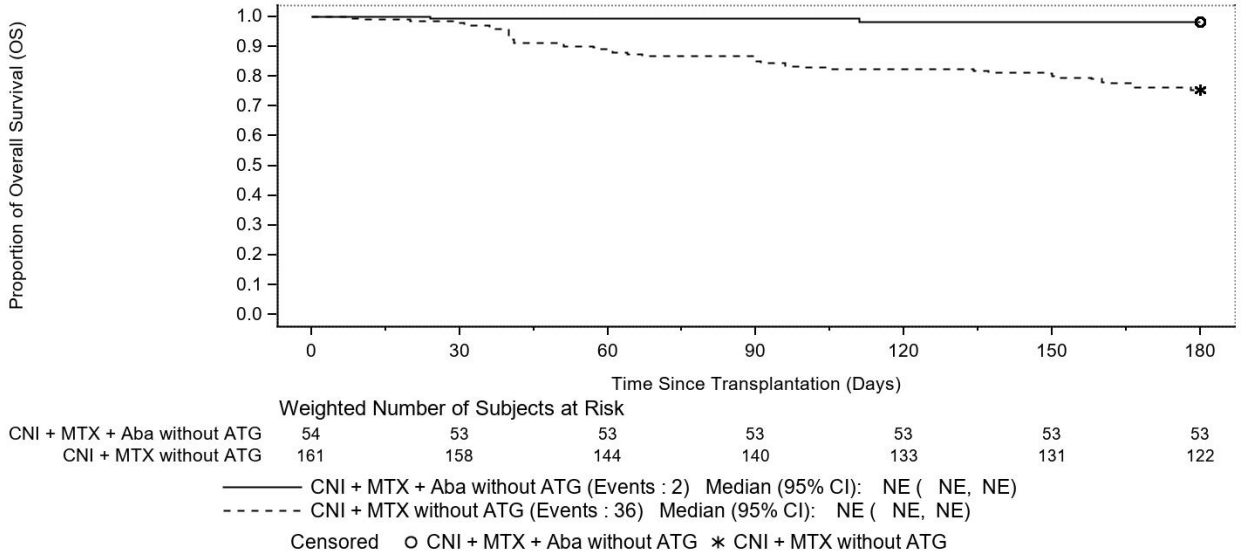
Abatacept + SOC (without ATG) also resulted in a statistically significant improvement in OS and GFS when compared to CNI + MTX+ATG (P-value = 0.0060; survival rate at Day 180: 98% vs 74%; HR: 0.08 [95% CI, 0.02, 0.36]). Given the potential promise of both abatacept-based and PT-Cy-based GVHD prophylaxis regimens compared to SOC, Study IM101841 included a direct comparison of abatacept + CNI + MTX versus PT-Cy. OS was slightly higher up to Day 180 in the abatacept regimen group than in the PT-Cy group, but the difference was not significant (P-value=0.1097; survival rate at Day 180: 98% vs 88%; HR: 0.15 [95% CI, 0.03, 0.67]).

In the abatacept + CNI + MTX without ATG group compared to the CNI + MTX without ATG group, the GFS rates at Day 100 and Day 180 were higher, there were fewer events of Gr III-IV aGVHD or death, and the RFS rate at Day 100 and Day 180 was higher. Findings from the supplemental and sensitivity analyses were similar to the those in the primary analysis. With the PS using 1:1 matching, the

survival rate at Day 180 was higher in subjects treated with abatacept + CNI + MTX without ATG, compared to subjects treated with CNI + MTX without ATG.

In the secondary analysis population, OS rate through 180 days was significantly higher (P-value = 0.0043) in the subgroup of subjects receiving abatacept + tacrolimus + MTX without ATG group compared to subjects receiving tacrolimus + MTX without ATG.

Figure 1: Kaplan-Meier Plot of OS During 180 Days of Follow-up Post-treatment Weighting (IPTW) Scores (PS) in the Primary Objective Cohort



Propensity scores obtained from a logistic regression model including gender, disease, age, HSCT graft source, conditioning intensity, performance score, and CNI type as covariates. Based on weighted Kaplan-Meier method. Symbols represent censored observation. OS time is defined as the time between the date of transplant to the date of death. Subjects are censored at 181 days post-transplant or at time of last follow-up, whichever is earlier. NE: Not Estimable. Source: Figure 8.2-1 of the IM101841 CSR.

Table 5 *Summary of OS During 180 Days of Follow-up Post-Transplant Using Stabilized IPTW with Propensity Scores in the Primary Objective Cohort (PS Model1)*

Measure	CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162
PROPORTION WITH EVENT (n/m, %)	2/ 54 (3.7)	36/162 (22.2)
MEDIAN TIME TO EVENT (A)	NE	NE
95% CI OF MEDIAN TIME	(NE, NE)	(NE, NE)
SURVIVAL RATE AT DAY 180 (A)	0.98	0.75
95% CI OF SURVIVAL RATE	(0.78, 1.00)	(0.67, 0.82)
P-VALUE FROM LOG-RANK TEST (A)	0.0028	NA
HAZARD RATIO VS. COMPARATOR GROUP (B)	0.06	NA
95% CI OF HAZARD RATIO	(0.01, 0.27)	NA
HAZARD RATIO VS. COMPARATOR GROUP (C)	0.07	NA
95% CI OF HAZARD RATIO	(0.01, 0.30)	NA

n = Number of subjects who died of any cause, m = Number of subjects in the analysis Propensity scores obtained from a logistic regression model including gender, disease, age, HSCT graft source, conditioning intensity, performance score, and CNI type as covariates (A) Based on weighted Kaplan-Meier method. (B) Marginal hazard ratio based on weighted Cox proportional hazards model with treatment as the only covariate using a robust variance estimator that accounts for the sample weights. Ties are handled using the Breslow method. (C) Marginal hazard ratio based on weighted Cox proportional hazards model with treatment and disease status as covariates using a robust variance estimator that accounts for the sample weights. Ties are handled using the Breslow method. OS time is defined as the time between the date of transplant to the date of death. Subjects are censored at 181 days post-transplant or at time of last follow-up, whichever is earlier. NA: Not Applicable. NE: Not Estimable. Source: Table 8.2-1 of the IM101841 CSR27

Safety results

The CIBMTR database (from which the data for Study IM101841 was collected) does not include reports of individual adverse events (AEs) and causality assessment at the individual case level is not feasible.

The occurrence of PTLD after transplant is a datapoint captured in the CIBMTR database and was chosen as an exploratory safety outcome. Given the small sample size, data was collected among patients with available results at 2 timepoints: up to the first 100 and 180 days after transplant. There were no cases of PTLD reported at Day 100 or at Day 180 in the primary objective cohort of Study IM101841 (Table 6).

Table 6 Proportion of Subjects who Developed PTLD During 180 Days of Follow-up Post-transplant

Study Day	CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162
DAY 100		
NUMBER OF SUBJECTS <n/m> (%)	0/ 20 (0.0)	0/ 45 (0.0)
95% CI	(0.0, 16.8)	(0.0, 7.9)
DAY 180		
NUMBER OF SUBJECTS <n/m> (%)	0/ 20 (0.0)	0/ 45 (0.0)
95% CI	(0.0, 16.8)	(0.0, 7.9)

Note: n = Number of subjects who developed PTLD, m = Number of subjects in the analysis. Subjects with available CRF data are included.

2.3.2. Discussion on clinical aspects

The MAH has submitted the final clinical study report (CSR) for the company-sponsored observational paediatric study IM101841 for ORENCIA (abatacept), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended:

"Overall Survival in 7/8 HLA-matched Hematopoietic Stem Cell Transplantation Patients Treated with Abatacept Combined with a Calcineurin Inhibitor and Methotrexate - An Analysis of the Center for the International Blood and Marrow Transplant Research (CIBMTR) Database"

Study IM101841 was a retrospective observational study evaluating registry data on adult and paediatric patients (6 years of age or older) who received an unrelated donor (URD) allogeneic hematopoietic stem cell transplantation (HSCT) and abatacept (ORENCIA) in addition to standard of care acute Graft Versus Host Disease (GVHD) prophylaxis regimens. The population selected included 216 patients. In the study of 7/8 HLA-matched patients treated with background GVHD prophylaxis CNI + MTX ± abatacept without ATG, the OS at Day 180 was statistically significantly greater in the CNI + MTX with abatacept without ATG group compared to patients treated with background CNI + MTX without ATG (98% vs 75%, HR: 0.07 [0.01, 0.30]; P value = 0.0028).

By design, the CIBMTR database (from which the data for Study IM101841 was collected) does not include reports of individual adverse events and in this setting causality assessment at the individual case level is not feasible. The occurrence of PTLD after transplant was chosen as an exploratory safety outcome and showed that there were no cases of PTLD reported at Day 100 or at Day 180 in the primary objective cohort of Study IM101841.

Overall, study IM101841 retrospectively analyzed patient information recorded in the CIBMTR registry database. The accrued data suggest a clinical benefit on OS in 7/8 HLA-matched HSCT patients treated

with abatacept combined with a calcineurin inhibitor and methotrexate. The accrued safety data was exploratory in nature. Due to the nature of the data, firm overall conclusion cannot be made. For the regulatory purpose of this P46 submission these data are, however, considered adequate and sufficient.

On the regulatory background of the MAH abatacept aGVHD development program, the MAH states that in the US, initial discussions of possible registrational intent pathways began with the US Food and Drug Administration (FDA) in Jun-2017 with early data from a Phase 2 investigator-sponsored research study, ABA2 (IM1091311). The FDA granted orphan drug designation to abatacept for the prevention of GVHD in Dec-2017 (DRU-2017-6141) and Breakthrough Therapy Designation in Oct-2019, based on the results of the ongoing study IM101311. Additional interactions on the subsequent development program occurred, including discussion on the FDA's Real-World Evidence (RWE) Program that focuses on exploring the potential of RWE to support regulatory decisions about product effectiveness.

According to the MAH, in support of the RWE program, the company-sponsored registry study IM101841 was submitted to the FDA on 23 June 2021 as an efficacy supplement to the development program. Study IM101841 protocol and analytical plan were then prospectively discussed with the FDA under BTD, following consideration of the ABA2 study. Accordingly, these studies have been submitted to the FDA on 23 June 2021 and are currently under review for this indication.

The study IM 101841 is not part of a specific pediatric investigation plan. Accordingly, the EU submission plan has not yet been decided on and will be evaluated after the conclusion of the FDA assessment.

On this background, the Applicant provided, on request, clarification on the following two questions 1 and 2:

1. The MAH is requested to complete the Annex 1 (Line listing of all the studies included in the development program).

   MAH Response: see attached the completed Annex 1.

   Assessment of response: A completed Annex 1 has been provided, as requested.

   Conclusion: Issue resolved

2. The MAH states that the study IM101841 is not part of a specific paediatric investigation plan and the EU submission plan has not yet been decided on and will be evaluated after the conclusion of FDA's assessment. (The MAH has stated that studies, including study IM101841, are currently under review by the FDA). This can be taken as reasonable considering the stated timelines and is thus acceptable, if done in a timely manner. However,

   a) the MAH should submit the timelines for all future submissions concerning the company aGVHD development programme and commit to these submissions in a timely manner (due date).

   MAH Response

   The MAH does not have an aGVHD development program beyond the two studies listed in Annex 1. In this context, currently, the MAH has not yet made a decision to file for a new indication in EU based on results from these studies. Nevertheless, should an aGVHD prevention indication be approved in the US, BMS commits to submit this indication in EU so that the SmPC covers this information, as a US approval could promote some desire to use ORENCIA in this setting in EU irrespective of the approved indications. This submission would

then occur in Q4-2022 (due date by 30 November 2022, based on EMA's timetable) i.e. after patent expiry (23 November 2022), and would therefore not require a previously agreed PIP.

Assessment of response: The MAH has provided the requested timelines and a commitment on future submissions.

Conclusion: Issue resolved

b) the MAH is requested to clarify the exact current status of the study IM101311. Is a P46 procedure planned for this study?

Response: the investigator-sponsored Phase 2 ABA2 study (IM101311) is currently ongoing, in the 5-year long-term follow-up phase. An Art. 46 submission is not planned for this study. As this is not a BMS-sponsored study, the MAH's understanding is that it does not fall under the scope of the Art. 46 requirement.

Assessment of response: The CHMP recommends the MAH to submit the results of study IM101311 when available.

Conclusion: Issue resolved

In an overall conclusion, all issues requiring clarification were adequately and sufficiently addressed. No open issues remain. This P46 can be considered fulfilled.

3. CHMP overall conclusion and recommendation

Based on the provided data on the company-sponsored observational study IM101841:

"Overall Survival in 7/8 HLA-matched Hematopoietic Stem Cell Transplantation Patients Treated with Abatacept Combined with a Calcineurin Inhibitor and Methotrexate - An Analysis of the Center for the International Blood and Marrow Transplant Research (CIBMTR) Database",

This article P46 submission is considered fulfilled.

☒ Fulfilled:

No further action required based on the results of the study IM101841 and no amendment to the product information is required at this point of time. However, the CHMP recommends the MAH to submit the results of study IM101311 when available.

4. Request for supplementary information

None

Annex 1. Line listing of all the studies included in the development program

Clinical studies (listed by chronological date of completion):

Product Name: Orencia Active substance: abatacept

Study title	Study number	Date of completion	Date of submission of final study report
BMS sponsored study IM101841: Overall Survival in 7/8 HLA-matched Hematopoietic Stem Cell Transplantation Patients Treated with Abatacept Combined with a Calcineurin Inhibitor and Methotrexate - An Analysis of the Center for the International Blood and Marrow Transplant Research (CIBMTR) Database	IM101841	31 March 2021 (date of the CSR)	30 September 2021 (EMEA/H/C/000701/P46/067)
Investigator-sponsored Phase 2 ABA2 study (IM101311): Abatacept Combined With a Calcineurin Inhibitor and Methotrexate for Graft Versus Host Disease Prophylaxis: A Randomized Controlled Trial	IM101311	N/A (ongoing study)	N/A