19 February 2024
EMA/74789/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Orencia

International non-proprietary name: Abatacept

Procedure No. EMEA/H/C/000701/0152

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion [2]**
☐	Start of procedure	31 Dec 2022	31 Dec 2022	☐
☐	CHMP Rapporteur Assessment Report	24 Feb 2023	24 Feb 2023	☐
☐	PRAC Rapporteur Assessment Report	03 Mar 2023	02 Mar 2023	☐
☐	PRAC members comments	08 Mar 2023	08 Mar 2023	☐
☐	CHMP Co-Rapporteur Critique	08 Mar 2023	10 Mar 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	09 Mar 2023	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	16 Mar 2023	16 Mar 2023	☐
☐	CHMP members comments	20 Mar 2023	20 Mar 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 Mar 2023	23 Mar 2023	☐
☐	Request for supplementary information	30 Mar 2023	30 Mar 2023	☐
☐	Submission of MAH responses	11 Aug 2023	10 Aug 2023	☐
☐	Re-start of procedure	14 Aug 2023	14 Aug 2023	☐
☐	CHMP Rapporteur Assessment Report	12 Sept 2023	12 Sep 2023	☐
☐	PRAC Rapporteur Assessment Report	15 Sept 2023	12 Sep 2023	☐
☐	PRAC members comments	20 Sept 2023	20 Sept 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	21 Sept 2023	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	28 Sept 2023	28 Sept 2023	☐
☐	CHMP members comments	02 Oct 2023	02 Oct 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	05 Oct 2023	05 Oct 2023	☐
☐	Request for supplementary information	12 Oct 2023	12 Oct 2023	☐
☐	Submission of MAH responses	21 Dec 2023	20 Dec 2023	☐
☐	Re-start of procedure	25 Dec 2023	25 Dec 2023	☐
☐	CHMP Rapporteur Assessment Report	23 Jan 2024	23 Jan 2024	☐
☐	PRAC Rapporteur Assessment Report	26 Jan 2024	23 Jan 2024	☐
☐	PRAC members comments	31 Jan 2024	31 Jan 2024	☐
☐	Updated PRAC Rapporteur Assessment Report	01 Feb 2024	n/a	☐
☐	PRAC endorsed relevant sections of the	08 Feb 2024	08 Feb 2024	☐

Status of this report and steps taken for the assessment				
	assessment report[3]			
☐	CHMP members comments	12 Feb 2024	12 Feb 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 Feb 2024	15 Feb 2024	☐
☐	Request for supplementary information/opinion	22 Feb 2024		☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
Rapporteur: Co-Rapporteur:	Outi Mäki-Ikola (FI) Róbert Pórszász (HU)

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
aGvHD	Acute GvHD
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
AR	Assessment Report
(r)/(h)ATG	(rabbit)/(horse) Anti-thymocyte globulin
AUC	Area under the curve
BLA	Biologics License Application
BM	Bone marrow
BMS	Bristol Myers Squibb
Cav	Time averaged serum concentration
cGvHD	Chronic GvHD
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CL	Clearance
Cmax	Peak serum concentration
Cmin	Trough serum concentration
Cminss	Trough serum concentration at steady state
CML	Chronic myelogenous leukaemia
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CRF	Case report form
CsA	Ciclosporin
CSR	Clinical study report
CTLA-4	Cytotoxic T lymphocyte (T cell)-associated antigen 4
DBL	Database lock
DFS	Disease-free survival
EBMT	European Society for Blood and Marrow Transplantation
E-R	Exposure-response
FDA	United States Food and Drug Administration
GFS	GvHD-free survival

GI	Gastrointestinal
Gr	Grade
GRFS	Severe aGvHD (Grade III-IV) Free-Relapse Free Survival
GvHD	Graft vs. host disease
GvT	Graft vs. tumour
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HM	Haematologic malignancyHR Hazard ratio
HSCT	Haematopoietic stem cell transplantation
IND	Investigational new drug
IPTW	Inverse probability of treatment weighting
ISR/T	Investigator-sponsored research/trial
IV	Intravenous
JIA	Juvenile idiopathic arthritis
LPLV	Last patient last visit
MAC	Myeloablative conditioning
MITT	Modified Intent-to-treat
MDS	Myelodysplastic syndrome
MMUD	Mismatched unrelated donors
MTX	Methotrexate
MUD	Matched unrelated donors
NA	Not applicable
NE	Not estimable
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PB	Peripheral blood
PBMTC	Pediatric Blood and Marrow Transplant Consortium
PD	Pharmacodynamic
PK	Pharmacokinetics
Pm	Pharmacometric
PPK	Population pharmacokinetic
PS	Propensity score
PT-Cy	Post-transplant cyclophosphamide

RA	Rheumatoid arthritis
RIC	Reduced-intensity conditioning
RFS	Relapse-free survival
RMP	Risk Management Plan
RWD	Real-world data
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	Standard of care
TED	Transplant Essential Data
TRM	Transplant-related mortality
URD	Unrelated donor

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 28 November 2022 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include the prophylaxis of acute Graft versus Host Disease (aGvHD) in the adult and paediatric population for Orencia, based on final results from studies IM101311 - Abatacept Combined With a Calcineurin Inhibitor and Methotrexate for Graft Versus Host Disease Prophylaxis and 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 International Blood And Marrow Transplant Research (CIBMTR) Database. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 28.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

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☐ is recommended for approval.

☐ is not recommended for approval.

☒ is subject to a request for supplementary information (please refer to the RSI section <and the proposed Changes to the Product Information in a separate document>) before a recommendation can be made.

The responses timetable to the Request for Supplementary Information will be[1] [2]:

- ☐ 30 days (15 days to assess with clock-stop, 8 days to assess with immediate responses)
- ☒ 60 days (36 days to assess)

3. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

[1] Instructions to assessor: please select one of the two options. If no option is selected, a default 30-day assessment timetable will be applied.
[2] Note to MAH: this timetable refers to the assessment of the responses to the RSI and is determined by the Rapporteur/assessor; it does not refer to the clock-stop necessary for the preparation and submission of the responses which is determined by the MAH and communicated to the Procedure Assistant upon receipt of the assessment report.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No'

4. Scientific discussion

4.1. Introduction

4.1.1. Problem statement

Within the current variation application, the MAH is seeking an extension of indication for abatacept in addition to calcineurin inhibitor + methotrexate standard of care (SOC) for prevention of acute graft-versus-host disease (aGvHD) prophylaxis in allogeneic haematopoetic stem cell transplantation (HSCT) recipients.

The indication initially proposed by the MAH read as follows:

ORENCIA in combination with a calcineurin inhibitor and methotrexate is indicated for the prophylaxis for acute graft versus host disease (aGvHD) in adult and paediatric patients 2 years of age and older undergoing haematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor.

The proposed posology is:

Adults

The recommended dose of abatacept for adult patients is 10 mg/kg (maximum dose of 1,000 mg) and should be administered as a 60-minute IV infusion on the day before transplantation (Day -1), followed by a dose on Days 5, 14, and 28 after transplantation.

Paediatric Population

- *The recommended dose of abatacept for patients 6 to 17 years of age is the same as for adults, 10 mg/kg (maximum dose of 1,000 mg). Abatacept should be administered on the day before transplantation (Day -1), followed by a dose on Days 5, 14, and 28 after transplantation.*
- *The recommended dose of abatacept for patients 2 to less than 6 years of age is 15 mg/kg on the day before transplantation (Day -1), followed by 12 mg/kg on Days 5, 14, and 28 after transplantation.*

Abatacept should be administered as a 60-minute intravenous infusion.

At CHMP's request in the 1st RSI, the MAH revised the indication to align with the population studied. The revised indication reads as follows (addition in bold):

ORENCIA in combination with a calcineurin inhibitor and methotrexate is indicated for the prophylaxis for acute graft versus host disease (aGvHD) in adult and paediatric patients 2 years of age and older ***with haematologic malignancies*** *undergoing haematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor.*

Disease characteristics

Allogeneic HSCT (aHSCT) is an effective treatment for aggressive haematologic malignancies, often representing the only option for cure. However, some of its benefit, especially in the case of unrelated donor (URD) transplantation, is offset by a high rate of transplant-related mortality (TRM) stemming largely from severe aGvHD and infection. aGvHD occurs when reconstituted 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 GI tract being the most common targets. aGvHD-mediated damage to these vital organs has been associated with increased morbidity and death. Chronic graft-versus-host disease (cGvHD) is also a major complication of HSCT and can lead to debilitating consequences and mortality; it has features resembling autoimmune and other immunologic disorders such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency. Whereas cGvHD is often preceded by a history of aGVHD, it can also occur in the absence of antecedent aGvHD.

GvHD is the leading cause (20%) of non-relapse mortality in HSCT recipients. Both aGvHD and cGvHD are common complications of HSCT. aGvHD and cGvHD variants have been classically characterised based upon the time of onset, with aGvHD occurring within the first 100 days post-transplant, and cGvHD occurring thereafter. However, clinical findings, rather than a set time period, have increasingly been used to differentiate between acute and chronic GvHD.

Among the many factors that impact the risk of severe aGvHD, the degree of matching between recipient and donor human leukocyte antigen (HLA) alleles is the most important variable affecting the incidence and severity of this disease. The preferred transplant donor is a fully HLA-matched sibling; however, only a minority of subjects (<20%) have a fully-matched sibling. Hence, a majority of prospective transplant subjects turn to Center for International Blood and Marrow Transplant Research (CIBMTR) and European Society for Blood and Marrow Transplantation (EBMT) registries of potential unrelated donors (URD), to screen for matches for the 8 alleles at the HLA -A, -B, and -DRB1 loci. With a fully-matched (8/8) unrelated donor (MUD), the risk to subjects is lower than with donors who have even a single HLA mismatch. Subjects with a 7/8 mismatched unrelated donor (MMUD) are at high risk for development of severe aGvHD and consequently, aGvHD-related mortality, which is the largest driver of non-relapse deaths after 7/8 MMUD transplants. Currently, the risk of failure associated with 7/8 MMUD HSCT is sufficiently high to deny many patients access to this potentially life-saving procedure, particularly those belonging to ethnic minorities (non-Caucasians), for whom an 8/8 HLA matched donor often cannot be identified. Thus, while the likelihood of identifying a suitable 8/8 MUD for prospective recipients of Caucasian ancestry is >70%, it is far lower for those from minority groups. This is particularly true for Black patients, for whom the probability of finding an 8/8 donor in the US National Marrow Donor Program registry was < 20%. Moreover, these patients often lack other donor options (including haplo-identical and cord blood donors). In a recent publication in the New England Journal of Medicine, it was shown that rendering 7/8 MMUD HSCT safer and more effective, by reducing the risk of severe aGvHD, could significantly increase the number of available donors for all ethnicities (for example, to >70% for African Americans).

Current treatment options and unmet medical need

Current transplant management focuses on prophylactic GvHD regimens aimed to either suppress donor T cell function with immunomodulatory agents or deplete T cells from the donor graft; the target is to balance between maximising the reduction of GvHD and minimising the risk of relapse, fatal infections (especially viral reactivation) as well as delayed engraftment. The backbone of the current standard of care (SOC) for GvHD prophylaxis is the use of a calcineurin inhibitor [CNI; either cyclosporine (CsA) or tacrolimus (TAC)] plus methotrexate (MTX). In addition, anti-thymocyte globulin (ATG) has

been used for prophylaxis of GvHD in the setting of aHSCT for many years. Other immunomodulatory agents are also being used to augment the basic CNI+MTX GvHD prophylaxis regimen. In addition to abatacept, these agents include mycophenolate mofetil, sirolimus and post-transplant cyclophosphamide (PT-Cy).

The European Society for Blood and Marrow Transplantation (EBMT) has in 2020 issued updated consensus recommendations for prophylaxis and management of GvHD (Penack et al, Lancet Haematol 2020); these focus on allogeneic stem-cell transplantation in adult patients with standard risk haematological malignant disease using an HLA-matched sibling or URD and bone marrow or peripheral blood as stem-cell source. According to the published recommendations:

- Patients undergoing matched related donor or matched URD allogeneic transplant should receive GvHD prophylaxis with a calcineurin inhibitor plus an antimetabolite.
- TAC or CsA can be used in the setting of sibling or matched unrelated donor transplants. The choice should be made based on experience at the centre (e.g., CsA is the standard calcineurin inhibitor adopted in most European centres).
- MTX is the recommended antimetabolite for patients receiving myeloablative conditioning (MAC).
- Mycophenolate mofetil can be used instead of MTX for patients receiving MAC in case of contraindications to MTX or for those patients who need rapid engraftment (e.g., those with aspergillosis).
- Mycophenolate mofetil is the recommended antimetabolite for patients receiving non-MAC conditioning and reduced-intensity conditioning (RIC).
- rATG [Thymoglobulin (Sanofi, Paris, France) or Grafalon (Neovii, St Gallen, Switzerland)] is recommended for preventing GvHD in patients undergoing matched URD allogeneic stem-cell transplantation.
- rATG can also be recommended for preventing GvHD in patients undergoing matched related donor (MRD) allogeneic peripheral blood allogeneic stem-cell transplantation; rATG is recommended for patients who are at a high risk of GvHD.

The recommendations recognise that there are divergent views concerning paediatric transplantations, MMUD transplantations and haploidentical transplantations, and the recommendations therefore do not cover these situations. It is however mentioned that in children (<18 years), many centres use calcineurin inhibitor as a single agent, and many centres also use rATG in MUD allogeneic stem-cell transplant. Moreover, while not covered in the recommendations, rATG is also very commonly used as part of prophylactic regimens in HLA-mismatched transplantations.

The recommendations also acknowledge that while a high consensus was reached during their development regarding the underlying principles for drug management of GvHD prophylaxis, the level of evidence for each specific recommendation (regarding e.g. timing, dose and duration) is low, mainly because comparative analyses are absent. From a regulatory perspective, it is furthermore noted that in the EU, GvHD prophylaxis is quite variably covered among the authorised indications for the medicinal products included in the recommendations, with cornerstone products such as CNI, MTX and rATG being authorised primarily through national / decentralised procedures and consequently with variable Product Information.

Considering the limited evidence base, an unmet need for prophylaxis of GvHD can be considered to exist in the majority of HSCT recipients who do not have a fully matched sibling donor, and this unmet need is even greater for the 7/8 MMUD population who are considered to be inherently at higher risk of GvHD. Consequently, additional products with a favourable benefit-risk profile and a well-documented

basis for their use would be an important addition to the current treatment armamentarium. From a European perspective, where rATG holds an established position as part of the prophylactic regimen in many instances, it should be borne in mind that abatacept would likely be viewed as an alternative to rATG rather than the two agents being used together, as this combination would very likely lead to profound and excessive immunosuppression.

4.1.2. About the product

Abatacept (Orencia®), a selective costimulation modulator, is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T cell-associated CTLA-4 linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human IgG1. 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. Abatacept is approved for the intravenous (IV) treatment of moderate to severe adult rheumatoid arthritis (RA) and psoriatic arthritis (PsA) in the US, the EU, Japan, Latin America, and other countries/regions. A subcutaneous (SC) formulation of abatacept in a prefilled syringe and autoinjector has been approved for adult RA and PsA patients in the US, EU, and several other countries. SC abatacept is approved for the treatment of juvenile idiopathic arthritis (JIA) in paediatric patients 2 years of age and older in the US and EU. Abatacept is also approved for IV treatment of JIA in paediatric patients 6 years of age and older in the US, EU, and other countries/regions, as well as for prophylaxis of aGvHD in adult and paediatric patients 2 years of age and older in the US and 6 years of age and older in Canada and Israel.

According to the MAH, 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 contributing to the pathogenesis of GvHD become activated and utilise CD28:CD80/86 costimulation to propagate the immune response. As such, studies in both murine and non-human primate models have shown that 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 two diseases, T cells are thought to play a critical role in the diverse clinical manifestations of each disease.

4.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek scientific advice in relation to this development programme.

Paediatric requirements do not apply, as the submission occurs after patent expiry.

4.1.4. General comments on compliance with GCP

Study IM101311 was performed in accordance with GCP as claimed by the MAH.

Study IM101841 was conducted in accordance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices as claimed by the MAH.

The MAH has also provided a statement confirming that Study IM101311, conducted outside of the European Union, was conducted in accordance with the ethical principles underlying EU Directive 2001/20/EC.

4.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

4.2.1. Ecotoxicity/environmental risk assessment

Abatacept is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk to the environment. According to Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00 Corr2.), specific ERA studies are not required for proteins.

Abatacept and the product excipients do not pose a significant risk to the environment.

4.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of abatacept.

4.3. Clinical aspects

4.3.1. Introduction

GCP

Clinical trial IM101311 was performed in accordance with GCP as claimed by the MAH.

The MAH has also provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 Tabular overview of clinical studies

Study/Key Dates/ Study Report	Study Design/ Duration/ Status	Subject Population	Treatment groups/ Background Therapy	No. Subjects Randomized	Efficacy Endpoints
IM101311 (also known as **ABA2**) Phase 2 Pivotal Study **Study initiation: 15-Apr-2013** **Study Completion (LPLV): 17-Nov-2018** **DBL: 06-Nov-2020 for Primary CSR**[1] **and Primary CSR Addendum**[10]	**Study Design:** Phase 2 trial with 2 cohorts: a randomized, double blind, placebo-controlled cohort (8/8 MUD cohort) for subjects who received a HSCT from 8/8 MUD and a single arm cohort (7/8 MMUD cohort) for subjects who received a HSCT from 7/8 MMUD. **Duration:** up to Day 180 (primary endpoint), and then 5 years of long-term follow-up **Status:** Ongoing	Subjects had hematologic malignancies, were at least 6 years old, and had a unrelated BM or PB stem cell donor who was HLA matched at no fewer than 7/8 HLA loci (A, B, C, DRB1).	**8/8 MUD Cohort:** • Abatacept+CNI+MTX • Placebo+CNI+ MTX **7/8 MMUD Cohort:** • Abatacept+CNI+MTX	**8/8 MUD:** All 146 enrolled subjects were randomized and 142 subjects were treated with study medication and transplanted (73 with abatacept and 69 with placebo) **7/8 MMUD:** Of the 46 subjects enrolled, 44 were treated with study medication and transplanted; 43 subjects were treated with abatacept	**8/8 MUD - Primary:** To compare severe (Gr III-IV) GFS up to Day 180 post-transplantation between a cohort with abatacept+SOC prophylaxis of aGvHD and a cohort with SOC (only) prophylaxis of aGvHD **7/8 MMUD**: to evaluate severe (Gr III-IV) GFS up to Day 180 post-transplantation in subjects receiving open-label abatacept+SOC aGvHD prophylaxis
IM101841 **Study initiation: 10-Oct-2020** **Study Completion: 15-Feb-2021** **Study period: 01-Jan-2011 to 31-Dec-2018** **Primary Non-interventional Study Report**[2]	**Study Design:** Retrospective cohort study evaluating subjects that received abatacept in addition to SOC aGvHD prophylaxis, compared to subjects receiving SOC aGvHD prophylaxis, using data routinely collected into the CIBMTR database. **Duration:** up to 180 days post-transplant **Status:** Completed	Subjects were at least 6 years old, had a BM or PB stem cell donor who was HLA-matched at 7/8 loci (A, B, C, DRB1).	• Abatacept+CNI+MTX without ATG **or** • CNI+MTX without ATG	**Abatacept+CNI+MTX without ATG:** 54 **CNI+MTX without ATG:** 162	**Primary:** to compare the OS with 180 days of follow-up post-HSCT in 7/8 HLA-matched subjects treated with abatacept+CNI+MTX without ATG to those treated with CNI+MTX without ATG

To confirm GCP compliance, the MAH performed a risk assessment of the IM101311 Investigator Sponsored Research. The purpose was to identify study integrity, data quality, and GCP risks for the study. The scope of the assessment included review and evaluation of the following topics: organization and personnel, vendor management, quality management system, trial management and oversight, data management and handling, randomization and unblinding, safety reporting, investigational product, statistical analysis and reporting, computer systems and record management (Trial Master File). To address identified risk areas, the Sponsor provided a mitigation plan that was deemed acceptable by the MAH.

An inspection was also conducted by the FDA on 20-27 September 2021 in support of the US submission for abatacept in the prevention of aGvHD. In addition, two site inspections were performed. The FDA inspections did not raise negative findings and no Form 483s were issued.

4.3.2. Pharmacokinetics

Analytical methods

Bioanalytical reports were provided for abatacept quantitation by ELISA, Anti-BMS-188667 antibodies by ECL and Anti-BMS-188667 neutralizing antibodies by a cell-based assay.

Abatacept quantitation in human serum by ELISA

The assay is a quantitative sandwich enzyme immunoassay using monoclonal anti-CTLA4 antibody (clone 7F8) for capturing abatacept and biotinylated monoclonal anti-CTLA4 antibody (clone 11D4) for detection. The signal is measured using a TMB substrate after streptavidin-horseradish peroxidase. The

quantitation range is 1.00-30.0 ng/ml. Dilutional linearity was confirmed up to 1:1000000 and selectivity in GvHD patient serum.

Electro chemiluminescent (ECL) immunoassay for the detection of anti-BMS-188667 antibodies in human serum

Anti-abatacept antibodies are detected by a MSD electrochemiluminescence method using biotinylated abatacept for capture, ruthenium labeled abatacept for detection and anti-CTL4Ig as positive control. Of the 840 samples, 15 samples were confirmed positive for ADA with 'CTLA4 and possibly Ig' reactivity, 5 samples were confirmed positive for ADA with 'Ig and/or junction region' reactivity.

Detection of anti-BMS-188667 neutralizing antibodies in human serum by a cell-based assay

Abatacept consists of the extracellular domain of human CTLA-4 linked to the Fc (hinge, CH2 and CH3 domains) portion of human IgG1, is a recombinant DNA-derived protein that binds to CD80 and CD86 on antigen presenting cells blocking the CD28 costimulatory pathway for T-cell activation. Jurkat T cells were transfected with the luciferase gene under the control of the IL2 promoter and co-stimulated with Daudi B cells in the presence of anti-CD3. The co-stimulation activates the IL-2 promoter which in turn produces luciferase protein. The resulting luminescent signal is measured using a Luciferase assay system. Abatacept produces a dose-dependent decrease in luciferase activity by blocking the T-cells functional interaction with CD28 and preventing the co-stimulatory signal that is necessary for IL-2 production. The method uses anti-human CTLA4 mouse Mab 11D4 as positive control (Nab working solution) and anti-CD3 Mab (mixed with Daudi cell culture medium). Abatacept concentration range was 0.002-100 µg/ml.

Seven samples were run in the NAb assay. These samples were confirmed as positive in ADA analysis, belonged to post-dose samples (visit after baseline) and a corresponding baseline sample was available. Eight samples were not analysed as they were baseline samples.

CHMP's comments

The PK and immunogenicity samples were analysed at Wuxi App Tec. The methods and the analysis site were the same as for the currently approved indications. The samples were appropriately stored and handled. Bioanalytical reports including ISR for the abatacept assay method were provided.

The new PK data are for patients with hematologic malignancy (HM) treated with abatacept (plus standard GvHD prophylaxis regimen) for the prophylaxis of aGvHD (study IM101311). Descriptive statistics of the observed abatacept concentrations are shown in Table 2. Patients with 8/8 HLA match had 24% to 28% lower geometric mean abatacept concentration on D14 (predose), D28 (predose), D35, D42, and D63 compared with patients with 7/8 HLA match.

Table 2 ***Summary Statistics of observed Abatacept Concentrations (study IM101311)***

		8/8 HLA MATCH		7/8 HLA MATCH	
TREATMENT	STUDY DAY	STATISTIC	CONCENTRATION (ug/mL)	STATISTIC	CONCENTRATION (ug/mL)
ABATACEPT	D-1 PRE	N	72	N	42
		MEAN	1.305	MEAN	4.572
		SD	11.007	SD	29.626
		GEO.MEAN	0.001	GEO.MEAN	0.001
		%CV	843.5	%CV	648.0
		MEDIAN	0.001	MEDIAN	0.001
		MIN	0.00	MIN	0.00
		MAX	93.40	MAX	192.00
	D-1 POST	N	64	N	40
		MEAN	232.497	MEAN	222.551
		SD	285.440	SD	67.437
		GEO.MEAN	189.058	GEO.MEAN	176.446
		%CV	122.8	%CV	30.3
		MEDIAN	183.500	MEDIAN	219.500
		MIN	81.60	MIN	0.03
		MAX	2270.00	MAX	365.00
	D5 PRE	N	32	N	18
		MEAN	43.359	MEAN	59.233
		SD	11.772	SD	21.980
		GEO.MEAN	41.869	GEO.MEAN	55.532
		%CV	27.2	%CV	37.1
		MEDIAN	43.000	MEDIAN	54.900
		MIN	25.00	MIN	26.00
		MAX	72.60	MAX	112.00
	D14 PRE	N	68	N	40
		MEAN	44.957	MEAN	60.155
		SD	16.496	SD	17.955
		GEO.MEAN	42.484	GEO.MEAN	57.536
		%CV	36.7	%CV	29.8
		MEDIAN	42.250	MEDIAN	58.650
		MIN	20.70	MIN	27.10
		MAX	122.00	MAX	109.00
	D28 PRE	N	68	N	38
		MEAN	51.415	MEAN	67.561
		SD	26.304	SD	21.507
		GEO.MEAN	46.902	GEO.MEAN	63.482
		%CV	51.2	%CV	31.8
		MEDIAN	47.700	MEDIAN	63.900
		MIN	12.70	MIN	14.10
		MAX	214.00	MAX	103.00
	D28 POST	N	66	N	39
		MEAN	237.258	MEAN	324.718
		SD	67.741	SD	78.246
		GEO.MEAN	227.565	GEO.MEAN	315.624
		%CV	28.6	%CV	24.1
		MEDIAN	235.500	MEDIAN	315.000
		MIN	128.00	MIN	159.00
		MAX	386.00	MAX	530.00
	D35	N	63	N	33
		MEAN	86.756	MEAN	114.145
		SD	27.055	SD	32.603
		GEO.MEAN	82.662	GEO.MEAN	109.155
		%CV	31.2	%CV	28.6
		MEDIAN	82.100	MEDIAN	111.000
		MIN	41.10	MIN	46.30
		MAX	160.00	MAX	171.00
	D42	N	62	N	34
		MEAN	61.781	MEAN	85.921
		SD	23.556	SD	46.567
		GEO.MEAN	57.621	GEO.MEAN	77.283
		%CV	38.1	%CV	54.2
		MEDIAN	58.300	MEDIAN	77.300
		MIN	27.70	MIN	20.90
		MAX	141.00	MAX	304.00
	D63	N	69	N	35
		MEAN	28.858	MEAN	38.792
		SD	14.140	SD	18.261
		GEO.MEAN	22.504	GEO.MEAN	31.132
		%CV	49.0	%CV	47.1
		MEDIAN	25.800	MEDIAN	38.000
		MIN	0.00	MIN	0.78
		MAX	90.00	MAX	75.50
	D100	N	64	N	37
		MEAN	9.271	MEAN	12.971
		SD	5.919	SD	8.711
		GEO.MEAN	7.567	GEO.MEAN	6.429
		%CV	63.8	%CV	67.2
		MEDIAN	7.950	MEDIAN	12.400
		MIN	0.57	MIN	0.00
		MAX	30.60	MAX	30.90

4.3.3. Pharmacodynamics

No separate new data relevant to the pharmacodynamic effects of abatacept have been provided within the documentation.

4.3.4. PK/PD modelling

Population PK analyses

Two population PK (PPK) modelling reports were included in the submission material. The objective of the PPK model dated 26-Mar-2020 was to describe the PK of abatacept in patients ≥6 years of age with RA or JIA or receiving URD HSCT due to HM (hereafter referred to as **2020 PPK model**). Subsequently, the MAH developed a refined PPK model dated 20-Jul-2022 (hereafter referred to as **2022 PPK model**) to simulate abatacept exposure in a virtual paediatric patient population (2 to <6 years old) to support dose selection in this age group for prevention of aGvHD.

The 2022 PPK model is pivotal for extrapolation of PK and prediction of exposure in children 2 to <6 years old; this age group was not enrolled in Study IM101311. The 2020 PPK model is important for the current application because the structure and covariates of the 2022 model are based on the 2020 model.

2020 PPK model

Dataset: The 2020 PPK model dataset included PK data from 8 studies in which abatacept was administered intravenously (IV):

- Studies IM103002, IM101100, IM101101, IM101102, IM101029, and IM101031 (Phase 2 and Phase 3 studies in adult patients with RA)
- Study IM101033 (Phase 3 study in paediatric patients 6-17 years of age with JIA)
- Study IM101311 (Phase 2 study in paediatric and adult patients aged ≥6 years receiving URD HSCT for HM)

The initial PK database included 5225 abatacept concentration samples from 689 patients. Of these samples, 208 were flagged and excluded as anomalous values using the same criteria as in previous PPK analyses, and 144 samples were below the lower limit of quantitation (BLQ). A total of 4873 samples (93.26%) from 685 patients were included in the final dataset.

Missing dosing information in Study IM101311 was imputed as follows:

1. If the infusion stop time was missing, it was imputed using the infusion start time and the median infusion duration (that is, 1 hour).
2. If the infusion start time was missing, it was imputed using the infusion stop time and the median infusion duration. If the imputed start time was prior to a trough sample, the trough sampling time was used as the infusion start time.
3. If both start and stop times of infusion were missing and if a trough sample was taken on the same day, the trough sampling time was used as the infusion start time and the infusion stop time was imputed using the imputed infusion start time and the median infusion duration.
4. If both start and stop times of infusion were missing and if no trough sample was taken, then the previous occasion's dosing time was used as the current dosing time. If the time of the previous dose was not available, this step was repeated until the dosing time or a trough sample taken on that occasion were available.

Concentrations missing an actual sample time were common in study IM101311 (427 out of 938 samples). For samples collected up to 28 days after HSCT, missing times of pre-dose samples were imputed using the start time of the infusion directly following the sample; missing times of post-infusion samples were imputed using the end time of infusion. For samples collected beyond 28 days after HSCT, the missing times of samples were imputed by carrying the last available sample time forward.

Selected subject characteristics are shown in Table 3.

Table 3 ***Subject Characteristics in the 2020 PPK Analysis Dataset***

Subject Characteristic		RA (N = 386)	JIA (N = 184)	HM		Overall (N = 685)
				Cohort 7/8 (N = 42)	Cohort 8/8 (N = 73)	
Baseline Age [yrs]	Mean (SD)	53.3 (12.1)	12.5 (2.9)	36.3 (22.9)	40.8 (19.5)	40.0 (21.5)
	Median	54.0	13.0	39.5	44.0	45.0
	Min, Max	17, 84	6, 17	6, 76	6, 71	6, 84
Baseline Body Weight [kg]	Mean (SD)	78.25 (21.02)	42.06 (15.29)	72.27 (27.97)	74.16 (23.37)	67.72 (25.71)
	Median	75.65	41.75	74.80	71.30	67.90
	Min, Max	38.1, 186.8	14.4, 100.0	22.0, 127.3	23.1, 142.7	14.4, 186.8
Baseline Calculated GFR [mL/min/1.73 m^2]	Mean (SD)	86.677 (28.872)	202.446 (81.290)	128.754 (52.643)	122.475 (46.083)	124.180 (71.440)
	Median	80.035	184.978	119.580	112.545	103.390
	Min, Max	36.99, 245.88	82.50, 578.21	50.99, 307.69	68.03, 315.18	36.99, 578.21
	Missing N (%)	0 (0.0)	0 (0.0)	1 (2.4)	7 (9.6)	8 (1.2)
Baseline Albumin [g/dL][a]	Mean (SD)	3.94 (0.30)	4.27 (0.37)	3.20 (0.35)	3.44 (0.34)	4.02 (0.36)
	Median	3.90	4.30	3.30	3.20	4.00
	Min, Max	2.7, 4.7	3.0, 5.1	2.6, 3.5	3.2, 3.9	2.6, 5.1
	Missing N (%)	8 (2.1)	35 (19.0)	37 (88.1)	68 (93.2)	148 (21.6)
Baseline Aspartate Aminotransferase [U/L]	Mean (SD)	20.9 (8.6)	23.6 (17.8)	32.0 (18.0)	26.0 (13.0)	22.8 (13.1)
	Median	19.0	20.0	27.0	24.0	20.0
	Min, Max	7, 90	9, 181	11, 84	8, 83	7, 181
	Missing N (%)	0 (0.0)	0 (0.0)	2 (4.8)	9 (12.3)	11 (1.6)
Baseline Alanine Aminotransferase [U/L]	Mean (SD)	20.3 (11.3)	17.3 (18.4)	44.2 (44.2)	36.9 (32.9)	22.5 (20.9)
	Median	17.0	13.0	29.0	26.5	17.0
	Min, Max	5, 93	2, 188	11, 223	7, 187	2, 223
	Missing N (%)	0 (0.0)	0 (0.0)	2 (4.8)	9 (12.3)	11 (1.6)
Baseline Total Bilirubin [mg/dL]	Mean (SD)	0.425 (0.192)	0.419 (0.268)	0.550 (0.319)	0.577 (0.357)	0.447 (0.247)
	Median	0.400	0.400	0.500	0.400	0.400
	Min, Max	0.10, 2.00	0.10, 2.60	0.10, 1.80	0.20, 1.80	0.10, 2.60
	Missing N (%)	8 (2.1)	35 (19.0)	2 (4.8)	9 (12.3)	54 (7.9)
Sex, N (%)	Male	109 (28.2)	53 (28.8)	26 (61.9)	41 (56.2)	229 (33.4)
	Female	277 (71.8)	131 (71.2)	16 (38.1)	32 (43.8)	456 (66.6)
Baseline Use of Methotrexate, N (%)	No	132 (34.2)	40 (21.7)	42 (100.0)	73 (100.0)	287 (41.9)
	Yes	254 (65.8)	136 (73.9)	0 (0.0)	0 (0.0)	390 (56.9)
	Missing N (%)	0 (0.0)	8 (4.3)	0 (0.0)	0 (0.0)	8 (1.2)
Baseline Use of NSAIDs, N (%)[a]	No	72 (18.7)	12 (6.5)	0 (0.0)	0 (0.0)	84 (12.3)
	Yes	314 (81.3)	164 (89.1)	0 (0.0)	0 (0.0)	478 (69.8)
	Missing N (%)	0 (0.0)	8 (4.3)	42 (100.0)	73 (100.0)	123 (18.0)
Baseline Use of Corticosteroids, N (%)[a]	No	272 (70.5)	89 (48.4)	0 (0.0)	0 (0.0)	361 (52.7)
	Yes	114 (29.5)	87 (47.3)	0 (0.0)	0 (0.0)	201 (29.3)
	Missing N (%)	0 (0.0)	8 (4.3)	42 (100.0)	73 (100.0)	123 (18.0)

Model development: A PPK model for abatacept was previously developed using data from adult subjects with RA and subjects with JIA aged 6 to 17 years. This model was a 2-compartment, zero-order IV infusion, and first-order elimination model with an additive plus proportional residual error model, parameterized in terms of CL, VC, intercompartmental clearance (Q), and VP. Power relationships between weight and CL, VC, and VP were included in the base structural PPK model. The parameters of this base structural model were re-estimated using the pooled analysis dataset which expanded on the previous set by including data collected in subjects with HM enrolled in Study IM101311. Table 4 presents the parameter estimates for this 2020 base model.

Table 4 ***Parameter Estimates (2020 Base PPK Model)***

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability[a]	
	Population Mean	%RSE	Final Estimate	%RSE
$CL_{TV,ref}$: Clearance [L/h][b]	0.0224	1.60	0.0776	6.73
CL_{BWT}: Power of Weight on CL [-][c]	0.558	5.46		
$VC_{TV,ref}$: Central Volume [L][b]	3.13	1.42	0.0446	17.2
VC_{BWT}: Power of Weight on VC [-][c]	0.734	4.25		
Q: Distribution Clearance [L/h]	0.0324	6.46	NE	NA
$VP_{TV,ref}$: Peripheral Volume [L][b]	5.25	3.36	0.172	12.9
VP_{BWT}: Power of Weight on VP [-][c]	0.779	6.11		
Proportional Component of RV			0.0610	5.58
Additive Component of RV			0.00240	56.0
Minimum Value of the Objective Function = 24185.065				

[a] ETA shrinkage: ETA CL: 6.79%, ETA VC: 38.5%, ETA VP: 26.0%; Epsilon Shrinkage: Proportional Component: 11.8%, Additive Component: 11.8%.

[b] $CL_{TV,ref}$, $VC_{TV,ref}$, and $VP_{TV,ref}$ are typical values of CL, VC, and VP at the reference covariate values. Covariate effects were estimated relative to a reference weight of 67.9 kg.

[c] $CL_{TV} = CL_{TV,ref}\left(\frac{BWT_b}{67.9}\right)^{CLBWT}$

$VC_{TV} = VC_{TV,ref}\left(\frac{BWT_b}{67.9}\right)^{VCBWT}$

$VP_{TV} = VP_{TV,ref}\left(\frac{BWT_b}{67.9}\right)^{VPBWT}$

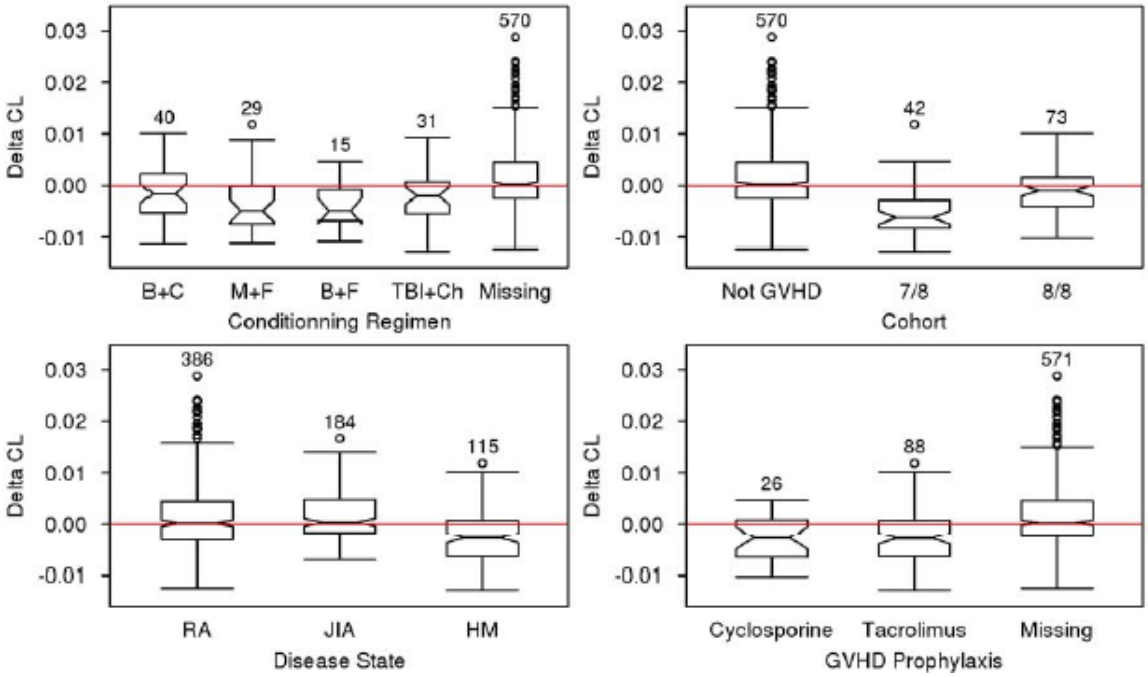
NA: not applicable; NE: not estimated

Goodness-of-fit plots demonstrated generally good agreement between the observed and model-predicted concentrations in the overall population, although the model tended to slightly underpredict very low concentrations (below 0.1 µg/ml). However, multiple trends were observed in the subset of data collected in Study IM101311, including the underprediction of concentrations below 10 µg/mL at the population level and clear differences in the central tendency lines associated with each cohort of Study IM101311 (Cohort 8/8 vs Cohort 7/8), consistent with the observed data (see section 5.3.2 of this AR).

Alternative IIV and residual variability (RV) models were tested but were not found to provide improvement. They included the addition of IIV in Q and switching to constant coefficient of variation (CV) or log RV models.

Covariates: Graphical analyses were conducted to explore potential covariate effects on CL. Results for covariates specifically related to Study IM101311 are shown in Figure 1. Patients in Study IM101311 appeared to have lower CL compared with patients with RA and JIA, and among patients in Study IM101311 Cohort 7/8 appeared to have lower CL compared with Cohort 8/8. CL appeared not to be affected by aGvHD prophylaxis (cyclosporine vs tacrolimus) and conditioning regimen (busulfan + cyclophosphamide [B+C]; busulfan + fludarabine [B+F]; melphalan + fludarabine [M+F]; total body irradiation and chemotherapy [TBI+Ch]).

Figure 1 ***Categorical covariates vs clearance (2020 Base PPK model)***



Formal covariate analysis was conducted next. A single round of forward selection was performed to select covariates determined to be statistically significant when evaluated univariately using a significance level of 0.01 (corresponding to a decrease in the objective function of 6.63 for 1 df). Based upon the comparison of univariate models to the reference base PPK model, the effects of disease status, baseline AST, baseline CGFR, non-usage of MTX, and sex on CL and the effects of disease status and sex on VC were considered statistically significant at the 0.01 level and were incorporated into the first full model. The effect of baseline ALT on CL, also found to be statistically significant, was not included in the full model because baseline ALT and AST were highly correlated (Pearson correlation coefficient = 0.737) and because the effect of baseline AST was more statistically significant.

Parameter estimates from the first full covariate model are provided in Table 5.

Table 5 ***Parameter Estimates (2020 Full PPK Model)***

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability[a]	
	Population Mean	%RSE	Final Estimate	%RSE
$CL_{TV,ref}$: Clearance (L/h)[b]	0.0254	3.27		
CL_{BWT}: Power of Weight on CL (-)[c]	0.659	6.36		
CL_{JIA}: Exponent of JIA Effect on CL (-)[c]	-0.0512	82.5	0.0616	6.66
CL_{HM}: Exponent of HM Effect on CL (-)[c]	-0.242	15.8		
CL_{AST}: Power of Baseline AST Effect on CL (-)[c]	-0.133	22.2		
CL_{CGFR}: Power of Baseline CGFR Effect on CL (-)[c]	0.206	16.7		
CL_{MTX}: Exponent of Effect of Non-Methotrexate Use on CL (-)[c]	-0.00343	677		
CL_{SEX}: Exponent of Sex Effect in Female on CL (-)[c]	-0.0947	25.9		
$VC_{TV,ref}$: Central Volume (L)[b]	3.32	3.14		
VC_{BWT}: Power of Weight on VC (-)[c]	0.666	6.54		
VC_{JIA}: Exponent of JIA Effect on VC (-)[c]	-0.0445	103	0.0379	17.2
VC_{HM}: Exponent of HM Effect on VC (-)[c]	0.113	33.6		
VC_{SEX}: Exponent of Sex Effect in Female on VC (-)[c]	-0.123	23.2		
Q: Distribution Clearance (L/h)[c]	0.0341	6.67	NE	NA
$VP_{TV,ref}$: Peripheral Volume (L)[b]	5.37	3.45	0.160	12.5
VP_{BWT}: Power of Weight on VP (-)[c]	0.778	6.16		
Proportional Component of RV			0.0612	5.60
Additive Component of RV			0.00242	55.5
Minimum Value of the Objective Function = 23994.277				

[a] ETA shrinkage: ETA CL: 8.06%, ETA VC: 40.6%, ETA VP: 26.1%; Epsilon Shrinkage: Proportional Component: 11.4%, Additive Component: 11.4%.

[b] $CL_{TV,ref}$, $VC_{TV,ref}$, and $VP_{TV,ref}$ are typical values of CL, VC, and VP at the reference covariate values. Covariate effects were estimated relative to a reference male RA subject with a baseline weight of 67.9 kg, baseline AST of 20 U/L, baseline CGFR of 103 mL/min/m^2 and receiving concomitant administration of methotrexate.

[c] $$CL_{TV} = CL_{TV,ref}\left(\frac{BWT_b}{67.9}\right)^{CL_{BWT}}\left(\frac{AST_b}{20}\right)^{CL_{AST}}\left(\frac{CGFR_b}{103}\right)^{CL_{CGFR}} e^{JIA\times CL_{JIA}+HM\times CL_{HM}+SEX\times CL_{SEX}+(1-MTX)\times CL_{MTX}}$$

$$VC_{TV} = VC_{TV,ref}\left(\frac{BWT_b}{67.9}\right)^{VC_{BWT}} e^{JIA\times VC_{JIA}+HM\times VC_{HM}+SEX\times VC_{SEX}}$$

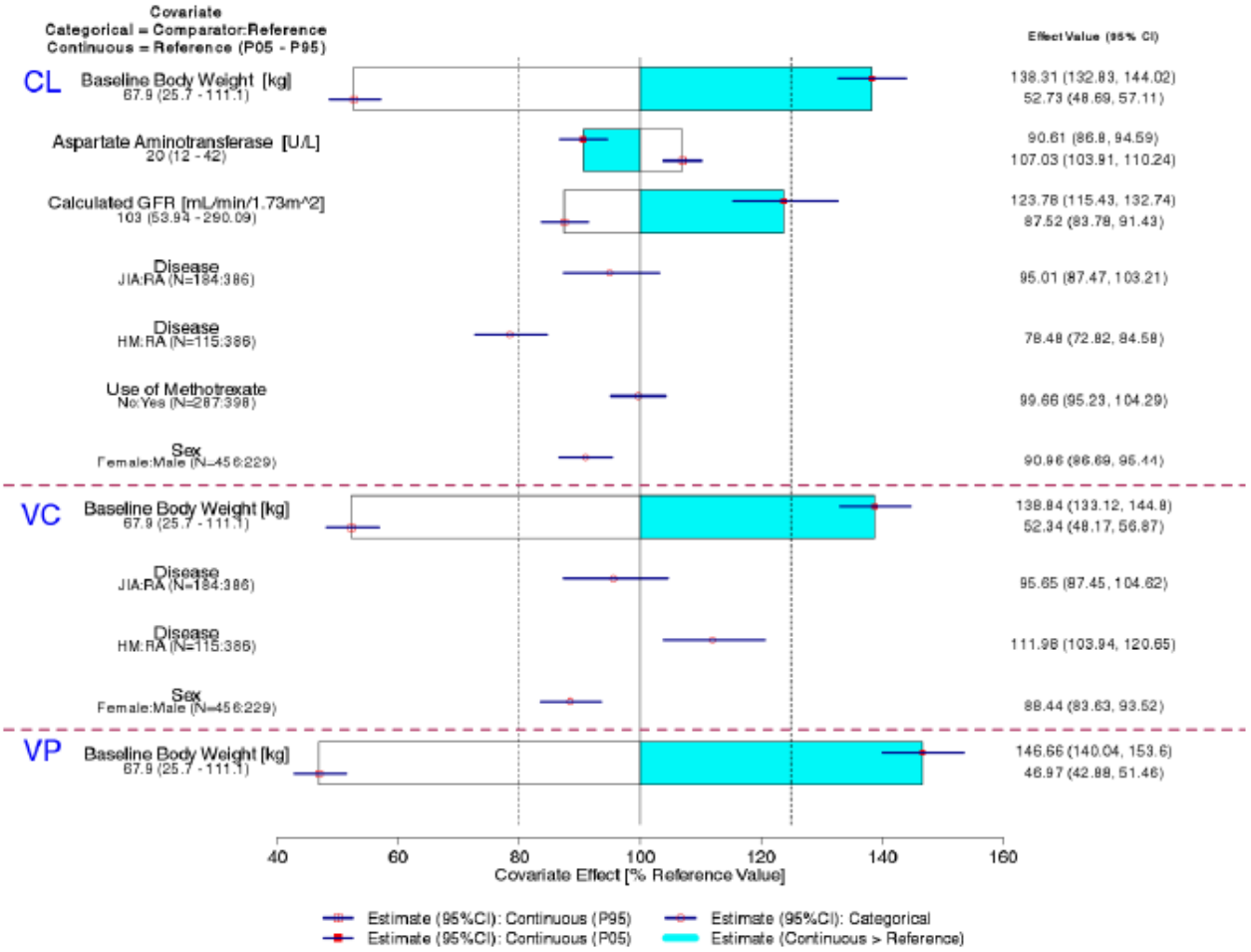
$$VP_{TV} = VP_{TV,ref}\left(\frac{BWT_b}{67.9}\right)^{VP_{BWT}}$$

NA: not applicable; NE: not estimated

Clinical relevance of covariates was evaluated with a forest plot (Figure 2). Baseline weight was associated with a 38%, 39%, and 47% increase in CL, VC, and VP at the 95th percentile of weight (111 kg), respectively, and these covariate effects were considered clinically relevant. Similarly, subjects with HM were predicted to exhibit a 22% reduction in CL, although the upper bound of the associated 95% CI fell within the reference range. Additionally, although the effect of baseline calculated GFR (CGFR) was within the reference range for the 5th and 95th percentile of CGFR, the upper bound of the 95% CI

associated with the 95th percentile of CGFR was larger than 125%. The magnitude of all other covariate effects (AST, JIA vs RA, MTX use, gender on CL; disease status and gender on VC) was completely contained within the 80% to 125% range and, therefore, none of these effects were considered clinically relevant.

Figure 2 ***Clinical Relevance of Covariate Effects (2020 Full PPK Model)***



Note 1: Categorical covariate effects (95% CI) are represented by open circles (horizontal lines).

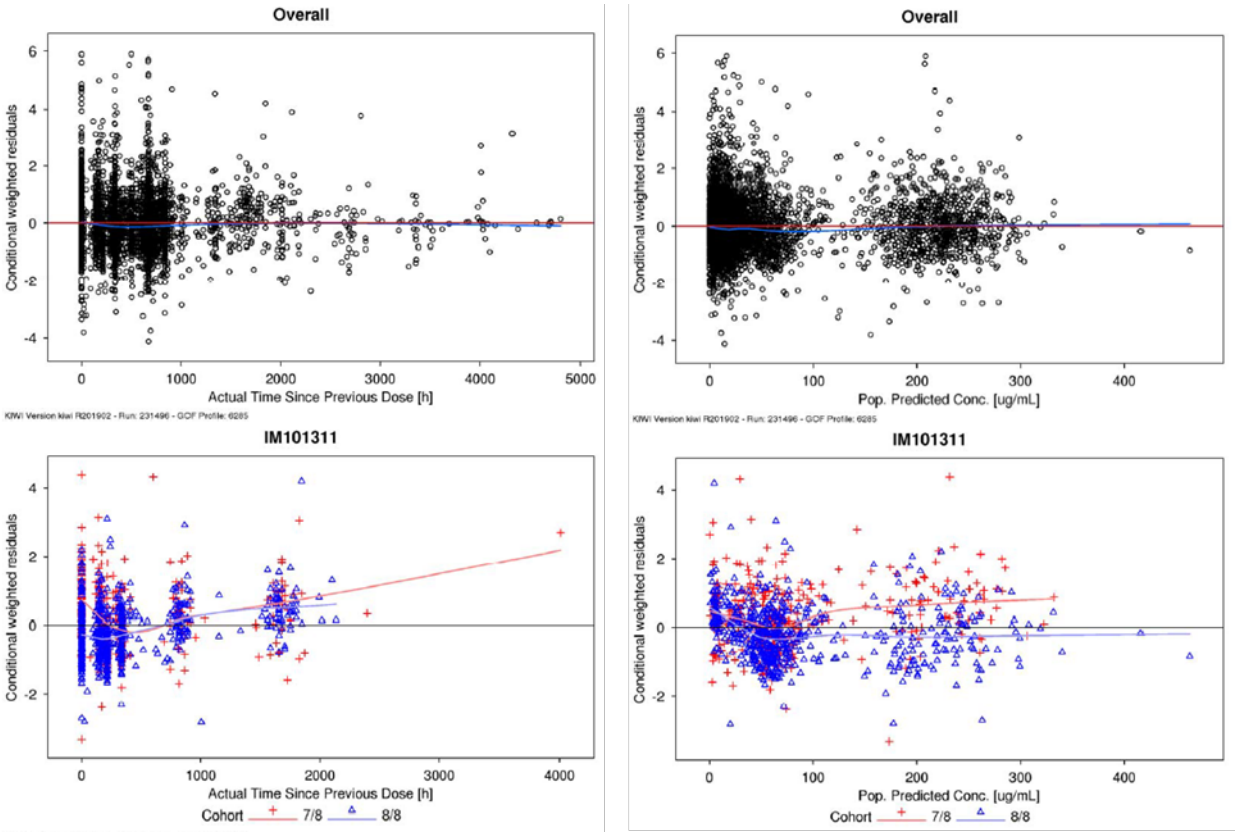
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represent the range of covariate effects from the median to the 5th/95th percentiles of the covariate.

Note 3: The reference subject is a male subject with RA, receiving concomitant MTX at baseline and with BWT = 67.9 kg, AST = 20 U/L, and CGFR = 103 mL/min/1.73 m^2. Parameter estimate in the reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

A reduced model was obtained by stepwise backward elimination of covariate effects from the full PPK model. A significance level of 0.001 was used for the backward elimination (which corresponds to an increase in the objective function of 10.83 for 1 df). Covariates were removed by backward elimination until all remaining covariates were statistically significant ($P < 0.001$). After 4 steps, 3 effects were removed from the model: on the effect of JIA disease status CL and VC and the non-usage of MTX on CL. All other covariate effects were found to be statistically significant, in particular the effect of HM disease status on both CL and VC. However, the covariate effects included in the reduced

model did not correct the differences in fit between the cohorts of Study IM101311 (Figure 3). This warranted the assessment of cohort effect in a subsequent sensitivity analysis.

Figure 3 ***CWRESI Versus Time After Previous Dose (Left panel) and CWRESI Versus Population Predicted Concentration (Right panel) Overall and in Study IM101311, Stratified by Cohort. (2020 PPK model after backward elimination step)***



To assess the effect of Study IM101311 cohorts (7/8 and 8/8) on abatacept PK the effects of HM disease on CL and VC were removed from the reduced model. Next, a single round of forward selection was performed for Study IM101311 cohort effects on CL and VC. Cohort effects were statistically significant on both CL and VC ($P<0.01$) and, therefore, were incorporated into the sensitivity analysis model. The parameter estimates of the sensitivity analysis model are shown in Table 6 and graphical representations of the effect of categorical and continuous covariates on the typical values of structural model parameters are presented in Figure 4. Of note, the reference subject used for this evaluation was not defined as a subject with RA (as done in previous 2020 models) but as a subject with JIA or RA, referred to as non-PHM (i.e., not a subject receiving URD HSCT due to HM). Combining the JIA and RA patients was considered appropriate because, as discussed above, the effect of JIA vs RA disease status on CL and VC was considered not clinically relevant and it was not statistically significant in the backward elimination at the selected significance level.

Table 6 ***Parameter Estimates (2020 Sensitivity Analysis PPK Model)***

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability[a]	
	Population Mean	%RSE	Final Estimate	%RSE
$CL_{TV,ref}$: Clearance (L/h)[b]	0.0250	2.55		
CL_{BWT}: Power of Weight on CL (-)[c]	0.677	5.57		
CL_{AST}: Power of AST Effect on CL (-)[c]	-0.120	23.4		
CL_{CGFR}: Power of GFR Effect on CL (-)[c]	0.187	15.1		
CL_{SEX}: Exponent of Sex Effect in Female on CL (-)[c]	-0.0969	26.3	0.0592	6.87
$CL_{COHORT7}$: Exponent of Cohort 7/8 Effect on CL (-)[c]	-0.383	13.6		
$CL_{COHORT8}$: Exponent of Cohort 8/8 Effect on CL (-)[c]	-0.133	24.4		
$VC_{TV,ref}$: Central Volume (L)[b]	3.25	2.71		
VC_{BWT}: Power of Weight on VC (-)[c]	0.687	4.48		
VC_{SEX}: Exponent of Sex Effect in Female on VC (-)[c]	-0.123	23.8	0.0343	17.9
$VC_{COHORT7}$: Exponent of Cohort 7/8 Effect on VC (-)[c]	-0.0543	74.4		
$VC_{COHORT8}$: Exponent of Cohort 8/8 Effect on VC (-)[c]	0.252	15.1		
Q: Distribution Clearance (L/h)	0.0345	7.44	NE	NA
$VP_{TV,ref}$: Peripheral Volume (L)[b]	5.38	3.69	0.159	12.3
VP_{BWT}: Power of Weight on VP (-)[c]	0.776	6.18		
Proportional Component of RV			0.0611	5.66
Additive Component of RV			0.00242	55.9
Minimum Value of the Objective Function = 23944.455				

[a] ETA shrinkage: ETA CL: 8.33%, ETA VC: 41.9%, ETA VP: 26.0%; Epsilon Shrinkage: Proportional Component: 11.3%, Additive Component: 11.3%.

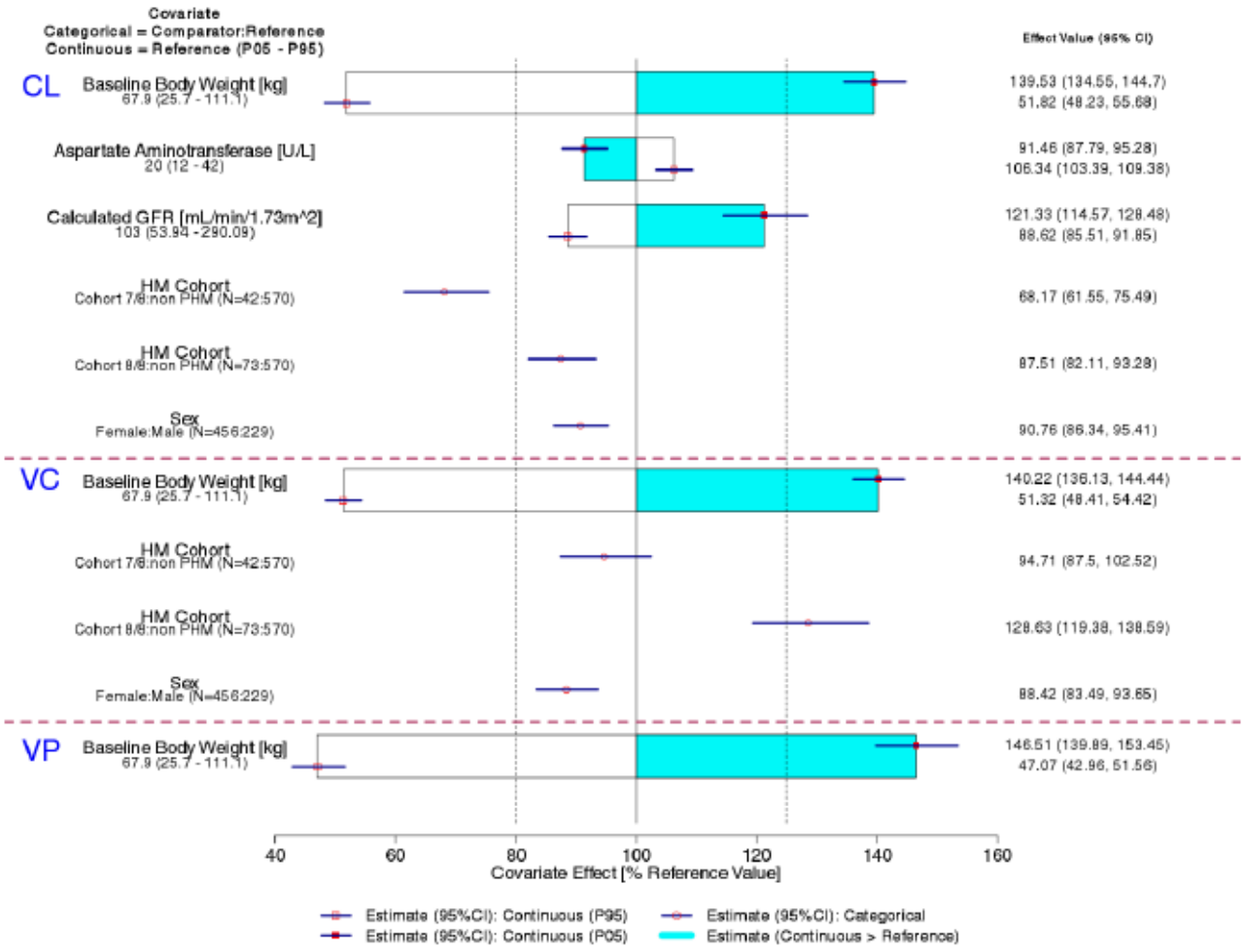
[b] $CL_{TV,ref}$, $VC_{TV,ref}$, and $VP_{TV,ref}$ are typical values of CL, VC, and VP at the reference covariate values. Covariate effects were estimated relative to a reference male subject not enrolled in Study IM101311 and with a baseline weight of 67.9 kg, baseline AST of 20 U/L, and baseline CGFR of 103 mL/min/m^2.

[c] $$CL_{TV} = CL_{TV,ref}\left(\frac{BWT_b}{67.9}\right)^{CL_{BWT}}\left(\frac{AST_b}{20}\right)^{CL_{AST}}\left(\frac{CGFR_b}{103}\right)^{CL_{CGFR}} e^{SEX\times CL_{SEX}+\text{COHORT7}\times CL_{COHORT7}+\text{COHORT8}\times CL_{COHORT8}}$$

$$VC_{TV} = VC_{TV,ref}\left(\frac{BWT_b}{67.9}\right)^{VC_{BWT}} e^{SEX\times VC_{SEX}+\text{COHORT7}\times VC_{COHORT7}+\text{COHORT8}\times VC_{COHORT8}}$$

$$VP_{TV} = VP_{TV,ref}\left(\frac{BWT_b}{67.9}\right)^{VP_{BWT}}$$

Figure 4 ***Clinical Relevance of Covariate Effects (2020 Sensitivity Analysis PPK Model)***



Note 1: Categorical covariate effects (95% CI) are represented by open circles (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represent the range of covariate effects from the median to the 5th/95th percentiles of the covariate.

Note 3: The reference subject is a male subject with RA or JIA (referred to as non-PHM in the plot above, ie, not a subject receiving URD HSCT due to HM), BWT = 67.9 kg, AST = 20 U/L, and CGFR = 103 mL/min/1.73 m^2. Parameter estimate in the reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

As shown in Figure 4, baseline weight was associated with a 40%, 40%, and 47% increase in CL, VC, and VP at the 95th percentile of weight (111 kg), respectively. Subjects from the Study IM101311 Cohort 7/8 were predicted to exhibit a 32% reduction in CL, while the 12% reduction in CL (including the associated 95% CI) predicted for Cohort 8/8 was completely contained within the reference range. In contrast, subjects from the Study IM101311 Cohort 8/8 were predicted to exhibit a clinically relevant 29% increase in VC, while the 5% reduction in VC (including the associated 95% CI) predicted for Cohort 7/8 was completely contained within the reference range. Additionally, although the effect of baseline CGFR was within the reference range for the 5th and 95th percentile of CGFR (54 and 290 mL/min/m^2), the upper bound of the 95% CI associated with the 95th percentile of CGFR was larger than 125%. All other covariate relationships (AST and gender on CL; gender on VC) were completely contained within the 80% to 125% range and, therefore, not considered to be clinically relevant.

The final PPK model was obtained by stepwise backward elimination of cohort effects from the sensitivity analysis model. The effect of Cohort 7/8 on VC was removed from the model. All the other cohort effects were found to be statistically significant at the 0.001 level.

The final model was a 2-compartment model with zero-order IV infusion, linear distribution and elimination parameterized in terms of CL, VC, Q, and VP. The data supported the estimation of IIV on CL, VC, and VP. Residual variability was described using a combined additive and constant CV model. The final PPK model, given the data, included effects of baseline body weight, CGFR, AST, sex, and Study IM101311 cohorts on CL; baseline BWT and Study IM101311 Cohort 8/8 on VC; and baseline BWT on VP. Baseline BWT and the Study IM101311 cohorts are the only variables that were considered potentially clinically relevant. Parameter estimates for the final 2020 PPK model are provided in Table 7. The fixed and random effect parameters were generally estimated with good precision (%RSE ≤ 25.8%), except for the additive component of RUV (%RSE = 55.6%). The condition number of the final model was 45.8, indicating that the model was not over-parameterized.

Table 7 ***Parameter Estimates (Final 2020 PPK Model)***

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability[a]	
	Population Mean	%RSE	Final Estimate	%RSE
$CL_{TV,ref}$: Clearance (L/h)[b]	0.0250	2.53		
CL_{BWT}: Power of Weight on CL (-)[c]	0.676	5.54		
CL_{AST}: Power of AST Effect on CL (-)[c]	-0.120	23.4		
CL_{CGFR}: Power of GFR Effect on CL (-)[c]	0.187	15.1		
CL_{SEX}: Exponent of Sex Effect in Female on CL (-)[c]	-0.0962	25.8	0.0592	6.87
$CL_{COHORT7}$: Exponent of Cohort 7/8 Effect on CL (-)[c]	-0.380	13.6		
$CL_{COHORT8}$: Exponent of Cohort 8/8 Effect on CL (-)[c]	-0.133	24.8		
$VC_{TV,ref}$: Central Volume (L)[b]	3.22	2.46		
VC_{BWT}: Power of Weight on VC (-)[c]	0.683	4.48		
VC_{SEX}: Exponent of Sex Effect in Female on VC (-)[c]	-0.117	23.4	0.0345	17.7
$VC_{COHORT8}$: Exponent of Cohort 8/8 Effect on VC (-)[c]	0.260	14.2		
Q: Distribution Clearance (L/h)	0.0346	6.92	NE	NA
$VP_{TV,ref}$: Peripheral Volume (L)[b]	5.39	3.52	0.159	12.4
VP_{BWT}: Power of Weight on VP (-)[c]	0.776	6.14		
Proportional Component of RV			0.0611	5.61
Additive Component of RV			0.00242	55.6
Minimum Value of the Objective Function = 23945.886				

[a] ETA shrinkage: ETA CL: 8.33%, ETA VC: 41.9%, ETA VP: 26.0%; Epsilon Shrinkage: Proportional Component: 11.3%, Additive Component: 11.3%

[b] $CL_{TV,ref}$, $VC_{TV,ref}$, and $VP_{TV,ref}$ are typical values of CL, VC, and VP at the reference covariate values. Covariate effects were estimated relative to a reference male subject not enrolled in Study IM101311 and with a baseline weight of 67.9 kg, baseline AST of 20 U/L, and baseline CGFR of 103 mL/min/m^2.

[c]
$$CL_{TV} = CL_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{CL_{BWT}}\left(\frac{AST_b}{AST_{ref}}\right)^{CL_{AST}}\left(\frac{CGFR_b}{CGFR_{ref}}\right)^{CL_{CGFR}} e^{SEX\times CL_{SEX}+COHORT7\times CL_{COHORT7}+COHORT8\times CL_{COHORT8}}$$

$$VC_{TV} = VC_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VC_{BWT}} e^{SEX\times VC_{SEX}+COHORT8\times VC_{COHORT8}}$$

$$VP_{TV} = VP_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VP_{BWT}}$$

NA: not applicable; NE: not estimated

Diagnostic goodness-of-fit plots for the final 2020 PPK model are presented in Figure 5 and Figure 6. In the overall dataset, there was generally good agreement between the observed and model-predicted abatacept serum concentrations. Additionally, the introduction of cohort-specific effects on CL and VC reduced the differences in the central tendency lines associated with each cohort of Study IM101311. The pcVPC plots indicated that the model predictions tracked the observed concentrations (after prediction-correction) reasonably well in terms of central tendency and variability for patients in Study IM101311 (Figure 7). However, the abatacept concentrations collected late after the previous dose in

subjects with HM tended to be slightly underpredicted, especially after more than 1,000 hours after the previous dose. The pcVPC plots for RA and JIA patients are omitted from this AR.

Figure 5 ***Observed Versus Population Predicted and Individual Predicted Concentration overall (Left panel) and in Study IM101311 Stratified by Cohort (Right panel). (Final 2020 PPK Model)***

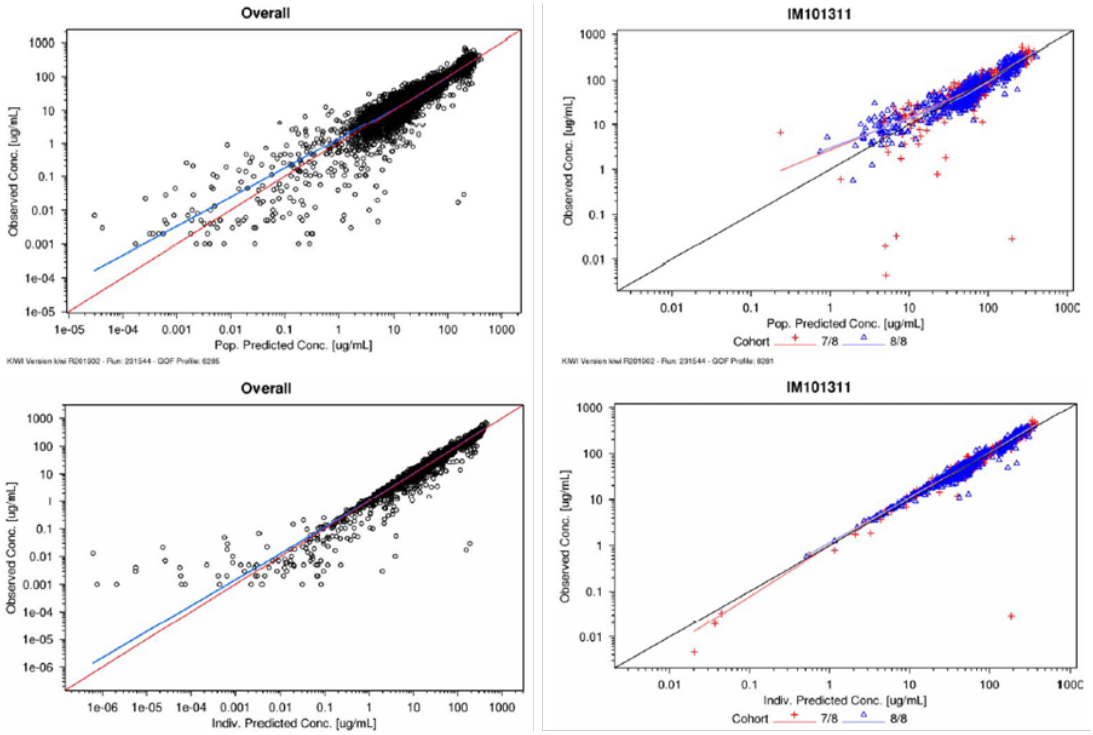


Figure 6 ***CWRESI Versus Time After Previous Dose (Left) and CWRESI Versus Population Predicted Concentration (Right) Overall and in Study IM101311 Stratified by Cohort. (2020 Final PPK model)***

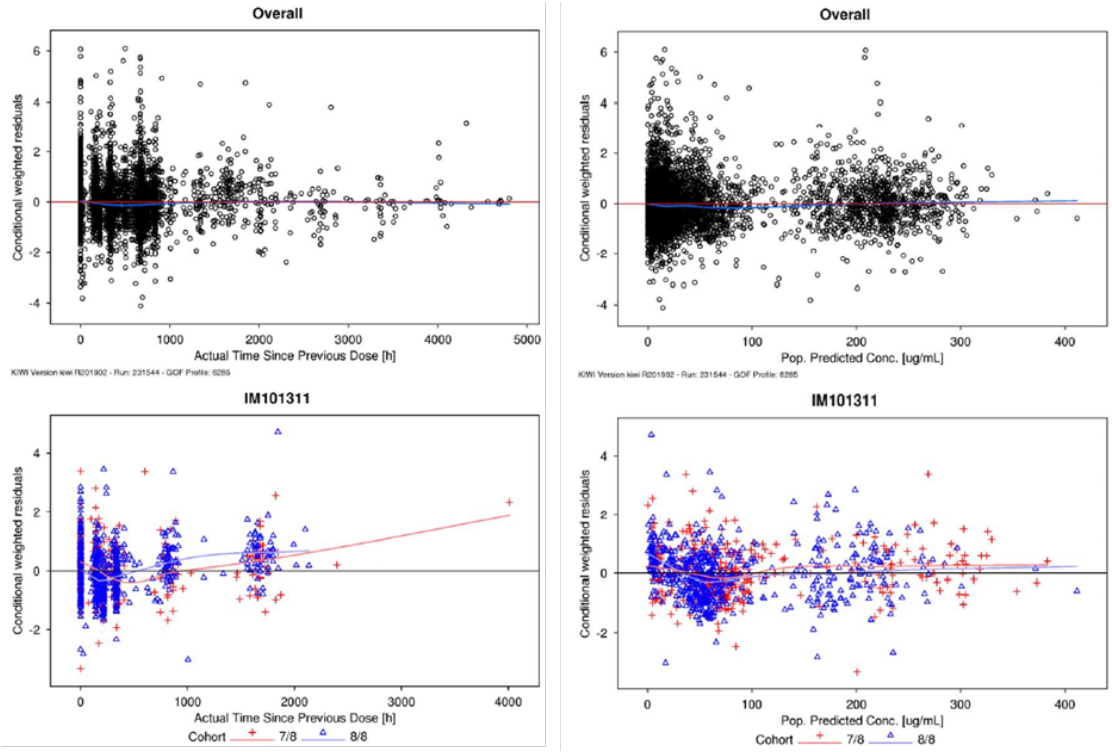
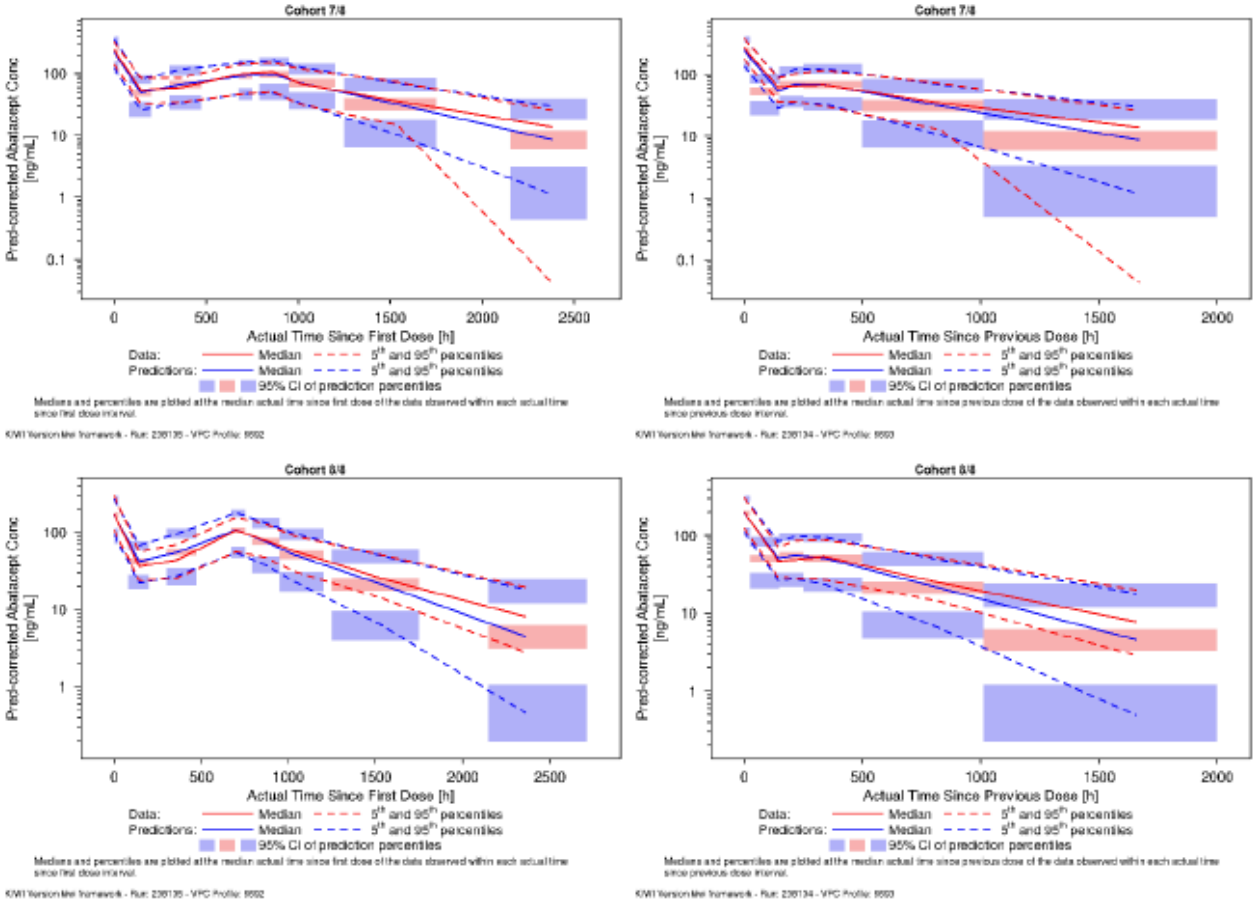


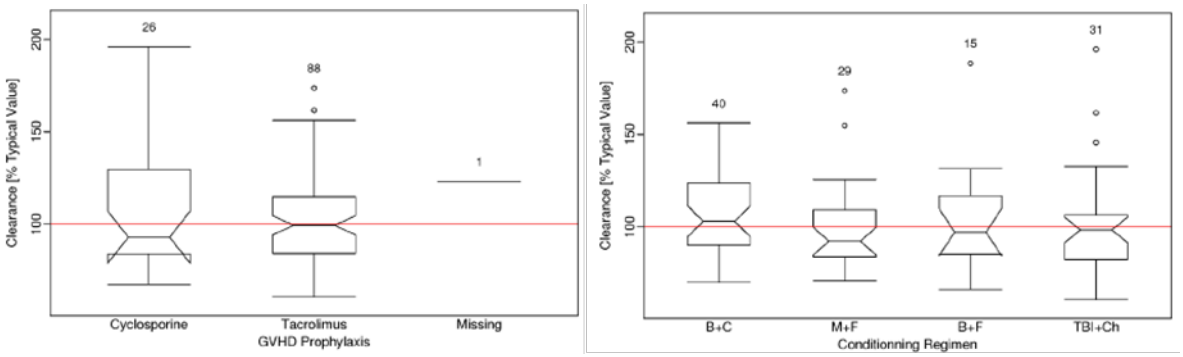
Figure 7 ***pcVPC Plots for Study IM101311 Stratified by Cohort. (2020 Final PPK model)***



Conc: concentration; Pred: prediction

Finally, graphical exploration was performed to assess the effect of aGvHD prophylaxis treatment and conditioning regimen on CL. The distributions of individual Bayesian CL values (expressed as a percentage of the typical value) indicated that aGvHD prophylaxis treatment (cyclosporine vs tacrolimus) and conditioning regimen (busulfan + cyclophosphamide; busulfan + fludarabine; melphalan + fludarabine; total body irradiation and chemotherapy) did not have significant effect on predicted CL (Figure 8).

Figure 8 ***Distribution of Clearance by aGvHD Prophylaxis Treatment and Conditioning Regimen in Study IM101311***



B+C: busulfan + cyclophosphamide; B+F: busulfan + fludarabine; ID: identification; M+F: melphalan + fludarabine; TBI+Ch, total body irradiation and chemotherapy

2022 PPK model

The main purpose of the 2022 PPK analysis was to refine the 2020 PPK model to include additional PK data for paediatric subjects (2 to 17 years of age) and to use the updated model to simulate abatacept exposure in a virtual paediatric patient population (2 to <6 years old) to support dose selection in prevention of aGvHD in this age group, which was not investigated in Study IM101311.

The 2022 model PK dataset included the 8 studies that were in the 2020 PPK model dataset plus PK data from Study IM101301, which was a Phase 3 study to evaluate the safety and efficacy of subcutaneously administered abatacept in paediatric patients 2-17 years old with JIA. A total of 1482 concentrations from 219 paediatric patients from Study IM101301 were added to the dataset.

The parameters of the previous 2020 PPK model were re-estimated using the 2022 pooled analysis dataset. Following re-estimation, the model was also updated to include absorption parameters (KA and F1), since the patients in Study IM101301 were administered SC abatacept. The F1, interindividual variability (IIV) on F1, and covariate effects on F1 were all fixed to the final estimates from the previous JIA PPK model that was submitted and assessed in variation procedure EMEA/H/C/000701/II/0117/G, while KA was able to be estimated using the updated dataset. No other refinements were made to the abatacept PPK model.

The parameter estimates for the 2022 PPK model are shown in Table 8.

Table 8 ***Parameter Estimates (2022 PPK Model)***

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL	Clearance (L/h)	0.0230	2.32	26.7 %CV	6.33
	Power of weight on CL (-)	0.876	3.08		
	Power of AST effect (-)	-0.115	24.2		
	Power of GFR effect (-)	0.279	9.12		
	Exponent of sex effect in female (-)	-0.0572	41.2		
	Exponent of GVHD Cohort 7 effect (-)	-0.326	16.8		
	Exponent of GVHD Cohort 8 effect (-)	-0.0934	36.8		
VC	Central volume (L)	3.19	2.48	17.7 %CV	20.0
	Power of weight on VC (-)	0.712	4.30		
	Exponent of sex effect in female (-)	-0.0967	28.6		
	Exponent of GVHD Cohort 8 effect (-)	0.257	14.5		
Q	Distribution clearance (L/h)	0.0303	5.23	NE	NA
VP	Peripheral volume (L)	5.07	3.11	42.2 %CV	12.0
	Power of weight on VP (-)	0.839	5.24		
KA	Absorption rate constant (1/h)	0.00705	19.2	117 %CV	39.9
F1	Bioavailability of SC formulation	1.21	FIXED	0.718 SD	FIXED
	Power of weight on F1	-0.506			
	Power of age on F1	0.487			
	Exponent of JIA on F1	3.08			
Proportional Component of RV		0.0724	4.77	2290 - 26.9 %CV F [0.001 - 700][a]	NA
Additive Component of RV		5.26E-04	66.9		
Minimum Value of the Objective Function = 33065.229					

[a] The magnitude of residual variability (%CV) was calculated using the following equation: (SQRT(0.0724×F2+5.26E-04)/F)×100.

Shrinkage estimates: 7.7% for IIV in CL, 51.5% for IIV in VC, 32.8% for IIV in VP, 59.8% for IIV in KA, and 100.0% for IIV in F1.

Abbreviations: AST = aspartate aminotransferase; %CV = coefficient of variation expressed as a percent; F = bioavailability; GFR = glomerular filtration rate; GVHD = graft versus host disease; JIA = juvenile idiopathic arthritis; NA = not applicable; NE = not estimated; %RSE = relative standard error expressed as a percent; RV = residual variability; SC = subcutaneous; SD = standard deviation.

Table 9 shows a comparison of the parameter estimates from the 2020 and 2022 PPK models. Compared to the previous 2020 PPK model, the inclusion of the data collected in Study IM101301 resulted in minimal changes in CL, VC, Q and VP (|% change| all ≤12.43%). More significant, but reasonable, differences in the estimates for covariate effects were observed in the refined model, which would be expected given that the additional data provided by patients ages 2 to 5 years old with a lower range of body weights. Particularly, the effects of weight and GFR on CL increased (29.59% and 49.2%, respectively), while the effects of female gender on VC and CL decreased (-17.35% and -40.54%, respectively). Of note, the GFR was calculated for paediatric and adult subjects using the Schwartz equation and the MDRD equation, respectively.

Table 9 ***Comparison of the 2020 and 2022 PPK model parameter estimates***

Label	Previous GVHD Final Model	Updated Model With Study IM101301	Percent Change (%)
Value of Objective Function	23945.886	33065.229	NA
CL: Clearance (L/h)	0.025	0.023	-8.00
VC: Central Volume (L)	3.22	3.19	-0.93
Q: Distribution Clearance (L/h)	0.0346	0.0303	-12.43
VP: Peripheral Volume (L)	5.39	5.07	-5.94
CL: Power of Weight on CL (-)	0.676	0.876	29.59
VC: Power of Weight on VC (-)	0.683	0.712	4.25
VP: Power of Weight on VP (-)	0.776	0.839	8.12
CL: Power of AST Effect (-)	-0.12	-0.115	-4.17
CL: Power of GFR Effect (-)	0.187	0.279	49.20
VC: Exponent of Sex Effect in Female (-)	-0.117	-0.0967	-17.35
CL: Exponent of Sex Effect in Female (-)	-0.0962	-0.0572	-40.54
CL: Exponent of GVHD Cohort 7 Effect (-)	-0.38	-0.326	-14.21
CL: Exponent of GVHD Cohort 8 Effect (-)	-0.133	-0.0935	-29.70
VC: Exponent of GVHD Cohort 8 Effect (-)	0.26	0.257	-1.15
KA: Absorption Rate Constant (1/h)	NA	0.00705	NA
F1: Bioavailability of SC formulation	NA	1.21	NA
F1: Power of weight on F1	NA	-0.506	NA
F1: Power of age on F1	NA	0.487	NA
F1: Exponent of JIA on F1	NA	3.08	NA
IIV in CL	0.0592	0.0689	16.39
IIV in VC	0.0345	0.0309	-10.43
IIV in VP	0.159	0.164	3.14
IIV in KA	NA	0.861	NA
IIV in F1	NA	0.516	NA
Proportional Component of RV	0.0611	0.0724	18.49
Additive Component of RV	0.00242	0.000526	-78.26

Abbreviations: AST = aspartate aminotransferase; GFR = glomerular filtration rate; GVHD = graft versus host disease; IIV = interindividual variability; JIA = juvenile idiopathic arthritis; NA = not applicable; RV = residual variability; SC = subcutaneous.

The goodness-of-fit plots and pcVPC plots are shown in Figure 9 and Figure 10, respectively. The MAH concluded that there was generally good agreement between the observed and model-predicted abatacept serum concentrations, although there was a slight underprediction at higher concentrations (>300 µg/ml).

Figure 9 ***Goodness-of-Fit Plots (2022 PPK Model)***

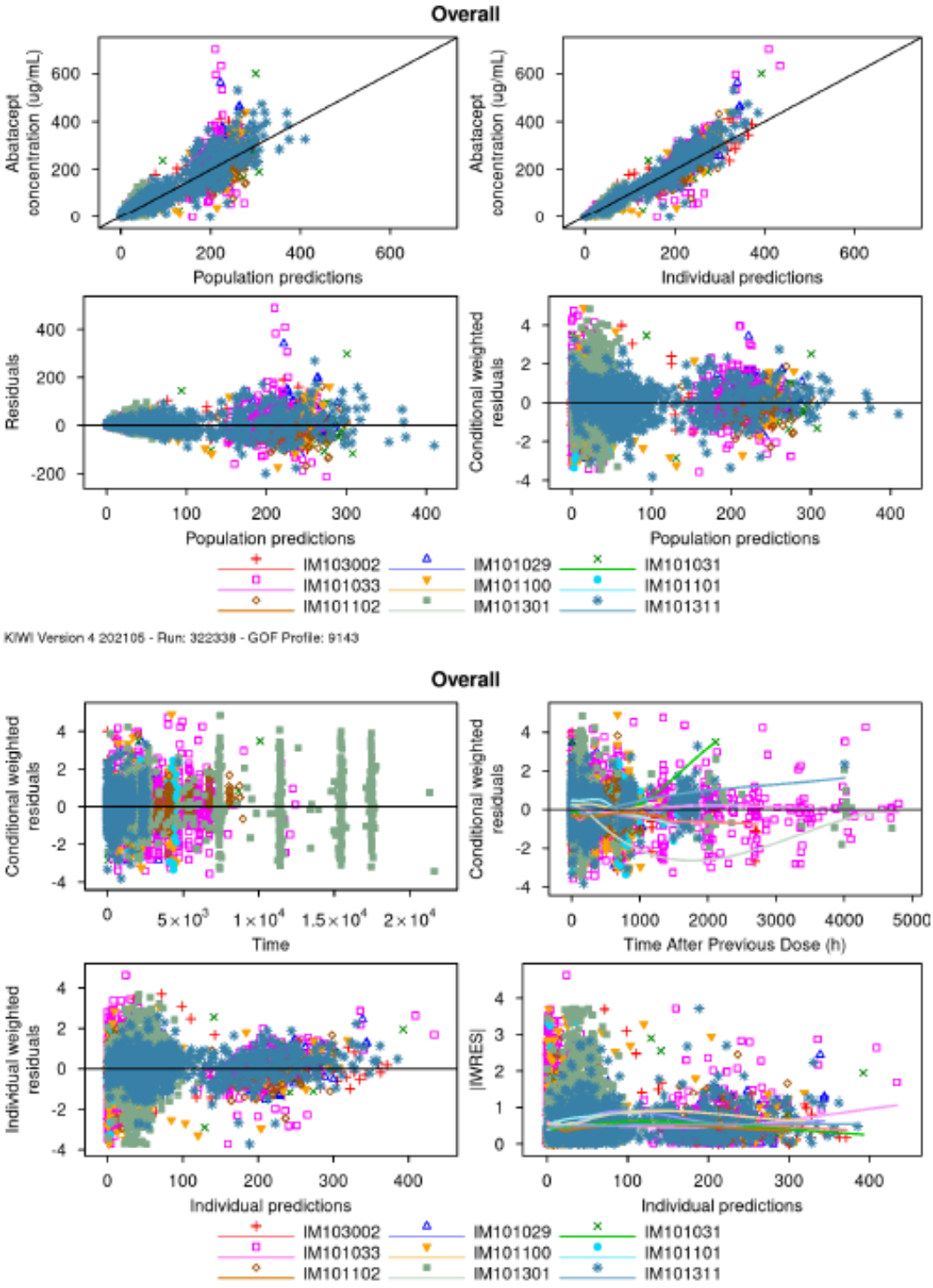
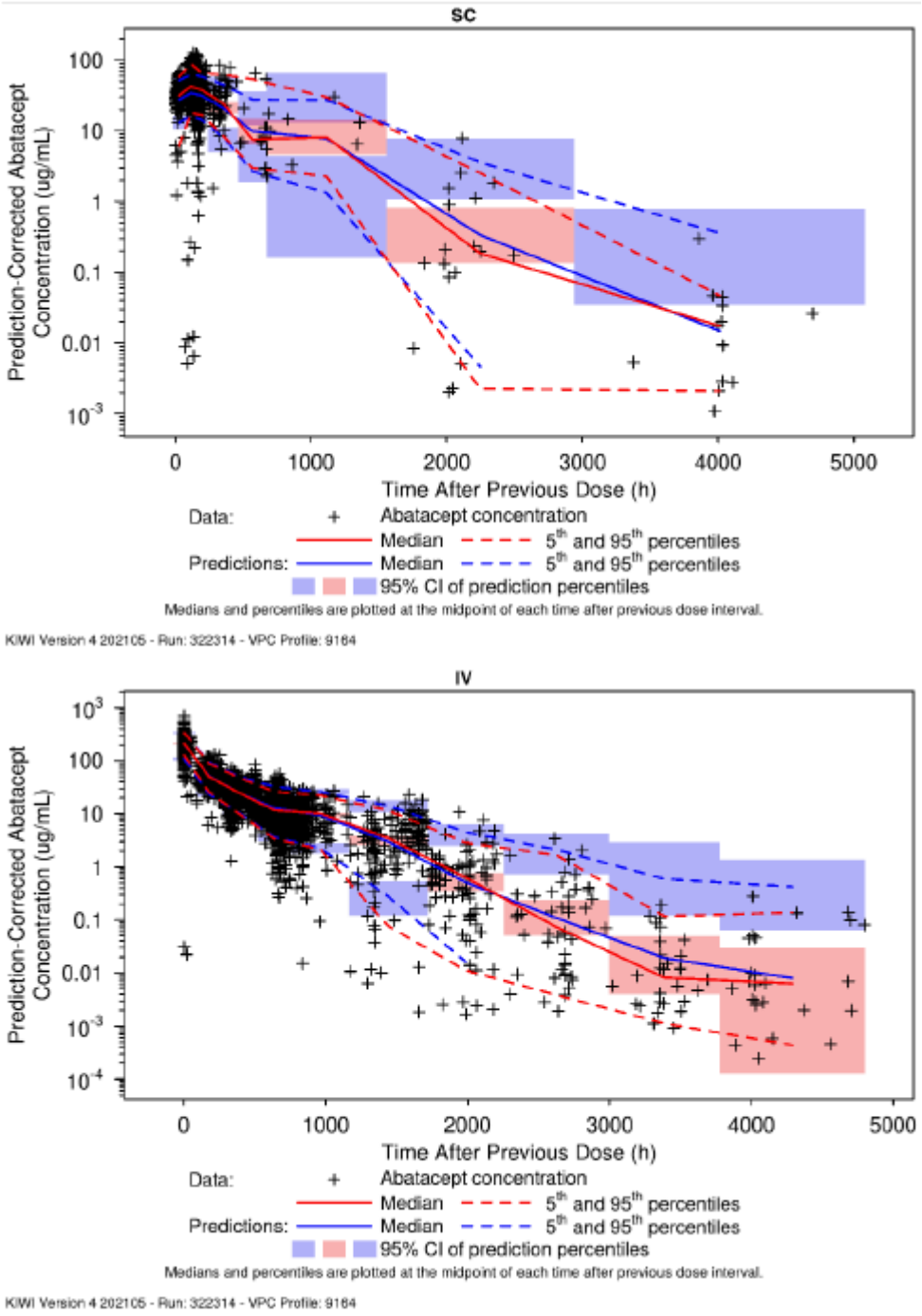


Figure 10 ***pcVPC Plots for the 2022 PPK Model, Stratified by Route of Administration***



Pharmacokinetic simulations

A range of doses were simulated to determine the optimal IV abatacept regimen for aGvHD prophylaxis in paediatric patients ages 2 to less than 6 years old to achieve exposures similar to the distributions observed in adults and paediatric patients following 10 mg/kg in Study IM101311 of aGvHD prophylaxis with URD HSCT treatment due to HM. A total of 10,000 virtual paediatric patients were generated. The age (in months) for each virtual paediatric patient was simulated using a uniform distribution from 2 to less than 6 years old. Sex was randomly assigned with equal probability. Weight was simulated from the

CDC growth chart based on each virtual patient's age and sex. Baseline GFR and AST were set to the median values of 158.97 ml/min/1.73 m^2 and 29 U/L from the 6- to 13-year-old patients from Study IM101311, respectively. Cohort was randomly assigned using the distribution observed from Study IM101311 (36% Cohort 7/8 and 64% Cohort 8/8). The 2022 PPK model was then applied to the virtual paediatric patient data to simulate individual PK parameters for each virtual patient. Interindividual variability was introduced into the simulations based on the estimated random effect distributions in the PPK model.

Fixed dosing regimens were evaluated first in virtual paediatric patients (i.e., 10, 12, 15, and 20 mg/kg administered as 1-hour IV infusions on Days -1 (0 hour), Day 5 (144 hours), Day 14 (360 hours), and Day 28 (696 hours)). Exposures measures (AUC, Cmin, and Cmax) after the first and last dose were computed by continuous numerical integration of the model-predicted abatacept concentrations using NONMEM for the 10,000 virtual paediatric patients and the 115 patients with HM from Study IM101311. Abatacept concentrations after the last dose (on Day 28) were simulated until 360 hours after the last dose (Day 42).

Summary statistics of predicted abatacept exposure measures in virtual paediatric patients 2 to <6 years of age (by fixed dosing regimen) and in patients with HM from Study IM101311 (by age group) are shown in Table 10 and Table 11, respectively. Boxplots of abatacept exposure measures are shown in Figure 11.

Table 10 ***Exposure Measures in Virtual Paediatric Patients, by Regimen***

Exposures		10 mg/kg n = 10000	12 mg/kg n = 10000	15 mg/kg n = 10000	20 mg/kg n = 10000
Abatacept AUC1 [µg • h/mL]	Mean (SD)	8015.62 (1375.70)	9618.73 (1650.97)	12023.82 (2063.72)	16031.89 (2751.73)
	Median	7880.00	9450.00	11800.00	15800.00
	Min, Max	4580.0, 15500.0	5490.0, 18600.0	6870.0, 23300.0	9160.0, 31000.0
Abatacept AUC After Last Dose [µg • h/mL]	Mean (SD)	29682.52 (7281.28)	35618.57 (8738.43)	44523.32 (10922.97)	59364.44 (14563.98)
	Median	29000.00	34800.00	43500.00	58000.00
	Min, Max	10800.0, 69900.0	12900.0, 83800.0	16200.0, 105000.0	21500.0, 140000.0
Abatacept Cmax1 [µg/mL]	Mean (SD)	126.12 (28.62)	151.35 (34.35)	189.18 (42.94)	252.24 (57.24)
	Median	122.00	147.00	183.00	244.00
	Min, Max	59.4, 273.0	71.3, 328.0	89.1, 409.0	119.0, 546.0
Abatacept Cmax After Last Dose [µg/mL]	Mean (SD)	182.78 (36.09)	219.34 (43.31)	274.16 (54.13)	365.55 (72.18)
	Median	178.00	214.00	267.00	356.00
	Min, Max	92.8, 366.0	111.0, 439.0	139.0, 549.0	186.0, 731.0
Abatacept Cmin1 [µg/mL]	Mean (SD)	38.31 (8.80)	45.98 (10.56)	57.47 (13.20)	76.63 (17.61)
	Median	37.60	45.10	56.40	75.20
	Min, Max	15.5, 85.3	18.6, 102.0	23.2, 128.0	31.0, 171.0
Abatacept Cmin After Last Dose [µg/mL]	Mean (SD)	54.54 (18.45)	65.45 (22.14)	81.81 (27.68)	109.08 (36.91)
	Median	52.85	63.40	79.30	106.00
	Min, Max	6.2, 149.0	7.5, 179.0	9.3, 224.0	12.4, 299.0

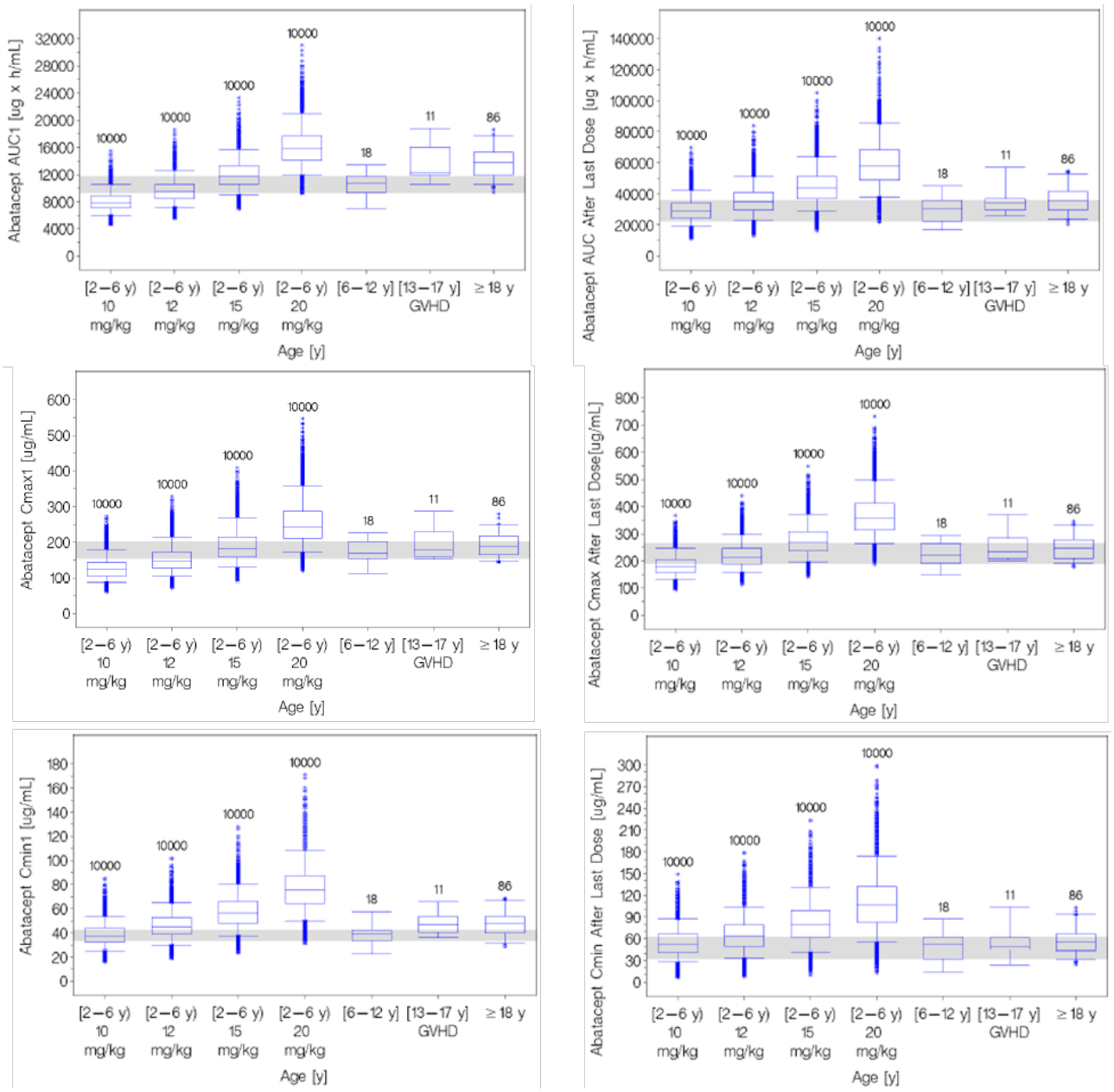
Abbreviations: AUC = area under the concentration-time curve; AUC1 = area under the concentration-time curve following the first dose; Cmax = peak serum concentration; Cmax1 = peak serum concentration following the first dose; Cmin = trough serum concentration; Cmin1 = minimum concentration following the first dose; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

Table 11 ***Exposure Measures in Patients with HM From Study IM101311, by Age Group***

Exposures		[6-12 y] n = 18	[13-17 y] n = 11	≥18 y n = 86	Overall n = 115
Abatacept AUC1 [µg • h/mL]	Mean (SD)	10367.78 (1911.73)	13518.18 (2580.24)	13797.56 (2251.77)	13234.00 (2540.50)
	Median	10700.00	12300.00	13700.00	13100.00
	Min, Max	6990.0, 13400.0	10600.0, 18800.0	9370.0, 18600.0	6990.0, 18800.0
Abatacept AUC After Last Dose [µg • h/mL]	Mean (SD)	30516.67 (8916.49)	35890.91 (9685.71)	36427.91 (8778.42)	35451.30 (9062.31)
	Median	30500.00	34300.00	35800.00	34500.00
	Min, Max	16800.0, 45100.0	26000.0, 57100.0	20400.0, 54700.0	16800.0, 57100.0
Abatacept Cmax1 [µg/mL]	Mean (SD)	170.22 (34.50)	196.55 (45.68)	193.05 (32.91)	189.81 (35.23)
	Median	168.00	177.00	189.00	184.00
	Min, Max	112.0, 226.0	151.0, 287.0	144.0, 279.0	112.0, 287.0
Abatacept Cmax After Last Dose [µg/mL]	Mean (SD)	222.39 (45.71)	252.91 (59.76)	249.16 (44.71)	245.33 (47.06)
	Median	220.00	233.00	247.00	245.00
	Min, Max	147.0, 293.0	200.0, 368.0	177.0, 345.0	147.0, 368.0
Abatacept Cmin1 [µg/mL]	Mean (SD)	38.65 (8.75)	47.56 (9.25)	47.41 (10.29)	46.05 (10.40)
	Median	38.65	46.70	47.80	46.70
	Min, Max	22.3, 57.5	35.8, 65.6	28.0, 68.5	22.3, 68.5
Abatacept Cmin After Last Dose [µg/mL]	Mean (SD)	50.43 (21.17)	55.91 (21.59)	57.56 (18.78)	56.29 (19.42)
	Median	52.40	49.10	55.35	54.10
	Min, Max	14.1, 86.9	24.0, 104.0	24.6, 103.0	14.1, 104.0

Abbreviations: AUC = area under the concentration-time curve; AUC1 = area under the concentration-time curve following the first dose; Cmax = peak serum concentration; Cmax1 = peak serum concentration following the first dose; Cmin = trough serum concentration; Cmin1 = minimum concentration following the first dose; HM = hematologic malignancies; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

Figure 11 ***Boxplots of Abatacept Exposure in Virtual Paediatric Patients by Fixed Dose Regimens and Patients at Risk for aGvHD (10 mg/kg dose) by Age Group from Study IM101311***



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles. Asterisks shod data points outside this range. The number of subjects is above each box. The shaded region represents the 25th to 75th percentiles of exposure for aGvHD subjects 6-12 years of age.

AUC = area under the concentration-time curve; **AUC1** = AUC following the first dose; **Cmax** = peak serum concentration; **Cmax1** = Cmax following the first dose; **Cmin** = minimum serum concentration; **Cmin1** = Cmin following the first dose; **aGvHD** = graft versus host disease; **y** = years.

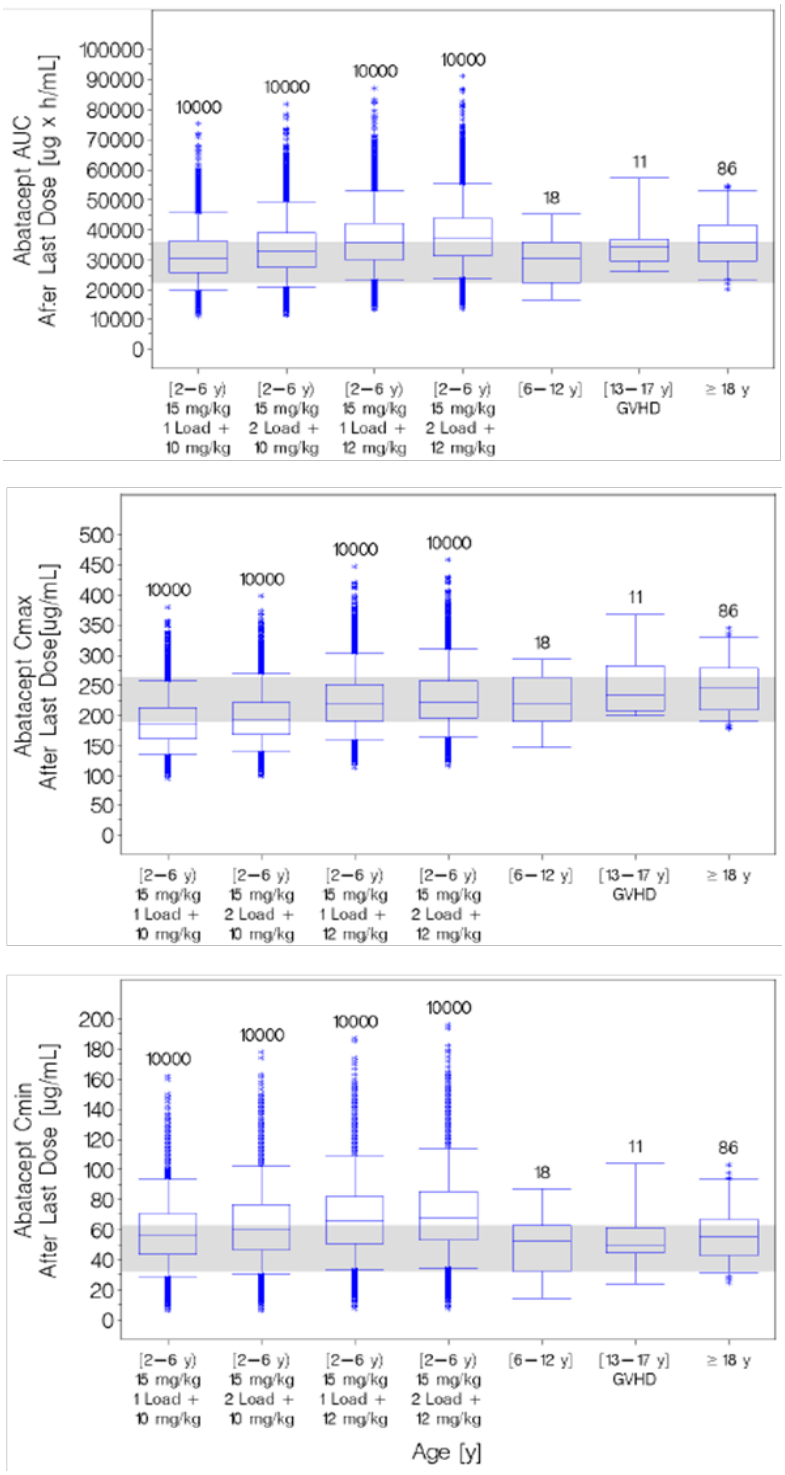
The 15 mg/kg fixed dose regimen provided the best match after the first dose (comparable AUC and Cmax, slightly higher Cmin), but higher than reference exposure after the last dose. Therefore, loading followed by maintenance dosing regimens were considered to assess whether the exposure targets could be achieved more precisely over the duration of treatment. The evaluated scenarios were as follows:

- Loading Dose 15 mg/kg on Day -1 and Maintenance Dose 10 mg/kg on Days 5, 14, and 28

- Loading Dose 15 mg/kg on Day -1 and Maintenance Dose 12 mg/kg on Days 5, 14, and 28
- Loading Dose 15 mg/kg on Days -1, 5 and Maintenance Dose 10 mg/kg on Days 14 and 28
- Loading Dose 15 mg/kg on Days -1, 5 and Maintenance Dose 12 mg/kg on Days 14 and 28

Boxplots of abatacept exposure after the last dose are shown in Figure 12. In all four scenarios, 15 mg/kg was the first dose, hence exposure measures following the first dose are the same in all scenarios. Of all the scenarios tested, loading dose 15 mg/kg on Day -1 followed by maintenance dose 12 mg/kg on Days 5, 14, and 28 was considered to provide the best balance between potential risks of administering doses that deliver exposures that are either insufficient or unnecessarily high to achieve a similar benefit-risk profile as that observed in adults.

Figure 12 ***Boxplots of Abatacept Exposure in Virtual Paediatric Patients by Loading/Maintenance Dose Regimens and Patients at Risk for aGvHD (10 mg/kg dose) by Age Group from Study IM101311***



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles. Asterisks shod data points outside this range. The number of subjects is above each box. The shaded region represents the 25th to 75th percentiles of exposure for aGvHD subjects 6-12 years of age.

AUC = area under the concentration-time curve; **Cmax** = peak serum concentration; **Cmin** = minimum serum concentration; **aGvHD** = graft versus host disease; **y** = years.

Exposure-response analysis for efficacy

Abatacept exposure-efficacy response in subjects receiving URD HSCT due to HM was characterized by describing the relationships between abatacept exposure measures following the first and last dose ($AUC_{0\text{-}t}$, C_{min}, C_{max}, and C_{av}) and the time to first severe (Grade III-IV) aGvHD-free survival (aGFS) up to Day 180 post-transplantation and time to overall survival (OS). Abatacept exposure parameters were obtained with the 2020 PPK model. A total of 185 patients randomized to abatacept or placebo were included in the analyses.

Exposure-response (E-R) for efficacy described the time to first event as function of abatacept exposure using semiparametric Cox proportional hazards (CPH) models. The time to event in the models was expressed as:

$$\lambda(t) = \lambda_0(t)exp(\boldsymbol{\beta}^T \boldsymbol{X}_i)$$

where $\lambda_0(t)$ is the baseline hazard function and $\boldsymbol{X}_i$ is a vector of predictor variables. The parameter vector $\boldsymbol{\beta}$ is estimated by maximum partial-likelihood. The exponential function $exp(\boldsymbol{\beta}^T)$ represents the hazard ratio for each parameter.

Time to first severe aGFS

Two, 10, and 17 patients in abatacept 7/8 cohort, abatacept 8/8 cohort, and placebo group, respectively, experienced severe aGvHD during the first 180 days after transplantation. The base model was developed first to characterise the marginal effect of various abatacept exposure measures on time to first severe aGFS without consideration of covariates. Abatacept C_{min} after the last dose as a linear functional form was selected as the exposure measure. The base model parameter estimates are presented in Table 12.

Table 12 ***Parameter Estimates of E-R Efficacy for Time to First Severe aGFS (Base Model)***

Variable	Coefficient	SE	RSE	P value	Hazard Ratio	Lower 95% CI	Upper 95% CI	Hazard Ratio (95% CI)
CMINL	-0.017	0.006723	39.55	0.01146	0.9831	0.9703	0.9962	0.9831 (0.9703, 0.9962)

CMINL: minimum concentration after last dose; SE: standard error

Next, a single round of forward selection was used to select covariates determined to be statistically significant when evaluated univariately using an alpha level of 0.01 for inclusion in each full model. The pre-specified covariates were as follows: age, body weight, baseline serum IgG, sex, race (Caucasian vs non-Caucasian), GVHD prophylaxis, conditioning regimen, subject's pre-transplant cytomegalovirus (CMV) status, donor's pre-transplant CMV status, subject's pre-transplant Epstein-Barr virus (EBV) status, type of graft received, relapse of underlying malignancy to Day 180, and cohort. Baseline performance status and donor's pre-transplant EBV status were pre-specified covariates but not assessed due to 39% and 79.5% missing data. The only covariate with a P value < 0.01 in the univariate step was relapse of malignancy. The full model parameter estimates are presented in Table 13.

Table 13 ***Parameter Estimates of E-R Efficacy for Time to First Severe aGFS (Full Model)***

Predictor[a]	Estimate	SE	%RSE	Hazard Ratio (95% CI)
Abatacept Cmin After the Last Dose [µg/mL]	-0.01521	0.006639	43.66	0.9849 (0.9722, 0.9978)
Relapse	1.079	0.4202	38.94	2.942 (1.291, 6.704)

[a] Reference values: Relapse=No.
SE: standard error

The final model was developed by backward elimination of covariates from the full model based on likelihood ratio test (LRT) P values. A significance level of 0.001 was used for the backward elimination The full model was reduced to the base model after 1 step of backward elimination. Only abatacept C_{min} after the last dose was retained in the final model, as this effect was not subjected to backward elimination. The final model suggests that higher C_{min} is associated with lower risk of severe aGVHD.

The final model was evaluated using VPC (Figure 13, Figure 14, Figure 15). There was good agreement between the observed and predicted median aGFS-free survival over time, except for in the lowest and highest quartiles of C_{min}.

Figure 13 ***VPC of Time to First Severe aGFS (Final Model), by Treatment***

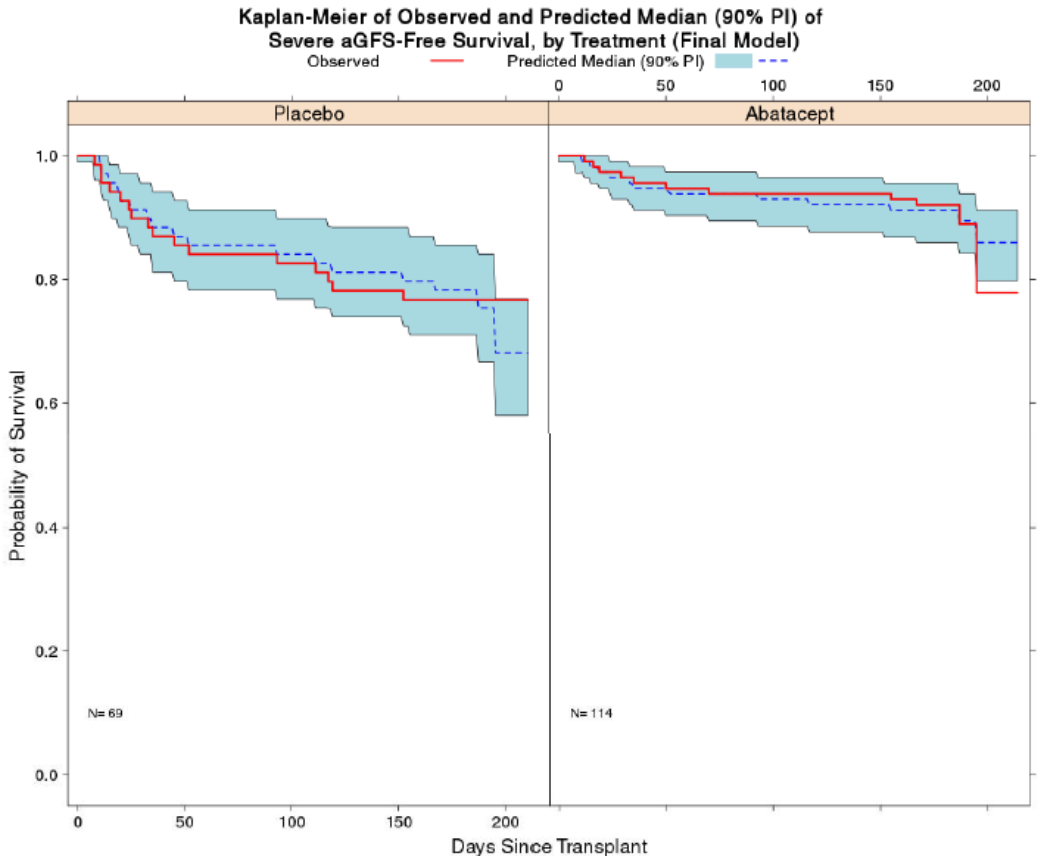


Figure 14 ***VPC of Time to First Severe aGFS (Final Model), by Placebo and Quartiles of C_{min} after the last dose***

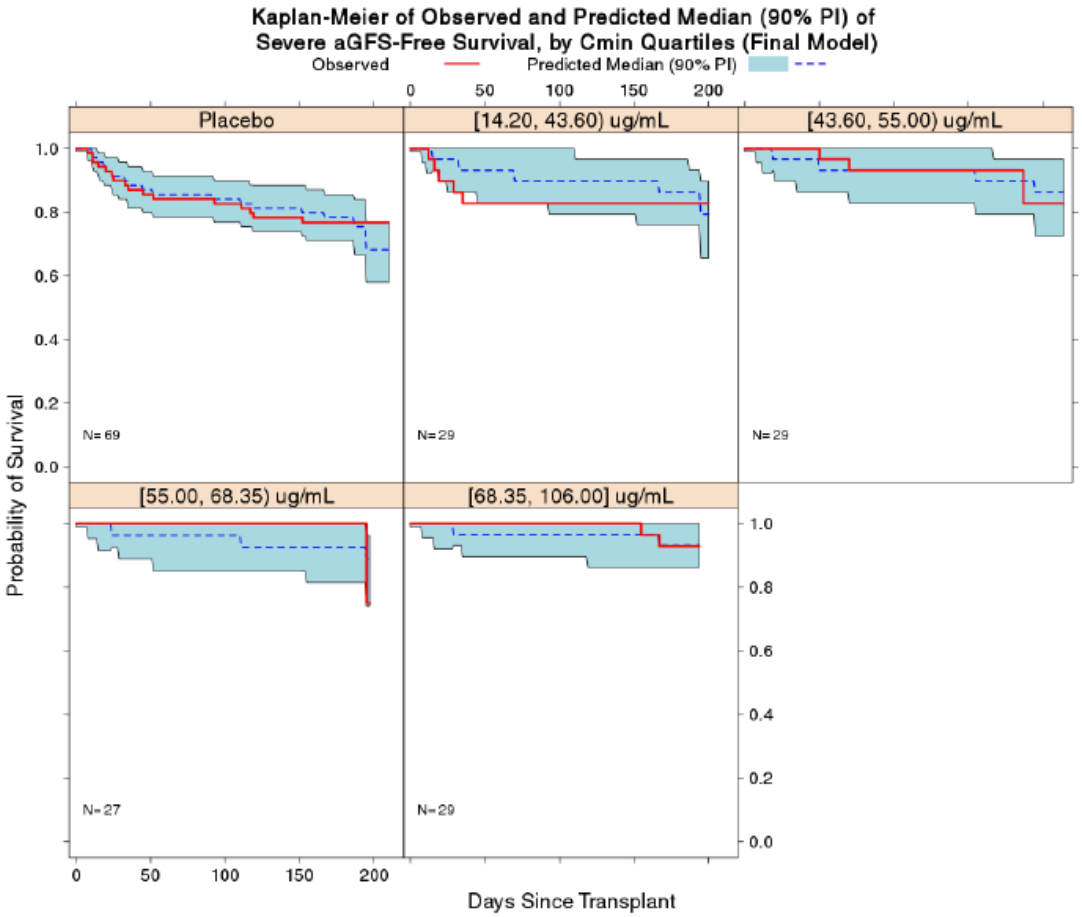
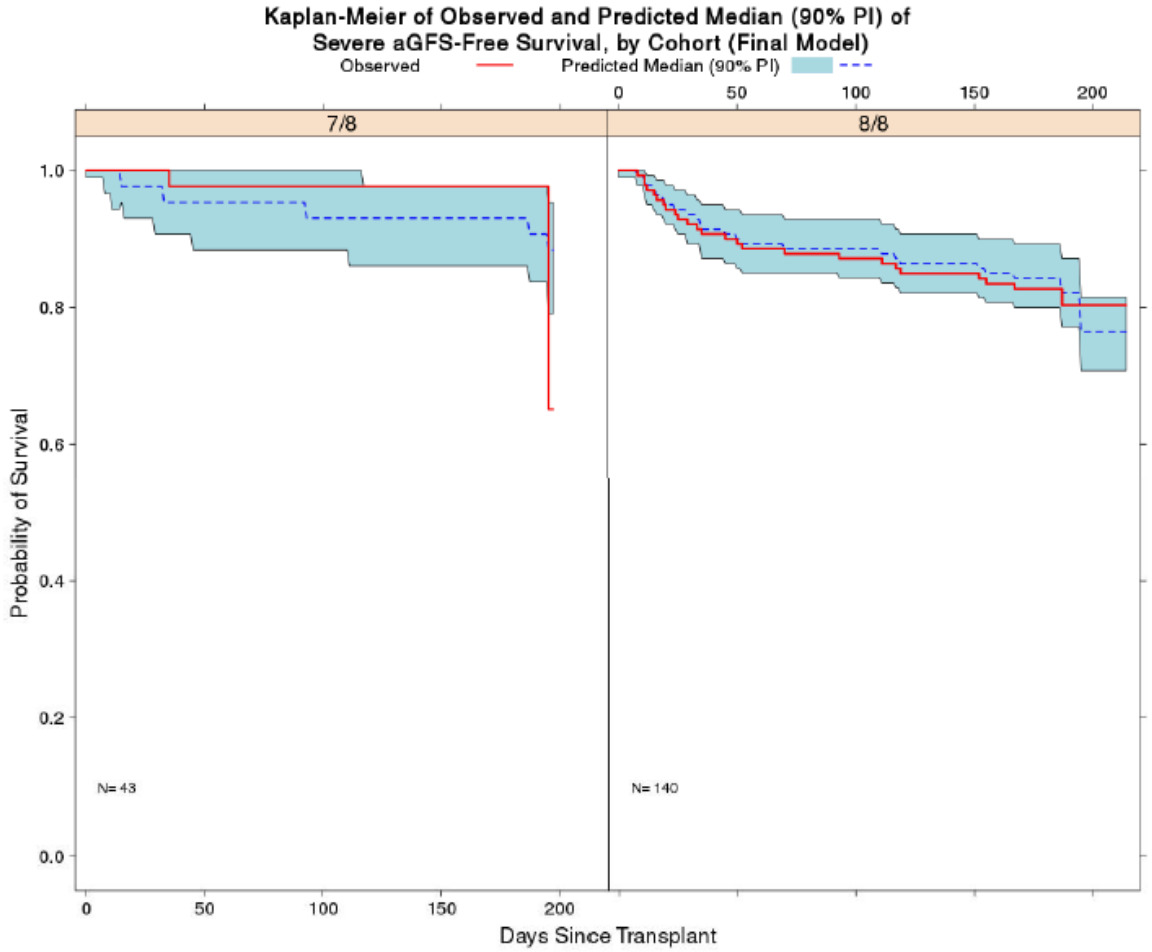

Kaplan-Meier of Observed and Predicted Median (90% PI) of
Severe aGFS-Free Survival, by Cmin Quartiles (Final Model)
Observed
Predicted Median (90% PI)
Placebo
[14.20, 43.60) ug/mL
[43.60, 55.00) ug/mL
[55.00, 68.35) ug/mL
[68.35, 106.00] ug/mL
N= 69
N= 29
N= 29
N= 27
N= 29
Probability of Survival
Days Since Transplant
0
50
100
150
200
0.0
0.2
0.4
0.6
0.8
1.0

Figure 15 ***VPC of Time to First Severe aGFS (Final Model), by Cohort***



Overall survival

Two, 5, and 13 patients in abatacept 7/8 cohort, abatacept 8/8 cohort, and placebo group, respectively, experienced death during the first 180 days after transplantation. C_{max} after the first dose was the most significant exposure measure for OS, but C_{min} after the last dose was included in the base model since C_{max} and C_{min} were highly correlated and to be consistent with the exposure measure selected in the time to aGFS analysis. The base model parameter estimates are presented in Table 14.

Table 14 ***Parameter Estimates of E-R Efficacy for OS (Base Model)***

Variable	Coefficient	SE	RSE	P value	Hazard Ratio	Lower 95% CI	Upper 95% CI	Hazard Ratio (95% CI)
Abatacept Cmin After the Last Dose [µg/mL]	-0.01796	0.00811	45.14	0.02672	0.9822	0.9667	0.9979	0.9822 (0.9667, 0.9979)

SE: standard error

The full model and the final model were developed exactly as with the time to first severe aGFS model. The only covariate with a P value < 0.01 in the univariate step and included in the full model was relapse of malignancy. The full model was not reduced after 1 step of backward elimination as the P value for relapse was below the 0.001 threshold. Hence, the full model was the final model. The parameter estimates are presented in Table 15.

Table 15 ***Parameter Estimates of E-R Efficacy for OS (Full and Final Model)***

Variable[a]	Coefficient	SE	RSE	P value	Hazard Ratio	Lower 95% CI	Upper 95% CI	Hazard Ratio (95% CI)
Abatacept Cmin After the Last Dose [µg/mL]	-0.01607	0.007772	48.38	0.03872	0.9841	0.9692	0.9992	0.9841 (0.9692, 0.9992)
Relapse	1.868	0.4517	24.18	3.54E-05	6.475	2.672	15.69	6.475 (2.672, 15.69)

[a] Reference values: Relapse=No.

SE: standard error

The final model was evaluated using VPC (Figure 16, Figure 17, Figure 18). There was good agreement between the observed and predicted median OS over time. Similar VPC plots were obtained with the alternative model with C_{max} after the first dose as the exposure parameter (not shown in this AR).

Figure 16 ***VPC of Overall Survival (Final Model), by Treatment***

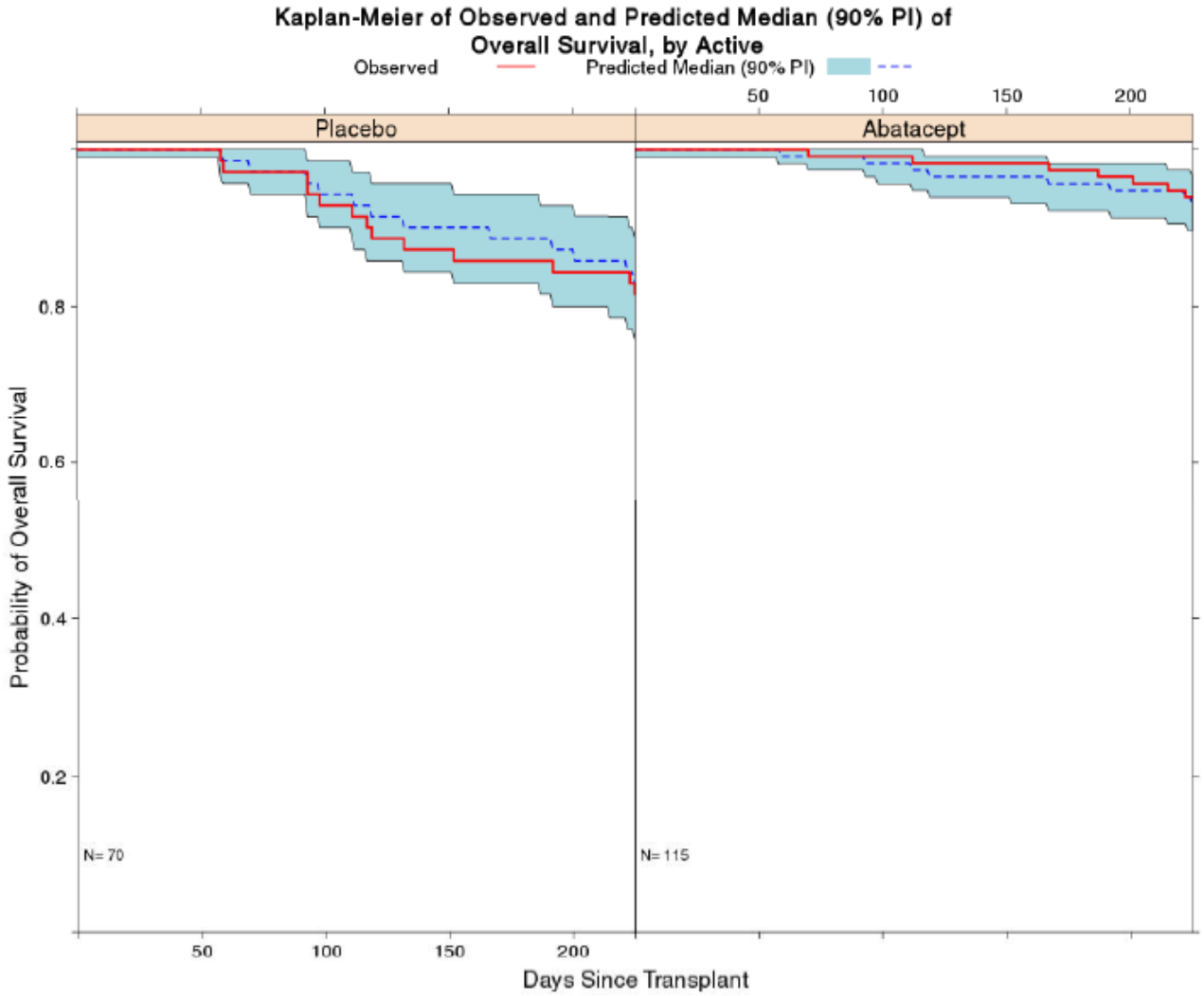


Figure 17 ***VPC of Overall Survival (Final Model), by Placebo and Quartiles of C_{min} after the last dose***

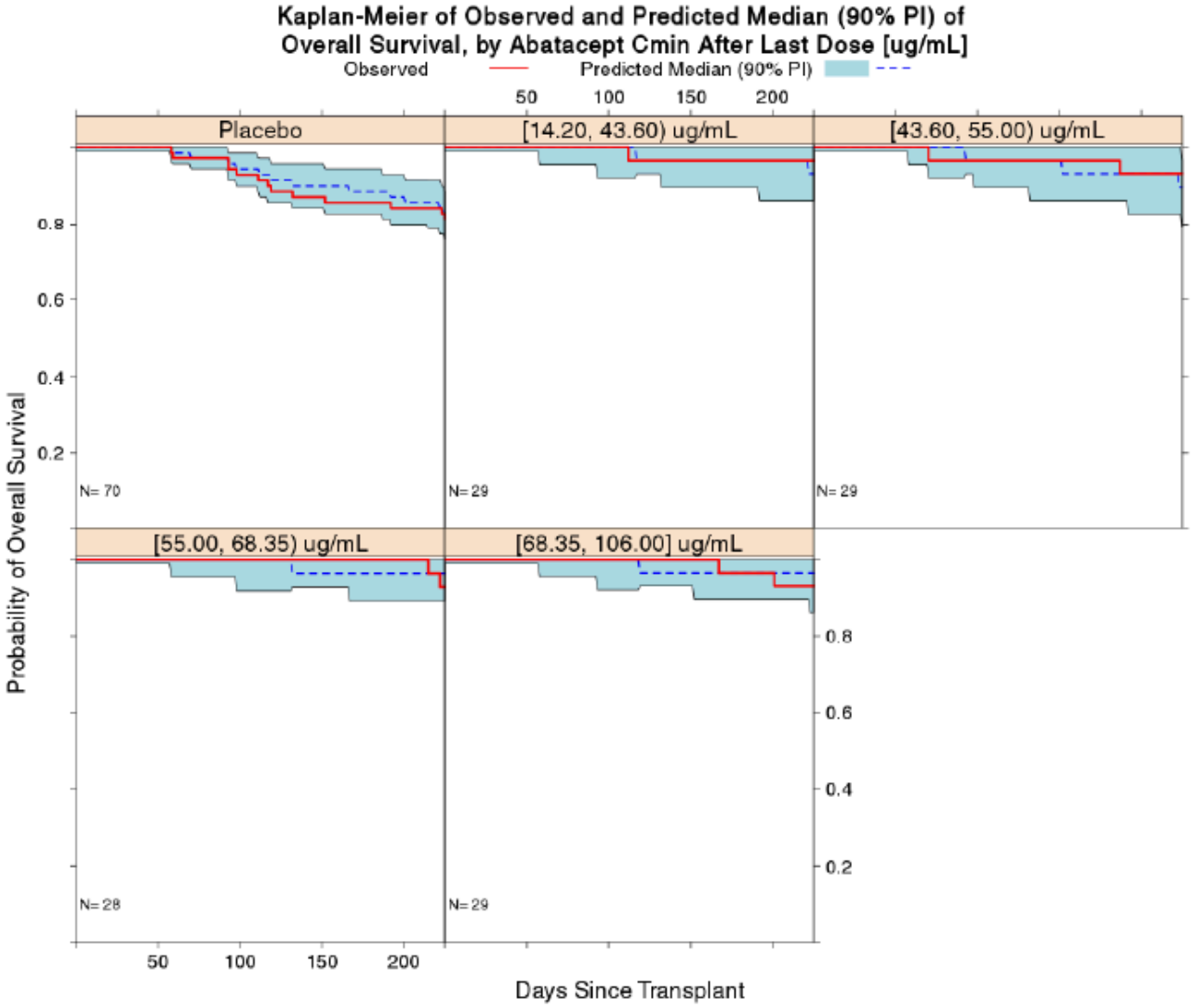
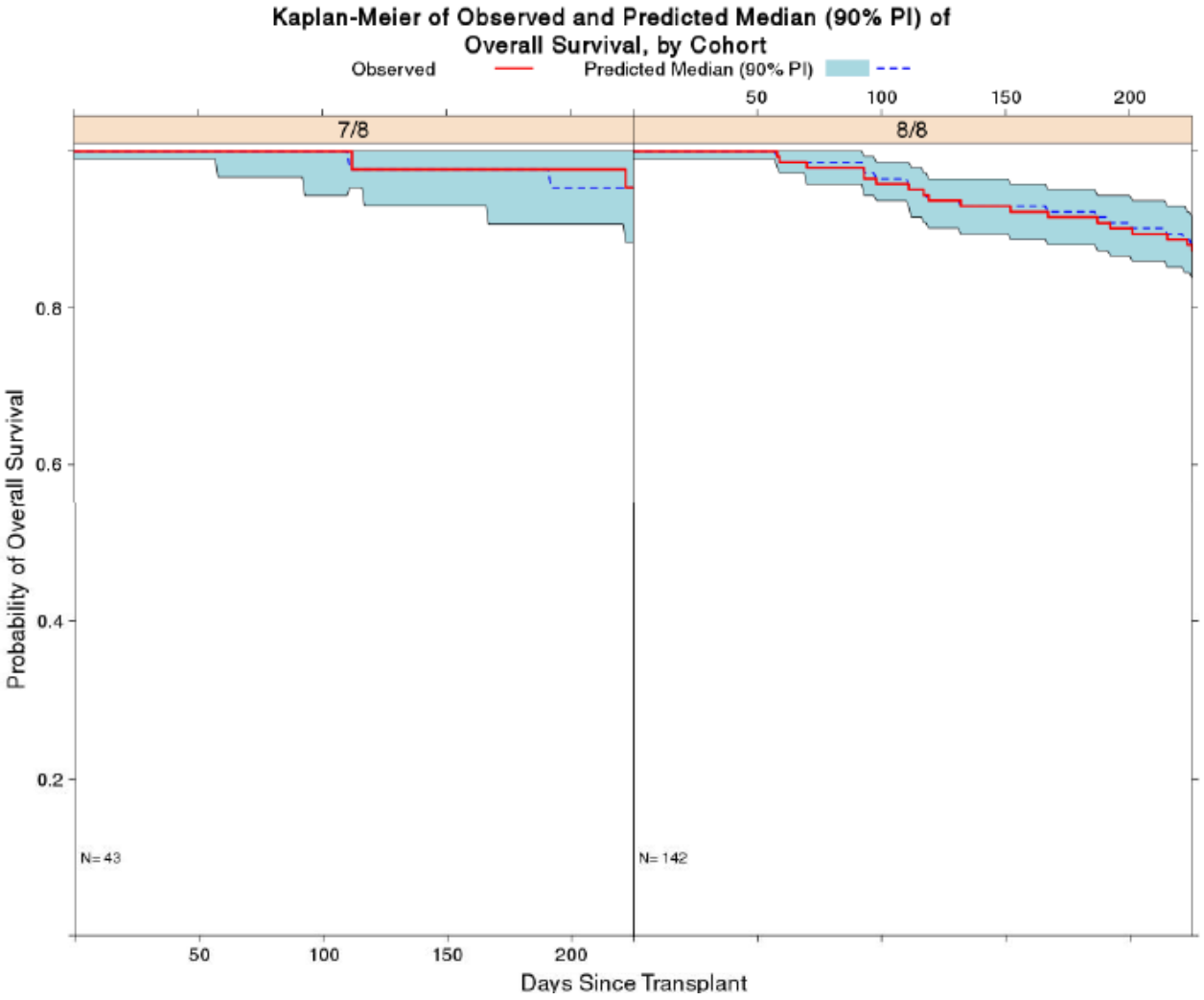


Figure 18 ***VPC of Overall Survival (Final Model), by Cohort***



Exposure-response analysis for safety

The 2020 pharmacometric report

The E-R abatacept safety evaluation for Study IM101311 consisted of the following safety endpoints: time to first infection regardless of seriousness (the most common expected adverse event) and time to first CMV disease (invasive and viremia). Kaplan-Meier (K-M) plots were used to graphically evaluate the relationships between abatacept exposure and the three safety endpoints. Abatacept exposure parameters were obtained with the 2020 PPK model.

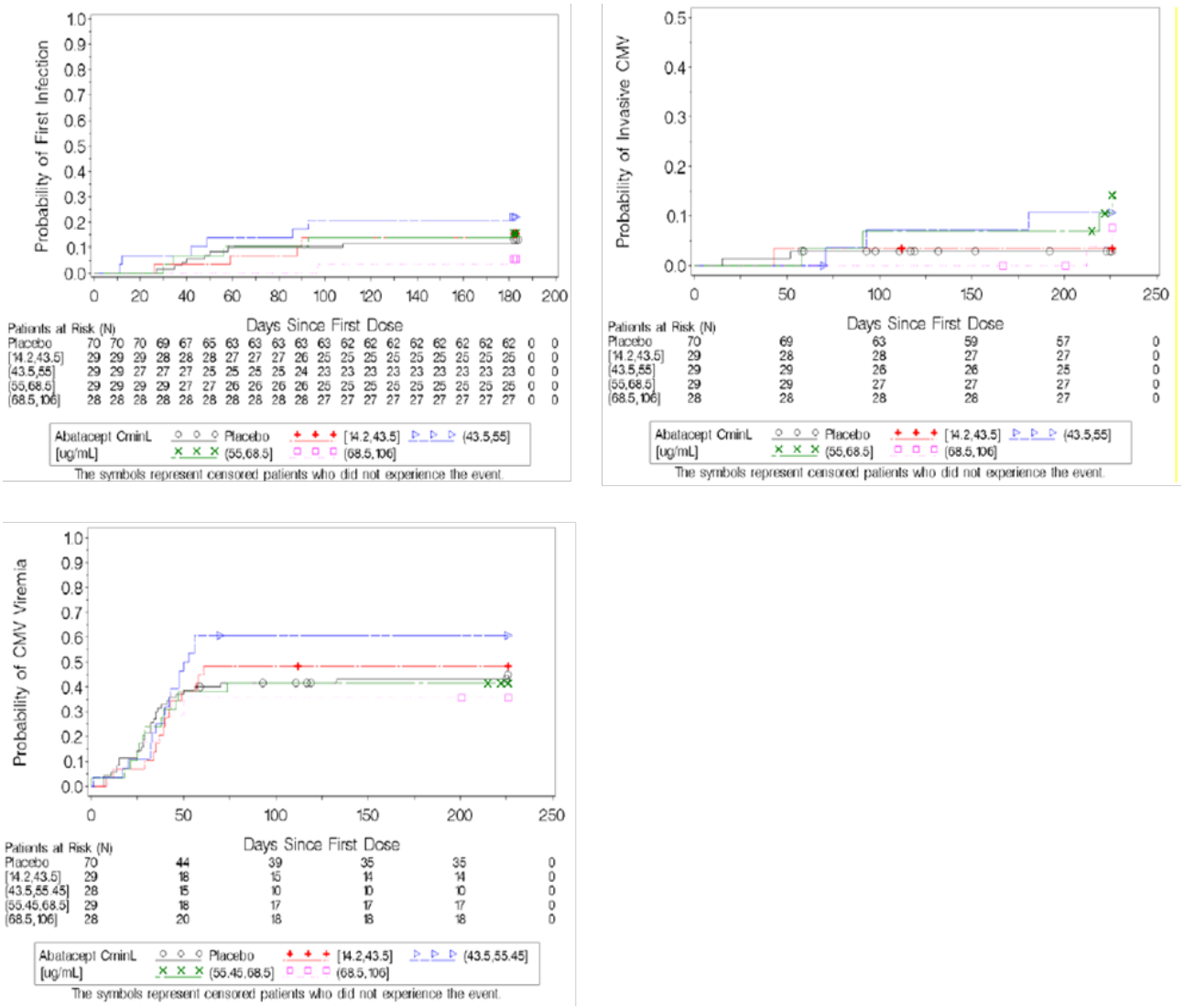
At least one infection was reported for 12.4% of subjects in Study IM101311 (n = 23 events, 8 events (11.4%) in placebo group and 15 events (12.9%) in abatacept group).

Invasive CMV disease was reported for 6.5% of subjects in Study IM101311 (n = 12 events, 2 events (2.9%) in placebo group and 10 events (8.7%) in abatacept group).

CMV viremia was reported for 45.9% of subjects in Study IM101311 (n = 85 events, 31 events (44.3%) in placebo group and 54 events (47.0%) in abatacept group).

Kaplan-Meier (K-M) plots were used to graphically evaluate the relationships between abatacept exposure and the three safety endpoints. K-M curves of the probability of the events by quartiles of C_{min} after the last dose are shown in Figure 19, similar results were obtained for all exposure parameters (C_{min}, C_{max}, C_{av}, and AUC after the first and the last dose). There did not appear to be a relationship between abatacept exposure and time to first infection, invasive CMV disease, and CMV viremia.

Figure 19 ***Kaplan-Meier Plots of Probability of First Infection, Invasive CMV Disease, and CMV Viremia versus Days by Quartiles of C_{min} After the Last Dose***



"The E-R relationship for the occurrence of infection was explored graphically. Overall, 12.4% of patients (n = 23 events) had at least 1 occurrence of an infection. There was a similar rate of occurrence of infection among patients receiving placebo (11.4%) and abatacept (12.9%). The median exposure measures for the patients who experienced infections were similar to the medians for those patients who did not experience an infection. When abatacept exposure measures were grouped by the median and quartiles, no apparent E-R relationship was identified as the survival probabilities for all exposure quartiles largely overlapped over time. The Cox proportional hazard model for each abatacept exposure and time to first infection regardless of seriousness were evaluated. No abatacept exposures were

significant predictors of the time to first infection regardless of seriousness indicating no E-R relationship."

4.3.5. Discussion on clinical pharmacology

Bioanalytical methods

The PK and immunogenicity samples were analysed at the same site and using the same methods as in previous application. The samples were appropriately stored and handled.

Observed pharmacokinetics

Observed abatacept concentrations in Study IM101311 showed that patients with 8/8 HLA match tended to have approximately 25% lower abatacept exposure compared with patients with 7/8 HLA match. The MAH did not explore potential reasons for this difference (e.g., if the body weight distribution was different between the cohorts). This is not pursued because the PK data were used in population PK (PPK) analyses, which are more important for this application.

Population PK modelling and simulations

The MAH conducted two population PK (PPK) analyses. The first one, 2020 PPK analysis, was conducted to describe the PK of abatacept in patients ≥6 years of age with RA or JIA or receiving URD HSCT due to HM. In the second, 2022 PPK analysis, the dataset was extended to include paediatric patients ≥2 years of age with JIA and the parameters of the 2020 model were re-estimated. The 2022 model was used to simulate the PK of abatacept in a virtual paediatric patient population (2 to <6 years old) to support dose selection in this age group for prevention of aGvHD.

The development of the 2020 PPK model was conducted similarly as the development of models previously used to support the approved MAA and variation applications (e.g., exclusion of anomalous concentrations in the dataset and development of the covariate model). Initially, the population was categorised by background disease as RA/JIA/HM, and patients with HM were found to have 22% lower CL and 12% higher VC compared to patients with RA; patients with JIA had similar (4% to 5% lower) CL and VC as those with RA. However, goodness-of-fit plots indicated differences in fit between the cohorts (7/8 and 8/8 match) of Study IM101311 even when covariates like body weight were taken into account. Therefore, the disease category was refined as Cohort 7/8 vs Cohort 8/8 vs RA or JIA. The cohort effect was statistically significant (P<0.001) on CL and VC. The final 2020 PPK model was a 2-compartment model with zero-order IV infusion, linear distribution and elimination parameterized in terms of CL, VC, Q, and VP. Interindividual variability was estimated on CL, VC, and VP. Residual variability was described using a combined additive and constant CV model. Statistically significant covariates were baseline body weight (BWT), calculated GFR (CGFR), AST, sex, and Study IM101311 cohorts on CL; baseline BWT and Study IM101311 Cohort 8/8 on VC; and baseline BWT on VP. Cohorts 7/8 and 8/8 were estimated to have 31.8% and 12.5% lower CL, respectively, and 5.3% lower and 28.6% higher VC, respectively, than patients with RA or JIA. The covariates with potential clinical relevance (95% CI of the estimate not entirely contained within 80% to 125% of the reference value) were baseline BWT on CL, VC, and VP; Cohort 7/8 on CL; Cohort 8/8 on VC; and CGFR on CL. Graphical exploration indicated that aGvHD prophylaxis treatment and conditioning regimen did not have meaningful effect on CL, which supports the proposed statement on concomitant medications in section 5.2 of the SmPC.

The 2020 pharmacometric report was written well and clearly described and justified the decisions made during model development. Concentrations missing an actual sample time were common in study IM101311 (427/938 samples, 46%). The rules used to impute the sampling time were acceptable. Given the relatively slow elimination of abatacept (mean terminal half-life 13.1 days according to the SmPC),

it is unlikely that imputed sampling times would affect the parameter estimates to a significant degree. It is agreed with the MAH that the selected final categorisation of the background disease (Cohort 7/8 vs Cohort 8/8 vs RA or JIA) provided the best fit for the observed data, even though some underprediction at low concentrations can still be observed. The underlying reasons for the lower clearance in Cohort 7/8 (corresponding with higher observed concentrations in Cohort 7/8 in Study IM101311) could not be clarified by the model.

The primary aim of the 2022 PPK model is to simulate abatacept exposure in a virtual paediatric patient population (2 to <6 years old) to support dose selection in prevention of aGVDH in this age group, which was not investigated in Study IM101311. The 2022 model is based on the 2020 model, and includes the previous dataset extended with PK data from Study IM101301, which was a Phase 3 study to evaluate the safety and efficacy of subcutaneously administered abatacept in paediatric patients 2-17 years old with JIA. A total of 1482 concentrations from 219 paediatric patients from Study IM101301 were added to the dataset.

The parameters of the previous 2020 PPK model were re-estimated using the 2022 pooled analysis dataset and the model was also updated to include absorption parameters, since the patients in Study IM101301 were administered SC abatacept. The differences between the models in CL, VC, Q and VP estimates were small (|% change| all ≤12.43%). More significant changes were observed in covariates (weight, GFR, sex), but it is agreed with the MAH that these would be expected following the inclusion of subjects aged 2 to <6 years.

Estimated allometric exponents for clearance and volume parameters were used in the 2022 PPK model. The MAH conducted supplementary analyses during the assessment upon request, including sensitivity analysis with an alternative model with fixed theoretical allometric exponents (0.75 for clearance; 1.0 for volume). The alternative PK model with fixed allometric exponents resulted in minimal changes in clearance and volume parameter estimates and no overall improvement of the model; however, simulations using the model with fixed exponents suggested that with the proposed dose regimen for aGVHD indication, children [2-6) years of age are predicted to have a higher exposure after the first dose than older children and adults in study IM101311. The dataset of the year 2022 PPK model contained observations from 471 adult subjects and 433 paediatric (2 to < 18 years of age) subjects. Given the large number of paediatric patients in the dataset, it is considered appropriate to use the initially presented year 2022 population PK model with estimated allometric exponents to simulate the exposure for paediatric patients from 2 to less than 6 years of age in the current application.

PK simulations in virtual paediatric patients ages 2 to less than 6 years old using the 2022 PPK model indicated that to achieve exposures similar to those observed in patients ≥6 years of age in study IM101311, the younger children (2 to <6 years of age) should be administered higher doses of abatacept per kg body weight. This is in line with the approved posology for SC abatacept in treatment of JIA and might be related to body size and composition and protein catabolism rate. The proposed regimen for prophylaxis for aGvHD in patients 2 to <6 years of age is 15 mg/kg on the day before transplantation (Day -1), followed by 12 mg/kg on Day 5, 14, and 28 after transplantation. In patients ≥6 years of age (including adults), the proposed regimen is 10 mg/kg on Days -1, 5, 14 and 28, which is the regimen used in study IM101311.

As discussed above, the PK simulations come with some degree of uncertainty. In addition, the target exposure for children 2 to <6 years of age in the applied indication is based on limited observed efficacy and safety data from one clinical study (IM101311) where only one dose level was used. However, the proposed regimen for prophylaxis for aGvHD in patients 2 to <6 years of age is considered acceptable from pharmacokinetic perspective. Orencia is approved in children 2 to <6 years of age for treatment of JIA. It is challenging to extrapolate safety information from patients with JIA to those undergoing HSCT but the available data do not indicate concerns specific to young children. Predicted C_{max} and C_{avg} in

children 2 to <6 years of age are higher in aGvHD prophylaxis indication than in JIA indication but on the other hand, duration of treatment is only four doses in aGvHD prophylaxis. Given the seriousness of aGvHD, consequences are expected to be greater with a too low exposure compared to a too high exposure, the proposed posology in children 2-5 years of age is considered acceptable. It is also acknowledged that the MAH will collect additional safety and PK data in patients 2 to less than 6 years of age in a clinical study using the proposed dose regimen.

Exposure-response analyses

Exposure-response (E-R) models for efficacy suggested that higher exposure to abatacept was associated with better response (longer time to first severe aGvHD and longer overall survival (OS)). As could be expected, relapse of the underlying malignancy predicted shorter OS. However, the number of events was relatively small, and it is intriguing that in patients treated with abatacept, those with 7/8 HLA match seemed to have better clinical response over the first 180 days post-transplantation compared with patients with 8/8 HLA match.

Three safety endpoints (time to first infection, first invasive CMV disease, and first CMV viremia) were used in graphical E-R safety analyses. The Kaplan-Meier plots indicated no relationship between abatacept exposure level and time to first infection, invasive CMV disease, and CMV viremia.

The numbers of efficacy and safety events were relatively small and, therefore, the E-R analyses should be considered exploratory at present.

4.3.6. Conclusions on clinical pharmacology

Bioanalytical methods appeared appropriate.

Results of population PK analysis indicated that clearance of abatacept is slightly lower in patients at least 6 years of age treated with allogeneic hematopoietic stem cell transplant due to haematologic malignancy compared to patients with RA or JIA. The proposed posology in patients 2 to less than 6 years of age is based on modelling and simulations and extrapolation from older patients. As discussed above, the simulations come with some degree of uncertainty. However, the presented PPK model is considered appropriate for PK simulations and dose recommendations for prophylaxis for aGvHD in patients 2 to <6 years of age. Although the E-R analyses for safety in aGvHD prophylaxis must be considered exploratory at present, it is acknowledged that no relationship between abatacept exposure level and safety endpoints were observed in paediatric patients 6 years of age and older and adults undergoing HSCT. Orencia is approved in children 2 to <6 years of age for treatment of JIA and the available data do not indicate concerns specific to young children. Predicted C_{max} and C_{avg} in children 2 to <6 years of age are higher in aGvHD prophylaxis indication than in JIA indication but on the other hand, duration of treatment is only four doses in aGvHD prophylaxis. Given the seriousness of aGvHD, it is expected that consequences are greater with a too low exposure compared to a too high exposure. Therefore, the proposed posology in children 2 to less than 6 years of age is considered acceptable. Finally, it should be noted that the MAH will collect additional safety and PK data in patients 2 to less than 6 years of age in a clinical study (ABA3, aka IM101790 or NCT04380740) to verify the model-predicted dose regimen in these patients.

4.4. Clinical efficacy

The application is based on the results of two partly overlapping studies:

- Study IM101311 (hereinafter Study 311) was an investigator-sponsored, multicentre Phase 2 trial with 2 treatment populations: a randomised, double-blind, placebo-controlled cohort for

patients receiving HSCT from 8 of 8 HLA-matched donors (the "8/8 matched unrelated donors (MUD) cohort"), and a single-arm cohort for patients receiving HSCT from 7 of 8 HLA-matched donors (the "7/8 mismatched unrelated donors (MMUD) cohort"). The primary objective of the study was to assess the impact of abatacept on the incidence of severe aGVHD, when added to a background GvHD prophylactic regimen (CNI + MTX) administered to patients with haematological malignancies receiving an unrelated-donor (URD) HSCT. In the documentation, the MAH has provided some additional analyses comparing outcomes in the 7/8 MMUD cohort to historical controls sourced from the Center for International Blood and Marrow Transplant Research (CIBMTR). Due to the overlap of these analyses with Study IM101841, these comparative analyses are not separately presented in this AR.

- Study IM101841 (hereinafter Study 841) was a registry study using data routinely collected into the Center for International Blood and Marrow Transplant Research (CIBMTR) database. CIBMTR collects data on all allogeneic (related and unrelated) HSCTs performed in the United States (US) and on all HSCTs done with products procured through the C. W. Bill Young Cell Transplantation Program but performed outside of the US. The primary objective of the registry study was to compare OS with 180 days of follow-up post-HSCT in 7/8 HLA-matched patients treated with CNI + MTX + abatacept without ATG to those treated with CNI + MTX without ATG. A number of other comparator groups were also included in the study. The study protocol was developed in consultation with and input from the FDA to supplement results obtained in Study 311.

As stated above, Study 311 was an investigator-sponsored study, and the MAH licensed the datasets of the study from the investigator. For purposes of submission of a supplemental NDA in the US, the MAH and the FDA agreed that the MAH could create a new SAP to analyse the data, and the results of the analyses could be used as the basis of a regulatory submission for the aGvHD prophylaxis indication. In the current Assessment Report (AR), Study 311 is described and assessed based on this SAP, without specific consideration to the Investigators' separate analyses or results published in scientific articles.

Furthermore, it should be noted that the 7/8 MMUD cohort of Study 311 was also included in Study 841 and indeed accounts for over 80% of patients in the "CNI + MTX + abatacept without ATG" group of Study 841. As such, the samples for the 7/8 MMUD cohorts in the two studies are not independent. As stated above, the results within the 7/8 MMUD cohort of Study 311 are presented as a single-arm study in this AR, and comparative analyses regarding 7/8 patients are presented within results for Study 841.

CHMP's comments:

In the response to the 1st RSI, the MAH provided additional data for both studies; these include 5-year outcomes data for Study 311, 1-year outcomes data for the 7/8 cohort in Study 841, and 1-year outcomes data from a new 8/8 MUD cohort that has been added into Study 841 comparing 71 abatacept + CNI+MTX patients with 355 patients with 3 different GVHD prophylaxis approaches. These data had become available to the MAH very recently, and in the response, were only summarised by means of selected graphical outputs or extracts from externally prepared abstracts. The data are considered potentially of significant relevance for assessment purposes; however, it would be expected that they undergo the same degree of quality assurance as data included in the initial submission and are made available to the same degree of detail, before they can be reliably included in the assessment. As such, a formal MO is raised in terms of the quality and regulatory suitability of the newly available data, and the MAH is expected to complete their quality assurance processes and provide appropriate supporting documentation for these new data before they can be adequately considered in the assessment. ***MO***

4.4.1. Dose response studies

No separate dose-response studies were conducted as part of the current development programme. For Study 311, the abatacept dose regimen of 10 mg/kg was based on experience from Rheumatoid Arthritis (RA) and Juvenile Idiopathic Arthritis (JIA) trials wherein abatacept was dosed at 10 mg/kg and was administered IV on days 1,15, and 29 (1 trial used day 30), and every 28 days thereafter for a total of 6 to 10 months of treatment. In these trials, abatacept was well tolerated. Furthermore, in a first-in-disease feasibility trial of abatacept for GvHD prevention (NCT01012492), 10 patients with high-risk haematologic malignancies were treated with 10 mg/kg abatacept IV on days -1, +5, +14, +28.

4.4.2. Main studies

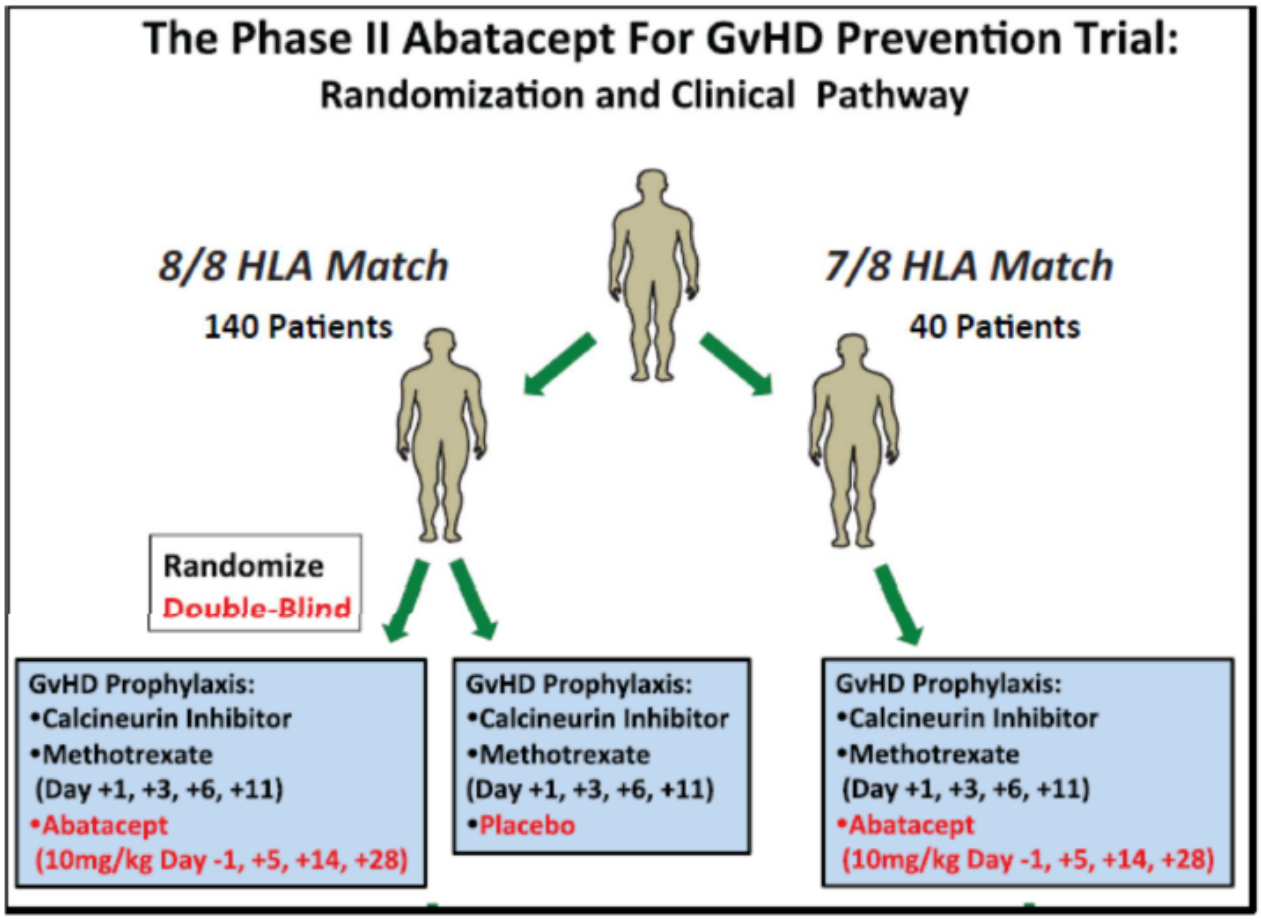
4.4.2.1. Study IM101311

The title of Study IM101311 was "Abatacept Combined With a Calcineurin Inhibitor and Methotrexate for Graft Versus Host Disease Prophylaxis"

Methods

As outlined above, Study 311 was an investigator-sponsored, multicentre Phase 2 trial, and its primary objective was to assess the impact of abatacept on the incidence of severe aGVHD, when added to a background GvHD prophylactic regimen (CNI + MTX) administered to patients with haematological malignancies receiving an URD HSCT. The study was conducted in 2 treatment populations: patients receiving HSCT from 8 of 8 HLA-matched donors (the 8/8 MUD cohort), and patients receiving HSCT from 7 of 8 HLA-matched donors (the 7/8 MMUD cohort). The original protocol required all subjects enrolled into the study (both 8/8 MUD cohort and 7/8 MMUD cohort) to be randomised to either study medication (abatacept + standard prophylaxis [CNI + MTX] regimen) or placebo + CNI + MTX regimen. In this AR, these treatment arms will be referred to as abatacept and placebo arms, respectively. However, following initiation of the study, but independent of it, a general impression began to emerge among members of the HSCT transplant community that addition of abatacept to a standard of care regimen for aGVHD prophylaxis appeared to be therapeutically beneficial. Consequently, investigators felt it was not ethical to enrol recipients of 7/8 MMUD if they could be randomised to the placebo arm of the study, given known high risks of transplant-related mortality with placebo; this emerging consensus resulted in a prolonged delay in enrolment of the 7/8 MMUD cohort that necessitated elimination of the placebo arm by protocol amendment (Amendment 04). After the implementation of Protocol Amendment 04, all subjects enrolled in the 7/8 MMUD cohort received open-label abatacept and the placebo arm was discontinued in the 7/8 MMUD cohort. A schematic of the study design (following Amendment 04) is displayed in Figure 20.

Figure 20 ***Study Design Schematic for IM101311***



CHMP's comments

The main study in the application was an investigator-sponsored Phase 2 study conducted in two treatment populations. Patients receiving HSCT from an 8 of 8 HLA-matched donor (the 8/8 MUD cohort) were included in a double-blind placebo-controlled study. Patients receiving HSCT from a 7 of 8 HLA-matched donor (the 7/8 MMUD cohort) were also initially intended to be studied in a placebo-controlled study, but due to an emerging consensus that patients randomised to placebo would in fact be undertreated, the 7/8 cohort was rapidly converted into a single arm study. Since the clinical outcomes of the 7/8 MMUD HSCTs plus Standard of Care therapies are generally much worse compared to 8/8 MUD transplantations when the patients are on Standard of Care therapies, the decision that all patients in the 7/8 MMUD cohort received open-label abatacept is accepted.

In principle, a placebo-controlled design is considered well suited for purposes of assessing the absolute effect of abatacept when added on top of standard of care.

Study participants

Prospective subjects for the study were recruited from transplant centres across the US and Canada. The main inclusion and exclusion criteria were:

Main inclusion criteria:

- Must be at least 6 years old and weigh 20 kg.
- Must have a willing unrelated adult donor (bone marrow or peripheral blood). Donors may have a single mismatch (i.e. be a 7/8) and this mismatch may be at the allele or antigen level; however, donors with allele level disparity should be given preference over those with antigen level disparity. The use of mismatched donors in which disparity is only in the host versus graft direction (because of recipient homozygosity) is discouraged because of the potentially heightened risk for graft rejection.
- All patients and/or their parents or legal guardians must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.
- Must have a high risk haematologic malignancy as defined below (further specifications regarding eligibility were provided in the protocol):
    - Acute myeloid leukaemia (AML)
    - Myelodysplastic syndrome (MDS)
    - Acute lymphoblastic leukaemia (ALL)
    - Patients with acute undifferentiated, biphenotypic, or bilineal leukaemia, which is in first or greater complete remission (CR) or partial remission (PR).
    - Chronic myelogenous leukaemia (CML)
    - Acute Lymphoblastic Lymphoma in second or greater complete remission
    - Peripheral T cell lymphoma (PTCL)
    - Chronic myelomonocytic leukaemia
    - Atypical (BCR-ABL negative) chronic myelogenous leukaemia
    - Hodgkin lymphoma that has recurred or progressed after an autologous BMT
    - Non-Hodgkin lymphoma (other than lymphoblastic or peripheral T cell lymphoma)

Main exclusion criteria

- Prior allogeneic HSCT.
- The patient is enrolled on a Children's Oncology Group (COG) trial that uses criteria for unrelated donor HSCT, which conflict with this study's eligibility criteria.
- The patient is enrolled on a COG trial that utilises unrelated donor HSCT and requires that patients be transplanted using an approach specified by the protocol that is in conflict with the approach specified in this protocol.
- Availability of a willing and suitable HLA identical related donor.
- Uncontrolled viral, bacterial, fungal or protozoal infection at the time of study enrolment.
- HIV infection.

- Serious psychiatric disease including schizophrenia, bipolar disorder and severe depression.
- Any patient with a known or suspected inherited predisposition to cancer should be discussed with the study team prior to screening for eligibility.
    - Patients with a known inherited or constitutional predisposition to transplant morbidities, including, but not limited to Fanconi Anemia, Dyskeratosis Congenita, Shwachman-Diamond Syndrome and Down Syndrome will be excluded.
    - Patients with known inherited or constitutional predisposition to non-haematologic cancers including, but not limited to Li-Fraumeni syndrome, BRCA1 and BRCA2 mutations will be excluded.
    - Patients with an inherited predisposition to leukaemia or otherwise haematologic malignancies that have not been associated with predisposition to transplant morbidities or non-hematologic cancers will not be excluded.
- Patient with a secondary malignancy who would be otherwise eligible for study, but for whom remission from the primary disease cannot be conclusively confirmed or for whom the chance of relapse of the primary disease is significant.
- Incompletely treated active tuberculosis Infection.
- Pregnancy (positive serum b-HCG) or breastfeeding.
- Estimated GFR of < 50 mL/min/1.73m^2.
- Cardiac ejection fraction < 50 (using M-Mode if assessment is done by ECHO).
- T.bilirubin > 2 × upper limit of normal or ALT > 4 × upper limit of normal or unresolved veno-occlusive disease.
- Pulmonary disease with FVC, FEV1 or DLCO parameters <45% predicted (corrected for haemoglobin) or requiring supplemental oxygen. Children who are developmentally unable to perform pulmonary function testing will be assessed solely on their need for supplemental oxygen.
- Karnofsky performance score or Lansky Play-Performance Scale score <80.
- Presence of antibodies to a mismatched donor HLA antigen.

CHMP's comments

The eligibility criteria are appropriately set in relation to the study objectives.

Treatments

Study treatments

Abatacept was administered at a dose of 10 mg/kg (to a maximum total of 1000 mg) on days -1, +5, +14, +28 (day of transplant is Day 1 of Study). The dosing regimen was selected based on targeting trough serum concentrations of abatacept of at least 10 µg/mL (considered optimal based on preclinical models) and on providing exposures similar to those achieved in RA and JIA studies. It had also been used in a first-in-disease feasibility trial of abatacept for GvHD prevention.

Abatacept was supplied as 250 mg lyophilised powder for IV infusion in single use vials. Each vial was reconstituted with 10 ml of Sterile Water for Injection, USP, and the reconstituted solution then further diluted in 0.9% Sodium Chloride USP (Normal Saline) to a final volume of 100 ml. The placebo consisted of 100 ml of 0.9% Sodium Chloride.

Study drug (abatacept or placebo) was administered as an IV infusion over 1 hour. Premedication with IV diphenhydramine was to be performed 30 minutes prior to each study drug dose.

Standard GvHD prophylactic regimen

CNI (CsA or TAC) administration was to be commenced no later than day –2 (at least 36 hours before the stem cell infusion). CsA doses were to be adjusted to maintain a level of 100-300 ng/ml, and TAC doses to maintain a level of 5-15 ng/ml. Centres were encouraged to administer CsA by continuous infusion, but intermittent infusion was permitted. Once the patient could tolerate oral medications, the CNI was to be converted to an oral formulation. Patients were to receive full dose CNI therapy through at least day 100 as tolerated. Tapering off the dose could be initiated between days 100 to 180 at the discretion of the treating physician. Once the taper had been initiated, it was to be gradually tapered (25-40% per month) and discontinued once the dose is 25% or less of the starting dose. The CNI could be interrupted or dose reduced at the discretion of the treating physician for renal toxicity, poorly controlled hypertension, neurotoxicity and other serious toxicities.

MTX was to be given at a dose of 15 mg/m2 IV on day 1, and a dose of 10 mg/m2 IV on days 3 and 6 and 11. Dosing was to be based on actual weight. For patients with a body mass index of 35 or higher, however, the dose could be adjusted for obesity according to institutional practices. The day 1 dose could not be administered until 24 hours following completion of the stem cell infusion. Monitoring of drug levels and leucovorin was permitted according to local institutional guidelines.

MTX dose modifications could be made at the discretion of the treating physician; the protocol contained non-binding guidelines to assist in decision-making. If more than one dose of MTX was completely held, mycophenolate mofetil was to be started in place of MTX: 15 mg/kg IV or PO (to maximum of 1000 mg) every 8 hours through day +30. It could be continued longer at the discretion of the treating physician, if there was evidence of GvHD.

Pre-HSCT conditioning regimens

Treating physicians were to select, from 1 of 4 conditioning approaches listed below and choose the regimen that he or she determined was best suited for the individual patient and the patient's malignancy. Subjects who had prior autologous HSCT, however, were to be conditioned with melphalan and fludarabine. Patients were not to receive lymphocyte depleting antibodies (either anti-thymocyte globulin [ATG] or alemtuzumab) with any of the conditioning regimens.

1) Total body irradiation (TBI) based conditioning plus chemotherapy

2) Busulfan and cyclophosphamide (recommended for myeloid malignancies only)

3) Melphalan and fludarabine

4) Busulfan and fludarabine (recommended for myeloid malignancies)

CHMP's comments

The abatacept dose and posology resembles the previously authorised posology in rheumatoid arthritis and JIA, with one extra dose added at about 1 week after the initial dose. No separate studies evaluating dose response or different lengths of the treatment period were undertaken.

The background prophylactic regimen, comprising a combination of a calcineurin inhibitor and

methotrexate, is a well-established backbone also in current European guidelines. It should however be noted that antithymocyte globulin (ATG) is broadly used as part of the regimen in both 8/8 and 7/8 matched transplantations. In this context, the decision to transition into a single arm design in the 7/8 cohort is understandable, but even the control group in the 8/8 cohort could be considered somewhat undertreated compared to current European practice. In their response to the 1st RSI, the MAH provided data from an 8/8 cohort in the registry study 841, comparing abatacept and ATG when added to a CNI/MTX backbone in this patient group, which could be considered to implicitly address this limitation.

The MAH has provided a thorough discussion of the literature data on the use of ATGs as part of the SOC in HSCT. Based on the discussion, while ATG is broadly used in the prophylactic regimens in Europe, its effect in the prophylaxis of acute GvHD after HSCT seems somewhat inconclusive. Instead, its main benefit seems to be in prophylaxis of chronic GvHD.

Objectives

The primary objective of Study 311 (as pre-specified in the MAH's SAP) was to compare severe (Gr III-IV) aGvHD-free survival (GFS) up to Day 180 post-transplantation between the abatacept + standard GvHD prophylaxis and standard GvHD prophylaxis regimen only in URD HSCT for subjects with haematologic malignancies.

The key secondary objective was to compare the cumulative incidence of adjudicated severe Gr III-IV aGvHD up to Day 180 post-transplant between the abatacept + standard GvHD prophylaxis and standard GvHD prophylaxis regimen only in unrelated-donor HSCT for subjects with haematologic malignancies.

Other secondary objectives related to efficacy were to assess, within the 8/8 matched unrelated donors (MUD) Cohort:

- overall survival (OS) during the post-transplantation follow-up period
- GFS up to Day 180 using Gr II-IV GvHD as the GvH component; it will include all Gr II-IV aGvHD events and all cause deaths up to Day 180 post-transplant follow-up in the study
- disease-free survival (DFS) and transplant-related mortality (TRM) during the post-transplantation follow-up period
- relapse of underlying malignancy during the post-transplantation follow-up period
- early onset (occurring on or before Day 100 post-transplantation) (all grades [Gr I-IV, Gr II-IV and Gr III-IV]) aGvHD
- late onset aGvHD (occurring after Day 100 post-transplantation) (all grades [Gr I-IV, Gr II-IV and Gr III-IV]) during the post-transplantation follow-up period.
- cGvHD (defined using the 2005 NIH Consensus Criteria for cGvHD scoring) during the post-transplantation follow-up period
- Immune Suppression-free survival and Immune Suppression-free/Disease-free survival during the post-transplantation follow-up period
- severe aGvHD Free – Relapse Free survival (GRFS) during the post-transplantation follow-up to database lock

Corresponding objectives were set for analyses within the 7/8 mismatched unrelated donors (MMUD) Cohort. All of these were considered secondary objectives.

Outcomes/endpoints

The primary efficacy endpoint (corresponding to the primary objective) was Severe (Gr III-IV) GFS up to Day 180, defined as the time between the date of transplant and the onset date of documented severe (Gr III-IV) aGvHD, or death due to any cause up to Day 180 post-transplant, whichever occurs first. Day 225 was the upper limit of the Day 180 window and used for censoring.

The key secondary endpoint (corresponding to the key secondary objective) was the cumulative incidence of severe Gr III-IV aGvHD up to Day 180 post-transplantation.

Other secondary endpoints were formulated to correspond to the secondary objectives. The following additional definitions were applied:

- OS was defined as survival with or without relapse of underlying malignancy.
- DFS was defined as survival without relapse of underlying malignancy.
- TRM was defined as any death occurring in a continuous complete remission, i.e. death without relapse of underlying malignancy.
- Relapse was defined as either morphological or cytogenetic evidence of acute leukaemia or MDS consistent with pre transplant feature, or radiologic evidence of lymphoma, documented or not by biopsy.
- Overlap syndrome was included for analyses of cGvHD.
- Immune Suppression-Free Survival and Immune Suppression-Free/Disease-Free Survival were Defined as survival and disease-free survival off of all immunosuppressive agents.
- For the secondary endpoint of severe aGvHD Free - Relapse Free Survival, severe aGvHD, relapse, and death were considered events.

A centralised GvHD adjudication sub-committee reviewed and adjudicated study data provided by investigational sites for accuracy and completeness related to GvHD grading and scoring.

In their response to the RSI, the MAH clarified that the diagnosis of subtypes of GvHD were assessed as follows:

- classic aGvHD (before day 100), including all grades, and stratified by grades
    - Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005, section 1) using the NIH consensus criteria.
- late onset (after day 100) aGvHD
    - Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005, section 1) using the NIH 2005 consensus criteria.
- cGvHD, including overlap syndrome
    - Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005, section 2) using the NIH consensus criteria. This assessment was continued through Year 5 post-transplant.

CHMP's comments

The primary objective of the study was to evaluate efficacy against acute GvHD, and the timing of primary efficacy assessment at D180 post transplant is selected accordingly. Other more general endpoints related to treatment benefit, including overall survival, were primarily evaluated within the

same timeframe. Whereas it can be agreed that most instances of acute GvHD could be caught within this timeframe, this approach has limitations for other endpoints. Moreover, it is not clear that capturing prevention of acute GvHD as an isolated phenomenon is sufficient demonstration of efficacy in the context of aHSCT, and it could be expected that clinically relevant effects on other endpoints, including overall survival, should also be shown to sufficiently support a claim of actual clinical benefit. As such, the additional analyses up to database lock, provided as supplementary analyses by the MAH, are considered of equal importance compared to the D180 analyses.

Late onset acute GvHD and chronic GvHD seem to be somewhat overlapping conditions. The MAH was therefore requested to clarify how late onset aGvHD and cGvHD were differentiated in the study (noting also that the frequency of early onset (before day 100) aGvHD was proposed as the primary endpoint in the Investigator sponsored research protocol). In the MAH's response, the requested clarification was provided, and the numbers of late onset acute GvHD events were provided separately by cohorts and treatment groups, as requested in the RSI. See section "Outcomes and estimation" for corresponding results.

Sample size

In the original investigator-sponsored protocol, a sample size of approximately 140 subjects (~70 subjects per arm) for the 8/8 MUD cohort was originally planned based on the protocol-defined primary comparison of cumulative incidence of severe Gr III-IV aGVHD event up to Day 100 post-transplantation. The trial was originally designed as a phase 2 trial with one-sided alpha of 0.2 and power of 80%.

For the purpose of the pre-planned analysis per the MAH's SAP, GFS up to Day 180 has been defined as the primary endpoint. The following power calculations for the GFS endpoint are based on a sample size of 70 subjects per treatment arm in the 8/8 MUD cohort and an alpha level of 0.05:

- Assuming an exponential GFS distribution in each arm, the sample size of 140 subjects (70 per arm) required at least 28 severe aGVHD events or deaths to be observed across both arms. This was required for a two-sided log-rank test at alpha of 5% to show statistical difference in GFS with approximately 81% power when the true hazard ratio (HR) of the abatacept arm relative to control is 0.34.
- The sample of 140 subjects (70/arm) would yield approximately 80% power, assuming a HR of 0.30 in the incidence of aGVHD up to Day 180 post-transplantation in the abatacept arm relative to the standard treatment only arm. This required approximately 23 severe Gr III-IV aGVHD events to be observed across both arms up to Day 180 post-transplantation to show a statistically significant difference at 5% 2-sided alpha assuming a follow-up period of 6 months post-transplantation.

This power estimate was based on a two-sided log rank test.

Randomisation

Subjects in the 8/8 MUD cohort were randomly assigned to the standard GVHD prophylaxis arm (placebo) or to the investigational abatacept arm of the study. The randomization was performed by the Cedars-Sinai Statistical Analysis Core, who conveyed the randomization details to the central research pharmacist at Children's Healthcare of Atlanta/Emory University, who, in turn, conveyed the information to the treating centre's investigational pharmacist.

Non-adaptive randomization was performed with a block size of 8 and an allocation ratio of 1:1. Randomization was stratified by baseline age category (≤ 21 years versus > 21 years). There was no stratification by center. Randomization was performed using the open source randomization software RANDI2 via a secure web-browser, hosted and maintained by the Cedars-Sinai Statistical Analysis Core.

Blinding (masking)

For the blinded 8/8 MUD cohort the Cedars-Sinai Statistical Analysis Core, the central research pharmacist, the treating center research pharmacist, the study monitors, and members of the Data Safety and Monitoring Committee (DSMC) of the Pediatric Blood and Marrow Transplant Consortium (PBMTC) were not blinded to study treatment assignment at the patient level. All participating subjects, their families, all medical providers, and all investigators and study personnel other than those listed above were initially blinded to treatment assignment. Unblinding for analysis of the Day 180 data took place prior to full completion of the retrospective data collection. The BMS Global Biometric Sciences department was provided with the database and the unblinding assignments on 11-Oct-2018. Other BMS study personnel remained blinded to patient level treatment assignment. All other study team members other than those listed above were blind to treatment assignment at the patient level until all patients reached at least day +365 post-transplant and remained blinded until 17-Jul-2020.

The 7/8 MMUD cohort was not blinded apart from the first 5 participants enrolled in this cohort. At the time of meeting the accrual goal for the 7/8 MMUD cohort, the sponsor requested from the DSMC that the 5 subjects be unblinded for data analysis and publication to which DSMC agreed.

Statistical methods

Analysis populations

The efficacy analyses of the 8/8 MUD cohort were based on the "Modified Intent-to-treat (MITT) analysis population" that consisted of all randomized and transplanted subjects who received one dose of study medication. Subjects were analysed according to the treatment arm to which they were randomized. The 3 subjects randomised to placebo and 1 subject randomised to abatacept were not treated with study medication and were excluded. All the subjects treated with study medication received the transplant in the study.

The statistical efficacy (and safety) analyses of 7/8 MMUD cohort were based on dataset labelled as "7/8 Cohort Treated analysis population" and consisted of all subjects in the 7/8 MMUD cohort who received at least one dose of abatacept. This population was used for all the efficacy and safety analyses for the 7/8 MMUD cohort. All treated subjects in the 7/8 MMUD cohort also received a transplant in the study.

Analysis Timepoints

The CSR included in the submission is based on data that cover the period when all subjects had a chance to be followed at least up to the planned assessment on Day 365. The CSR body presented the results until nominal Day 180 timepoint, but due to inconsistent CRF collection time points may include all events up to Day 225, which is the upper limit of the Day 180 visit interval as defined in the SAP. The supplementary CSR tables and figures include time-to-event analyses up to database lock, i.e., use all available information in the locked database of 06-Nov-2020. Most subjects were censored around 1 year after transplantation.

Statistical methods

Analyses of primary endpoint GFS

GFS was defined as the time between the date of transplant and the onset date of documented severe (Gr III-IV) aGvHD, or death due to any cause up to Day 180 post-transplant, whichever occurs first. Notably, for the GFS analysis chronic GVHD (cGVHD) events would not be considered as an event.

Concerning censoring,

- Subjects who, by the time of the database lock for the primary analysis were continuing in the study but did not have occurrence of severe Gr III/IV aGVHD and did not die will be censored at Day 180 for the primary analysis or, if the Day 180 CRF collection time was later than that, data were censored at latest on Day 225, the upper bound of the time window. These censoring events were tabulated "On-study" in respective summaries.
- Subjects who discontinued early from the study prior to their Day 180 post-transplant follow-up visit and did not have a severe GR III/IV aGVHD prior to discontinuing but had at least one GVHD assessment were censored at their date of last GVHD assessment prior to discontinuation from the study. These censoring events were tabulated "Off-study" in respective summaries.

Distribution of GFS was estimated using Kaplan-Meier techniques. When appropriate, the median along with 95% CI were estimated based on Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Medians could only be estimated in any treatment arm if at least 50% of subjects in that arm experience the event prior to the database lock. Survival rates at fixed time points (e.g., Day 100, at Day 180, etc.) were derived from the Kaplan-Meier estimate along with their corresponding log-log transformed 95% confidence intervals).

An estimate of the hazard ratio of events between the two arms and the corresponding two-sided, 95% CI were computed using a stratified Cox proportional model that includes treatment arm as unique covariate, stratified for age group (≤ 21 years versus > 21 years) at randomization. Ties were handled using the exact method.

Stratified log-rank test was performed to test the comparison in the GFS distributions between the two treatment arms, tested at two-sided 5% significance level.

Supportive analyses were conducted, e.g. analysis with censoring at relapse of underlying malignancy (otherwise identical to the primary analysis). The MAH's justification for this analysis was that relapse will trigger a start of change in medication that will impact the probability of aGVHD occurrence.

Consistency of the effect (HR) was assessed by various subgroups determined by demographics, disease characteristics and treatments.

<u>Analyses of key secondary endpoint cumulative Incidence of severe aGvHD</u>

Time to severe aGvHD was defined as the time between the date of transplant and the onset date of documented severe (Gr III-IV) aGvHD. Death for reasons other than severe GvHD were considered as competing risk. The censoring rules were the same as in the analysis of GFS with the exception that relapse of the underlying malignancy was considered as competing risk.

The hazard ratio and corresponding 95% confidence interval of aGVHD was estimated using the stratified Fine and Gray model. The models were fit using version 9.4 (SAS/STAT 13.1) of SAS software by specifying the 'eventcode' option and 'STRATA=' in PROC PHREG, or alternatively using the % CIF macro in SAS with the 'STRATA=' parameter. Age group was specified as stratification factor. P-value for the Wald test from the PROC PHREG was reported. Cumulative incidence rates and function plots by treatment arm were obtained from the unstratified Fine and Gray model. Cumulative incidence rates and the cumulative incidence function plots per strata were provided.

The other secondary endpoints were analysed with methods analogous to those described above. The relevant details are provided with the respective results.

Control for type I error

In order to protect the overall significance level at 0.05, a hierarchical testing procedure was specified for the treatment comparison using the primary and key secondary efficacy variable.

The results for the 7/8 MMUD Cohort are presented descriptively using estimates as per Kaplan-Meier or unstratified Fine & Gray model without covariates.

CHMP's comments

The analysis of 8/8 MUD cohort's data was prespecified as being based on Day 180 database (allowing an assessment window up to Day 225). Although the majority of acute aGvHD events are expected with the first few months, an assessment of GFS for a full year is considered necessary and is anyway available in the submission. The assessment needs to consider the possibility that after the most intense period of aGvHD during the first few months, GFS distribution may be driven by deaths not related to aGvHD and likely unrelated to whether abatacept was or was not used which will reduce the sensitivity of the study to detect an effect on GvHD as measured by GFS.

Conventional time-to-event analysis methods were used for the primary endpoint GFS. Arguably, the question could be also posed in a binary way: instead of asking how soon the problems started, one could evaluate whether severe GFS events occurred during, and whether the subject survived e.g. the full first year after the transplant. Indeed, the goal of the prophylaxis is not to postpone the inevitable severe aGvHD events but to prevent them altogether. The benefit of time-to-event methods, however, is their ability to handle incomplete follow-ups. In the current study, the analysis timings were set to ensure complete follow-up of all enrolled subjects up to the respective milestone. Given that few subjects dropped out intermittently, evaluation of simple proportions would have done little injustice to the data. Nevertheless, the proportions of subjects with GFS at, e.g., Day 365 can be descriptively compared based on the time-to-event analysis provided by the MAH. The use of time-to-events methods are ever more important in later analysis time points where subjects have variable durations of long-term follow-up.

Severe aGvHD events were analysed as the key secondary endpoint using competing risks methods. When focusing on abatacept's effect specifically on severe aGvHD prevention it is appropriate to acknowledge that death not related to severe aGvHD is a competing risk that precludes occurrence of subsequent severe aGvHD. The same is not true for the other competing risk considered: relapse of underlying malignancy. The MAH has justified this approach stating that other medications are used in case the underlying malignancy relapses which may trigger aGVHD event and withdrawal of immunosuppression. It is questionable as to whether severe aGvHD events following disease relapse no longer matter. To this end, the MAH was requested to provide an analysis of severe aGvHD incidence without considering disease relapse a competing event. In response, the MAH provided analyses of severe aGvHD incidence in which subjects were either censored or not censored on the date of relapse considering disease recurrence. The results of these analyses (see section 5.4.2) were rather consistent, and it can be concluded that censoring at the time of disease relapse did not have a great impact on the severe aGvHD results up to Day 180 visit. The same can be said about the comparison of modelling approach: whether disease relapse is treated as a competing risk, as done in the primary CSR analyses, or censored as done in the analysis provided in response to the RSI.

The MAH has plotted cumulative incidence curves over time from the Fine & Gray model sub-distribution hazard model. These plots suggest the sub-distribution hazard ratio between treatments as being constant over time in both age categories identically with the events happening at the same time in both arms. Notably, this reflects a premise of Fine & Gray model as implemented rather than observed events.

Results

Participant flow

In total, 146 subjects were enrolled into the 8/8 MUD cohort of Study 311 and randomly assigned 1:1 to abatacept or placebo treatment groups. Of these, 142 subjects were treated with study medication and transplanted; 73 received abatacept and 69 received placebo. (Table 16). Among the treated subjects, 14 (19.2%) subjects in the abatacept group and 18 (26.1%) in the placebo group discontinued treatment. The most frequent reason for discontinuation of treatment in both groups was relapse. Subject disposition post-transplant is summarised in Table 17.

Table 16 ***Subject Disposition during the Screening Period: All Enrolled Subjects in the 8/8 MUD Cohort***

	NUMBER OF SUBJECTS
SCREEN FAILURE	0
ENROLLED	146
ENROLLED BUT NEVER RANDOMIZED	0
RANDOMIZED	146
ABATACEPT	74
PLACEBO	72
RANDOMIZED BUT NOT TREATED WITH STUDY MEDICATION (A)	4
ABATACEPT	1
PLACEBO	3
RANDOMIZED AND TREATED WITH STUDY MEDICATION (B)	142
ABATACEPT	73
PLACEBO	69
RANDOMIZED, TREATED WITH STUDY MEDICATION, AND TRANSPLANTED (C)	142
ABATACEPT	73
PLACEBO	69

(A) Randomized subjects not included in the MITT population
(B) Treated population, (C) MITT population

Table 17 ***Subject Disposition during the Post-transplantation Period - 8/8 MUD Cohort MITT Analysis Population***

	Number (%) of Subjects		
	Abatacept N = 73	Placebo N = 69	Total N = 142
NUMBER OF SUBJECTS WHO DISCONTINUED TREATMENT	14 (19.2)	18 (26.1)	32 (22.5)
REASONS FOR DISCONTINUATION OF TREATMENT			
RELAPSE	12 (16.4)	15 (21.7)	27 (19.0)
REFUSAL OF FURTHER PROTOCOL THERAPY BY PATIENT/PARENT/GUARDIAN	0	1 (1.4)	1 (0.7)
COMPLETION OF PLANNED THERAPY	0	0	0
PHYSICIAN DETERMINES IT IS IN PATIENT'S BEST INTEREST	0	0	0
OTHER	2 (2.7)	2 (2.9)	4 (2.8)
NUMBER OF SUBJECTS COMPLETING DAY 180 VISIT	71 (97.3)	63 (91.3)	134 (94.4)
NUMBER OF SUBJECTS DISCONTINUED STUDY PRIOR TO THE DAY 180 VISIT	1 (1.4)	6 (8.7)	7 (4.9)
REASONS FOR DISCONTINUATION OF STUDY PRIOR TO THE DAY 180 VISIT			
DEATH	1 (1.4)	6 (8.7)	7 (4.9)
LOST TO FOLLOW-UP	0	0	0
WITHDRAWAL OF CONSENT FOR ANY FURTHER DATA SUBMISSION	0	0	0
OTHER	0	0	0
NUMBER OF SUBJECTS DISCONTINUED STUDY POST DAY 180 VISIT	9 (12.3)	5 (7.2)	14 (9.9)
REASONS FOR DISCONTINUATION OF STUDY POST DAY 180 VISIT			
DEATH	9 (12.3)	5 (7.2)	14 (9.9)
LOST TO FOLLOW-UP	0	0	0
WITHDRAWAL OF CONSENT FOR ANY FURTHER DATA SUBMISSION	0	0	0
OTHER	0	0	0

8/8 Cohort MITT Analysis Population includes all enrolled subjects in the 8/8 HLA-matched cohort randomized and transplanted who took at least 1 dose of study medication

Duration of the post-transplantation period in the 8/8 MUD cohort at the time of database lock (06 November 2020) is summarised in Table 18.

Table 18 ***Duration of the Post-transplantation Period at Database Lock: 8/8 MUD Cohort MITT Analysis Population***

	Number (%) of Subjects		
Days in the Post-transplantation Period	Abatacept N = 73	Placebo N = 69	Total N = 142
0-60	0	2 (2.9)	2 (1.4)
61-120	1 (1.4)	7 (10.1)	8 (5.6)
121-180	1 (1.4)	2 (2.9)	3 (2.1)
181-270	7 (9.6)	4 (5.8)	11 (7.7)
271-360	3 (4.1)	1 (1.4)	4 (2.8)
>360	61 (83.6)	53 (76.8)	114 (80.3)

For subjects who discontinued, duration is calculated as date of last contact (or lost to follow-up) - date of transplant + 1.

For subjects who completed the study, duration is calculated as last date of assessment - date of transplant + 1.

For subjects who are continuing in the study beyond the data collected in the database lock, duration is > 360 days.

In the 7/8 MMUD cohort, of the 46 subjects that were enrolled, 44 were treated with study medication and transplanted; 43 subjects were treated with abatacept (including 3 prior to Amendment 04) and 1 subject was randomised to the placebo group prior to Amendment 04. Among the treated subjects, 8 (18.6%) discontinued treatment; relapse was the most frequent reason for discontinuation. Disposition in the 7/8 MMUD cohort is summarised in Table 19 and Table 20.

Table 19 ***Subject Disposition during the Screening Period: All Enrolled Subjects in the 7/8 MMUD Cohort***

	NUMBER OF SUBJECTS
SCREEN FAILURE	0
ENROLLED (A)	46
ENROLLED (A) BUT NOT TREATED WITH STUDY MEDICATION (B)	2
ENROLLED (A), TREATED WITH STUDY MEDICATION AND TRANSPLANTED	44
RANDOMIZED BUT NOT TREATED WITH STUDY MEDICATION (B)	1
ABATACEPT	0
PLACEBO	1
RANDOMIZED AND TREATED WITH STUDY MEDICATION (C)	4
ABATACEPT	3
PLACEBO	1
RANDOMIZED, TREATED WITH STUDY MEDICATION, AND TRANSPLANTED	4
ABATACEPT	3
PLACEBO	1

(A) Subjects enrolled after amendment 4: all subjects were assigned to abatacept
(B) Assignment failures
(C) Subjects randomized prior to amendment 4. Subjects randomized to Abatacept and treated with study medication are included in the 7/8 HLA-Matched Cohort. Subject randomized to placebo and treated with study medication are included in the analysis with the CIBMTR cohort.

Table 20 ***Subject Disposition during the Post-transplantation Period: 7/8 MMUD Cohort Treated Analysis Population***

	Number (%) of Subjects Abatacept N = 43
NUMBER OF SUBJECTS WHO DISCONTINUED TREATMENT	8 (18.6)
REASONS FOR DISCONTINUATION OF TREATMENT	
RELAPSE	4 (9.3)
REFUSAL OF FURTHER PROTOCOL THERAPY BY PATIENT/PARENT/GUARDIAN	2 (4.7)
COMPLETION OF PLANNED THERAPY	0
PHYSICIAN DETERMINES IT IS IN PATIENT'S BEST INTEREST	0
OTHER	2 (4.7)
NUMBER OF SUBJECTS COMPLETING DAY 180 VISIT	43 (100.0)
NUMBER OF SUBJECTS DISCONTINUED STUDY PRIOR TO THE DAY 180 VISIT	0
REASONS FOR DISCONTINUATION OF STUDY PRIOR TO THE DAY 180 VISIT	
DEATH	0
LOST TO FOLLOW-UP	0
WITHDRAWAL OF CONSENT FOR ANY FURTHER DATA SUBMISSION	0
OTHER	0
NUMBER OF SUBJECTS DISCONTINUED STUDY POST DAY 180 VISIT	6 (14.0)
REASONS FOR DISCONTINUATION OF STUDY POST DAY 180 VISIT	
DEATH	6 (14.0)
LOST TO FOLLOW-UP	0
WITHDRAWAL OF CONSENT FOR ANY FURTHER DATA SUBMISSION	0
OTHER	0

The 7/8 Cohort Treated Analysis Population includes all enrolled subjects in the 7/8 HLA-matched cohort who received transplant and took at least 1 dose of Abatacept

Duration of the post-transplantation period in the 7/8 MMUD cohort at the time of database lock (06 November 2020) is summarised in Table 21.

Table 21 ***Duration of the Post-transplantation Period at Database Lock: 7/8 MMUD Cohort Treated Analysis Population***

Days in the Post-transplantation Period	Number (%) of Subjects Abatacept N = 43
0-60	0
61-120	1 (2.3)
121-180	0
181-270	1 (2.3)
271-360	3 (7.0)
>360	38 (88.4)

For subjects who discontinued, duration is calculated as date of last contact (or lost to follow-up) - date of transplant + 1.

For subjects who completed the study, duration is calculated as last date of assessment - date of transplant + 1.

For subjects who are continuing in the study beyond the data collected in the database lock, duration is > 360 days.

CHMP's comments

In the 8/8 MUD cohort, the number of deaths reported as a reason for study discontinuation until D180 was higher in the placebo group than in the abatacept group [1 (1.4%) vs. 6 (8.7%)]. On the other hand, the number of such deaths reported after D180 is higher in the abatacept group than in the placebo group [9 (12.3%) vs. 5 (7.2%)]. Relapses leading to discontinuation of treatment were slightly higher for placebo than abatacept [15 (21.7%) vs. 12 (16.4%].

In the 7/8 MMUD cohort, there were no deaths reported as a reason for study discontinuation until D180; after D180, 6 such deaths (14%) have been reported. Relapses leading to discontinuation of treatment occurred in 4 subjects (9.3%).

In their response to the 1st RSI, the MAH provided updated summaries for duration of follow-up in the post-transplantation period for Study 311. It is however unclear which data lock point has been used for the summaries; considering that median durations in the > 1400 day range are reported, whereas in the efficacy analyses, most patients were censored between 300 and 400 days, it seems likely that a DLP beyond November 2020 has been used. This should be confirmed. ***OC*** *To avoid confusion regarding potentially multiple DLPs, updated tables have currently not been inserted into the AR.*

Recruitment

For the 8/8 MUD cohort of Study 311, subjects were enrolled at 13 sites in the US and 1 site in Canada. For the 7/8 MMUD cohort, subjects were enrolled at 9 sites in the US.

Conduct of the study

The original protocol for the investigator-sponsored study was dated 12 May 2012. First patient first visit date was 15 April 2013 and the last patient last visit (LPLV) for purposes of preparation of the MAH's CSR was 17 November 2018. The clinical database lock for the MAH's CSR occurred on 06 November 2020. At the time of the initial submission, the investigator-sponsored study remained ongoing, with a planned total duration of follow-up of 5 years and LPLV expected in February 2023.

As of the 06 November 2020 database lock, there had been a total of 17 global revisions (with 17 global amendments) made into the protocol. Most of these amendments implemented changes in planned sample size, plans for interim analyses and stopping rules. In Amendment 04 (dated 09 August 2014), the formerly randomised 7/8 cohort was converted into a single arm in whom all subjects received abatacept. In this amendment, the primary endpoint was also changed from Grade III-IV to Grade II-IV aGvHD; however, in a subsequent amendment (dated 08 October 2015), a change back to the original endpoint was implemented.

According to the CSR, no important protocol deviations (defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being) occurred in the study.

CHMP's comments

The study protocol underwent several substantial changes, including a change in primary endpoint and subsequent return to the original primary endpoint and a conversion of the 7/8 cohort into a single arm. Most of the changes were related to changes in assumptions with impact on sample size, planned interim analyses and stopping rules. In total, while the changes are substantial, they appear to have been managed adequately and do not seem to adversely impact study integrity or reliability of the results.

Baseline data

In the 8/8 MUD cohort, median age was 44 years (range 6-71 years), 55% of subjects were male and 45% were female, and 87% were White. Twenty-seven (19%) randomised subjects in the 8/8 MUD cohort were 6 to 17 years old; 14 were randomised to abatacept and 13 were randomised to placebo. In the abatacept group, there were 4 subjects in the 6-11 year age range and 10 subjects in the 12-17 year age range, while in the placebo group, there were 6 subjects in the 6-11 year age range and 7 subjects in the 12-17 year age range.

The most common types of malignancy among subjects were AML (37%), ALL (30%) and MDS (19%). A large majority of subjects (84%) received tacrolimus for GvHD prophylaxis. Baseline demographic characteristics for the 8/8 MUD cohort are summarised in Table 22 and baseline disease characteristics in Table 23.

Table 22 ***Baseline Demographic Characteristics: 8/8 MUD Cohort MITT Analysis Population***

		Abatacept N = 73	Placebo N = 69	Total N = 142
AGE (YEARS)	N	73	69	142
	MEAN	40.7	39.8	40.3
	SD	19.47	20.29	19.81
	MEDIAN	44.0	40.0	43.5
	MIN	6	7	6
	MAX	71	74	74
AGE GROUP	<= 21 (PEDIATRIC)	18 (24.7)	17 (24.6)	35 (24.6)
	> 21 (ADULT)	55 (75.3)	52 (75.4)	107 (75.4)
GENDER	MALE	41 (56.2)	37 (53.6)	78 (54.9)
	FEMALE	32 (43.8)	32 (46.4)	64 (45.1)
RACE	WHITE	63 (86.3)	61 (88.4)	124 (87.3)
	BLACK OR AFRICAN AMERICAN	3 (4.1)	2 (2.9)	5 (3.5)
	AMERICAN INDIAN OR ALASKA NATIVE	1 (1.4)	0	1 (0.7)
	ASIAN	4 (5.5)	2 (2.9)	6 (4.2)
	OTHER	1 (1.4)	2 (2.9)	3 (2.1)
	UNKNOWN	1 (1.4)	2 (2.9)	3 (2.1)
ETHNICITY	HISPANIC OR LATINO	4 (5.5)	2 (2.9)	6 (4.2)
	NOT HISPANIC OR LATINO	68 (93.2)	66 (95.7)	134 (94.4)
	NOT REPORTED	1 (1.4)	1 (1.4)	2 (1.4)
WEIGHT (KG)	N	73	69	142
	MEAN	74.16	75.43	74.78
	SD	23.367	22.546	22.899
	MEDIAN	71.30	76.70	74.25
	MIN	23.1	26.3	23.1
	MAX	142.7	131.7	142.7
WEIGHT CATEGORY	20 - 30 KG	3 (4.1)	3 (4.3)	6 (4.2)
	> 30 - 40 KG	2 (2.7)	2 (2.9)	4 (2.8)
	> 40 - 50 KG	2 (2.7)	3 (4.3)	5 (3.5)
	> 50 KG	66 (90.4)	61 (88.4)	127 (89.4)
GEOGRAPHIC REGION	NORTH AMERICA	73 (100.0)	69 (100.0)	142 (100.0)
	SOUTH AMERICA	0	0	0
	EUROPE	0	0	0
	ROW	0	0	0

Abbreviations: ROW = Rest of World.

Table 23 ***Baseline Disease Characteristics: 8/8 MUD Cohort MITT Analysis Population***

	Abatacept N = 73	Placebo N = 69	Total N = 142
BASELINE SERUM IGG (G/L)			
N	69	66	135
MEAN (SD)	8.052 (3.2501)	7.783 (4.3157)	7.920 (3.7964)
MEDIAN (RANGE)	7.760 (1.11 - 17.82)	7.365 (1.28 - 30.20)	7.470 (1.11 - 30.20)
PRE-TRANSPLANT CMV (PATIENT)			
POSITIVE	44 (60.3)	36 (52.2)	80 (56.3)
NEGATIVE	27 (37.0)	31 (44.9)	58 (40.8)
INCONCLUSIVE	0	2 (2.9)	2 (1.4)
NOT REPORTED	2 (2.7)	0	2 (1.4)
PRE-TRANSPLANT CMV (DONOR)			
POSITIVE	32 (43.8)	27 (39.1)	59 (41.5)
NEGATIVE	41 (56.2)	42 (60.9)	83 (58.5)
INCONCLUSIVE	0	0	0
PRE-TRANSPLANT EBV (PATIENT)			
POSITIVE	65 (89.0)	62 (89.9)	127 (89.4)
NEGATIVE	5 (6.8)	4 (5.8)	9 (6.3)
INCONCLUSIVE	0	1 (1.4)	1 (0.7)
NOT REPORTED	3 (4.1)	2 (2.9)	5 (3.5)
PRE-TRANSPLANT EBV (DONOR)			
POSITIVE	43 (58.9)	40 (58.0)	83 (58.5)
NEGATIVE	9 (12.3)	9 (13.0)	18 (12.7)
INCONCLUSIVE	1 (1.4)	1 (1.4)	2 (1.4)
NOT TESTED	19 (26.0)	19 (27.5)	38 (26.8)
NOT REPORTED	1 (1.4)	0	1 (0.7)
TYPE OF MALIGNANCY			
ACUTE MYELOID LEUKEMIA (AML)	30 (41.1)	22 (31.9)	52 (36.6)
MYELODYSPLASTIC SYNDROME (MDS)	15 (20.5)	12 (17.4)	27 (19.0)
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)	20 (27.4)	22 (31.9)	42 (29.6)
ACUTE LEUKEMIA OF AMBIGUOUS LINEAGE (UNDIFFERENTIATED, BIPHENOTYPIC, OR BILINEAGE)	0	1 (1.4)	1 (0.7)
HODGKIN AND NON-HODGKIN LYMPHOMA	1 (1.4)	1 (1.4)	2 (1.4)
ACUTE LYMPHOBLATIC LYMPHOMA IN 2ND OR GREATER COMPLETE REMISSION	4 (5.5)	1 (1.4)	5 (3.5)
CHRONIC MYELOMONOCYTIC LEUKEMIA	1 (1.4)	4 (5.8)	5 (3.5)
ATYPICAL (BCR-ABL NEGATIVE) CHRONIC MYELOGENOUS LEUKEMIA	0	0	0
CHRONIC MYELOGENOUS LEUKEMIA	1 (1.4)	5 (7.2)	6 (4.2)
NOT REPORTED	1 (1.4)	1 (1.4)	2 (1.4)
GVHD PROPHYLAXIS			
CYCLOSPORINE	11 (15.1)	11 (15.9)	22 (15.5)
TACROLIMUS	62 (84.9)	58 (84.1)	120 (84.5)
PERFORMANCE SCORE			
N	73	69	142
MEAN (SD)	89.2 (7.02)	90.1 (7.17)	89.6 (7.09)
MEDIAN (RANGE)	90.0 (80 - 100)	90.0 (80 - 100)	90.0 (80 - 100)
TYPE OF GRAFT RECEIVED			
BONE MARROW (BM)	33 (45.2)	26 (37.7)	59 (41.5)
CYTOKINE MOBILIZED PERIPHERAL BLOOD (PBSC)	40 (54.8)	43 (62.3)	83 (58.5)
CYTOKINE MOBILIZED BONE MARROW (CMBM)	0	0	0
CONDITIONING REGIMEN			
TBI AND CHEMOTHERAPY	20 (27.4)	26 (37.7)	46 (32.4)
BUSULFAN AND CYCLOPHOSPHAMIDE	28 (38.4)	21 (30.4)	49 (34.5)
BUSULFAN AND FLUDARABINE	7 (9.6)	2 (2.9)	9 (6.3)
MELPHALAN AND FLUDARABINE	18 (24.7)	20 (29.0)	38 (26.8)

In the 7/8 MMUD cohort, median age was 38 years (range 6-76 years), 63% of subjects were male and 37% were female; 72% were White and 16% were Black. In the 7/8 MMUD cohort, 16 (37%) randomised subjects were 6 to 17 years old; 8 subjects each were in the 6-11 year and 12-17 year age ranges.

The most common types of malignancy among subjects were AML (35%), MDS (26%) and ALL (19%). Also in this cohort, the majority of subjects (63%) received tacrolimus for GvHD prophylaxis. Baseline demographic characteristics for the 7/8 MMUD cohort are summarised in Table 24 and baseline disease characteristics in Table 25.

Table 24 ***Baseline Demographic Characteristics: 7/8 MMUD Cohort Treated Analysis Population***

		Abatacept N = 43
AGE (YEARS)	N	43
	MEAN	35.7
	SD	22.87
	MEDIAN	38.0
	MIN	6
	MAX	76
AGE GROUP	<= 21 (PEDIATRIC)	18 (41.9)
	> 21 (ADULT)	25 (58.1)
GENDER	MALE	27 (62.8)
	FEMALE	16 (37.2)
RACE	WHITE	31 (72.1)
	BLACK OR AFRICAN AMERICAN	7 (16.3)
	AMERICAN INDIAN OR ALASKA NATIVE	1 (2.3)
	ASIAN	2 (4.7)
	OTHER	0
	UNKNOWN	2 (4.7)

Table 25 ***Baseline Disease Characteristics: 7/8 MMUD Cohort Treated Analysis Population***

	Abatacept N = 43
PRE-TRANSPLANT CMV (PATIENT)	
POSITIVE	28 (65.1)
NEGATIVE	15 (34.9)
INCONCLUSIVE	0
PRE-TRANSPLANT CMV (DONOR)	
POSITIVE	20 (46.5)
NEGATIVE	23 (53.5)
INCONCLUSIVE	0
PRE-TRANSPLANT EBV (PATIENT)	
POSITIVE	39 (90.7)
NEGATIVE	4 (9.3)
INCONCLUSIVE	0
PRE-TRANSPLANT EBV (DONOR)	
POSITIVE	15 (34.9)
NEGATIVE	6 (14.0)
INCONCLUSIVE	2 (4.7)
NOT TESTED	20 (46.5)
TYPE OF MALIGNANCY AS COLLECTED IN CRF	
ACUTE MYELOID LEUKEMIA (AML)	15 (34.9)
MYELODYSPLASTIC SYNDROME (MDS)	11 (25.6)
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)	8 (18.6)
ACUTE LEUKEMIA OF AMBIGUOUS LINEAGE (UNDIFFERENTIATED, BIPHENOTYPIC, OR BILINEAGE)	1 (2.3)
HODGKIN AND NON-HODGKIN LYMPHOMA	1 (2.3)
ACUTE LYMPHOBLATIC LYMPHOMA IN 2ND OR GREATER COMPLETE REMISSION	1 (2.3)
CHRONIC MYELOMONOCYTIC LEUKEMIA	1 (2.3)
ATYPICAL (BCR-ABL NEGATIVE) CHRONIC MYELOGENOUS LEUKEMIA	0
CHRONIC MYELOGENOUS LEUKEMIA	4 (9.3)
NOT REPORTED	1 (2.3)
TYPE OF MALIGNANCY AS COLLECTED IN CIBMTR DATABASE	
ACUTE MYELOID LEUKEMIA (AML)	16 (37.2)
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)	9 (20.9)
CHRONIC MYELOID LEUKEMIA (CML)	4 (9.3)
MYELODYSPLASTIC SYNDROME (MDS)	12 (27.9)
HODGKIN'S LYMPHOMA (HL)	1 (2.3)
NOT REPORTED	1 (2.3)
DISEASE STATUS AS COLLECTED IN CIBMTR DATABASE	
EARLY	26 (60.5)
INTERMEDIATE	9 (20.9)
ADVANCED	6 (14.0)
HODGKIN'S LYMPHOMA (HL) - CHEMOSENSITIVE	1 (2.3)
NOT REPORTED	1 (2.3)
GVHD PROPHYLAXIS	
CYCLOSPORINE	16 (37.2)
TACROLIMUS	27 (62.8)
PERFORMANCE SCORE(%)	
90 - 100	30 (69.8)
< 90	12 (27.9)
NOT REPORTED	1 (2.3)
TYPE OF GRAFT RECEIVED	
BONE MARROW (BM)	21 (48.8)
CYTOKINE MOBILIZED PERIPHERAL BLOOD (PBSC)	22 (51.2)
CYTOKINE MOBILIZED BONE MARROW (CMBM)	0
PERIPHERAL BLOOD	0
CONDITIONING REGIMEN	
TBI AND CHEMOTHERAPY	11 (25.6)
TBI AND CYCLOPHOSPHAMIDE	0
BUSULFAN AND CYCLOPHOSPHAMIDE	13 (30.2)
BUSULFAN AND FLUDARABINE	8 (18.6)
MELPHALAN AND FLUDARABINE	11 (25.6)
OTHER	0

CHMP's comments

In the 8/8 MUD cohort, median age was 44 years, both genders were approximately equally represented, and a large majority of subjects (87%) were White. In the 7/8 MMUD cohort, median age was 38 years and the proportion of males was 63%. While White subjects also accounted for 72% of total in the 7/8 MMUD cohort, a higher proportion of subjects were Black (16%, vs. 4% in the 8/8 MUD cohort).

The spectrum of diseases serving as the indication for aHSCT can be considered overall representative as compared to current treatment strategies. The majority of patients received a myeloablative conditioning regimen. As regards the CNI component of the GvHD prophylaxis regimen, a majority of subjects in both cohorts received TAC; this seems to reflect a practice that differs from EU, where CsA is the more commonly used CNI.

Numbers analysed

All treated subjects received the treatment to which they were randomised, and efficacy and safety data from all subjects were analysed according to the treatment group assignment in accordance with the randomization schedule. Analysis populations are summarised in Table 26.

Table 26 ***Analysis Populations for Study 311***

	Number of Subjects		
Population	**Abatacept**	**Placebo**	**Total**
8/8 Cohort Modified Intent-to-treat (MITT) analysis population	73	69	142
8/8 Cohort Per-protocol (PP) analysis population	73	69	142
As-treated analysis population	8/8 Cohort: 73 7/8 Cohort: 43	69 NA	142
Immunogenicity analysis population	8/8 Cohort: 73 7/8 Cohort: 41	NA	
Evaluable PK analysis population	8/8 Cohort: 72 7/8 Cohort: 42	NA	

Outcomes and estimation

Results for 8/8 MUD cohort

A tabular overall summary of efficacy results for the 8/8 MUD cohort in Study 311 is displayed in Table 27.

Table 27 ***Summary of Efficacy: 8/8 MUD Cohort MITT Analysis Population***

	8/8 MUD Cohort MITT Analysis Population	
Efficacy Parameters	**Abatacept (N =73)**	**Placebo (N = 69)**
Gr III-IV aGvHD-Free Survival		
Events, n (%)	10 (13.7)	17 (24.6)
Survival Rate[a] (95% CI)		
Day 100	0.92 (0.83, 0.96)	0.83 (0.71, 0.90)
Day 180	0.89 (0.79, 0.94)	0.77 (0.65, 0.85)
HR[b] (95% CI)	0.54 (0.25, 1.19; P-value = 0.1223[c])	
Sensitivity analysis		
GFS rate		
Day 180	93.0%	80.0%
HR (95% CI)	0.34 (0.12, 0.96); P-value = 0.0324	
Gr III-IV aGvHD-Free Survival (Based on date of aGvHD Diagnosis)		
Events, n (%)	10 (13.7)	17 (24.6)
Survival Rate[a] (95% CI)		
Day 100	0.93 (0.84, 0.97)	0.84 (0.73, 0.91)
Day 180	0.89 (0.79, 0.94)	0.77 (0.65, 0.85)
HR[b] (95% CI)	0.54 (0.25, 1.19; p = 0.1231)[c]	
Gr III-IV Severe aGvHD - Cumulative Incidence Rate		
Cumulative Incidence Rate (95% CI)		
≤ 21 years of age		
Day 100	0.05 (0.02, 0.15)	0.12 (0.04, 0.36)
Day 180	0.05 (0.02, 0.15)	0.12 (0.04, 0.36)
> 21 years of age		
Day 100	0.07 (0.03, 0.18)	0.17 (0.10, 0.30)
Day 180	0.07 (0.03, 0.18)	0.17 (0.10, 0.30)
HR (95% CI)	0.41 (0.14, 1.16); P-value = 0.0942[d]	
Gr II-IV aGvHD-Free Survival		
Events, n (%)	36 (49.3)	47 (68.1)
Median Time to GFS Event (days)[a]	NE (59.00, NE)	48 (34.00, 91.00)

Efficacy Parameters	8/8 MUD Cohort MITT Analysis Population Abatacept (N =73)	 Placebo (N = 69)
(95% CI)		
Survival Rate (95% CI)[a]		
Day 100	0.56 (0.44, 0.67)	0.36 (0.25, 0.47)
Day 180	0.50 (0.38, 0.61)	0.33 (0.22, 0.44)
HR[b] (95% CI)	0.55 (0.36, 0.86); P-value = 0.0069[c]	
Gr II-IV aGvHD Free Survival (Based on Date of aGvHD Diagnosis)		
Events, n (%)	36 (49.3)	47 (68.1)
Median Time to GFS Event (days) (95%CI)[a]	181.00 (72.00, NE)	55 (36.00, 99.00)
Survival Rate (95% CI)[a]		
Day 100	0.58 (0.45, 0.68)	0.38 (0.26, 0.49)
Day 180	0.52 (0.40, 0.63)	0.33 (0.22, 0.44)
HR[b] (95% CI)	0.54 (0.35, 0.84); p = 0.0052[c]	
Overall Survival		
Deaths, n (%) (Up to Day 180)	5 (6.8)	13 (18.8)
HR[b] (95% CI)	0.33 (0.12, 0.93); P-value = 0.0281[c]	
Deaths, n (%) (up to last contact prior to DBL)	24 (32.9)	29 (42.0)
Survival Rate[a] (95% CI)		
Day 100 (95% CI), %	0.99 (0.91, 1.00)	0.93 (0.83, 0.97)
Day 180 (95% CI), %	0.97 (0.89, 0.99)	0.84 (0.73, 0.91)
Day 365 (95% CI), %	0.84 (0.73, 0.90)	0.77 (0.65, 0.85)
Disease-Free Survival		
Relapse or Death, n (%)	10 (13.7)	19 (27.5)
HR (95% CI)[b]	0.46 (0.21, 0.99); P-value= 0.0408[c]	
Survival Rate[a](95% CI)		
Day 100 (95% CI), %	0.93 (0.84, 0.97)	0.87 (0.76, 0.93)
Day 180 (95% CI), %	0.88 (0.78, 0.93)	0.77 (0.65, 0.85)
Transplant Related Mortality		
Cumulative Incidence Rate (95% CI)		

Efficacy Parameters	8/8 MUD Cohort MITT Analysis Population	
	Abatacept (N =73)	Placebo (N = 69)
Day 100	< 0.01 (< 0.01,0.04)	0.05 (0.02,0.14)
Day 180	0.01 (< 0.01,0.06)	0.10 (0.05,0.22)
HR (95% CI)[d]	0.11 (0.01,0.87); P-value = 0.0359[d]	

[a] Based on Kaplan-Meier estimates

[b] Cox proportional hazards model stratified by age group at randomization (<=21 years versus > 21 years) with treatment as the only covariate. Hazard ratio is abatacept over placebo.

[c] Log-Rank test stratified by age group at randomization (<=21 years versus > 21 years).

[d] Wald confidence interval and P-value are presented

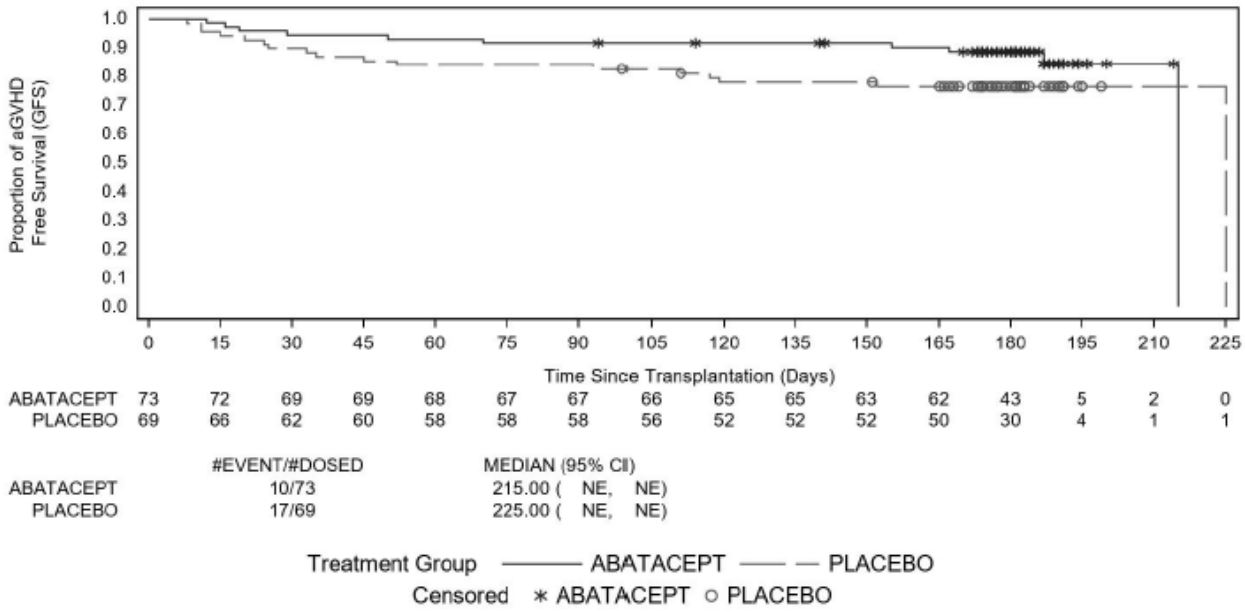
Primary efficacy endpoint: Severe (Gr III-IV) GFS up to Day 180

In 8/8 MUD cohort MITT subjects, the severe (Gr III-IV) GFS rate for abatacept vs. placebo was 89% vs. 77%, HR: 0.54 [95% CI: 0.25, 1.19]. The associated P-value was 0.1223 and thus not statistically significant at the 0.05 level. The Kaplan-Meier plot is shown in Figure 21. The results of a post-hoc analysis of severe (Gr III-IV) GFS based on the date of aGvHD diagnosis were consistent with those of the pre-specified analysis.

In a pre-specified sensitivity analysis where subjects were censored at the time of relapse, severe GFS rate up to Day 180 in the 8/8 MUD cohort was numerically higher in the abatacept group compared with the placebo group (93% vs. 80.0%; HR: 0.34 [95% CI: 0.12, 0.96]; P = 0.0324; not part of the hierarchical testing strategy).

At Day 180, 84.9% of abatacept and 75.4% of placebo subjects were on-study. One subject (1.4%) in the abatacept group was lost to follow up after relapse and was alive at Day 180. Of the 10 events in the abatacept group, 6 (8.2%) were severe Gr III-V aGvHD and 4 (5.5%) were death. Of the 17 events in the placebo group, 11 (15.9%) were severe Gr III-V aGvHD and 6 (8.7%) were death.

Figure 21 ***Kaplan Meier Plot of Gr III-IV GFS up to Day 180 Visit: 8/8 MUD Cohort MITT Analysis Population***



Symbols represent censored observation.
Due to high censoring percentage, median estimator in both treatment groups may be misleading.

Longer-term analysis: Severe (Gr III-IV) GFS up to database lock

When analysed with data until database lock, the severe (Gr III-IV) GFS rate at Day 365 was 72% for both abatacept and placebo. At database lock, the proportion of subjects with a severe (Gr III-IV) GFS event was 41% for abatacept and 45% for placebo, and the HR estimate for severe (Gr III-IV) GFS for abatacept vs. placebo was 0.80 (0.48, 1.34). The analysis is summarised in Table 28 and the Kaplan-Meier plot is shown in Figure 22.

Table 28 ***Severe Grade III/IV aGvHD Free Survival (GFS) up to Database Lock: 8/8 Cohort MITT Analysis Population***

Endpoints	Abatacept n / N (%)	Placebo n / N (%)	Hazard Ratio Estimate (B)	Estimate 95% CI	p-values Log-Rank Test (C)
GFS EVENT	30/73 (41.1%)	31/69 (44.9%)	0.80	0.48, 1.34	0.3928
MEDIAN TIME TO GFS EVENT (DAYS) (A)	958.00	511.00			
95% CI OF MEDIAN TIME	(654.00, 1014.00)	(412.00, 680.00)			
SURVIVAL RATE (A) (95% CI)					
DAY 100	0.86 (0.76, 0.92)	0.81 (0.70, 0.89)			
DAY 180	0.82 (0.71, 0.89)	0.75 (0.63, 0.84)			
DAY 365	0.72 (0.60, 0.81)	0.72 (0.60, 0.81)			

n = Number of subjects with GFS event (Grade III/IV aGvHD or death), N = Total number of subjects in the Treatment Group.

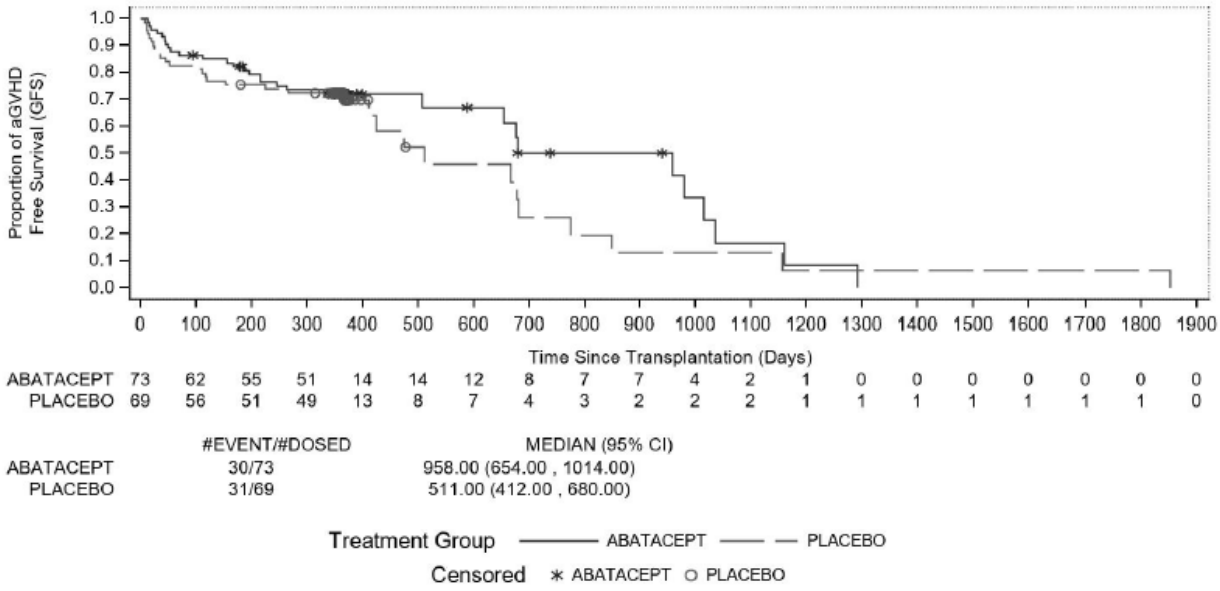
(A) Based on Kaplan-Meier estimates

(B) Cox proportional hazards model stratified by age group at randomization (<=21 years versus > 21 years) with treatment as the only covariate. Hazard ratio is Abatacept over placebo.

(C) Log-Rank test stratified by age group at randomization (<=21 years versus > 21 years).

Due to high censoring percentage, median estimator in both treatment groups may be misleading.

Figure 22 ***Kaplan Meier Plot of Gr III-IV GFS up to Database Lock: 8/8 MUD Cohort MITT Analysis Population***



Symbols represent censored observation

Due to high censoring percentage, median estimator in both treatment groups may be misleading.

CHMP's comments

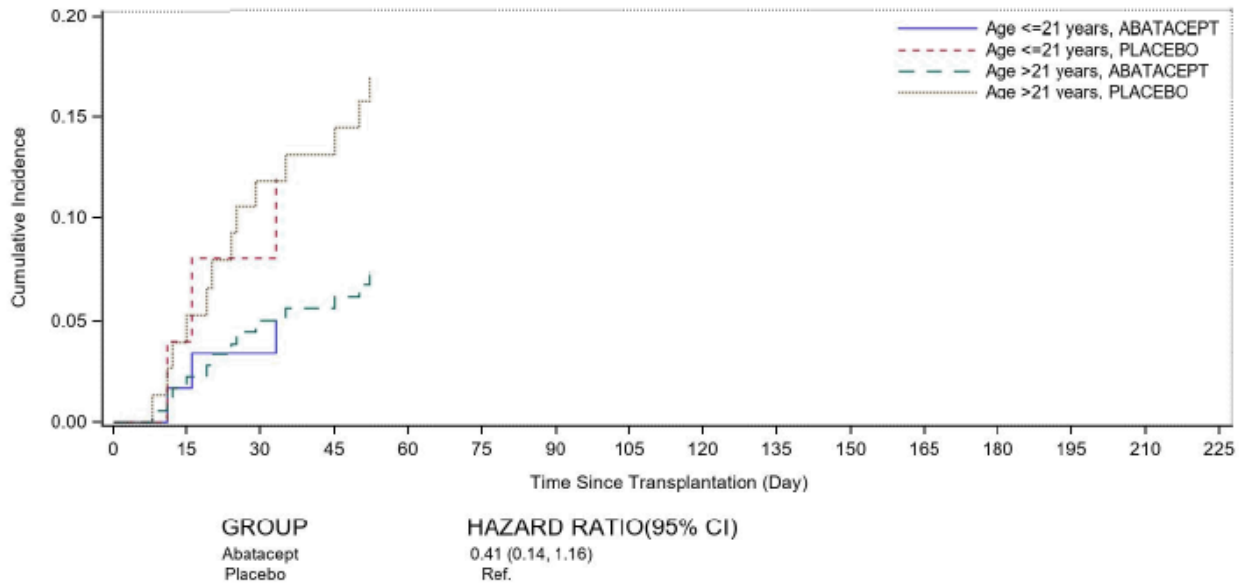
In the 8/8 MUD cohort, the primary endpoint was severe (Gr III-IV) GFS at Day 180. The survival rate was higher for abatacept than placebo (89% vs. 77%), but the difference was not statistically significant. The study thus formally failed on its primary endpoint, demoting the subsequent analysis in the hierarchical testing scheme (cumulative incidence of severe (Gr III-IV) aGvHD up to Day 180) as an exploratory analysis. Analyses for other endpoints were conducted outside of a Type I error -controlled framework.

The database was complete for the comparison of GFS through Day 365. By then, the Kaplan-Meier estimated GFS rate equated 0.72 in both treatment arms, although the HR estimate was 0.80 (0.48, 1.34) due to the events having occurred sooner in the placebo arm. Thus, in addition to the primary analysis formally failing, there appears to be a decrease in treatment effect over time. This seems concerning, and the MAH was requested to further discuss the implications of the observations.

Key secondary efficacy endpoint: Cumulative incidence of severe (Gr III-IV) aGvHD up to Day 180

Up to Day 180, the cumulative incidence of severe aGvHD (stratified by age group at randomisation) for the abatacept group compared to the placebo group was: ≤ 21 years: 5% vs 12%; > 21 years: 7% vs 17%; HR: 0.41 (95% CI: 0.14, 1.16), P = 0.0942. A graphical representation is displayed in Figure 23.

Figure 23 ***Cumulative Incidence Rate of Severe aGvHD up to Day 180 Using a Competing Risk Analysis: 8/8 Cohort MITT Analysis Population***



The cumulative incidence function is estimated using the Fine and Gray sub-distribution hazard model stratified by age.
group at randomization (<= 21 years, > 21 years) with treatment as covariate.
Event of interest includes severe (Gr III-IV) aGVHD up to Day 180 Visit.
Competing events include death not related to severe (Gr III-IV) aGVHD and relapse of the disease.

Using unstratified competing risk analysis (the competing risks were non-aGvHD -related death and relapse), the cumulative incidence of severe aGvHD up to Day 180 visit was 7% for abatacept and 16% for placebo; HR: 0.41 (95% CI 0.14, 1.17)(Table 29).

In response to the RSI, related analyses were provided where disease relapse was not considered as competing risk: the analysis was provided with or without censoring of severe aGvHD assessment on the date of relapse. Up to Day 180, 1 additional severe aGvHD event post disease relapse was considered in abatacept arm (as occurring post disease relapse) and contributed to change of HR (95% CI) from 0.40 (0.14, 1.15) to 0.49 (0.18, 1.31).

Table 29 ***Cumulative Incidence of Severe aGvHD up to Day 180 Visit Using Unstratified Competing Risk Analysis: 8/8 Cohort MITT Analysis Population***

Treatment	N	Time Point	Number of Event of Interest	Number of Competing Event	Number of Censor	Cumulative Incidence (95% CI)	Hazard Ratio (95% CI) (A)	P-value (A)
ABATACEPT	73	DAY 100	5	5	1	0.07 (0.03, 0.15)	0.41 (0.14, 1.17)	0.0964
		DAY 140	5	7	1	0.07 (0.03, 0.15)		
		DAY 180	5	8	23	0.07 (0.03, 0.15)		
		DAY 225	5	9	59	0.07 (0.03, 0.15)		
PLACEBO	69	DAY 100	11	5	1	0.16 (0.09, 0.28)		
		DAY 140	11	6	2	0.16 (0.09, 0.28)		
		DAY 180	11	9	21	0.16 (0.09, 0.28)		
		DAY 225	11	12	46	0.16 (0.09, 0.28)		

Unstratified Fine and Gray model with treatment as covariate. Hazard ratio is Abatacept over Placebo.

(A) Wald confidence interval and P-value are presented.

Event of interest includes severe (grade III/IV) acute GvHD up to Day 180 Visit.

Competing events include death not related to severe (grade III/IV) acute GvHD and relapse of the disease.

In additional analyses of early onset (before Day 100) and late onset (after Day 100) aGvHD (in which the events of interest included Gr I-IV aGvHD and death related to aGvHD), the cumulative incidence of early onset moderate/severe aGvHD was numerically lower in the abatacept group compared to the placebo group, whereas the opposite was true for late onset aGvHD. By Day 365, 7 of 26 patients at risk in the abatacept group vs. 0 of 14 patients at risk in the placebo group had developed late-onset (after Day 100) aGvHD. Of the 7 events in the abatacept group, 3 were Grade III-IV.

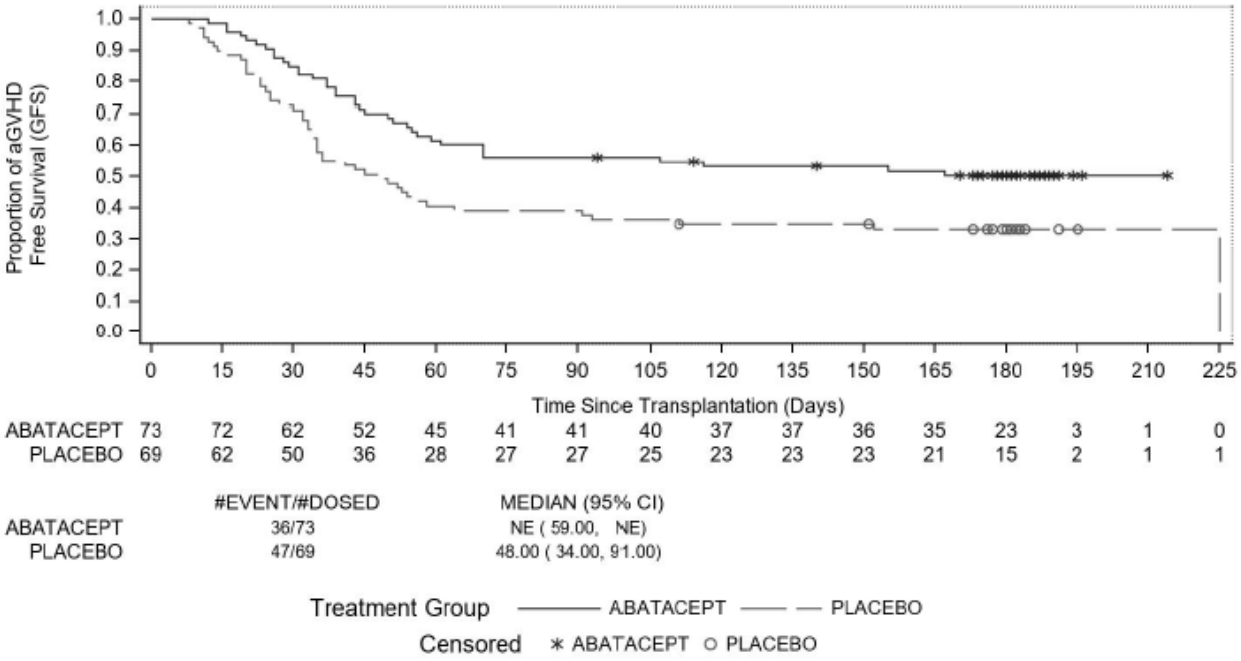
CHMP's comments

The cumulative incidence analysis of severe (Gr III-IV) aGvHD shows aGvHD events occurring quite soon after transplant (all events occurring by D100), whereas competing events cumulate more gradually. Even on a nominal level of testing, the difference between treatment groups on this pre-specified key secondary endpoint was not statistically significant.

Secondary efficacy endpoints: Moderate to severe (Gr II-IV) GFS

Up to Day 180, the moderate-to-severe (Gr II-IV) GFS rate was 50% for abatacept vs. 33% for placebo (HR: 0.55 (95% CI: 0.36, 0.86); nominal P = 0.0069). The corresponding Kaplan-Meier curve is shown in Figure 24.

Figure 24 ***Kaplan Meier Plot of Grade II-IV GFS up to Day 180 Visit – 8/8 Cohort MITT Analysis Population***



Symbols represent censored observation.
NE: Not Estimable.

CHMP's comments

At Day 180, the rate of Grade II-IV GFS was higher with abatacept than placebo. However, while this is in itself reassuring, Grade II aGvHD is mostly manageable, and the importance of the finding should be balanced against the finding of no significant difference in Grade III-IV GFS.

Secondary efficacy endpoints: Overall survival

Up to Day 180 visit, 5 (6.8%) subjects in the abatacept group and 13 (18.8%) subjects in the placebo group had died. The OS HR for abatacept vs placebo was 0.33 (95% CI: 0.12, 0.93), stratified log-rank test P = 0.0281 (nominal).

When analysed with data until database lock, there were 24 (32.9%) and 29 (42.0%) deaths reported in abatacept and placebo groups, respectively. The OS rates were higher for abatacept compared to placebo at Day 180 (97% vs 84%) and at Day 365 (84% vs 77%). The OS HR for abatacept vs. placebo (using all the data available in the 06- Nov-2020 database lock) was 0.81 (95% CI: 0.46, 1.42), stratified log-rank test P = 0.4610. In this dataset, 67.1% and 58.0% of subjects in the abatacept and placebo groups, respectively, were censored at their last contact date available in the database, with "on-study" as the reason for censoring, i.e., continuing the study and censored administratively.

The analysis is summarised in Table 30 and the Kaplan-Meier curve is shown in Figure 25.

Table 30 ***Summary of Overall Survival up to Database Lock: 8/8 Cohort MITT Analysis Population***

Endpoints	Abatacept n / N (%)	Placebo n / N (%)	Hazard Ratio Estimate (B)	Estimate 95% CI	P-value Log-Rank Test (C)
OS	24/ 73 (32.9%)	29/ 69 (42.0%)	0.81	0.46, 1.42	0.4610
MEDIAN TIME TO DEATH (DAYS) (A)	958.00	677.00			
95% CI OF MEDIAN TIME	(676.00, 1034.00)	(475.00, 1157.00)			
SURVIVAL RATE (A) (95% CI)					
DAY 100	0.99 (0.91, 1.00)	0.93 (0.83, 0.97)			
DAY 180	0.97 (0.89, 0.99)	0.84 (0.73, 0.91)			
DAY 365	0.84 (0.73, 0.90)	0.77 (0.65, 0.85)			

n = Number of subjects who have died, N = Total number of subjects in the Treatment Group.

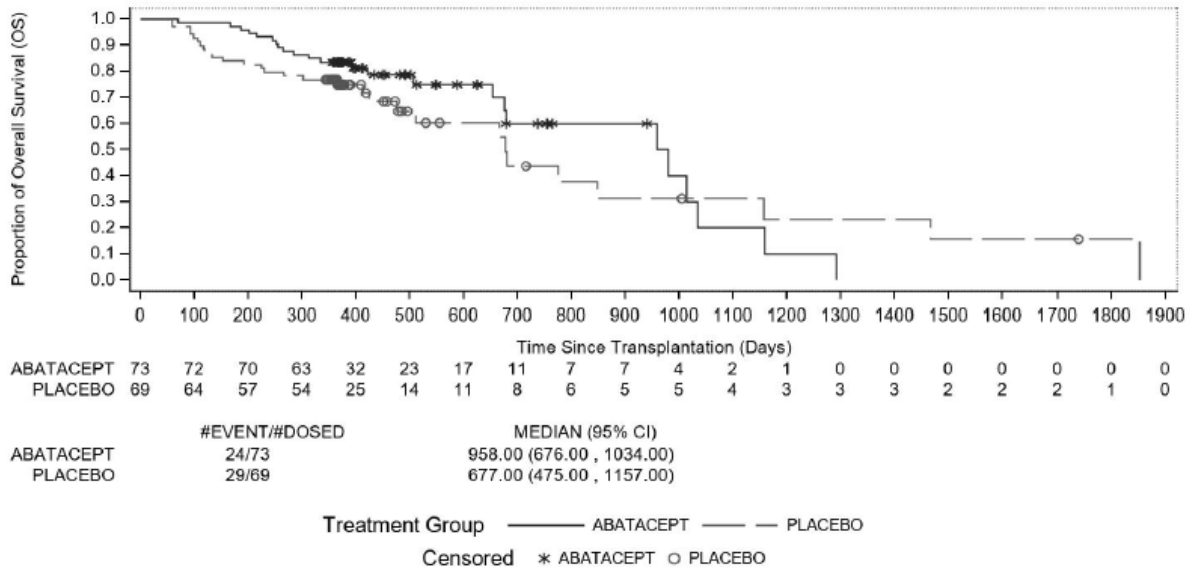
(A) Based on Kaplan-Meier estimates

(B) Cox proportional hazards model stratified by age group at randomization (<=21 years versus > 21 years) with treatment as the only covariate. Hazard ratio is Abatacept over placebo.

(C) Log-Rank test stratified by age group at randomization (<=21 years versus > 21 years).

Due to high censoring percentage, median estimator in both treatment groups may be misleading.

Figure 25 ***Kaplan Meier Plot of Overall Survival up to Database Lock: 8/8 MUD Cohort MITT Analysis Population***



Symbols represent censored observation

Due to high censoring percentage, median estimator in both treatment groups may be misleading.

CHMP's comments

In the analysis of OS until Day 180, a numerical advantage was seen for abatacept over placebo. Although a small numerical OS advantage favouring abatacept remains at Day 365, the HR at Day 365 is much closer to 1 than at Day 180. Most subjects remain censored in the final analysis. The results provide little direct evidence that abatacept improves survival through the first year after transplant. However, subjects in this population may die for the underlying malignancy, which is unlikely related to abatacept. In order to contextualise the attenuated difference in OS between the arms, the MAH was requested to present a tabular summary and discuss the reasons for deaths and to provide updated long-term results based on the longest feasible follow-up. While various survival analyses were discussed in the MAH's response to the RSI, tabular summaries of reasons for death were not provided, and the request is thereby reiterated. ***OC***

Secondary efficacy endpoints: Disease-free survival, transplant-related mortality and relapse

Up to Day 180, 13.7% of subjects in the abatacept group and 27.5% subjects in the placebo group had relapsed or died. The DFS HR for abatacept vs. placebo was 0.46 (95% CI: 0.21, 0.99), stratified log-rank test P = 0.0408 (nominal).

When analysed with data until database lock, the DFS rate at Day 365 was 79% for abatacept and 65% for placebo. At database lock, the number and proportion of subjects who had relapsed or died was 29/73 (40%) for abatacept and 31/69 (45%) for placebo, and the HR estimate for DFS for abatacept vs. placebo was 0.81 (0.48, 1.35). The analysis is summarised in Table 31 and the Kaplan-Meier plot is shown in Figure 26.

Table 31 ***Disease Free Survival up to Database Lock: 8/8 Cohort MITT Analysis Population***

Endpoints	Abatacept n / N (%)	Placebo n / N (%)	Hazard Ratio Estimate (B)	Estimate 95% CI	P-value Log-Rank Test (C)
RELAPSE OR DEATH	29/ 73 (39.7%)	31/ 69 (44.9%)	0.81	0.48, 1.35	0.4139
MEDIAN TIME TO RELAPSE OR DEATH (DAYS) (A)	679.00	569.00			
95% CI OF MEDIAN TIME	(588.00, 980.00)	(425.00, 1157.00)			
SURVIVAL RATE (A) (95% CI)					
DAY 100	0.93 (0.84, 0.97)	0.87 (0.76, 0.93)			
DAY 180	0.88 (0.78, 0.93)	0.77 (0.65, 0.85)			
DAY 365	0.79 (0.68, 0.87)	0.65 (0.53, 0.75)			

n = Number of subjects with relapse or death, N = Total number of subjects in the Treatment Group.

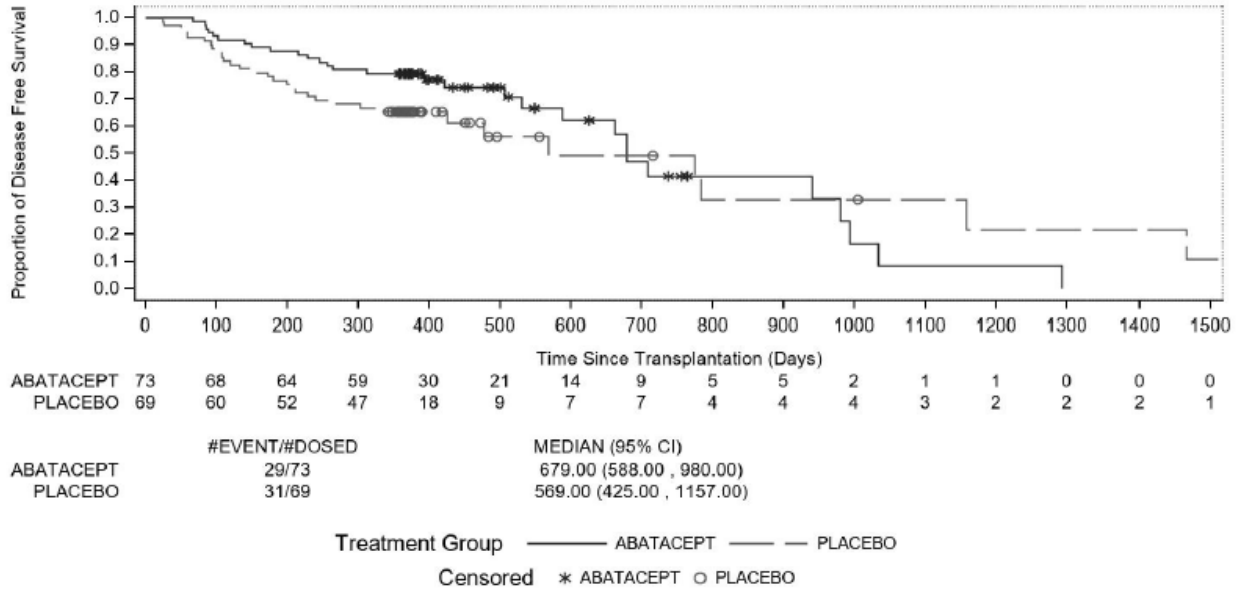
(A) Based on Kaplan-Meier estimates

(B) Cox proportional hazards model stratified by age group at randomization (<=21 years versus > 21 years) with treatment as the only covariate. Hazard ratio is Abatacept over placebo.

(C) Log-Rank test stratified by age group at randomization (<=21 years versus > 21 years).

Due to high censoring percentage, median estimator in both treatment groups may be misleading.

Figure 26 ***Kaplan Meier Plot of Disease Free Survival up to Database Lock: 8/8 MUD Cohort MITT Analysis Population***



Symbols represent censored observation

Due to high censoring percentage, median estimator in both treatment groups may be misleading.

Up to Day 180 visit, the cumulative incidence rates of TRM were 1% for abatacept and 10% for placebo; HR = 0.11 (95% CI: 0.01, 0.87), P = 0.0359 (nominal).

An unstratified competing risk analysis, in which the event of interest was transplant-related death prior to relapse, and the competing events were relapse and death due to other (non-transplant) causes without a prior relapse, was performed in the dataset with all data until database lock. In this analysis, the cumulative incidence of TRM at Day 365 was 9% for abatacept and 12% for placebo; the overall HR was 0.72 (95% CI 0.35, 1.49)(Table 32).

Table 32 ***Cumulative Incidence of Transplant Related Mortality up to Database Lock Using Unstratified Competing Risk Analysis: 8/8 Cohort MITT Analysis Population***

Treatment	N	Time Point	Number of Event of Interest	Number of Competing Event	Number of Censor	Cumulative Incidence (95% CI)	Hazard Ratio (95% CI) (A)	P-value (A)
ABATACEPT	73	DAY 100	0	5	0	0.02 (0.01,0.05)	0.72 (0.35,1.49)	0.3719
		DAY 140	0	7	0	0.04 (0.02,0.08)		
		DAY 180	0	9	0	0.05 (0.03,0.08)		
		DAY 225	1	9	0	0.05 (0.03,0.10)		
		DAY 365	5	10	7	0.09 (0.05,0.17)		
		DAY 547	8	11	37	0.15 (0.09,0.26)		
PLACEBO	69	DAY 100	4	5	0	0.03 (0.01,0.10)		
		DAY 140	7	6	0	0.06 (0.02,0.15)		
		DAY 180	8	8	0	0.07 (0.03,0.16)		
		DAY 225	8	11	0	0.07 (0.03,0.16)		
		DAY 365	10	14	12	0.12 (0.07,0.23)		
		DAY 547	11	15	34	0.20 (0.12,0.33)		

Unstratified Fine and Gray model with treatment as covariate. Hazard ratio is Abatacept over Placebo.

(A) Wald confidence interval and P-value are presented.

Event of interest includes transplant-related death prior to relapse

Competing events include relapse and death due to other (non-transplant) causes without a prior relapse.

A similar unstratified competing risk analysis was performed for relapse. In the dataset with all data until database lock, the cumulative incidence of relapse at Day 365 was 16% for abatacept and 18% for placebo, and the overall HR was 0.87 (95% CI 0.45, 1.68)(Table 33).

Table 33 ***Cumulative Incidence of Relapse up to Database Lock Using Unstratified Competing Risk Analysis: 8/8 Cohort MITT Analysis Population***

Treatment	N	Time Point	Number of Event of Interest	Number of Competing Event	Number of Censor	Cumulative Incidence (95% CI)	Hazard Ratio (95% CI) (A)	P-value (A)
ABATACEPT	73	DAY 100	5	0	0	0.07 (0.03,0.13)	0.87 (0.45,1.68)	0.6714
		DAY 140	7	0	0	0.09 (0.04,0.16)		
		DAY 180	9	0	0	0.11 (0.06,0.20)		
		DAY 225	9	1	0	0.13 (0.08,0.21)		
		DAY 365	10	5	7	0.16 (0.11,0.23)		
		DAY 547	11	8	37	0.20 (0.13,0.31)		
PLACEBO	69	DAY 100	5	4	0	0.08 (0.04,0.15)		
		DAY 140	6	7	0	0.10 (0.06,0.17)		
		DAY 180	8	8	0	0.13 (0.08,0.21)		
		DAY 225	11	8	0	0.15 (0.09,0.24)		
		DAY 365	14	10	12	0.18 (0.11,0.28)		
		DAY 547	15	11	34	0.22 (0.14,0.36)		

Unstratified Fine and Gray model with treatment as covariate. Hazard ratio is Abatacept over Placebo.

(A) Wald confidence interval and P-value are presented.

Events of interest include relapse of underlying malignancy or death due to underlying malignancy complications.

Competing event includes death due to other causes.

CHMP's comments

There was no apparent difference in incidence of relapse of underlying malignancy. On the one hand, the numerically better result suggests that abatacept did not negatively modify the effect of transplant while, on the other hand, the small difference in favour of abatacept might have inflated the result of GFS if there were, perhaps by chance, higher mortality in the placebo arm related to underlying disease.

Secondary efficacy endpoint: Cumulative incidence of cGvHD up to database lock

Using unstratified competing risk analysis (the event of interest being cGhVD and competing risks including death and relapse of underlying malignancy), the cumulative incidence of cGvHD up to Day 365 was 49% for abatacept and 43% for placebo Table 34.

Table 34 ***Cumulative Incidence of cGvHD up to Database Lock Using Unstratified Competing Risk Analysis: 8/8 Cohort MITT Analysis Population***

Treatment	N	Time Point	Number of Event of Interest	Number of Competing Event	Number of Censor	Cumulative Incidence (95% CI)	Hazard Ratio (95% CI) (A)	P-value (A)
ABATACEPT	73	DAY 100	0	5	1	<0.01 (<0.01, 0.05)	1.19 (0.73, 1.94)	0.4835
		DAY 140	3	7	1	0.06 (0.03, 0.12)		
		DAY 180	10	9	1	0.15 (0.10, 0.24)		
		DAY 225	18	10	1	0.29 (0.22, 0.39)		
		DAY 365	36	14	10	0.49 (0.40, 0.61)		
		DAY 547	36	16	18	0.49 (0.40, 0.61)		
PLACEBO	69	DAY 100	1	9	0	<0.01 (<0.01, 0.05)		
		DAY 140	5	13	0	0.05 (0.02, 0.12)		
		DAY 180	10	16	0	0.13 (0.08, 0.20)		
		DAY 225	21	19	0	0.25 (0.17, 0.37)		
		DAY 365	29	22	8	0.43 (0.33, 0.57)		
		DAY 547	29	23	16	0.43 (0.33, 0.57)		

Unstratified Fine and Gray model with treatment as covariate. Hazard ratio is Abatacept over Placebo.

(A) Wald confidence interval and P-value are presented.

Event of interest includes chronic GvHD.

Competing events include death and relapse of underlying malignancy.

CHMP's comments

The incidence of cGvHD was substantial in both groups and slightly higher with abatacept than placebo. However, no analyses concerning e.g. the severity of cGvHD have been provided, and it remains unclear whether the slight increase in cGvHD with abatacept could be associated with clinically relevant detrimental effects. The MAH was requested to address this finding as part of the overall discussion regarding expected clinical benefit.

In their response, the MAH acknowledged the lack of effect on cGvHD and ascribed this to the short treatment course. To address this question, the MAH indicated that an investigator-sponsored study is currently underway to evaluate a longer course of treatment with abatacept.

Results for 7/8 MMUD cohort

A tabular overall summary of efficacy results for the 7/8 MMUD cohort in Study 311 is displayed in Table 35.

Table 35 ***Summary of Efficacy: 7/8 MMUD Cohort Treated Analysis Population***

Efficacy Parameters	Abatacept (N = 43)
Gr III-IV aGvHD-Free Survival	
Events, n (%)	2 (4.7)
Survival Rate[a] (95% CI)	
Day 100	0.98 (0.85, 1.00)
Day 180	0.98 (0.85, 1.00)
Gr III-IV aGvHD Free Survival (Based on Date of aGvHD Diagnosis)	
Events, n (%)	2 (4.7)
Survival Rate[a] (95% CI)	
Day 100	0.98 (0.85, 1.00)
Day 180	0.98 (0.85, 1.00)
Gr III-IV Severe aGvHD - Cumulative Incidence Rate	
Cumulative Incidence Rate (95% CI)[b]	
Day 100	0.02 (< 0.01, 0.11)
Day 180	0.02 (< 0.01, 0.11)
Gr II-IV aGvHD-Free Survival	
Events, n (%)	19 (44.2)
Survival Rate[a] (95% CI)	
Day 100	0.58 (0.42, 0.71)
Day 180	0.58 (0.42, 0.71)
Gr II-IV aGvHD-Free Survival (Based on date of aGvHD Diagnosis)	
Events, n (%)	19 (44.2)
Survival Rate[a] (95% CI)	
Day 100	0.58 (0.42, 0.71)
Day 180	0.58 (0.42, 0.71)
Overall Survival (up to last contact prior to DBL)	
Deaths, n (%) (up to Day 180 visit)	2 (4.7)
Deaths, n (%) (up to last contact prior to DBL)	12 (27.9)
Survival Rate[a] (95% CI)	
Day 180	0.98 (0.85, 1.00)
Day 365	0.88 (0.74, 0.95)

Efficacy Parameters	Abatacept (N = 43)
Disease-Free Survival	
Relapse or Death, n (%)	5 (11.6)
Survival Rate[a] (95% CI)	
Day 100 (95% CI), %	0.98 (0.85, 1.00)
Day 180 (95% CI), %	0.91 (0.77, 0.96)
Transplant-related Mortality	
Cumulative Incidence Rate (95% CI)[b]	
Day 100	0.00 (NA , NA)
Day 180	0.02 (< 0.01 , 0.11)

[a] Based on Kaplan-Meier estimates

[b] Cumulative incidence estimates based on unstratified Gray's model

Primary efficacy endpoint: Severe (Gr III-IV) GFS up to Day 180

In the 7/8 MMUD cohort Treated Analysis Population, the severe (Gr III-IV) GFS rate up to Day 180 was 98% [95% CI: 85%, 100%]. At Day 180, 41 (95.3%) of the subjects were on-study. There were 2 GFS events, 1 (2.3%) severe (Gr III-IV) aGvHD and 1 (2.3%) death.

Longer-term analysis: Severe (Gr III-IV) GFS up to database lock

When analysed with data until database lock, the severe (Gr III-IV) GFS rate at Day 365 was 88%. At database lock, there were 12/43 subjects (28%) with a severe (Gr III-IV) GFS event. The analysis is summarised in Table 36 and the Kaplan-Meier plot is shown in Figure 27.

Table 36 ***Severe Grade III/IV aGvHD Free Survival (GFS) up to Database Lock: 7/8 MMUD Cohort Treated Analysis Population***

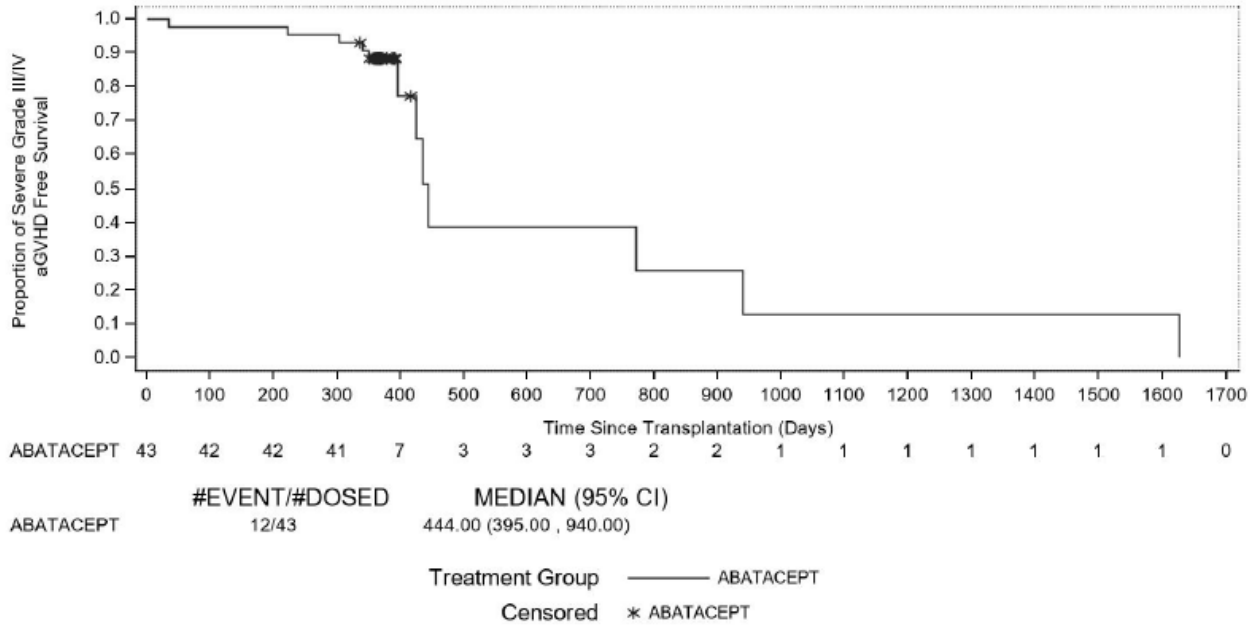
Endpoints	Abatacept n / N (%)
GFS EVENT	12/43 (27.9%)
MEDIAN TIME TO GFS EVENT (DAYS) (A)	444.00
95% CI OF MEDIAN TIME	(395.00 , 940.00)
SURVIVAL RATE (A) (95% CI)	
DAY 100	0.98 (0.85, 1.00)
DAY 180	0.98 (0.85, 1.00)
DAY 365	0.88 (0.74, 0.95)

n = Number of subjects with GFS event (Grade III/IV aGvHD or death), N = Total number of subjects in the Treatment Group.

(A) Based on Kaplan-Meier estimates

Due to high censoring percentage, median estimator in both treatment groups may be misleading.

Figure 27 ***Kaplan Meier Plot of Gr III-IV GFS up to Database Lock: 7/8 MMUD Cohort Treated Analysis Population***



Symbols represent censored observation.

Due to high censoring percentage, median estimator in Abatacept group may be misleading.

CHMP's comments

The results at Day 180 in this small cohort are strikingly positive. It is not immediately clear why results in the 7/8 cohort clearly outperform those observed in the 8/8 cohort. Although the GFS rate decreases over time (from 98% at Day 180 to 88% at Day 365), the GFS rate of 88% remains far greater than the corresponding rate (72%) in the 8/8 cohort. Owing to the small sample size and as indicated by the nominal confidence intervals, the results are not entirely incompatible with the prior expectation that there would be lower risk of GFS events in the 8/8 MUD population than in the 7/8 MMUD population treated with abatacept. While the results of the 7/8 MMUD cohort may be considered a priori as the most accurate way of estimating respective results in the target population (with no consideration of the 8/8 MUD cohort), the difference between the 7/8 and 8/8 cohorts suggests that random chance may have given results that are better than the eventual outcomes to be expected, on average, in the target population. The MAH was requested to discuss the plausibility and rationale for these findings as part of the general discussion concerning clinical benefit.

Key secondary efficacy endpoint: Cumulative incidence of severe (Gr III-IV) aGvHD

In the 7/8 MMUD cohort Treated Analysis Population, the cumulative incidence of severe (Gr III-IV) aGVHD up to Day 180 was 2% (95% CI: < 1%, 11%).

Using a competing risk analysis (the competing risks were non-aGvHD -related death and relapse), the cumulative incidence of severe aGvHD up to Day 180 visit was 2% (95% CI <0.01, 0.11)(Table 37).

Table 37 ***Cumulative Incidence of Severe aGvHD up to Day 180 Visit Using a Competing Risk Analysis: 7/8 MMUD Cohort Treated Analysis Population***

Treatment	N	Time Point	Number of Event of Interest	Number of Competing Event	Number of Censor	Cumulative Incidence (95% CI) (A)
ABATACEPT	43	DAY 100	1	1	0	0.02 (<0.01, 0.11)
		DAY 140	1	2	0	0.02 (<0.01, 0.11)
		DAY 180	1	3	14	0.02 (<0.01, 0.11)
		DAY 225	1	3	39	0.02 (<0.01, 0.11)

Event of interest includes severe (grade III/IV) acute GvHD up to Day 180 Visit.

Competing events include death not related to severe (grade III/IV) acute GvHD and relapse of the disease.

(A) Cumulative incidence estimates based on unstratified Gray's model.

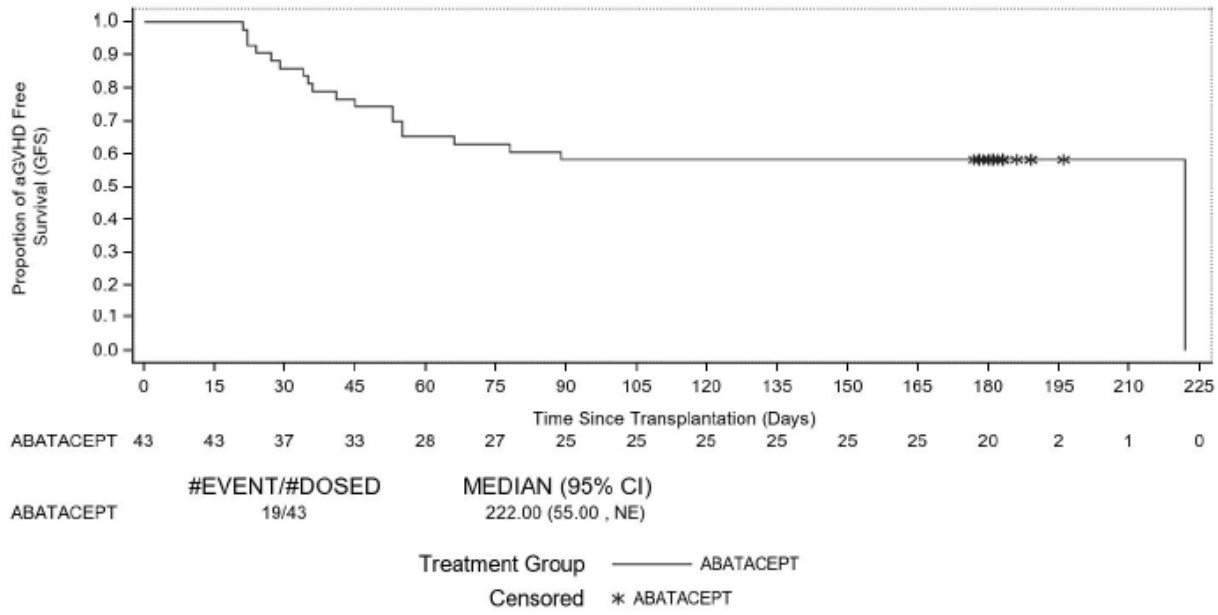
In response to the RSI, a related analysis was provided where disease relapse was not considered as a competing risk: the analysis was provided with or without censoring of severe aGvHD assessment on the date of relapse. Up to Day 180, no additional severe aGvHD events post disease relapse were seen.

In an additional analysis of late onset (after Day 100) aGvHD (in which the events of interest included Gr I-IV aGvHD and death related to aGvHD), there were 2 events of interest at Day 180 and 3 events of interest at Day 365 among 16 patients at risk, with 1 and 2 events, respectively, in the Grade III-IV category.

Secondary efficacy endpoints: Moderate to severe (Gr II-IV) GFS

In the 7/8 MMUD cohort Treated Analysis Population, the moderate-severe (Gr II-IV) GFS rate up to Day 180 was 58% (95% CI: 42%, 71%). The corresponding Kaplan-Meier curve is shown in Figure 28.

Figure 28 ***Kaplan Meier Plot of Grade II-IV GFS up to Day 180 Visit – 7/8 MMUD Cohort Treated Analysis Population***



Symbols represent censored observation.
NE: Not Estimable.
Due to high censoring percentage, median estimator in Abatacept group may be misleading.

Secondary efficacy endpoints: Overall survival

Up to Day 180 visit, 2 (4.7%) abatacept-treated subjects in the 7/8 MMUD cohort Treated Analysis Population had died. The OS rate at Day 180 was 98% (95% CI: 85, 100).

When analysed with data until database lock, 12 (27.9 %) deaths had been reported. The OS rate at Day 365 was 88% (95% CI: 74%, 95%). In this dataset, 31 (72.1%) subjects were on-study and censored at their last contact date.

The analysis is summarised in Table 38 and the Kaplan-Meier curve is shown in Figure 29.

Table 38 ***Summary of Overall Survival up to Database Lock: 7/8 MMUD Cohort Treated Analysis Population***

Endpoints	Abatacept n / N (%)
OS	12/43 (27.9%)
MEDIAN TIME TO DEATH (DAYS) (A)	940.00
95% CI OF MEDIAN TIME	(771.00 , NE)
SURVIVAL RATE (A) (95% CI)	
DAY 100	1.00
DAY 180	0.98 (0.85, 1.00)
DAY 365	0.88 (0.74, 0.95)

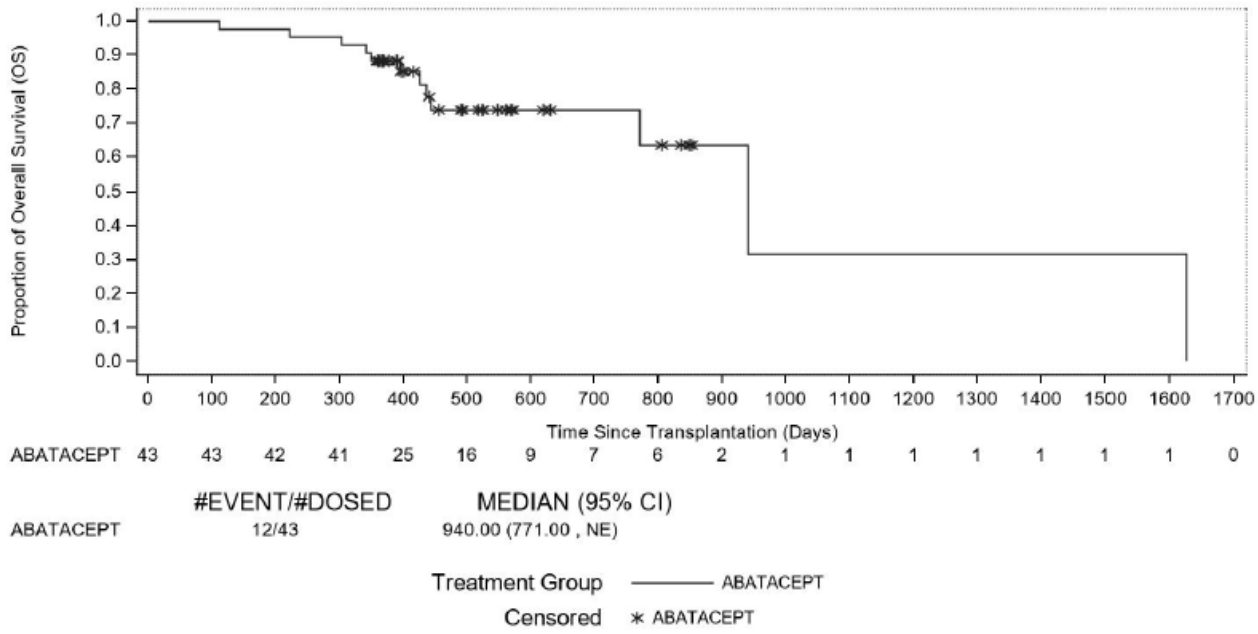
n = Number of subjects who have died, N = Total number of subjects in the Treatment Group.

(A) Based on Kaplan-Meier estimates.

NE: Not Estimable.

Due to high censoring percentage, median estimator in Abatacept group may be misleading.

Figure 29 ***Kaplan Meier Plot of Overall Survival up to Database Lock: 7/8 MMUD Cohort Treated Analysis Population***



Symbols represent censored observation

Due to high censoring percentage, median estimator in Abatacept group may be misleading.

CHMP's comments

Results on overall survival paralleled the GFS results, with a very high 98% survival rate at Day 180 decreasing to 88% at Day 365. Similar to the 8/8 cohort, the MAH was requested to present a summary and discuss the reasons for deaths.

Secondary efficacy endpoints: Disease-free survival, transplant-related mortality and relapse

Up to Day 180 visit, 11.6% of subjects had relapsed or died. The DFS rate at Day 180 was 91% (95% CI: 77%, 96%).

When analysed with data until database lock, the DFS rate at Day 365 was 81%. At database lock, the number and proportion of subjects who had relapsed or died was 13/43 (30%). The analysis is summarised in Table 39 and the Kaplan-Meier plot is shown in Figure 30.

Table 39 ***Disease Free Survival up to Database Lock: 7/8 MMUD Cohort Treated Analysis Population***

Endpoints	Abatacept n / N (%)
RELAPSE OR DEATH	13/43 (30.2%)
MEDIAN TIME TO RELAPSE OR DEATH (DAYS) (A)	940.00
95% CI OF MEDIAN TIME	(771.00 , NE)
SURVIVAL RATE (A) (95% CI)	
DAY 100	0.98 (0.85, 1.00)
DAY 180	0.91 (0.77, 0.96)
DAY 365	0.81 (0.66, 0.90)

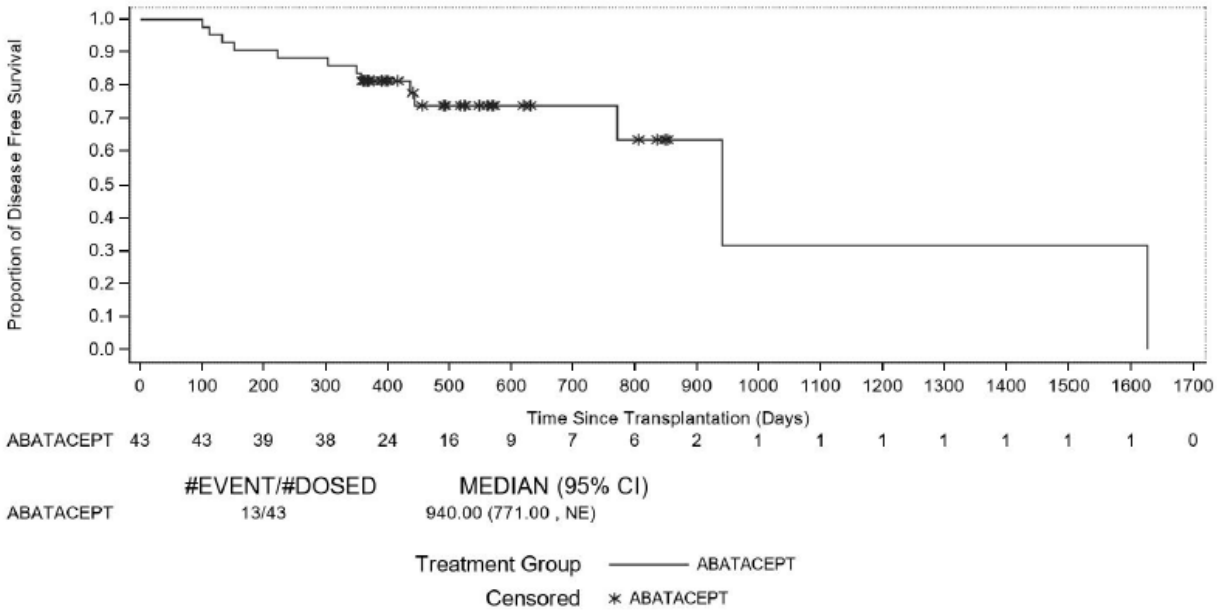
n = Number of subjects with relapse or death, N = Total number of subjects in the Treatment Group.

(A) Based on Kaplan-Meier estimates.

NE: Not Estimable.

Due to high censoring percentage, median estimator in Abatacept group may be misleading.

Figure 30 ***Kaplan Meier Plot of Disease Free Survival up to Database Lock: 7/8 MMUD Cohort Treated Analysis Population***



Symbols represent censored observation.

Due to high censoring percentage, median estimator in Abatacept group may be misleading.

Up to Day 180 visit, the cumulative incidence of TRM was 2% (95% CI: < 1%, 11%).

A competing risk analysis, in which the event of interest was transplant-related death prior to relapse, and the competing events were relapse and death due to other (non-transplant) causes without a prior relapse, was performed in the dataset with all data until database lock. In this analysis, the cumulative incidence of TRM at Day 365 was 9% (95% CI 3%, 20%)(Table 40).

Table 40 ***Cumulative Incidence of Transplant Related Mortality up to Database Lock Using a Competing Risk Analysis: 7/8 MMUD Cohort Treated Analysis Population***

Treatment	N	Time Point	Number of Event of Interest	Number of Competing Event	Number of Censor	Cumulative Incidence (95% CI) (A)
ABATACEPT	43	DAY 100	0	1	0	0.00 (NA , NA)
		DAY 140	1	2	0	0.02 (<0.01 , 0.11)
		DAY 180	1	3	0	0.02 (<0.01 , 0.11)
		DAY 225	2	3	0	0.05 (<0.01 , 0.14)
		DAY 365	4	4	3	0.09 (0.03 , 0.20)
		DAY 547	6	4	20	0.17 (0.06 , 0.32)

Event of interest includes transplant-related death prior to relapse.

Competing events include relapse and death due to other (non-transplant) causes without a prior relapse.

(A) Cumulative incidence estimates based on unstratified Gray's model.

NA: Not Applicable.

A similar competing risk analysis was performed for relapse. In the dataset with all data until database lock, the cumulative incidence of relapse at Day 365 was 9% Table 41.

Table 41 ***Cumulative Incidence of Relapse up to Database Lock Using a Competing Risk Analysis: 7/8 MMUD Cohort Treated Analysis Population***

Treatment	N	Time Point	Number of Event of Interest	Number of Competing Event	Number of Censor	Cumulative Incidence (95% CI) (A)
ABATACEPT	43	DAY 100	1	0	0	0.02 (<0.01 , 0.11)
		DAY 140	2	1	0	0.05 (<0.01 , 0.14)
		DAY 180	3	1	0	0.07 (0.02 , 0.17)
		DAY 225	3	2	0	0.07 (0.02 , 0.17)
		DAY 365	4	4	3	0.09 (0.03 , 0.20)
		~~DAY 547~~	~~4~~	~~6~~	~~20~~	~~0.09 (0.03 , 0.20)~~

Events of interest include relapse of underlying malignancy or death due to underlying malignancy complications.

Competing event includes death due to other causes.

(A) Cumulative incidence estimates based on unstratified Gray's model.

Secondary efficacy endpoint: Cumulative incidence of cGvHD up to database lock

Using competing risk analysis (the event of interest being cGhVD and competing risks including death and relapse of underlying malignancy), the cumulative incidence of cGvHD up to Day 365 was 63% (Table 42).

Table 42 ***Cumulative Incidence of cGvHD up to Database Lock Using a Competing Risk Analysis: 7/8 MMUD Cohort Treated Analysis Population***

Treatment	N	Time Point	Number of Event of Interest	Number of Competing Event	Number of Censor	Cumulative Incidence (95% CI) (A)
ABATACEPT	43	DAY 100	1	1	0	0.02 (<0.01 , 0.11)
		DAY 140	2	3	0	0.05 (<0.01 , 0.14)
		DAY 180	9	4	0	0.21 (0.10 , 0.34)
		DAY 225	15	4	0	0.35 (0.21 , 0.49)
		DAY 365	27	5	4	0.63 (0.46 , 0.76)
		DAY 547	27	5	11	0.63 (0.46 , 0.76)

Event of interest includes chronic GvHD.

Competing events include death and relapse of underlying malignancy.

(A) Cumulative incidence estimates based on unstratified Gray's model.

CHMP's comments

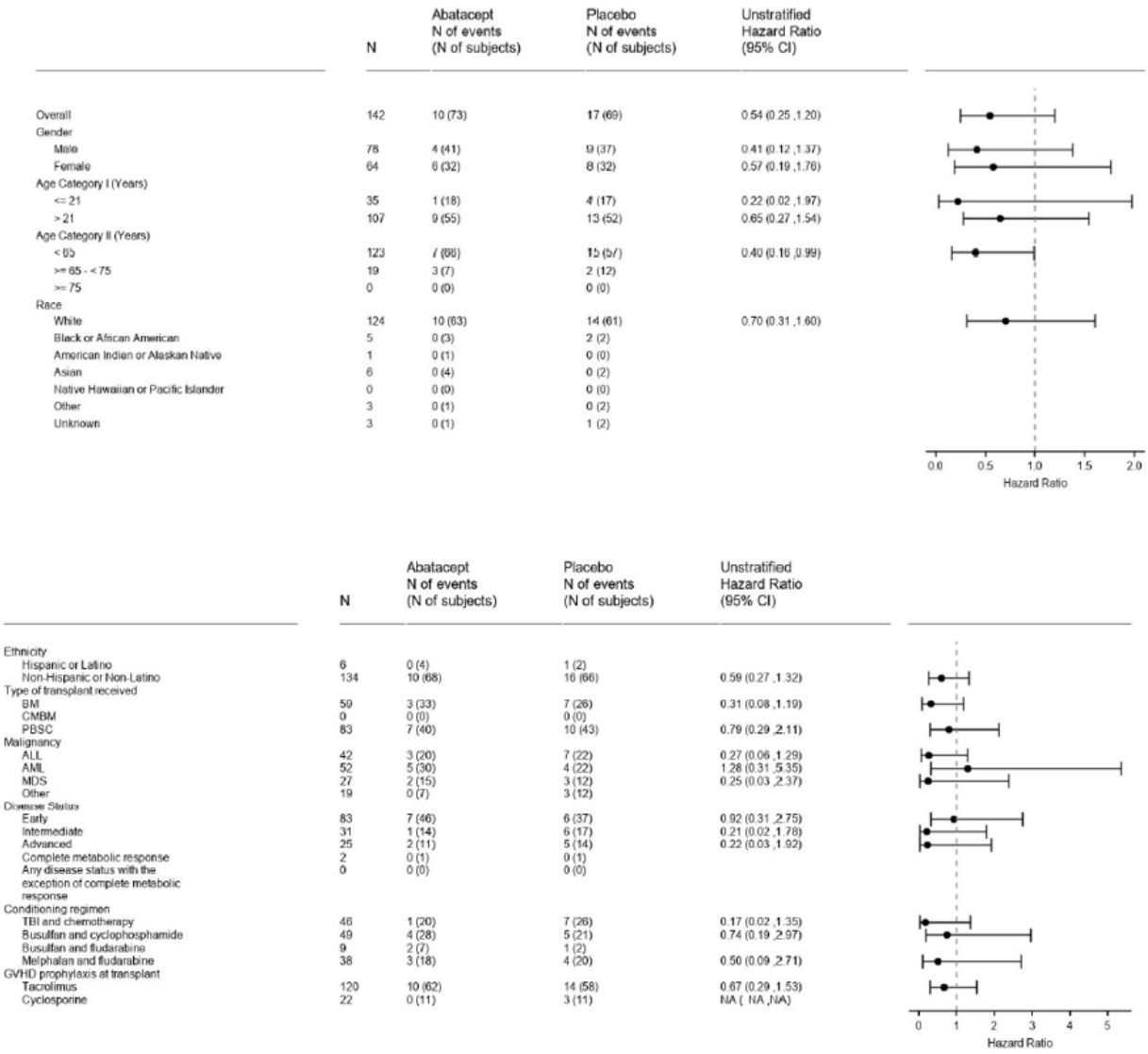
Chronic GvHD is the only endpoint in which the outcome is clearly inferior in the 7/8 MMUD cohort compared to abatacept-treated patients in the 8/8 MUD cohort. At Day 365, the cumulative incidence of cGvHD is estimated at 49% in the 8/8 cohort and 63% in the 7/8 cohort.

Ancillary analyses

Analysis of (Gr III-IV) GFS by subgroups in the 8/8 MUD cohort

An analysis of (Gr III-IV) GFS at Day 180 by subgroups is shown in Figure 31.

Figure 31 ***Grade III-IV GFS in Subsets During the Day 180 Analysis Period: 8/8 MUD Cohort MITT Analysis Population***



Unstratified Cox proportional hazards model, with treatment as covariate. Hazard ratio is Abatacept over placebo.
Hazard ratios are not computed for subgroups with less than 10 subjects in any treatment group.
Error bars represent 95% confidence intervals for the hazard ratio. Estimation of Hazard Ratio is Not Applicable (NA).

CHMP's comments

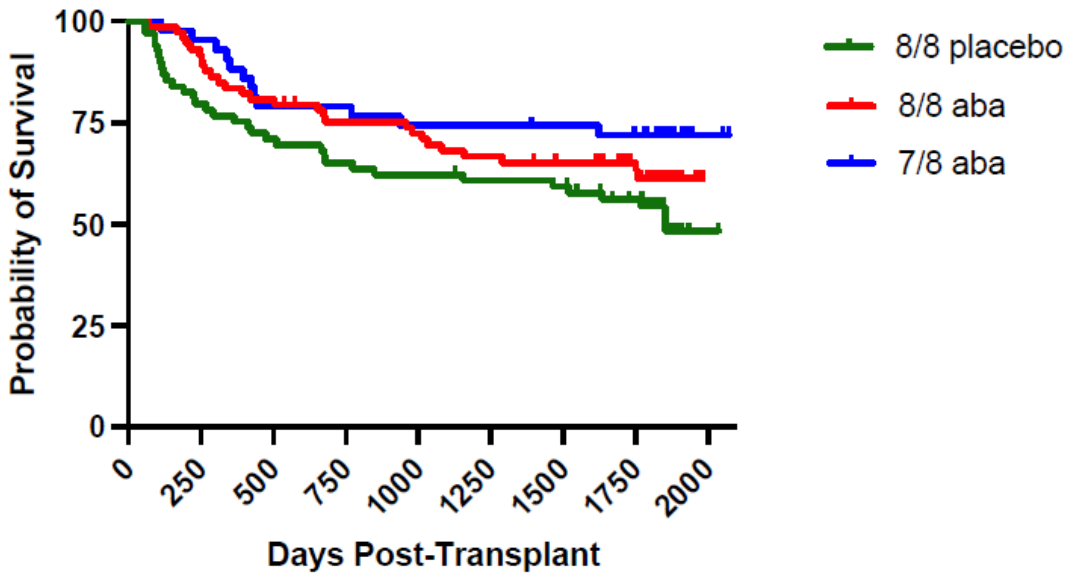
No striking aberrations were seen in subgroup analyses based on demographic and baseline characteristics. For patients with early disease, the HR was 0.92, and in patients with AML, the HR was 1.28. Due to the small number of subjects receiving CsA as the CNI component of the prophylaxis regimen, a HR could not be calculated in this subgroup.

5-year outcomes data provided in the MAH's response to the 1st RSI

In their response to the 1st RSI, the MAH indicated that 5-year outcomes data had become available to the MAH in June 2023. In the response, the MAH has provided graphs depicting OS and RFS results over 5 years of follow-up post transplant; these are displayed in Figure 32 and Table 43 for OS, and in Figure

33 for RFS. According to the MAH, while rates of cGvHD were not lower in the abatacept cohorts, these did not negate the early benefits associated with lower rates of aGvHD.

Figure 32 ***5-year OS Between ABA2 (Study 311) Strata***

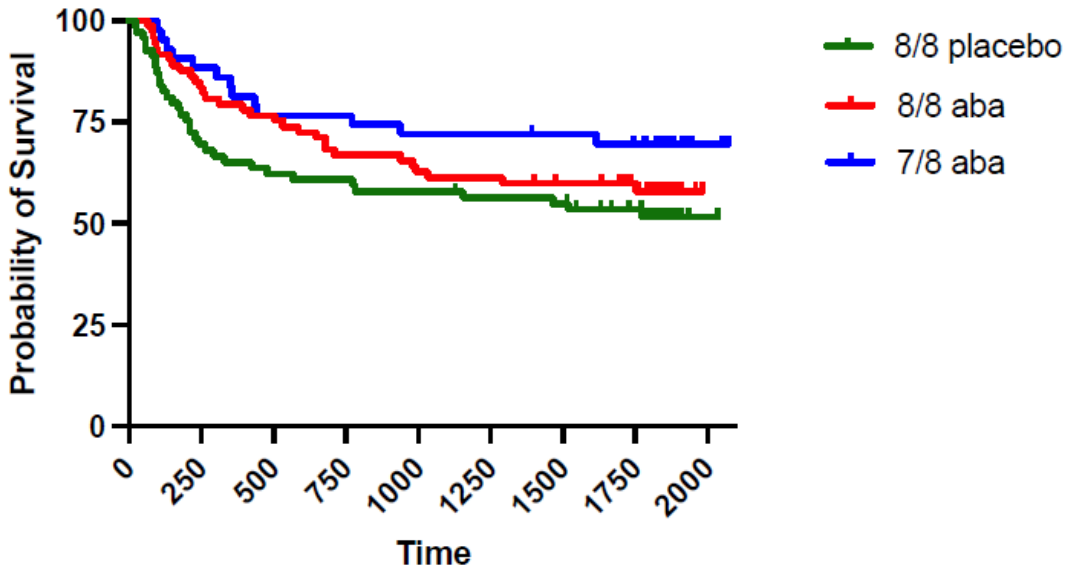


	8/8 placebo	8/8 aba	7/8 aba
# censored subjects	37	46	31
# deaths/events	32	27	12

Table 43 ***OS for the 5-year Timeframe in IM101311***

Group	N	# Deaths	# Alive	OS %
Pbo	69	32	37	53%
Aba 8/8	73	27	46	63%
Aba 7/8	43	12	31	72%

Figure 33 ***5-year RFS Between ABA2 (Study 311) Strata***



	8/8 placebo	8/8 aba	7/8 aba
# censored subjects	36	43	30
# deaths/events	33	30	13

At present, no other data, or materials supporting the graphical data outputs displayed above, have been provided for assessment.

CHMP's comments

In the initial assessment, a concern was raised regarding a potentially decreasing effect over time, as in the 8/8 cohort, the difference vs placebo seemed to decrease from Day 180 to Day 365. Moreover, a relative increase in the occurrence of cGvHD could not be ruled out.

The dataset for the initial assessment stemmed from a database lock of November 2020, at which time most subjects in long-term analyses were censored between 300 and 400 days of follow-up. The MAH has now gained access to data for the full 5 years of follow-up, and an initial snapshot has been provided for OS and RFS. The available data appear to show that on the OS and RFS level, a net benefit vs. placebo in the 8/8 cohort is maintained until 5 years, and that overall, the best results are still seen in the 7/8 cohort. Notably however, no results have been provided for frequency or severity of cGvHD.

The newly provided data are considered very useful in principle and could be used to mitigate the initially raised concerns. However, in the CHMP's opinion, the nature and quality of the information provided in the MAH's response is not adequate for purposes of regulatory decision-making. As pointed out in the introduction to clinical efficacy, the assessment has been based on the MAH's SAP and does not take into account or consider separate analyses by the Investigators or results published in scientific articles; the same standard should apply to follow-up information that has a significant bearing on final assessment of benefit-risk. A formal MO is therefore raised in terms of the quality and regulatory suitability of the newly available data, and the MAH is expected to complete this process and provide adequate documentation for these new data, including long-term data on the frequency and severity of cGvHD, before they can be formally considered in the assessment and a determination of benefit-risk duly completed. ***MO***

4.4.2.2. Study IM101841

The title of Study IM101841 was "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 International Blood and Marrow Transplant Research (CIBMTR) Database"

Methods

Study 841 was a retrospective registry study designed to examine real-world outcomes of abatacept + SOC aGvHD prophylaxis in patients undergoing aHSCT from 7/8 MMUD subjects. The study utilised data routinely collected for the CIBMTR database, which had the largest source of available historical data. The study sought to compare treatment outcomes among patients treated with abatacept + CNI + MTX to several comparator groups as displayed in Table 44. Propensity score methodology, based on established key prognostic factors for this population, was employed to reduce the effect of possible confounding. As indicated above, patients in the 7/8 MMUD cohort were included in the abatacept groups of Study 841 and account for over 80% of the total sample.

Table 44 ***Treatment Groups (with Corresponding Patient Numbers) Planned to be Included in the Registry Study IM101841***

Abatacept Groups[a]	**Abatacept+CNI+MTX without ATG**			**Abatacept + tacrolimus + MTX without ATG**	**Abatacept+ CsA + MTX + 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

[a] The abatacept groups include, but are not restricted to, patients who participated in the ABA2 trial.

Study participants

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 > 80%
- Patients whose first allogeneic transplant occurred from 01-Jan-2011 to 31-Dec-2018
- Patients with any of the following diseases: AML, ALL, CML, 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)

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 leukaemia [CMMoL] were included)
- Patients who did not consent to participate in research
- Patients treated at embargoed centres for research
- Patients treated with abatacept and ATG
- Among non-abatacept treated patients, patients transplanted at centres 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)

CHMP's comments

The eligibility criteria can overall be agreed to define a prospective population conforming to Study 311.

Treatments

No treatments were administered as part of 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

For brevity, results are only included for the primary objective cohort and the ATG comparison in this AR.

CHMP's comments

Compared to current European practice, the comparison within the primary objective cohort (i.e. abatacept vs. no abatacept on a CNI + MTX backbone) may not be optimal, as ATG has an established position as part of the prophylactic regimen particularly in 7/8 transplants; consequently, patients in the no abatacept group may be relatively undertreated compared to current standard of care. The secondary comparison of abatacept vs. ATG added to a CNI + MTX backbone would seem the most relevant comparison in this respect; however, as the best established benefit of ATG is on prevention of chronic GvHD, the 180 day time frame may be too short for a fair and comprehensive comparison of clinical benefit.

Objectives

Due to data constraints in the CIBMTR database, it was not feasible to evaluate GFS as a primary outcome. Based on consultation with the FDA, OS at Day 180 was used as the primary study outcome to evaluate the treatment effect of CNI + MTX + abatacept without ATG compared to CNI + MTX without ATG. OS was considered a more objective endpoint and was also recommended by the FDA.

The stated primary objective of Study 841 was to compare the OS with 180 days of follow-up post-HSCT in 7/8 HLA-matched patients treated with CNI + MTX + abatacept without ATG to those treated with CNI + MTX without ATG (i.e., comparison within the "primary objective cohort").

The secondary objectives were:

- 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

Exploratory objectives were to assess Gr II-IV aGvHD-free survival, Gr III-IV aGvHD-free survival and RFS at 100 and 180 days post-transplant.

Outcomes/endpoints

For OS, an event was defined as death by any cause, evaluated during 180 days of follow-up post-transplant. Subjects that were still alive were censored at 181 days after transplantation. OS time was defined as the time between the date from allogeneic transplant to the documented date of death as reported by treating physicians.

The primary endpoint was OS evaluated during 180 days of follow-up post-transplant, in subjects treated with CNI + MTX + abatacept without ATG vs. CNI + MTX without ATG; secondary endpoints were OS in subjects treated with CNI + MTX + abatacept without ATG compared to those treated with CNI + MTX with ATG, and OS in subjects treated with tacrolimus + MTX + abatacept without ATG and those treated with tacrolimus + MTX without ATG.

Proportions of subjects with Gr II-IV aGvHD and Gr III-IV aGvHD were reported for all subjects at Day 100 and Day 180. For a subset of subjects for whom the actual date of occurrence of aGvHD was available (approximately 25% of patients), GFS is also presented as a time-to-event analysis. Events considered for this analysis were Gr II-IV/Gr III-IV aGvHD or death for any cause. Due to the very small sample size, these time-to-event analyses are not included in this AR.

For RFS, relapse events were collected for all subjects up to 100 and 180 days post-transplant. RFS (also known as DFS) was presented as a time-to-event analysis. Events for this analysis were relapse, or death by any cause. RFS was defined as the time between date of allogeneic HSCT to the date of relapse or date of death, whichever occurred first. All subjects without events were censored at 181 days after transplantation.

Sample size

In Study IM101311, a placebo-controlled comparison arm was not feasible for the 7/8 MMUD HSCT recipient cohort due to concerns over the very high predicted rate of severe aGvHD. The initial results for this cohort were therefore compared to historical outcomes in a comparable population treated with SOC at the sponsoring institution.

The eligible patient population consisted of all abatacept patients and approximately 150 patients in each comparator group that fulfilled the inclusion and exclusion criteria for the study.

According to the MAH, for the 7/8 cohort, survival rates in IM101311 were 100% on abatacept and 72.5% on placebo. The number of patients in the CIMBTR database was estimated to be approximately N=50 for CNI + MTX + abatacept without ATG and approximately N=150 for CNI + MTX without ATG. When the analysis was completed, the N for each group was similar to what was anticipated: N = 54 for CNI + MTX + abatacept without ATG and N = 162 for CNI +MTX without ATG.

These estimates of sample size were based on 10,000 simulations of the study with varying survival rates at Day 180 using nQuery Advisor 7.0 software. The power estimates ranged from 76% to 99% with survival at Day 180 set at 95% and above for CNI + MTX + abatacept without ATG group and at 75% and 80% for the CNI + MTX without ATG group, based on a log-rank test and 2-sided alpha = 0.05. The actual analysis used in this study was a weighted log-rank test based on inverse probability of treatment weighting (IPTW), which had lower power but accounts for possible confounding at baseline.

CHMP's comments

In the MAH's protocol it is stated that for the 7/8 cohort, "survival rates in IM101311 were 100% on abatacept and 72.5% on placebo". This statement appears to be misleading, as there was no placebo group in the 7/8 cohort, and the survival rate estimate for the non-abatacept group is likely based on historical controls. The MAH should clarify. ***OC***

Randomisation and Blinding

The majority of patients contributing to CNI + MTX + abatacept without ATG arm originate from IM101311 study whose data were entered in CIBMTR registry. There was no randomisation to comparative treatments as part of IM101311 study.

Statistical methods

For the sample of patients in 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 is earlier. The primary comparison was evaluated at a 2-sided alpha of 0.05.

The marginal hazard ratio (HR) for OS and the corresponding 2-sided 95% confidence interval (CI) was 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.

The estimated survival probabilities over time were provided by weighted Kaplan-Meier curves up to 180 days after transplant.

Propensity Score

To address potential confounding and bias due to differences between the treatment groups in key characteristics at transplantation, propensity scores predicting the probability of abatacept treatment were generated separately for each of the comparison cohorts. The propensity scores were obtained using logistic regression models.

The following variables were included in each propensity score model:

- Gender: male, female
- Disease: AML, ALL, CML+CNL, MDS+MDS/MPN unclassifiable, HL+NHL
- Age (continuous)
- HSCT graft source: BM, PB
- Conditioning intensity: myeloablative, non-myeloablative / reduced intensity
- Karnofsky/Lansky Performance Score: 80%, 90-100%
- CNI type: tacrolimus, CsA (Note: this covariate was included for cohorts including CNI in both treatment arms)

Disease status at transplantation was originally planned to be included in the propensity score model but including this variable created problems with the model and was removed.

In supplementary analyses, propensity score matching was employed as additional analyses for the primary objective. In contrast to the IPTW approach, only patients that could be matched to abatacept-treated patients (and abatacept-treated patients with available matched comparator patients) were included in this analysis. Patients in the CNI + MTX + abatacept without ATG group were matched 1:1 to patients in the CNI + MTX without ATG with the smallest absolute difference in the logit of their propensity score (greedy nearest neighbor matching). A caliper width of 20% of the standard deviation of the logit of the propensity score was used. Abatacept patients were randomly ordered and then

matched without replacement. In the case of ties, patients were randomly matched. Abatacept patients without a matched comparator were excluded from the subsequent analysis.

CHMP's comments

Study IM101841 complements study IM101311 by providing a more thorough quantitative comparison with various historical reference arms representing different treatment combinations. Historical references were sourced from CIBMTR registry, but little information has been provided by the MAH about how control patients were selected from CIBMTR registry. Historical control patients were randomly drawn from CIBMTR database by CIBMTR staff. The number of control patients included in the analyses without ATG and with ATG (162 each) for the 7/8 MMUD cohort was determined by power calculation aiming at 3:1 ratio. The numbers of eligible control subjects in CIBMTR database, from which the sample was drawn, were 503 (CNI+MTX without ATG) and 623 (CNI+MTX with ATG). It may also be noteworthy that, when designing the study, the outcome in CNI + MTX + abatacept without ATG arm was almost completely known (due to the abatacept subjects being sourced from IM101311) which changes the role of sample size calculation as compared with a prospective study. It is not clear whether this was taken into account by the MAH.

The purpose of the historical reference arm is to provide an estimate of the counter-factual outcome that would have been observed if the abatacept-treated subjects (CNI + MTX + abatacept without ATG, in particular) would have been treated with specified alternative treatment combinations. Propensity score weights were estimated and used to create a pseudo-population where the abatacept-treated and control arm are balanced with respect to each of selected and measured potential confounders: gender, underlying disease, age, HSCT graft source, conditioning intensity, Karnofsky/Lansky Performance score and CNI type. Using the propensity weights, marginal treatment effect was estimated, i.e., difference of outcome in the population where everyone was treated with abatacept vs. the population where everyone was treated with the comparator treatment.

With respect to the resulting IPT weights estimated, among the small sample of 54 abatacept-treated, some subject had to be emphasized 15-fold as compared to another in order to eliminate correlation between treatment assignment and considered covariates. The downside of anticipatedly reduced confounding bias is that the variability in weights, further reduces the "effective sample size" (a measure not found in the submission), meaning that the amount of information is less than what would be gained from 54 subjects randomised to abatacept in an RCT. This is reflected in the standard errors, confidence intervals and p-values.

Despite the critical points made above, the MAH did put effort into anticipating and addressing issues in the evaluation of effect of CNI + MTX + abatacept without ATG relative to comparator treatments. The algorithm and individual methods used are theoretically fit for purpose but do not circumvent the main limitations from statistical point of view: the fact that few subjects treated with abatacept were studied. Furthermore, when deciding on the conduct and design of the retrospective study IM101841, the outcomes of the abatacept-treated subjects were already known to a great extent. Considering the OS results among the abatacept-treated subjects, no reasonable re-weighting scheme could transform the near complete survival in the sample already observed. From this perspective, IPT-weighted analysis of abatacept-treated subjects has value mainly as a methodological exercise. The main contribution of study IM101841 is the corroborative information on the outcomes in the comparative treatment combinations.

The supplementary analysis where subjects treated with CNI + MTX + abatacept without ATG were matched 1:1 with subjects CNI + MTX without ATG based on their probability of getting abatacept is considered to provide little added value to the IPTW analyses: while relying on the same assumption (that the fitted propensity score can make the abatacept-treated and -untreated groups exchangeable)

it appears to waste a lot of data. Furthermore, paired subjects (one treated and another not treated with abatacept) may have identical propensity score based on very different set of background characteristics.

Results

Participant flow

Patient disposition across the different study groups is displayed in Table 45.

Table 45 ***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.

[d] OS and Gr II-IV and Gr III-IV GFS in these 2 groups are exploratory objectives.

[e] Overall survival and Gr II-IV and Gr III-IV GFS in this group compared to CNI + MTX + abatacept without ATG is an exploratory objective.

Recruitment

Patient data for the registry study was obtained from the CIBMTR database. The CIBMTR collects data for approximately 23,000 new transplants annually in the US as well as follow-up data on previously reported recipients and donors.

All abatacept-exposed patients meeting the study's inclusion and exclusion criteria were to be included in the final study population. Unexposed patients were selected from all non-abatacept patients receiving care from sites that did not participate in the IM101311 trial and who met the study's inclusion and exclusion criteria. The pattern of use analysis showed that approximately 50 7/8 HLA-matched abatacept treated patients would be included in the primary analysis. In order to achieve adequate power, 150 patients treated with CNI + MTX without ATG, 150 patients treated with CNI + MTX with ATG, and 150 patients treated with PT-Cy without ATG were to be randomly selected.

Conduct of the study

The study protocol was amended once, mainly to incorporate changes and additions into the statistical methodology as proposed by the FDA.

Baseline data

In the primary objective cohort, using unweighted data, patients receiving CNI + MTX + abatacept without ATG were younger than patients receiving CNI + MTX without ATG based on mean age, and the proportion of male patients was higher in the CNI + MTX + abatacept without ATG group. The demographic characteristics were more comparable in the weighted samples. Table 46 displays key demographic characteristics using unweighted data, and weighted data are displayed in Table 47.

Table 46 ***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)

Table 47 ***Demographic Characteristics at Transplant for the Weighted Samples Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores***

		CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162	Total N = 216
AGE (YEARS)	N	54	162	216
	MEAN	47.1	45.9	46.2
	SD	19.2	17.0	17.5
	MEDIAN	51.0	49.0	49.0
	MIN	6	10	6
	MAX	76	74	76
GENDER (%)	MALE	33.4 (62.1)	95.5 (59.1)	128.9 (59.9)
	FEMALE	20.4 (37.9)	66.0 (40.9)	86.4 (40.1)
KARNOFSKY/LANSKY PERFORMANCE SCORE (%)	70	5.0 (9.2)	0	5.0 (2.3)
	80	11.4 (21.1)	50.9 (31.5)	62.2 (28.9)
	90-100	37.5 (69.7)	110.6 (68.5)	148.1 (68.8)
KARNOFSKY/LANSKY PERFORMANCE SCORE, COLLAPSED (%)	70 OR 80	16.3 (30.3)	50.9 (31.5)	67.2 (31.2)
	90-100	37.5 (69.7)	110.6 (68.5)	148.1 (68.8)
RACE (%)	WHITE	38.8 (72.1)	133.4 (82.6)	172.3 (80.0)
	BLACK OR AFRICAN AMERICAN	10.9 (20.3)	6.7 (4.1)	17.6 (8.2)
	ASIAN	2.4 (4.5)	5.4 (3.4)	7.8 (3.6)
	NOT REPORTED	1.7 (3.1)	16.0 (9.9)	17.6 (8.2)
ETHNICITY (%)	HISPANIC OR LATINO	5.9 (10.9)	24.6 (15.2)	30.5 (14.2)
	NOT HISPANIC OR LATINO	47.7 (88.5)	135.1 (83.7)	182.8 (84.9)
	NOT REPORTED	0.3 (0.5)	1.7 (1.1)	2.0 (0.9)

Propensity scores obtained from a logistic regression model including gender, disease, age, HSCT graft source, conditioning intensity, performance score, and CNI type as covariates.
Treatment header count (N) represents the unweighted number of subjects in the treatment group.
Percentages in this table are based on the weighted number of subjects in the treatment group.

Demographic data for the comparative analysis of CNI + MTX + abatacept vs. CNI + MTX + ATG are displayed in Table 48 using unweighted data, and corresponding weighted data are displayed in Table 49.

Table 48 ***Demographic Characteristics at Transplant – Comparator Group with ATG (unweighted)***

		CNI + MTX + Aba without ATG N = 54	CNI + MTX with ATG N = 162	Total N = 216
AGE (YEARS)	N	54	162	216
	MEAN	35.9	43.6	41.7
	SD	22.8	18.6	20.0
	MEDIAN	36.5	49.0	47.5
	MIN	6	7	6
	MAX	76	76	76
GENDER (%)	MALE	36 (66.7)	86 (53.1)	122 (56.5)
	FEMALE	18 (33.3)	76 (46.9)	94 (43.5)
KARNOFSKY/LANSKY PERFORMANCE SCORE (%)	70	2 (3.7)	0	2 (0.9)
	80	13 (24.1)	45 (27.8)	58 (26.9)
	90-100	39 (72.2)	117 (72.2)	156 (72.2)
KARNOFSKY/LANSKY PERFORMANCE SCORE, COLLAPSED (%)	70 OR 80	15 (27.8)	45 (27.8)	60 (27.8)
	90-100	39 (72.2)	117 (72.2)	156 (72.2)
RACE (%)	WHITE	39 (72.2)	124 (76.5)	163 (75.5)
	BLACK OR AFRICAN AMERICAN	9 (16.7)	15 (9.3)	24 (11.1)
	AMERICAN INDIAN OR ALASKA NATIVE	0	1 (0.6)	1 (0.5)
	ASIAN	3 (5.6)	7 (4.3)	10 (4.6)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	1 (0.6)	1 (0.5)
	NOT REPORTED	3 (5.6)	14 (8.6)	17 (7.9)

Table 49 ***Demographic Characteristics at Transplant for the Weighted Samples Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores – Comparator Group with ATG***

		CNI + MTX + Aba without ATG N = 54	CNI + MTX with ATG N = 162	Total N = 216
AGE (YEARS)	N	54	162	216
	MEAN	45.2	42.9	43.5
	SD	19.6	20.0	19.9
	MEDIAN	49.0	49.0	49.0
	MIN	6	7	6
	MAX	76	76	76
GENDER (%)	MALE	29.8 (60.1)	95.4 (58.1)	125.1 (58.6)
	FEMALE	19.8 (39.9)	68.7 (41.9)	88.5 (41.4)
KARNOFSKY/LANSKY PERFORMANCE SCORE (%)	70	6.0 (12.2)	0	6.0 (2.8)
	80	9.5 (19.2)	45.4 (27.7)	54.9 (25.7)
	90-100	34.0 (68.6)	118.6 (72.3)	152.6 (71.5)
KARNOFSKY/LANSKY PERFORMANCE SCORE, COLLAPSED (%)	70 OR 80	15.5 (31.4)	45.4 (27.7)	61.0 (28.5)
	90-100	34.0 (68.6)	118.6 (72.3)	152.6 (71.5)
RACE (%)	WHITE	35.2 (71.0)	125.9 (76.8)	161.1 (75.4)
	BLACK OR AFRICAN AMERICAN	10.7 (21.5)	14.6 (8.9)	25.3 (11.8)
	AMERICAN INDIAN OR ALASKA NATIVE	0	0.9 (0.6)	0.9 (0.4)
	ASIAN	2.1 (4.2)	6.9 (4.2)	9.0 (4.2)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0.8 (0.5)	0.8 (0.4)
	NOT REPORTED	1.6 (3.3)	14.9 (9.1)	16.5 (7.7)

Propensity scores obtained from a logistic regression model including gender, disease, age, HSCT graft source, conditioning intensity, performance score, and CNI type as covariates.
Treatment header count (N) represents the unweighted number of subjects in the treatment group.
Percentages in this table are based on the weighted number of subjects in the treatment group.

Baseline disease characteristics (unweighted) for the primary objective cohort are summarised in Table 50 and for the abatacept – ATG comparison in Table 51.

Table 50 ***Disease and Other Characteristics at Transplant - Primary Objective Cohort (unweighted)***

	CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162	Total N = 216
DISEASE (%)			
AML	20 (37.0)	81 (50.0)	101 (46.8)
ALL	13 (24.1)	31 (19.1)	44 (20.4)
MDS	11 (20.4)	32 (19.8)	43 (19.9)
CML	5 (9.3)	7 (4.3)	12 (5.6)
HL+NHL	3 (5.6)	11 (6.8)	14 (6.5)
MDS/MPN UNCLASSIFIABLE	1 (1.9)	0	1 (0.5)
CNL	1 (1.9)	0	1 (0.5)
DISEASE, COLLAPSED (%)			
AML	20 (37.0)	81 (50.0)	101 (46.8)
ALL	13 (24.1)	31 (19.1)	44 (20.4)
MDS OR MDS/MPN UNCLASSIFIABLE	12 (22.2)	32 (19.8)	44 (20.4)
CML OR CNL	6 (11.1)	7 (4.3)	13 (6.0)
HL+NHL	3 (5.6)	11 (6.8)	14 (6.5)
DISEASE STATUS (%)			
EARLY	33 (61.1)	84 (51.9)	117 (54.2)
INTERMEDIATE	13 (24.1)	28 (17.3)	41 (19.0)
ADVANCED	5 (9.3)	39 (24.1)	44 (20.4)
CHEMO-SENSITIVE	3 (5.6)	6 (3.7)	9 (4.2)
CHEMO-RESISTANT	0	5 (3.1)	5 (2.3)
DONOR AGE			
N	53	162	215
MEAN (SD)	31.2 (9.2)	32.1 (9.3)	31.9 (9.2)
MEDIAN (MIN-MAX)	28.3 (18.4 - 52.6)	30.0 (19.4 - 53.5)	29.7 (18.4 - 53.5)
DONOR-RECIPIENT SEX MATCH (%)			
MALE/MALE	22 (40.7)	55 (34.0)	77 (35.6)
MALE/FEMALE	10 (18.5)	40 (24.7)	50 (23.1)
FEMALE/MALE	14 (25.9)	32 (19.8)	46 (21.3)
FEMALE/FEMALE	8 (14.8)	35 (21.6)	43 (19.9)
DONOR-RECIPIENT CYTOMEGALOVIRUS (CMV) STATUS MATCH (%)			
+/+	18 (33.3)	46 (28.4)	64 (29.6)
+/-	9 (16.7)	26 (16.0)	35 (16.2)
-/+	19 (35.2)	48 (29.6)	67 (31.0)
-/-	8 (14.8)	41 (25.3)	49 (22.7)
NOT REPORTED	0	1 (0.6)	1 (0.5)
DONOR-RECIPIENT ABO MISMATCH (%)			
MATCHED	6 (11.1)	22 (13.6)	28 (13.0)
MINOR MISMATCH	7 (13.0)	12 (7.4)	19 (8.8)
MAJOR MISMATCH	5 (9.3)	10 (6.2)	15 (6.9)
BI-DIRECTIONAL	1 (1.9)	4 (2.5)	5 (2.3)
NOT COLLECTED (TED TRACK)	34 (63.0)	111 (68.5)	145 (67.1)
NOT REPORTED	1 (1.9)	3 (1.9)	4 (1.9)
HLA MATCHING (%)			
9/10	44 (81.5)	153 (94.4)	197 (91.2)
8/10	8 (14.8)	6 (3.7)	14 (6.5)
NOT REPORTED	2 (3.7)	3 (1.9)	5 (2.3)
CONDITIONING REGIMEN (%)			
TBI + CY +- OTHERS	15 (27.8)	38 (23.5)	53 (24.5)
BU + CY +- OTHERS	13 (24.1)	38 (23.5)	51 (23.6)
BU + FLU +- OTHERS	9 (16.7)	67 (41.4)	76 (35.2)
FLU + MEL +- OTHERS	16 (29.6)	19 (11.7)	35 (16.2)
TBI + ETOPOSIDE	1 (1.9)	0	1 (0.5)
CONDITIONING INTENSITY (%)			
MYELOABLATIVE	41 (75.9)	107 (66.0)	148 (68.5)
REDUCED INTENSITY OR NON-MYELOABLATIVE	13 (24.1)	55 (34.0)	68 (31.5)
STEM CELL SOURCE (%)			
BONE MARROW	31 (57.4)	44 (27.2)	75 (34.7)
PERIPHERAL BLOOD	23 (42.6)	118 (72.8)	141 (65.3)
YEAR OF TRANSPLANT (%)			
2011	0	2 (1.2)	2 (0.9)
2012	0	1 (0.6)	1 (0.5)
2013	2 (3.7)	21 (13.0)	23 (10.6)
2014	3 (5.6)	45 (27.8)	48 (22.2)
2015	16 (29.6)	39 (24.1)	55 (25.5)
2016	21 (38.9)	26 (16.0)	47 (21.8)
2017	7 (13.0)	15 (9.3)	22 (10.2)
2018	5 (9.3)	13 (8.0)	18 (8.3)
YEAR OF TRANSPLANT, GROUPED (%)			
2011-2013	2 (3.7)	24 (14.8)	26 (12.0)
2014-2018	52 (96.3)	138 (85.2)	190 (88.0)

	CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162	Total N = 216
TIME FROM DIAGNOSIS TO TRANSPLANT, MONTHS			
MEDIAN (MIN-MAX)	9.5 (1.9 - 231.7)	6.9 (2.3 - 213.2)	7.4 (1.9 - 231.7)
TIME FROM DIAGNOSIS TO TRANSPLANT, MONTHS, GROUPED (%)			
<6	16 (29.6)	66 (40.7)	82 (38.0)
6-<12	17 (31.5)	46 (28.4)	63 (29.2)
>=12	21 (38.9)	50 (30.9)	71 (32.9)
CNI TYPE (%)			
TAC	33 (61.1)	153 (94.4)	186 (86.1)
CSA	21 (38.9)	9 (5.6)	30 (13.9)
HCT-CI (%)			
0	16 (29.6)	50 (30.9)	66 (30.6)
1-2	13 (24.1)	32 (19.8)	45 (20.8)
>=3	25 (46.3)	80 (49.4)	105 (48.6)
ARRHYTHMIA (%)			
NO	52 (96.3)	157 (96.9)	209 (96.8)
YES	2 (3.7)	5 (3.1)	7 (3.2)
CARDIAC COMORBIDITY (%)			
NO	54 (100.0)	145 (89.5)	199 (92.1)
YES	0	17 (10.5)	17 (7.9)
CEREBROVASCULAR DISEASE (%)			
NO	52 (96.3)	161 (99.4)	213 (98.6)
YES	2 (3.7)	1 (0.6)	3 (1.4)
DIABETES (%)			
NO	49 (90.7)	148 (91.4)	197 (91.2)
YES	5 (9.3)	14 (8.6)	19 (8.8)
HEART VALVE DISEASE (%)			
NO	53 (98.1)	159 (98.1)	212 (98.1)
YES	1 (1.9)	3 (1.9)	4 (1.9)
MILD HEPATIC COMORBIDITY (%)			
NO	39 (72.2)	144 (88.9)	183 (84.7)
YES	15 (27.8)	17 (10.5)	32 (14.8)
NOT REPORTED	0	1 (0.6)	1 (0.5)
MODERATE/SEVERE HEPATIC COMORBIDITY (%)			
NO	53 (98.1)	156 (96.3)	209 (96.8)
YES	1 (1.9)	5 (3.1)	6 (2.8)
NOT REPORTED	0	1 (0.6)	1 (0.5)
INFECTION (%)			
NO	52 (96.3)	153 (94.4)	205 (94.9)
YES	2 (3.7)	9 (5.6)	11 (5.1)
INFLAMMATORY BOWEL DISEASE (%)			
NO	54 (100.0)	161 (99.4)	215 (99.5)
YES	0	1 (0.6)	1 (0.5)
OBESITY (%)			
NO	47 (87.0)	142 (87.7)	189 (87.5)
YES	7 (13.0)	20 (12.3)	27 (12.5)
PEPTIC ULCER (%)			
NO	54 (100.0)	161 (99.4)	215 (99.5)
YES	0	1 (0.6)	1 (0.5)
PSYCHIATRIC DISTURBANCE (%)			
NO	43 (79.6)	130 (80.2)	173 (80.1)
YES	11 (20.4)	32 (19.8)	43 (19.9)
MODERATE PULMONARY COMORBIDITY (%)			
NO	40 (74.1)	120 (74.1)	160 (74.1)
YES	14 (25.9)	42 (25.9)	56 (25.9)
SEVERE PULMONARY COMORBIDITY (%)			
NO	49 (90.7)	130 (80.2)	179 (82.9)
YES	5 (9.3)	32 (19.8)	37 (17.1)
MODERATE/SEVERE RENAL COMORBIDITY (%)			
NO	54 (100.0)	158 (97.5)	212 (98.1)
YES	0	3 (1.9)	3 (1.4)
NOT REPORTED	0	1 (0.6)	1 (0.5)
RHEUMATOLOGIC COMORBIDITY (%)			
NO	53 (98.1)	162 (100.0)	215 (99.5)
YES	1 (1.9)	0	1 (0.5)
PRIOR SOLID TUMOR (%)			
NO	48 (88.9)	137 (84.6)	185 (85.6)
YES	6 (11.1)	25 (15.4)	31 (14.4)
PARTICIPATION IN THE ABA2 CLINICAL TRIAL (%)			
NO	12 (22.2)	162 (100.0)	174 (80.6)
YES	42 (77.8)	0	42 (19.4)
PARTICIPATION IN ANY CLINICAL TRIAL (%)			
NO	12 (22.2)	139 (85.8)	151 (69.9)
YES	42 (77.8)	23 (14.2)	65 (30.1)

Table 51 ***Disease and Other Characteristics at Transplant – Comparator Group with ATG (unweighted)***

	CNI + MTX + Aba without ATG N = 54	CNI + MTX with ATG N = 162	Total N = 216
DISEASE (%)			
AML	20 (37.0)	78 (48.1)	98 (45.4)
ALL	13 (24.1)	43 (26.5)	56 (25.9)
MDS	11 (20.4)	29 (17.9)	40 (18.5)
CML	5 (9.3)	5 (3.1)	10 (4.6)
HL+NHL	3 (5.6)	7 (4.3)	10 (4.6)
MDS/MPN UNCLASSIFIABLE	1 (1.9)	0	1 (0.5)
CNL	1 (1.9)	0	1 (0.5)
DISEASE, COLLAPSED (%)			
AML	20 (37.0)	78 (48.1)	98 (45.4)
ALL	13 (24.1)	43 (26.5)	56 (25.9)
MDS OR MDS/MPN UNCLASSIFIABLE	12 (22.2)	29 (17.9)	41 (19.0)
CML OR CNL	6 (11.1)	5 (3.1)	11 (5.1)
HL+NHL	3 (5.6)	7 (4.3)	10 (4.6)
DISEASE STATUS (%)			
EARLY	33 (61.1)	88 (54.3)	121 (56.0)
INTERMEDIATE	13 (24.1)	41 (25.3)	54 (25.0)
ADVANCED	5 (9.3)	26 (16.0)	31 (14.4)
CHEMO-SENSITIVE	3 (5.6)	4 (2.5)	7 (3.2)
CHEMO-RESISTANT	0	3 (1.9)	3 (1.4)
DONOR AGE			
N	53	162	215
MEAN (SD)	31.2 (9.2)	32.8 (10.3)	32.4 (10.0)
MEDIAN (MIN-MAX)	28.3 (18.4 - 52.6)	29.2 (19.8 - 61.4)	29.1 (18.4 - 61.4)
DONOR-RECIPIENT SEX MATCH (%)			
MALE/MALE	22 (40.7)	65 (40.1)	87 (40.3)
MALE/FEMALE	10 (18.5)	40 (24.7)	50 (23.1)
FEMALE/MALE	14 (25.9)	21 (13.0)	35 (16.2)
FEMALE/FEMALE	8 (14.8)	36 (22.2)	44 (20.4)
DONOR-RECIPIENT CYTOMEGALOVIRUS (CMV) STATUS MATCH (%)			
+/+	18 (33.3)	70 (43.2)	88 (40.7)
+/-	9 (16.7)	13 (8.0)	22 (10.2)
-/+	19 (35.2)	46 (28.4)	65 (30.1)
-/-	8 (14.8)	31 (19.1)	39 (18.1)
NOT REPORTED	0	2 (1.2)	2 (0.9)
DONOR-RECIPIENT ABO MISMATCH (%)			
MATCHED	6 (11.1)	21 (13.0)	27 (12.5)
MINOR MISMATCH	7 (13.0)	7 (4.3)	14 (6.5)
MAJOR MISMATCH	5 (9.3)	6 (3.7)	11 (5.1)
BI-DIRECTIONAL	1 (1.9)	4 (2.5)	5 (2.3)
NOT COLLECTED (TED TRACK)	34 (63.0)	121 (74.7)	155 (71.8)
NOT REPORTED	1 (1.9)	3 (1.9)	4 (1.9)
HLA MATCHING (%)			
9/10	44 (81.5)	146 (90.1)	190 (88.0)
8/10	8 (14.8)	16 (9.9)	24 (11.1)
NOT REPORTED	2 (3.7)	0	2 (0.9)
CONDITIONING REGIMEN (%)			
TBI + CY +- OTHERS	15 (27.8)	36 (22.2)	51 (23.6)
BU + CY +- OTHERS	13 (24.1)	25 (15.4)	38 (17.6)
BU + FLU +- OTHERS	9 (16.7)	74 (45.7)	83 (38.4)
FLU + MEL +- OTHERS	16 (29.6)	27 (16.7)	43 (19.9)
TBI + ETOPOSIDE	1 (1.9)	0	1 (0.5)
CONDITIONING INTENSITY (%)			
MYELOABLATIVE	41 (75.9)	119 (73.5)	160 (74.1)
REDUCED INTENSITY OR NON-MYELOABLATIVE	13 (24.1)	43 (26.5)	56 (25.9)
STEM CELL SOURCE (%)			
BONE MARROW	31 (57.4)	35 (21.6)	66 (30.6)
PERIPHERAL BLOOD	23 (42.6)	127 (78.4)	150 (69.4)
YEAR OF TRANSPLANT (%)			
2013	2 (3.7)	11 (6.8)	13 (6.0)
2014	3 (5.6)	40 (24.7)	43 (19.9)
2015	16 (29.6)	45 (27.8)	61 (28.2)
2016	21 (38.9)	32 (19.8)	53 (24.5)
2017	7 (13.0)	19 (11.7)	26 (12.0)
2018	5 (9.3)	15 (9.3)	20 (9.3)
YEAR OF TRANSPLANT, GROUPED (%)			
2011-2013	2 (3.7)	11 (6.8)	13 (6.0)
2014-2018	52 (96.3)	151 (93.2)	203 (94.0)
TIME FROM DIAGNOSIS TO TRANSPLANT, MONTHS			
MEDIAN (MIN-MAX)	9.5 (1.9 - 231.7)	7.7 (0.5 - 255.7)	8.1 (0.5 - 255.7)
TIME FROM DIAGNOSIS TO TRANSPLANT, MONTHS, GROUPED (%)			
<6	16 (29.6)	55 (34.0)	71 (32.9)
6-<12	17 (31.5)	45 (27.8)	62 (28.7)
>=12	21 (38.9)	62 (38.3)	83 (38.4)
CNI TYPE (%)			
TAC	33 (61.1)	153 (94.4)	186 (86.1)
CSA	21 (38.9)	9 (5.6)	30 (13.9)

	CNI + MTX + Aba without ATG N = 54	CNI + MTX with ATG N = 162	Total N = 216
HCT-CI (%)			
0	16 (29.6)	49 (30.2)	65 (30.1)
1-2	13 (24.1)	44 (27.2)	57 (26.4)
>=3	25 (46.3)	69 (42.6)	94 (43.5)
ARRHYTHMIA (%)			
NO	52 (96.3)	160 (98.8)	212 (98.1)
YES	2 (3.7)	2 (1.2)	4 (1.9)
CARDIAC COMORBIDITY (%)			
NO	54 (100.0)	147 (90.7)	201 (93.1)
YES	0	15 (9.3)	15 (6.9)
CEREBROVASCULAR DISEASE (%)			
NO	52 (96.3)	159 (98.1)	211 (97.7)
YES	2 (3.7)	3 (1.9)	5 (2.3)
DIABETES (%)			
NO	49 (90.7)	142 (87.7)	191 (88.4)
YES	5 (9.3)	20 (12.3)	25 (11.6)
HEART VALVE DISEASE (%)			
NO	53 (98.1)	160 (98.8)	213 (98.6)
YES	1 (1.9)	2 (1.2)	3 (1.4)
MILD HEPATIC COMORBIDITY (%)			
NO	39 (72.2)	146 (90.1)	185 (85.6)
YES	15 (27.8)	16 (9.9)	31 (14.4)
MODERATE/SEVERE HEPATIC COMORBIDITY (%)			
NO	53 (98.1)	161 (99.4)	214 (99.1)
YES	1 (1.9)	1 (0.6)	2 (0.9)
INFECTION (%)			
NO	52 (96.3)	148 (91.4)	200 (92.6)
YES	2 (3.7)	14 (8.6)	16 (7.4)
INFLAMMATORY BOWEL DISEASE (%)			
NO	54 (100.0)	161 (99.4)	215 (99.5)
YES	0	1 (0.6)	1 (0.5)
OBESITY (%)			
NO	47 (87.0)	139 (85.8)	186 (86.1)
YES	7 (13.0)	23 (14.2)	30 (13.9)
PEPTIC ULCER (%)			
NO	54 (100.0)	162 (100.0)	216 (100.0)
PSYCHIATRIC DISTURBANCE (%)			
NO	43 (79.6)	135 (83.3)	178 (82.4)
YES	11 (20.4)	27 (16.7)	38 (17.6)
MODERATE PULMONARY COMORBIDITY (%)			
NO	40 (74.1)	127 (78.4)	167 (77.3)
YES	14 (25.9)	35 (21.6)	49 (22.7)
SEVERE PULMONARY COMORBIDITY (%)			
NO	49 (90.7)	132 (81.5)	181 (83.8)
YES	5 (9.3)	30 (18.5)	35 (16.2)
MODERATE/SEVERE RENAL COMORBIDITY (%)			
NO	54 (100.0)	161 (99.4)	215 (99.5)
YES	0	1 (0.6)	1 (0.5)
RHEUMATOLOGIC COMORBIDITY (%)			
NO	53 (98.1)	156 (96.3)	209 (96.8)
YES	1 (1.9)	6 (3.7)	7 (3.2)
PRIOR SOLID TUMOR (%)			
NO	48 (88.9)	138 (85.2)	186 (86.1)
YES	6 (11.1)	24 (14.8)	30 (13.9)
PARTICIPATION IN THE ABA2 CLINICAL TRIAL (%)			
NO	12 (22.2)	162 (100.0)	174 (80.6)
YES	42 (77.8)	0	42 (19.4)
PARTICIPATION IN ANY CLINICAL TRIAL (%)			
NO	12 (22.2)	151 (93.2)	163 (75.5)
YES	42 (77.8)	11 (6.8)	53 (24.5)

Outcomes and estimation

Overall survival

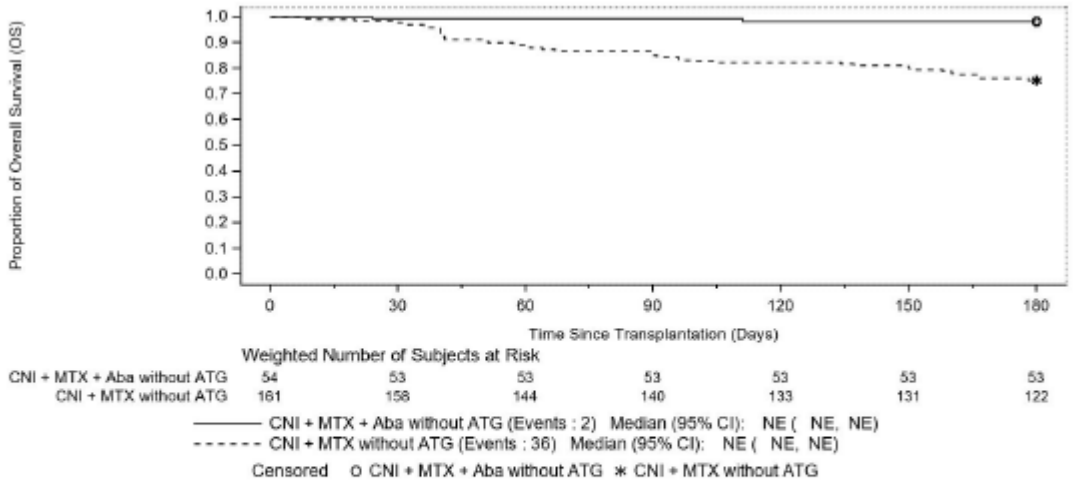
In the primary objective cohort, OS rate at 180 days after transplant was significantly higher in patients receiving CNI + MTX + abatacept without ATG compared to patients receiving CNI + MTX without ATG (Table 52). The corresponding Kaplan-Meier curves of OS up to Day 180 in each group are displayed in Figure 34. A supplementary analysis using propensity scoring with 1:1 matching was consistent with the primary analysis.

Table 52 ***Summary of OS During 180 Days of Follow-up Post-Transplant Using Stabilized IPTW with Propensity Scores in the Primary Objective Cohort***

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

Figure 34 ***Kaplan-Meier Plot of OS During 180 Days of Follow-up Posttransplant using IPTW with Propensity Scores 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

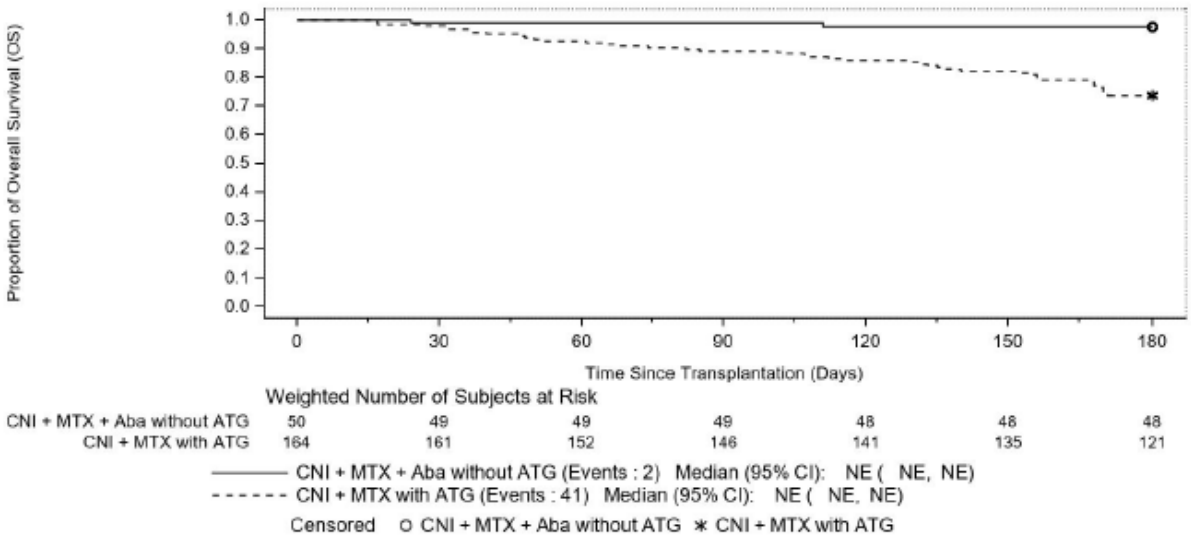
In the comparison of CNI + MTX + abatacept to CNI + MTX + ATG, the OS rate through 180 days was significantly higher in patients who received CNI + MTX + abatacept (Table 53). The corresponding Kaplan-Meier curves of OS up to Day 180 in each group are displayed in Figure 35.

Table 53 ***Summary of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the Comparator Group with ATG***

Measure	CNI + MTX + Aba without ATG N = 54	CNI + MTX with ATG N = 162
PROPORTION WITH EVENT (n/m, %)	2/ 54 (3.7)	41/162 (25.3)
MEDIAN TIME TO EVENT (A)	NE	NE
95% CI OF MEDIAN TIME	(NE, NE)	(NE, NE)
SURVIVAL RATE AT DAY 180 (A)	0.98	0.74
95% CI OF SURVIVAL RATE	(0.76, 1.00)	(0.65, 0.80)
P-VALUE FROM LOG-RANK TEST (A)	0.0060	NA
HAZARD RATIO VS. COMPARATOR GROUP (B)	0.08	NA
95% CI OF HAZARD RATIO	(0.02, 0.36)	NA
HAZARD RATIO VS. COMPARATOR GROUP (C)	0.10	NA
95% CI OF HAZARD RATIO	(0.02, 0.49)	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

Figure 35 ***K-M Plot of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the Comparator Group with ATG***



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

Grade II-IV and Grade III-IV aGvHD-free survival

The proportion of patients with Grade II-IV aGvHD or death, and Grade III-IV aGvHD or death at Day 100 and Day 180 in the primary objective cohort are shown in Table 54 and Table 55, respectively. Corresponding comparisons for CNI + MTX + abatacept vs. CNI + MTX + ATG are shown in Table 56 and Table 57, respectively.

Table 54 ***Weighted Proportion of Grade II-IV aGvHD or Death During 180 Days of Follow-up Post-transplant Using Stabilized IPTW Weights Based on Propensity Scores: Primary Objective Cohort***

Study Day		CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162
DAY 100	NUMBER OF SUBJECTS <n/m> (%) 95% CI	19.7/ 53.9 (36.5) (23.7, 49.4)	77.7/ 161.5 (48.1) (40.4, 55.8)
DAY 180	NUMBER OF SUBJECTS <n/m> (%) 95% CI	20.1/ 53.9 (37.3) (24.4, 50.2)	91.9/ 161.5 (56.9) (49.2, 64.5)

n = Number of subjects with event, m = Number of subjects in the analysis

Event is defined as Grade II-IV aGVHD or death of any cause.

Propensity scores obtained from a logistic regression model including gender, disease, age, HSCT graft source, conditioning intensity, performance score, and CNI type as covariates.

Table 55 ***Weighted Proportion of Grade III-IV aGvHD or Death During 180 Days of Follow-up Post-transplant Using Stabilized IPTW Weights Based on Propensity Scores: Primary Objective Cohort***

Study Day		CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162
DAY 100	NUMBER OF SUBJECTS <n/m> (%) 95% CI	3.6/ 53.9 (6.7) (0.1, 13.5)	42.7/ 161.5 (26.4) (19.6, 33.2)
DAY 180	NUMBER OF SUBJECTS <n/m> (%) 95% CI	4.4/ 53.9 (8.2) (0.8, 15.4)	58.3/ 161.5 (36.1) (28.7, 43.5)

n = Number of subjects with event, m = Number of subjects in the analysis

Event is defined as Grade II-IV aGVHD or death of any cause.

Propensity scores obtained from a logistic regression model including gender, disease, age, HSCT graft source, conditioning intensity, performance score, and CNI type as covariates.

Table 56 ***Weighted Proportion of Grade II-IV aGvHD or Death During 180 Days of Follow-up Post-transplant Using Stabilized IPTW Based on Propensity Scores: Comparator Group with ATG***

Study Day		CNI + MTX + Aba without ATG N = 54	CNI + MTX with ATG N = 162
DAY 100	NUMBER OF SUBJECTS <n/m> (%) 95% CI	18.3/ 49.5 (37.0) (23.5, 50.4)	78.7/ 164.0 (48.0) (40.3, 55.6)
DAY 180	NUMBER OF SUBJECTS <n/m> (%) 95% CI	18.8/ 49.5 (38.0) (24.4, 51.4)	96.0/ 164.0 (58.5) (51.0, 66.1)

n = Number of subjects with event, m = Number of subjects in the analysis

Event is defined as Grade II-IV aGVHD or death of any cause.

Propensity scores obtained from a logistic regression model including gender, disease, age, HSCT graft source, conditioning intensity, performance score, and CNI type as covariates.

Table 57 ***Weighted Proportion of Grade III-IV aGvHD or Death During 180 Days of Follow-up Post-transplant Using Stabilized IPTW Based on Propensity Scores: Comparator Group with ATG***

Study Day		CNI + MTX + Aba without ATG N = 54	CNI + MTX with ATG N = 162
DAY 100	NUMBER OF SUBJECTS <n/m> (%) 95% CI	3.0/ 49.5 (6.1) (0.0, 12.7)	42.4/ 164.0 (25.9) (19.2, 32.6)
DAY 180	NUMBER OF SUBJECTS <n/m> (%) 95% CI	3.8/ 49.5 (7.7) (0.2, 15.0)	61.7/ 164.0 (37.6) (30.2, 45.0)

n = Number of subjects with event, m = Number of subjects in the analysis

Event is defined as Grade II-IV aGVHD or death of any cause.

Propensity scores obtained from a logistic regression model including gender, disease, age, HSCT graft source, conditioning intensity, performance score, and CNI type as covariates.

Relapse-free survival

The relapse-free survival rates at Day 100 and Day 180 for the primary objective cohort are shown in Table 58.

Table 58 ***Summary of Relapse-free Survival During 180 Days of Follow-up Post-transplant: Primary Objective Cohort***

Measure	CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162
PROPORTION WITH EVENT (n/m, %)	7/ 54 (13.0)	51/ 162 (31.5)
MEDIAN TIME TO EVENT (A)	NE	NE
95% CI OF MEDIAN TIME	(NE, NE)	(NE, NE)
SURVIVAL RATE AT DAY 100 (A)	0.93	0.79
95% CI OF SURVIVAL RATE	(0.81, 0.97)	(0.72, 0.85)
SURVIVAL RATE AT DAY 180 (A)	0.87	0.69
95% CI OF SURVIVAL RATE	(0.75, 0.94)	(0.61, 0.75)
HAZARD RATIO VS. COMPARATOR GROUP (B)	0.37	NA
95% CI OF HAZARD RATIO	(0.17, 0.81)	NA

n = Number of subjects with event, m = Number of subjects in the analysis

Event is defined as relapse or death of any cause.

(A) Based on unweighted Kaplan-Meier method

(B) Marginal hazard ratio based on unweighted Cox proportional hazards model with treatment as the only covariate. Ties are handled using the Breslow method.

Relapse-free survival is defined as the time between date of transplant to date of death or relapse, whichever is earlier.

Subjects without event are censored at 181 days post-transplant or at time of last follow-up, whichever is earlier.

NA: Not Applicable

NE: Not Estimable

CHMP's comments

Based on a limited follow-up period of 180 days, the results of Study 841 suggest a beneficial effect on overall survival when abatacept was added to a CNI + MTX prophylactic regimen in 7/8 HLA-matched patients. Whereas the result is acknowledged, the study has some limitations. Firstly, the duration of follow-up is quite short and may be insufficient to cover the entire period of interest post-treatment. Secondly, European standard of care very routinely includes ATG as part of the prophylactic regimen in 7/8 transplants; consequently, in the primary comparison (CNI + MTX + abatacept vs. CNI + MTX only), patients in the control group are de facto undertreated compared to European practice. It should also be recognised that the favourable result in the abatacept group is driven by patients participating in IM101311, and the results can therefore not be considered to provide any independent support for a treatment benefit. As already stated above, considering the OS results among the abatacept-treated subjects, no reasonable re-weighting scheme could transform the near complete survival in the sample already observed, and from this perspective, the main contribution of study IM101841 is the corroborative information on the outcomes in the comparative treatment combinations.

A favourable effect of abatacept vs. ATG when added to a CNI + MTX regimen is also suggested. Nevertheless, the same caveats also apply to this comparison. Furthermore, the demonstrated benefit of ATG is particularly in the prevention of cGvHD, and the profile is thus somewhat different to abatacept as currently studied. The short-term analyses provided by the MAH may therefore be insufficient in particular for a comprehensive comparison of these two agents.

Reasons for death in the different study groups have not been clearly summarised in the documentation, and the MAH is requested to provide a tabular summary and discuss relevant differences for the primary objective cohort as well as for the ATG comparison. ***OC***

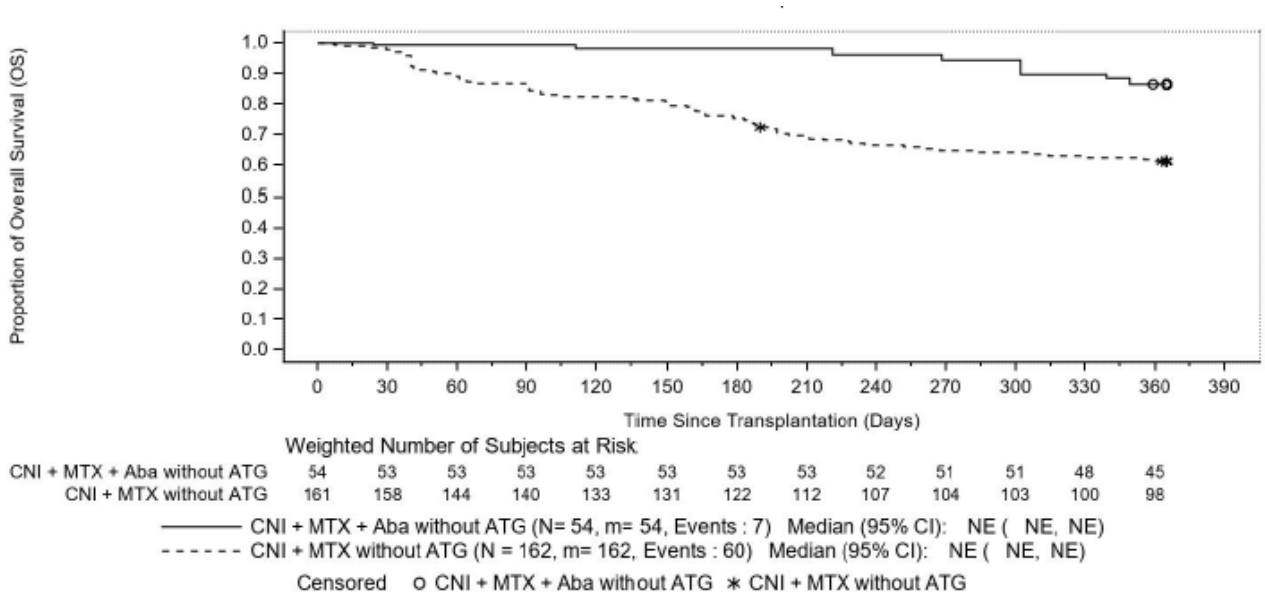
Additional 1-year outcomes data provided in the MAH's response to the 1st RSI

In their response to the 1st RSI, the MAH indicated that Study 841 has been expanded to cover outcomes observed over 1 year post transplant; furthermore, an 8/8 HLA-MUD cohort, using the same methodology described in the submitted 841 report, has been added. The 8/8 HLA-MUD cohort consists of a total of 426 patients (abatacept+CNI/MTX, 71 patients [17%]; CNI/MTX, 355 patients [83%]). The analyses provided in the response include comparison of abatacept+CNI/MTX to 3 different GvHD prophylaxis approaches, CNI/MTX, CNI/MTX+ATG and PT-Cy+Tac+MMF, for two outcomes: OS (the primary endpoint), and RFS (one of the exploratory endpoints).

1-year results in the 7/8 cohort

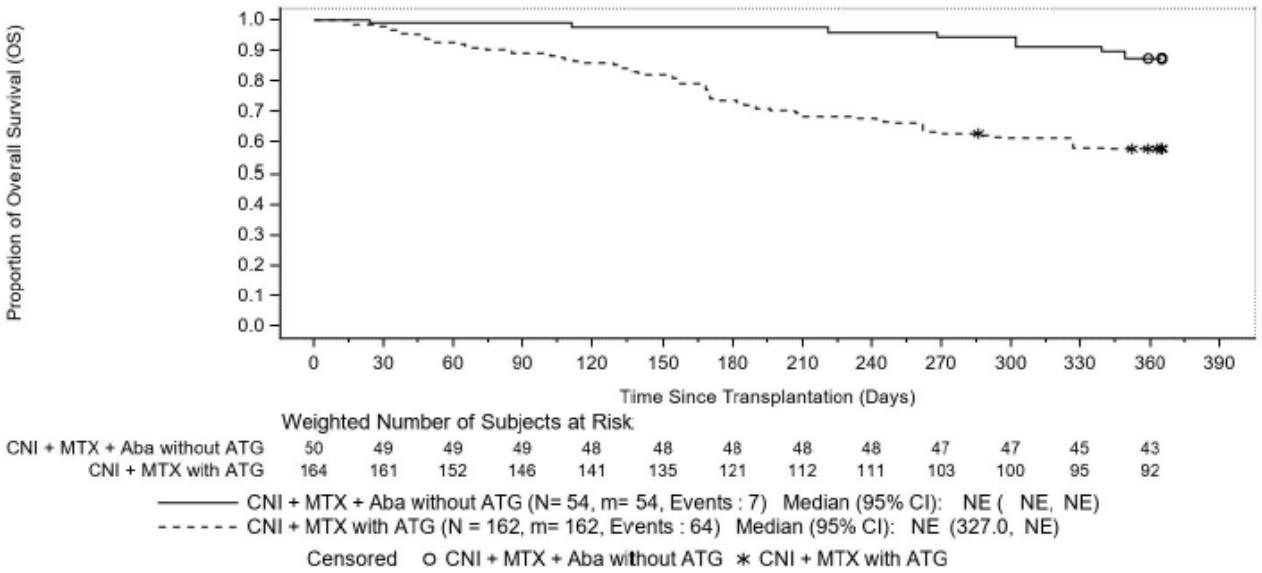
The OS K-M plot for 1 year, comparing abatacept+CNI/MTX against CNI/MTX in the 7/8 MMUD cohort, is displayed in Figure 36. The OS survival rate at Day 365 was 86% (95% CI 68, 95) for abatacept+CNI/MTX vs 61% (95% CI 53, 69) for CNI/MTX; p-value from logrank test: 0.0046; HR (95% CI): 0.28 (0.12-0.68) using treatment as covariate.

Figure 36 ***K-M Plot of OS During 365 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores, 7/8 HLA-MMUD cohort, abatacept+CNI/MTX vs CNI/MTX***



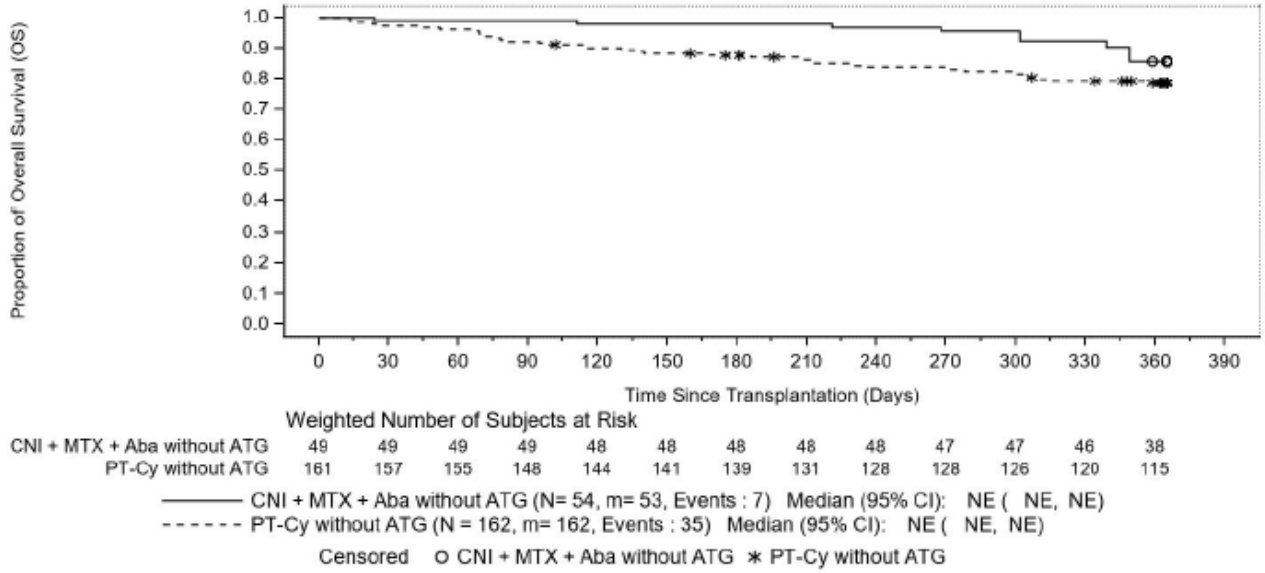
As seen in Figure 37, the comparison of abatacept+CNI/MTX to CNI/MTX with ATG also continued to favour abatacept at Day 365. OS survival rates were 87% (95% CI 67, 95) for abatacept+CNI/MTX vs 58% (95% CI 49, 66) for CNI/MTX with ATG; p-value from log-rank test: 0.0026; HR (95% CI): 0.24 (0.10-0.55) using treatment as covariate.

Figure 37 ***K-M Plot of OS During 365 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores, 7/8 HLA-MMUD cohort, abatacept+CNI/MTX to CNI/MTX with ATG***



In the comparison to prophylaxis with PT-Cy+Tac+MMF at Day 365 (Figure 38), OS survival rates at Day 365 were 86% (95% CI 66, 94) for abatacept+CNI/MTX vs 79% (95% CI 70, 85) for PT-Cy; p-value from log-rank test: 0.3376.

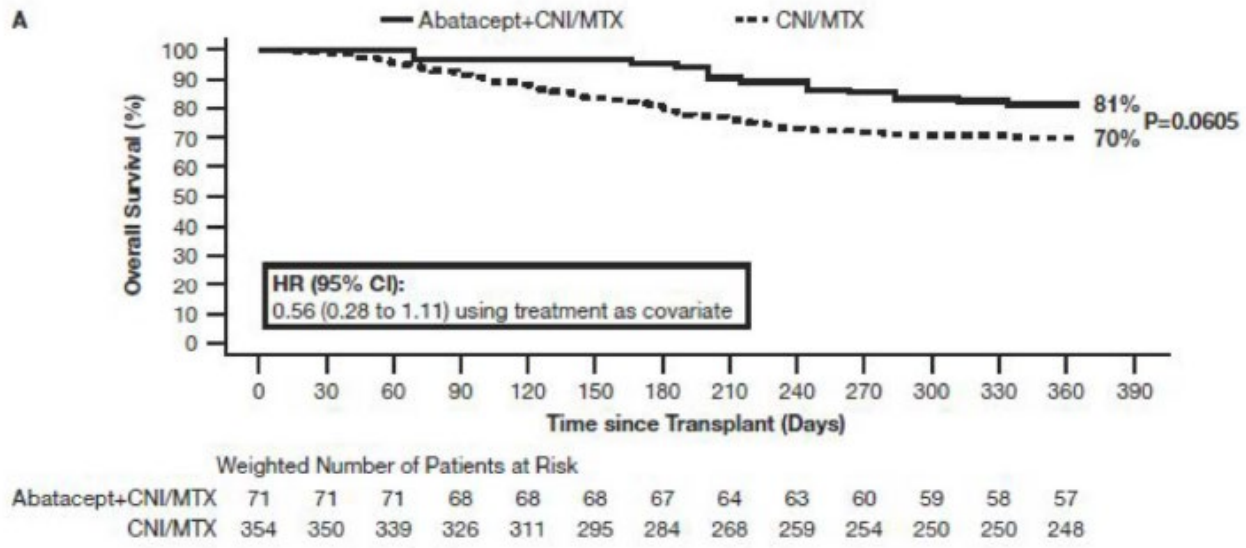
Figure 38 ***K-M Plot of OS During 365 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores, 7/8 HLA-MMUD, abatacept+CNI/MTX vs PT-Cy+Tac+MMF***



1-year results in the 8/8 cohort

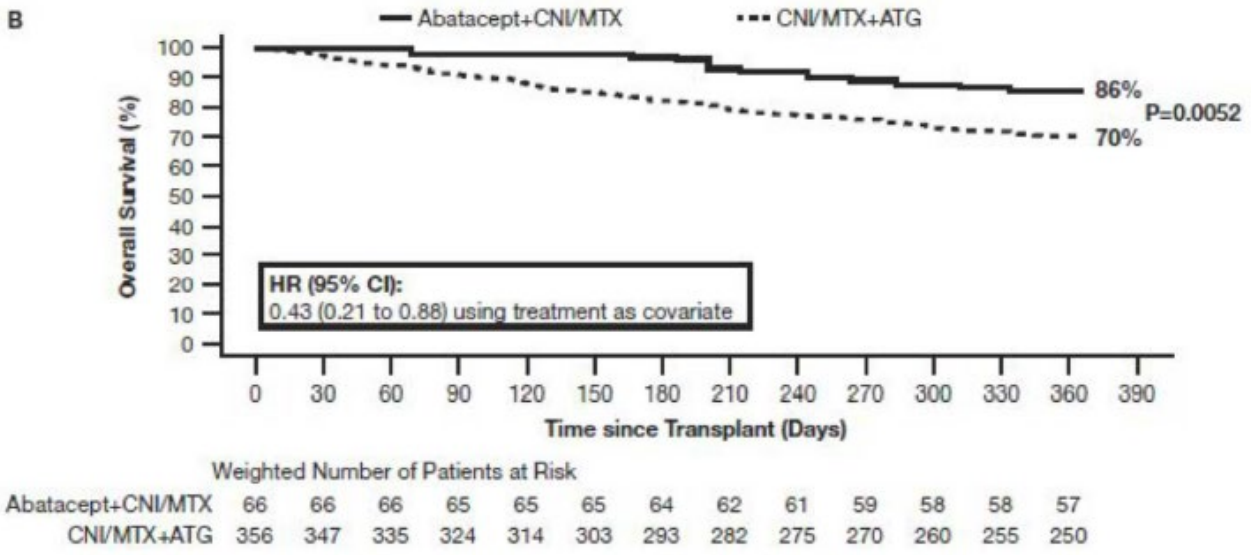
The OS K-M plot for 1 year, comparing abatacept+CNI/MTX against CNI/MTX in the 8/8 MUD cohort, is displayed in Figure 39. The OS survival rate at Day 365 was 81% (95% CI 68, 89] for abatacept+CNI/MTX vs. 70% (95% CI 65, 74) for CNI/MTX; p value = 0.0605.

Figure 39 ***K-M Plot of OS During 365 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores, 8/8 HLA-MUD cohort, abatacept+CNI/MTX vs CNI/MTX***



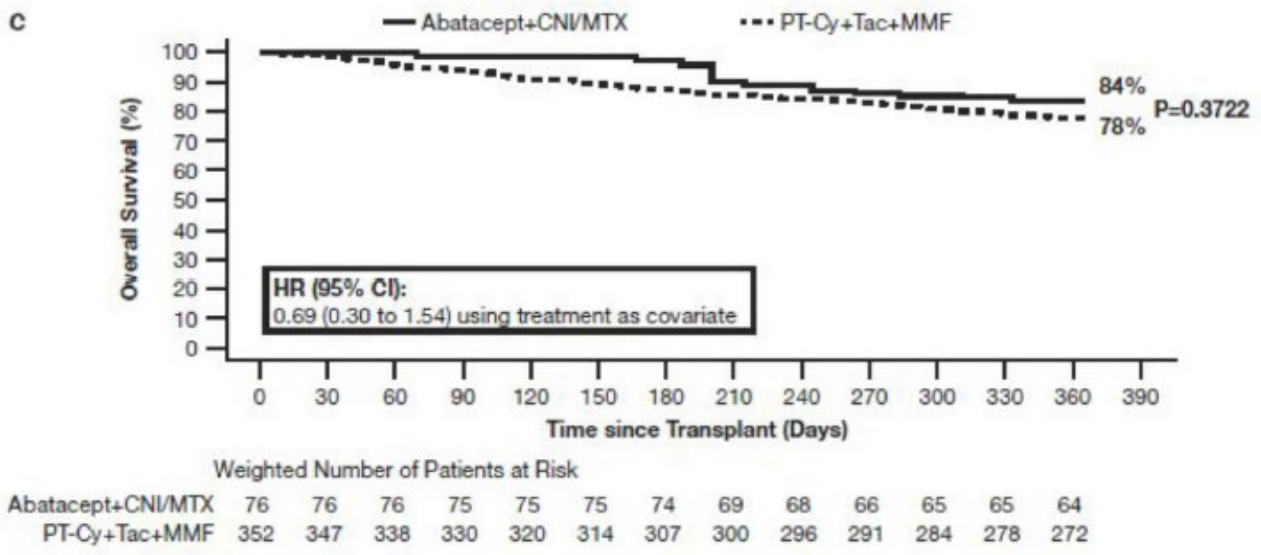
In the comparison to CNI/MTX+ATG (Figure 40), the OS rates at Day 365 were 86% (95% CI 72, 93) for abatacept+CNI/MTX vs. 70% (95% CI 65, 75) for CNI/MTX+ATG; p-value = 0.0052.

Figure 40 ***K-M Plot of OS During 365 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores, 8/8 HLA-MUD cohort, abatacept+CNI/MTX vs CNI/MTX with ATG***



In the comparison to PT-Cy+Tac+MMF (Figure 41), OS rates at Day 365 were 84% (95% CI 66, 93) for abatacept+CNI/MTX vs. 78% (95% CI 73, 82) for PT-Cy+Tac+MMF; p-value=0.3722.

Figure 41 ***K-M Plot of OS During 365 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores, 8/8 HLA-MUD cohort, abatacept+CNI/MTX vs PT-Cy+Tac+MMF***



At present, no other data, or materials supporting the graphical data outputs displayed above, have been provided for assessment.

CHMP's comments

Similar to Study 311, the newly provided data are considered very useful in principle and could be used to mitigate the initially raised concerns. In particular, the newly available 8/8 MUD cohort is significant in showing a beneficial net effect on OS vs ATG in this group of patients. It should however be noted that no data has been made available concerning GvHD, an endpoint that in relation to the sought indication would have more direct applicability than RFS. The origin of the 8/8 cohort is also currently not yet clear and it remains to be confirmed whether the abatacept group includes the patients participating in Study 311 (as is the case for the 7/8 cohort).

Overall, as also stated for Study 311, the nature and quality of the information provided in the MAH's response is, in the CHMP's opinion, inadequate for purposes of regulatory decision-making. The same quality standards should apply to all follow-up information that has a significant bearing on final assessment of benefit-risk, and the MO thus covers follow-up data for both studies. ***MO***

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 59 ***Summary of Efficacy for trial IM101311***

Title: Abatacept Combined with a Calcineurin Inhibitor and Methotrexate for Graft Versus Host Disease Prophylaxis		
Study Identifier	IM101311	
Design	Study IM101311 was a multicenter Phase 2 trial with 2 cohorts: a randomized, double blind, placebo-controlled cohort (8/8 matched unrelated donors [MUD] cohort) for subjects who received a hematopoietic stem cell transplantation (HSCT) from 8/8 MUD and a single arm cohort (7/8 mismatched unrelated donors [MMUD] cohort) for subjects who received a HSCT from 7/8 MMUD. The duration of the study for each cohort is 5 years post transplantation. The original protocol required all subjects enrolled into the study (both 8/8 MUD cohort and 7/8 MMUD cohort) to be randomized to either study medication (abatacept [intravenous] + standard prophylaxis regimen calcineurin inhibitor [CNI] + methotrexate [MTX]) or placebo arm (CNI + MTX). Following initiation of the study, but independent of it, a general impression began to emerge among members of the HSCT transplant community that addition of abatacept to a standard of care (SOC) regimen for acute graft vs host disease (aGvHD) prophylaxis appeared to be therapeutically beneficial. Investigators felt it was not ethical to enroll recipients of 7/8 MMUD if they could be randomized to the placebo arm of the study, given known high risks of transplant-related mortality with placebo; this emerging consensus resulted in a prolonged delay in enrolment of the 7/8 MMUD cohort that necessitated elimination of the placebo arm by protocol amendment (Amendment 04). After the implementation of Protocol Amendment 04, all subjects enrolled in the 7/8 MMUD cohort received open-label abatacept; the placebo arm was discontinued in the 7/8 MMUD cohort.	
	Duration: Study Initiation Date: 15-Apr-2013 Last Patient Last Visit for the Primary Clinical Study Report (CSR): 17-Nov-2018	
Hypothesis	Superiority of abatacept added to CNI +MTX SOC for aGvHD prophylaxis in allogeneic HSCT recipients.	
Treatment Groups	8/8 MUD Cohort: Abatacept+CNI+MTX Placebo+CNI+MTX 7/8 MMUD Cohort: Abatacept+CNI+MTX	
Endpoints and Definitions	Primary Endpoint	Severe (Grade [Gr] III-IV) aGvHD free survival (GFS) up to Day 180: Defined as the time between the date of transplant and the onset date of documented severe (Gr III-IV) aGvHD, or death due to any cause up to Day 180 post-transplant, whichever occurred first.
	Key Secondary Endpoint	Cumulative incidence of severe (Gr III/IV) aGvHD up to Day 180 post transplantation: For the purpose of the analysis plan for this submission, severe aGvHD events up to Day 180 were considered (instead of Day 100, which was the primary endpoint in the protocol) post-transplant to align with regulatory expectations. The aGvHD events in this definition of GFS are the adjudicated Gr III-IV aGvHD events.
Database Cutoff Date	Database Lock for the Primary CSR (primary analysis): 06-Nov-2020	
Analysis population	8/8 MUD cohort modified intent to treat (MITT) analysis population: all randomized and transplanted subjects who received at least one dose of study medication of either the abatacept or placebo treatment group. There were 146 subjects enrolled in the 8/8 MUD cohort of the study of which 142 were treated with study medication and transplanted; 73 with abatacept and 69 with placebo. 7/8 MMUD cohort treated analysis population: all 7/8 cohort subjects who received at least 1 dose of abatacept. There were 46 subjects enrolled in the 7/8 MMUD cohort of the study of which 44 were treated with study medication and transplanted; 43 subjects with abatacept (including 3 prior to Amendment 04) and 1 subject randomized to placebo group prior to Amendment 04.	

Summary of Primary and Key Secondary Efficacy Endpoints in Study IM101311 (8/8 MUD Cohort MITT Analysis Population)

Efficacy Parameter	Abatacept (N = 73)	Placebo (N = 69)
Primary Efficacy Endpoint		
Gr III-IV aGvHD-Free Survival		
Events, n (%)	10 (13.7)	17 (24.6)
Survival Rate (95% CI) [a]		
Day 100	0.92 (0.83, 0.96)	0.83 (0.71, 0.90)
Day 180	0.89 (0.79, 0.94)	0.77 (0.65, 0.85)
HR (95% CI) [b]	0.54 (0.25, 1.19; P-value = 0.1223) [c]	
Sensitivity analysis		
GFS rate		
Day 180	93.0%	80.0%
HR (95% CI) [b]	0.34 (0.12, 0.96); P-value = 0.0324 [c]	
Key Secondary Efficacy Endpoint		
Gr III-IV Severe aGvHD - Cumulative Incidence Rate		
Cumulative Incidence Rate (95% CI)		
≤ 21 years of age		
Day 100	0.05 (0.02, 0.15)	0.12 (0.04, 0.36)
Day 180	0.05 (0.02, 0.15)	0.12 (0.04, 0.36)
> 21 years of age		
Day 100	0.07 (0.03, 0.18)	0.17 (0.10, 0.30)
Day 180	0.07 (0.03, 0.18)	0.17 (0.10, 0.30)
HR (95% CI) [d]	0.41 (0.14, 1.16); P-value = 0.0942 [d]	

[a] Based on Kaplan-Meier estimates
[b] Cox proportional hazards model stratified by age group at randomization (<=21 years versus > 21 years) with treatment as the only covariate. Hazard ratio is abatacept over placebo
[c] Log-Rank test stratified by age group at randomization (<=21 years versus > 21 years)
[d] Wald confidence interval and p-value are presented

Summary of Primary and Key Secondary Efficacy Endpoints in Study IM101311 (7/8 MMUD cohort treated analysis population)

Efficacy Parameter	Abatacept (N = 43)
Primary Efficacy Endpoint	
Gr III-IV aGvHD-Free Survival	
Events, n (%)	2 (4.7)
Survival Rate (95% CI) [a]	
Day 100	0.98 (0.85, 1.00)
Day 180	0.98 (0.85, 1.00)
Key Secondary Efficacy Endpoint	
Gr III-IV Severe aGvHD - Cumulative Incidence Rate	
Cumulative Incidence Rate (95% CI) [b]	
Day 100	0.02 (< 0.01, 0.11)
Day 180	0.02 (< 0.01, 0.11)

[a] Based on Kaplan-Meier estimates
[b] Cumulative incident estimates based on unstratified Gray's model

Abbreviations: aGvHD = acute Graft vs Host Disease; CI = confidence interval; CNI = calcineurin inhibitor; CSR = clinical study report; GFS = aGvHD Free Survival; GvHD = graft vs. host disease; Gr = Grade; HR = hazard ratio; HSCT = hematopoietic stem cell transplantation; MITT = modified intent-to-treat; MTX = methotrexate; MUD = matched unrelated donors; MMUD = mismatched unrelated donors; SD = standard deviation; SOC = standard of care

Table 60 ***Summary of Efficacy for trial IM101841***

Title: 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 International Blood and Marrow Transplant Research Database		
Study Identifier	IM101841	
Design	Study IM101841 was a retrospective cohort study using data routinely collected into the Center for International Blood and Marrow Transplant Research (CIBMTR®) database. CIBMTR collects data on all allogeneic (related and unrelated) hematopoietic stem cell transplantation (HSCTs) performed in the United States (US) and on all HSCTs done with products procured through the C. W. Bill Young Cell Transplantation Program but performed outside of the US.	
	Duration: Study Initiation Date: 10-Oct-2020 Study Completion Date: 15-Feb-2021 Study Period: 01-Jan-2011 to 31-Dec-2018	
Primary Objective	To compare the overall survival (OS) with 180 days of follow-up post-HSCT in 7/8 human leukocyte antigen (HLA)-matched patients treated with calcineurin inhibitor (CNI) + methotrexate (MTX) + abatacept without anti-thymocyte globulin (ATG) to those treated with CNI + MTX without ATG	
Treatment Groups	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 one of the following graft vs. host disease (GvHD) prophylaxis regimens: • CNI + MTX + abatacept without ATG • CNI + MTX with ATG • Tacrolimus + MTX + abatacept without ATG • Tacrolimus + MTX without ATG • Post-transplant cyclophosphamide (PT-Cy) without ATG • Cyclosporin A (CsA) + MTX + abatacept without ATG • CsA + MTX without ATG	
Endpoints and Definitions	Primary Endpoint	Overall survival: Defined as death by any cause, evaluated during 180 days of follow-up post-transplant, in subjects treated with abatacept+CNI+MTX without ATG vs. CNI+MTX without ATG. Subjects that were still alive were censored at 181 days after transplantation. OS time was defined as the time between the date from allogeneic transplant to the documented date of death as reported by treating physicians.
	Secondary Endpoints	Overall survival in subjects treated with abatacept+CNI+MTX without ATG, compared to those treated with CNI+MTX with ATG: **e**valuated during 180 days of follow-up post-transplant. Subjects that were still alive were censored at 181 days after transplantation.
		Overall survival in subjects treated with abatacept+tacrolimus+MTX without ATG and those treated with tacrolimus+MTX without ATG: evaluated during 180 days of follow-up post-transplant. Subjects that were still alive were censored at 181 days after transplantation.
Abbreviations: ATG = anti-thymocyte globulin; CIBMTR = Center for International Blood and Marrow Transplant Research; CNI = calcineurin inhibitor; CsA = cyclosporin A; GvHD = graft vs. host disease; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplantation; OS = overall survival; PT-Cy = post-transplant cyclophosphamide; US = United States		
Analysis population	Patients from the CIBMTR database who were included in the analyses were those in the US who had received a first allogenic transplant from an unrelated donor with whom they were HLA-matched at 7/8 loci (A, B, C, DRB1). Patients with AML,	

	ALL, CML, MDS, HL, NHL were included. Analysis populations were based on GvHD prophylaxis treatment as follows: • GvHD prophylaxis treatments: – CNI + MTX (with or without ATG and with or without abatacept) – Tacrolimus + MTX ± abatacept – PT-Cy without ATG – CsA + MTX ± abatacept without ATG – CNI + MTX + abatacept without ATG who were enrolled in the IM101311 clinical trial – CNI + MTX + abatacept without ATG who were not enrolled in the IM101311 clinical trial (off-label use setting)

Summary of Primary and Secondary Efficacy Endpoints in Study IM101841		
Primary Efficacy Endpoint		
	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
Secondary Efficacy Endpoints		
Comparator Group with ATG		
	CNI+MTX+Aba without ATG (N = 54)	**CNI+MTX with ATG (N = 162)**
Proportion With Event (n/m, %)	2/54 (3.7)	41/162 (25.3)
Median Time to Event [a]	NE	NE
95% CI of Median Time	(NE, NE)	(NE, NE)
Survival Rate at Day 180 [a]	0.98	0.74
95% CI of Survival Rate	(0.76, 1.00)	(0.65, 0.80)
p-value from Log Rank Test [a]	0.0060	NA
Hazard Ratio vs. Comparator Group [b]	0.08	NA
95% CI of Hazard Ratio	(0.02, 0.36)	NA
Hazard Ratio vs. Comparator Group [c]	0.10	NA
95% CI of Hazard Ratio	(0.02, 0.49)	NA

[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.

Abbreviations: ATG = anti-thymocyte globulin; CIBMTR = Center for International Blood and Marrow Transplant Research; CI = confidence interval; CNI = calcineurin inhibitor; CsA = cyclosporin A; GvHD = graft vs. host disease; HLA = human leukocyte antigen; MTX = methotrexate; NA = not applicable; NE = not estimable; PT-Cy = post-transplant cyclophosphamide

Clinical studies in special populations

A post-hoc analysis was undertaken in the paediatric subgroup of Study 311. As outlined above, there were 27 randomised subjects in the 8/8 MUD cohort who were 6 to 17 years old; 14 were randomised to abatacept and 13 were randomised to placebo. In the single-arm 7/8 MMUD cohort, 16 randomised subjects were 6 to 17 years old. Distribution by age group is displayed in Table 61.

Table 61 ***Number of Paediatric Participants by Cohort and Age Group***

		N		
Age group (years old)		**6-11**	**12-17**	**Total**
7/8 cohort		8	8	16
8/8 cohort	abatacept	4	10	14
	placebo	6	7	13
Total		18	25	43

Severe GFS rates and OS rates by age group at 180 days post-transplant are displayed in Table 62 and Table 63 for the 8/8 MUD cohort, and Table 64 and Table 65 for the 7/8 MMUD cohort.

Table 62 ***Summary of Grade III/IV aGvHD Free Survival (GFS) During the Day 180 Analysis Period By Age Group in Paediatric Subjects: 8/8 MUD Cohort MITT Analysis Population***

Age Group: 6 - 11 YEARS

Endpoints	Abatacept n / N (%)	Placebo n / N (%)	Hazard Ratio Estimate (B)	Estimate 95% CI	p-value Log-Rank Test (C)
GFS EVENT	0/4	1/6 (16.7%)	NA	(NA, NA)	0.4142
MEDIAN TIME TO GFS EVENT (DAYS) (A)	NE	NE			
95% CI OF MEDIAN TIME	(NE , NE)	(33.00 , NE)			
SURVIVAL RATE (A) (95% CI)					
DAY 100	1.00 (1.00, 1.00)	0.83 (0.27, 0.97)			
DAY 180	1.00 (1.00, 1.00)	0.83 (0.27, 0.97)			

Age Group: 12 - 17 YEARS

Endpoints	Abatacept n / N (%)	Placebo n / N (%)	Hazard Ratio Estimate (B)	Estimate 95% CI	p-value Log-Rank Test (C)
GFS EVENT	0/10	1/7 (14.3%)	NA	(NA, NA)	0.2320
MEDIAN TIME TO GFS EVENT (DAYS) (A)	NE	NE			
95% CI OF MEDIAN TIME	(NE , NE)	(93.00 , NE)			
SURVIVAL RATE (A) (95% CI)					
DAY 100	1.00 (1.00, 1.00)	0.86 (0.33, 0.98)			
DAY 180	1.00 (1.00, 1.00)	0.86 (0.33, 0.98)			

n = Number of subjects with GFS event (Grade III/IV aGvHD or death), N = Total number of subjects in the Treatment Group.

(A) Based on Kaplan-Meier estimates

(B) Unstratified Cox proportional hazards model with treatment as the only covariate. Hazard ratio is Abatacept over placebo.

(C) Unstratified Log-Rank test

NE: Not Estimable.

Estimation of Hazard Ratio is Not Applicable (NA).

Table 63 ***Summary of Overall Survival (OS) up to Day 180 Visit By Age Group in Paediatric Subjects: 8/8 MUD Cohort MITT Analysis Population***

Age Group: 6 - 11 YEARS					
Endpoints	Abatacept n / N (%)	Placebo n / N (%)	Hazard Ratio Estimate (B)	Estimate 95% CI	p-value Log-Rank Test (C)
OS	0/4	0/6	NA	(NA, NA)	NA
MEDIAN TIME TO DEATH (DAYS) (A)	NE	NE			
95% CI OF MEDIAN TIME	(NE , NE)	(NE , NE)			
SURVIVAL RATE (A) (95% CI)					
DAY 100	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)			
DAY 180	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)			
Age Group: 12 - 17 YEARS					
Endpoints	Abatacept n / N (%)	Placebo n / N (%)	Hazard Ratio Estimate (B)	Estimate 95% CI	p-value Log-Rank Test (C)
OS	0/10	1/7 (14.3%)	NA	(NA, NA)	0.2320
MEDIAN TIME TO DEATH (DAYS) (A)	NE	NE			
95% CI OF MEDIAN TIME	(NE , NE)	(93.00 , NE)			
SURVIVAL RATE (A) (95% CI)					
DAY 100	1.00 (1.00, 1.00)	0.86 (0.33, 0.98)			
DAY 180	1.00 (1.00, 1.00)	0.86 (0.33, 0.98)			

n = Number of subjects who have died, N = Total number of subjects in the Treatment Group.

(A) Based on Kaplan-Meier estimates

(B) Unstratified Cox proportional hazards model with treatment as the only covariate. Hazard ratio is Abatacept over placebo.

(C) Unstratified Log-Rank test

NE: Not Estimable.

Estimation of Hazard Ratio is Not Applicable (NA).

Table 64 ***Summary of Grade III/IV aGvHD Free Survival (GFS) During the Day 180 Analysis Period By Age Group in Paediatric Subjects: 7/8 MMUD Cohort Treated Analysis Population***

Age Group: 6 - 11 YEARS	
Endpoints	Abatacept n / N (%)
GFS EVENT	0/8
MEDIAN TIME TO GFS EVENT (DAYS) (A)	NE
95% CI OF MEDIAN TIME	(NE , NE)
SURVIVAL RATE (A) (95% CI)	
DAY 100	1.00 (1.00, 1.00)
DAY 180	1.00 (1.00, 1.00)
Age Group: 12 - 17 YEARS	
Endpoints	Abatacept n / N (%)
GFS EVENT	1/8 (12.5%)
MEDIAN TIME TO GFS EVENT (DAYS) (A)	NE
95% CI OF MEDIAN TIME	(35.00 , NE)
SURVIVAL RATE (A) (95% CI)	
DAY 100	0.88 (0.39, 0.98)
DAY 180	0.88 (0.39, 0.98)

n = Number of subjects with GFS event (Grade III/IV aGvHD or death), N = Total number of subjects in the Treatment Group.

(A) Based on Kaplan-Meier estimates

NE: Not Estimable.

Table 65 ***Summary of Overall Survival (OS) up to Day 180 Visit By Age Group in Paediatric Subjects: 7/8 MMUD Cohort Treated Analysis Population***

Age Group: 6 - 11 YEARS	
Endpoints	Abatacept n / N (%)
OS	0/8
MEDIAN TIME TO DEATH (DAYS) (A)	NE
95% CI OF MEDIAN TIME	(NE , NE)
SURVIVAL RATE (A) (95% CI)	
DAY 100	1.00 (1.00, 1.00)
DAY 180	1.00 (1.00, 1.00)

Age Group: 12 - 17 YEARS	
Endpoints	Abatacept n / N (%)
OS	1/8 (12.5%)
MEDIAN TIME TO DEATH (DAYS) (A)	NE
95% CI OF MEDIAN TIME	(112.00 , NE)
SURVIVAL RATE (A) (95% CI)	
DAY 100	1.00 (1.00, 1.00)
DAY 180	0.88 (0.39, 0.98)

n = Number of subjects who have died, N = Total number of subjects in the Treatment Group.
(A) Based on Kaplan-Meier estimates
NE: Not Estimable.

CHMP's comments

The number of paediatric patients included in the study was very small, and no definitive conclusions can be made; moreover, the analyses are limited to the Day 180 data only. With due consideration to these limitations, the results seem generally consistent with those in the broader population and are not suggestive of inferior efficacy or detrimental effects among paediatric patients.

The MAH is requested to repeat the analyses by paediatric age group for the long-term data and provide the results, including data on cGvHD, as part of the response to the 2nd RSI. ***OC***

It is to be noted that no patients under 6 years of age were enrolled in the study; the proposal to extend the age group down to 2 years and above is thus completely dependent on extrapolation based on pharmacokinetic considerations.

4.4.3. Discussion on clinical efficacy

The current variation application is based on results from two partly overlapping studies:

- Study 311 was an investigator-sponsored, multicentre Phase 2 trial with 2 treatment populations: a randomised, double-blind, placebo-controlled cohort for patients receiving HSCT from 8 of 8 HLA-matched donors, and a single-arm cohort for patients receiving HSCT from 7 of 8 HLA-matched donors. The primary objective of the study was to assess the impact of abatacept on the incidence of severe aGVHD, when added to a background GvHD

prophylactic regimen (CNI + MTX) administered to patients with haematological malignancies receiving an unrelated-donor HSCT.

- Study 841 was a registry study using data routinely collected into the CIBMTR database. The primary objective of the registry study was to compare OS with 180 days of follow-up post-HSCT in 7/8 HLA-matched patients treated with CNI + MTX + abatacept without ATG to those treated with CNI + MTX without ATG. A number of other comparator groups were also included in the study. Notably, the 7/8 MMUD cohort of Study 311 was also included in Study 841 and indeed accounts for over 80% of patients in the "CNI + MTX + abatacept without ATG" group of Study 841.

Design and conduct of clinical studies

Study IM101311

The main study in the current application (IM101311) was an investigator-sponsored Phase 2 study conducted in two treatment populations. Patients receiving HSCT from an 8 of 8 HLA-matched donor (the 8/8 MUD cohort) were included in a double-blind placebo-controlled study. Patients receiving HSCT from a 7 of 8 HLA-matched donor (the 7/8 MMUD cohort) were also initially intended to be studied in a placebo-controlled study, but due to an emerging consensus that patients randomised to placebo would in fact be undertreated, the 7/8 cohort was rapidly converted into a single arm study. In principle, a placebo-controlled design is considered well suited for purposes of assessing the absolute effect of abatacept when added on top of standard of care. The main eligibility criteria were appropriately set in relation to the study objectives. Since the clinical outcomes of the 7/8 MMUD HSCTs plus Standard of Care therapies are generally much worse compared to 8/8 MUD transplantations when the patients are on Standard of Care therapies, the decision that all patients in the 7/8 MMUD cohort received open-label abatacept is accepted.

The abatacept dose (intravenous) and posology resembles the previously authorised posology in rheumatoid arthritis and JIA, with one extra dose added at about 1 week after the initial dose. No separate studies evaluating dose response or different lengths of the treatment period were undertaken.

The background prophylactic regimen, comprising a combination of a calcineurin inhibitor and methotrexate, is a well-established backbone also in current European guidelines. It should however be noted that antithymocyte globulin (ATG) is broadly used as part of the regimen in both 8/8 and 7/8 matched transplantations. In this context, the decision to transition into a single arm design in the 7/8 cohort is understandable, but even the control group in the 8/8 cohort could be considered somewhat undertreated compared to current European practice. In their response to the 1st RSI, the MAH provided data from an 8/8 cohort in the registry study 841, comparing abatacept and ATG when added to a CNI/MTX backbone in this patient group, which could be considered to implicitly address this limitation. The MAH has provided a thorough discussion of the literature data on the use of ATGs as part of the SOC in HSCT. Based on the discussion, while ATG is broadly used in the prophylactic regimens in Europe, its effect in the prophylaxis of acute GvHD after HSCT seems somewhat inconclusive. Instead, its main benefit seems to be in prophylaxis of chronic GvHD. From a European perspective, where rATG holds an established position as part of the prophylactic regimen in many instances, it should be borne in mind that abatacept would likely be viewed as an alternative to rATG rather than the two agents being used together, as this combination would very likely lead to profound and excessive immunosuppression.

The primary objective of the study was to evaluate efficacy against acute GvHD, and the timing of primary efficacy assessment at D180 post-transplant is selected accordingly. Other more general endpoints related to treatment benefit, including overall survival, were primarily evaluated within the same timeframe. Whereas it can be agreed that most instances of acute GvHD could be caught within

this timeframe, this approach has limitations for other endpoints. Moreover, it is not clear that capturing prevention of acute GvHD as an isolated phenomenon is sufficient demonstration of efficacy in the context of aHSCT, and it could be expected that clinically relevant effects on other endpoints, including overall survival, should also be shown to sufficiently support a claim of actual clinical benefit. As such, the additional analyses up to database lock, provided as supplementary analyses by the MAH, are considered of equal importance compared to the D180 analyses.

Late onset acute GvHD and chronic GvHD seem to be somewhat overlapping conditions. The MAH was therefore requested to clarify how late onset aGvHD and cGvHD were differentiated in the study (noting also that the frequency of early onset (before day 100) aGvHD was proposed as the primary endpoint in the Investigator sponsored research protocol). In the MAH's response, the requested clarification was provided, and the numbers of late onset acute GvHD events were provided separately by cohorts and treatment groups, as requested in the RSI.

The analysis of 8/8 MUD cohort's data was prespecified as being based on Day 180 database (allowing an assessment window up to Day 225). Although the majority of acute aGvHD events are expected with the first few months, an assessment of GFS for a full year is considered necessary and is anyway available in the submission. The assessment needs to consider the possibility that after the most intense period of aGvHD during the first few months, GFS distribution may be driven by deaths not related to aGvHD and likely unrelated to whether abatacept was or was not used which will reduce the sensitivity of the study to detect an effect on GvHD as measured by GFS.

Conventional time-to-event analysis methods were used for the primary endpoint GFS. Arguably, the question could be also posed in a binary way: instead of asking how soon the problems started, one could evaluate whether severe GFS events occurred during, and whether subject survived e.g. the full first year after the transplant. Indeed, the goal of the prophylaxis is not to postpone the inevitable severe aGvHD events but to prevent them altogether. The benefit of time-to-event methods, however, is their ability to handle incomplete follow-ups. In the current study, the analysis timings were set to ensure complete follow-up of all enrolled subjects up to the respective milestone. Given that few subjects dropped out intermittently, evaluation of simple proportions would have done little injustice to the data. Nevertheless, the proportions of subjects with GSF at, e.g., Day 365 can be descriptively compared based on the time-to-event analysis provided by the MAH. The use of time-to-events methods are ever more important in later analysis time points where subjects have variable durations of long-term follow-up.

Severe aGvHD events were analysed as the key secondary endpoint using competing risks methods. When focusing on the abatacept's effect specifically on severe aGvHD prevention it is appropriate to acknowledge that death not related to severe aGvHD is a competing risk that precludes occurrence of subsequent severe aGvHD. The same is not true for the other competing risk considered: relapse of underlying malignancy. The MAH has justified this approach stating that other medications are used in case the underlying malignancy relapses which may trigger aGVHD event and withdrawal of immunosuppression. It is questionable as to whether severe aGvHD events following disease relapse no longer matter. To this end, the MAH was requested to provide an analysis of severe aGvHD incidence without considering disease relapse a competing event. In response, the MAH provided analyses of severe aGvHD incidence in which subjects were either censored or not censored on the date of relapse considering disease recurrence. The results of these analyses (see section 5.4.2) were rather consistent, and it can be concluded that censoring at the time of disease relapse did not have a great impact on the severe aGvHD results up to Day 180 visit. The same can be said about the comparison of modelling approach: whether disease relapse is treated as a competing risk, as done in the primary CSR analyses, or censored as done in the analysis provided in response to the RSI.

The MAH has plotted cumulative incidence curves over time from the Fine & Gray model sub-distribution hazard model. These plots suggest the sub-distribution hazard ratio between treatments as being constant over time in both age categories identically with the events happening at the same time in both arms. Notably, this reflects a premise of Fine & Gray model as implemented rather than observed events.

The study was conducted at transplant centres in the US and Canada. For the 8/8 MUD cohort, subjects were enrolled at 13 sites in the US and 1 site in Canada. For the 7/8 MMUD cohort, subjects were enrolled at 9 sites in the US. The original protocol for the investigator-sponsored study was dated 12 May 2012. First patient first visit date was 15 April 2013 and the last patient last visit (LPLV) for purposes of preparation of the MAH's CSR was 17 November 2018. The clinical database lock for the MAH's CSR occurred on 06 November 2020. At the time of the initial submission, the investigator-sponsored study remained ongoing, with a planned total duration of follow-up of 5 years and LPLV expected in February 2023. The study protocol underwent several substantial changes, including a change in primary endpoint and subsequent return to the original primary endpoint and a conversion of the 7/8 cohort into a single arm. Most of the changes were related to changes in assumptions with impact on sample size, planned interim analyses and stopping rules. In total, while the changes are substantial, they appear to have been managed adequately and do not seem to adversely impact study integrity or reliability of the results.

In total, 146 subjects were enrolled into the 8/8 MUD cohort of Study 311 and randomly assigned 1:1 to abatacept or placebo treatment groups. Of these, 142 subjects were treated with study medication and transplanted; 73 received abatacept and 69 received placebo. In the 7/8 MMUD cohort, of the 46 subjects that were enrolled, 44 were treated with study medication and transplanted; 43 subjects were treated with abatacept and 1 subject was randomised to the placebo group prior to the cohort being converted into a single arm. Four subjects in the 8/8 MUD cohort, who did not get a single dose of study medication, were excluded from the efficacy analyses which is acceptable in a placebo-controlled trial as no bias could occur from such pre-treatment selection.

In the 8/8 MUD cohort, the number of deaths reported as a reason for study discontinuation until D180 was higher in the placebo group than in the abatacept group [1 (1.4%) vs. 5 (8.7%]. On the other hand, the number of such deaths reported after D180 is higher in the abatacept group than in the placebo group [9 (12.3%) vs. 5 (7.2%)]. Relapses leading to discontinuation of treatment were slightly higher for placebo than abatacept [15 (21.7%) vs. 12 (16.4%].

In the 7/8 MMUD cohort, there were no deaths reported as a reason for study discontinuation until D180; after D180, 6 such deaths (14%) have been reported. Relapses leading to discontinuation of treatment occurred in 4 subjects (9.3%).

In the 8/8 MUD cohort, median age was 44 years (range 6-71 years), 55% of subjects were male and 45% were female, and 87% were White. Twenty-seven (19%) randomised subjects in the 8/8 MUD cohort were 6 to 17 years old; 14 were randomised to abatacept and 13 were randomised to placebo. The most common types of malignancy among subjects were AML (37%), ALL (30%) and MDS (19%). A large majority of subjects (84%) received tacrolimus for GvHD prophylaxis.

In the 7/8 MMUD cohort, median age was 38 years (range 6-76 years), 63% of subjects were male and 37% were female; 72% were White and 16% were Black. In the 7/8 MMUD cohort, 16 (37%) randomised subjects were 6 to 17 years old. The most common types of malignancy among subjects were AML (35%), MDS (26%) and ALL (19%). Also in this cohort, the majority of subjects (63%) received tacrolimus for GvHD prophylaxis.

The spectrum of diseases serving as the indication for aHSCT can be considered overall representative as compared to current treatment strategies. The majority of patients received a myeloablative conditioning regimen. As regards the CNI component of the GvHD prophylaxis regimen, a majority of

subjects in both cohorts received TAC; this seems to reflect a practice that differs from EU, where CsA is the more commonly used CNI.

Study IM101841

Study 841 was a retrospective registry study designed to examine real-world outcomes of abatacept + SOC aGvHD prophylaxis in patients with haematological malignancies undergoing aHSCT from 7/8 MMUD subjects. The study utilised data routinely collected for the CIBMTR database and sought to compare treatment outcomes among patients treated with abatacept +CNI+MTX to several comparator groups; the primary comparison was between patients receiving CNI + MTX + abatacept without ATG and patients receiving only CNI + MTX (without ATG). As indicated above, patients in the 7/8 MMUD cohort were included in the abatacept group of Study 841 and account for over 80% of the total abatacept sample. The eligibility criteria for patient selection can overall be agreed to define a prospective population conforming to Study 311.

Due to data constraints in the CIBMTR database, it was not feasible to evaluate GFS as a primary outcome. Based on consultation with the FDA, OS at Day 180 was used as the primary study outcome to evaluate the treatment effect of CNI + MTX + abatacept without ATG compared to CNI + MTX without ATG. OS was considered a more objective endpoint and was also recommended by the FDA.

Compared to current European practice, the comparison within the primary objective cohort (i.e. abatacept vs. no abatacept on a CNI + MTX backbone) may not be optimal, as ATG has an established position as part of the prophylactic regimen particularly in 7/8 transplants; consequently, patients in the no abatacept group may be relatively undertreated compared to current standard of care. The secondary comparison of abatacept vs. ATG added to a CNI + MTX backbone would seem the most relevant comparison in this respect; however, as the best established benefit of ATG is on prevention of chronic GvHD, the 180 day time frame may be too short for a fair and comprehensive comparison of clinical benefit.

Study IM101841 complements study IM101311 by providing a more thorough quantitative comparison with various historical reference arms representing different treatment combinations. Historical control patients were randomly drawn from CIBMTR database by CIBMTR staff. The number of control patients included in the analyses without ATG and with ATG (162 each) for the 7/8 MMUD cohort was determined by power calculation aiming at 3:1 ratio. The numbers of eligible control subjects in CIBMTR database, from which the sample was drawn, were 503 (CNI+MTX without ATG) and 623 (CNI+MTX with ATG). It may also be noteworthy that, when designing the study, the outcome in CNI + MTX + abatacept without ATG arm was almost completely known (due to the abatacept subjects being sourced from IM101311) which changes the role of sample size calculation as compared with a prospective study. It is not clear whether this was taken into account by the MAH.

The purpose of the historical reference arm is to provide an estimate of the counter-factual outcome that would have been observed if the abatacept-treated subjects (CNI + MTX + abatacept without ATG, in particular) would have been treated with specified alternative treatment combinations. Propensity score weights were estimated and used to create a pseudo-population where the abatacept-treated and control arm are balanced with respect to each of selected and measured potential confounders: gender, underlying disease, age, HSCT graft source, conditioning intensity, Karnofsky/Lansky Performance score and CNI type. Using the propensity weights, marginal treatment effect was estimated, i.e., difference of outcome in the population where everyone was treated with abatacept vs. the population where everyone was treated with the comparator treatment.

With respect to the resulting IPT weights estimated, among the small sample of 54 abatacept-treated, some subject had to be emphasized 15-fold as compared to another in order to eliminate correlation between treatment assignment and considered covariates. The downside of anticipatedly reduced

confounding bias is that the variability in weights, effectively, further reduces the "effective sample size" (a measure not found in the submission), meaning that the amount of information is less than what would be gained from 54 subjects randomised to abatacept in an RCT. This is reflected in the standard errors, confidence intervals and p-values.

Despite the critical points made above, the MAH did put effort into anticipating and addressing issues in the evaluation of effect of CNI + MTX + abatacept without ATG relative to comparator treatments. The algorithm and individual methods used are theoretically fit for purpose but do not circumvent the main limitations from statistical point of view: the fact that few subjects treated with abatacept were studied. Furthermore, when deciding on the conduct and design of the retrospective study IM101841, the outcomes of the abatacept-treated subjects were already known to a great extent. Considering the OS results among the abatacept-treated subjects, no reasonable re-weighting scheme could transform the near complete survival in the sample already observed. From this perspective, IPT-weighted analysis of abatacept-treated subjects has value mainly as a methodological exercise. The main contribution of study IM101841 is the corroborative information on the outcomes in each of comparative treatment combinations.

Patients whose first allogeneic transplant occurred from 01-Jan-2011 to 31-Dec-2018 were included in the registry. A total of 54 patients were included in the CNI + MTX + abatacept without ATG group and 162 subjects in the CNI + MTX without ATG group (i.e., the primary objective cohort). There were also 162 subjects in the CNI + MTX with ATG group.

Efficacy data and additional analyses

Study IM101311, 8/8 cohort

In the 8/8 MUD cohort, the primary endpoint was severe (Gr III-IV) GFS at Day 180. The survival rate was higher for abatacept than placebo (89% vs. 77%), but the difference was not statistically significant. The study thus formally failed on its primary endpoint, demoting the subsequent analysis in the hierarchical testing scheme (cumulative incidence of severe (Gr III-IV) aGvHD up to Day 180) as an exploratory analysis. Analyses for other endpoints were conducted outside of a Type I error -controlled framework.

The database was complete for the comparison of GFS through Day 365. By then, the Kaplan-Meier estimated GFS rate equated 0.72 in both treatment arms, although the HR estimate was 0.80 (0.48, 1.34) due to the events having occurred sooner in the placebo arm. Thus, in addition to the primary analysis formally failing, there appears to be a decrease in treatment effect over time. This seems concerning, and the MAH was therefore requested to further discuss the implications of the observations.

The cumulative incidence analysis of severe (Gr III-IV) aGvHD shows aGvHD events occurring quite soon after transplant (all events occurring by D100), whereas competing events cumulated more gradually. Even on a nominal level of testing, the difference between treatment groups on this pre-specified key secondary endpoint was not statistically significant.

At Day 180, the rate of Grade II-IV GFS was higher with abatacept than placebo. However, while this is in itself reassuring, Grade II aGvHD is mostly manageable, and the importance of the finding should be balanced against the finding of no significant difference in Grade III-IV GFS.

In the analysis of OS until Day 180, a numerical advantage was seen for abatacept over placebo. Although a small numerical OS advantage favouring abatacept remains at Day 365, the HR at Day 365 is much closer to 1 than at Day 180. Most subjects remain censored in the final analysis. The results provide little direct evidence that abatacept improves survival through the first year after transplant. However, subjects in this population may die for the underlying malignancy, which is unlikely related to

abatacept. In order to contextualise the attenuated difference in OS between the arms, the MAH was requested to present a summary and discuss the reasons for deaths and to provide updated results based on the longest feasible follow-up. While various survival analyses were discussed in the MAH's response to the RSI, tabular summaries of reasons for death were not provided, and the request is thereby reiterated. **OC**

There was no apparent difference in incidence of relapse of underlying malignancy. On the one hand, the numerically better result suggests that abatacept did not negatively modify the effect of transplant while, on the other hand, the small difference in favour of abatacept might have inflated the result of GFS if there were, perhaps by chance, higher mortality in the placebo arm related to underlying disease.

The incidence of cGvHD was substantial in both groups and slightly higher with abatacept than placebo. However, no analyses concerning e.g., the severity of cGvHD have been provided, and it remains unclear whether the slight increase in cGvHD with abatacept could be associated with clinically relevant detrimental effects, and the MAH was requested to address this finding as part of the overall discussion regarding expected clinical benefit. In their response, the MAH acknowledged the lack of effect on cGvHD and ascribed this to the short treatment course. To address this question, the MAH indicated that an investigator-sponsored study is currently underway to evaluate a longer course of treatment with abatacept.

No striking aberrations were seen in subgroup analyses based on demographic and baseline characteristics. For patients with early disease, the HR was 0.92 (abatacept vs. placebo), and in patients with AML, the HR was 1.28. Due to the small number of subjects receiving CsA as the CNI component of the prophylaxis regimen, a HR could not be calculated in this subgroup.

Study 311, 7/8 MMUD cohort

The results at Day 180 in this small cohort are strikingly positive. It is not immediately clear why results in the 7/8 cohort clearly outperform those observed in the 8/8 cohort. Although the GFS rate decreases over time (from 98% at Day 180 to 88% at Day 365), the GFS rate of 88% remains far greater than the corresponding rate (72%) in the 8/8 cohort. Results on overall survival paralleled the GFS results, with a very high 98% survival rate at Day 180 decreasing to 88% at Day 365.

Owing to the small sample size and as indicated by the nominal confidence intervals, the results are not entirely incompatible with the prior expectation that there would be lower risk of GFS events in the 8/8 MUD population than in the 7/8 MMUD population treated with abatacept. While the results of the 7/8 MMUD cohort may be considered a priori as the most accurate way of estimating respective results in the target population (with no consideration of the 8/8 MUD cohort), the difference between the 7/8 and 8/8 cohorts suggests that random chance may have given results that are better than the eventual outcomes to be expected, on average, in the target population. The MAH was therefore requested to discuss the plausibility and rationale for these findings in the 7/8 cohort as part of the general discussion concerning clinical benefit.

Chronic GvHD was the only endpoint in which the outcome was clearly inferior in the 7/8 MMUD cohort compared to abatacept-treated patients in the 8/8 MUD cohort. At Day 365, the cumulative incidence of cGvHD was estimated at 49% in the 8/8 cohort and 63% in the 7/8 cohort.

Study 311, additional data provided in the MAHs response to the 1st RSI

The dataset for the initial assessment stemmed from a database lock of November 2020, at which time most subjects in long-term analyses were censored between 300 and 400 days of follow-up. The MAH has now gained access to data for the full 5 years of follow-up, and an initial snapshot has been provided for OS and RFS. The available data appear to show that on the OS and RFS level, a net benefit vs.

placebo in the 8/8 cohort is maintained until 5 years, and that overall, the best results are seen in the 7/8 cohort. Notably however, no results have been provided for frequency or severity of cGvHD.

The newly provided data are considered very useful in principle and could be used to mitigate the initially raised concerns. However, in the CHMP's opinion, the nature and quality of the information provided in the MAH's response is not adequate for purposes of regulatory decision-making. As pointed out in the introduction to clinical efficacy, the assessment has been based on the MAH's SAP and does not take into account or consider separate analyses by the Investigators or results published in scientific articles; the same standard should apply to follow-up information that has a significant bearing on final assessment of benefit-risk. A formal MO is therefore raised in terms of the quality and regulatory suitability of the newly available data, and the MAH is expected to complete this process and provide adequate documentation for these new data, including long-term data on the frequency and severity of cGvHD, before they can be formally considered in the assessment and a determination of benefit-risk duly completed. **MO**

Study 841

Based on a limited follow-up period of 180 days, the results of Study 841 suggest a beneficial effect on overall survival when abatacept was added to a CNI + MTX prophylactic regimen in 7/8 HLA-matched patients; the respective survival rates were 98% for abatacept vs. 75% for the control group. Whereas the result is acknowledged, the study has limitations. Firstly, the duration of follow-up is quite short and may be insufficient to cover the entire period of interest post-treatment. Secondly, European standard of care very routinely includes ATG as part of the prophylactic regimen in 7/8 transplants; consequently, in the primary comparison (CNI + MTX + abatacept vs. CNI + MTX only), patients in the control group are de facto undertreated compared to European practice. It should also be recognised that the favourable result in the abatacept group is driven by patients participating in IM101311, and the results can therefore not be considered to provide any independent support for a treatment benefit. As already stated above, considering the OS results among the abatacept-treated subjects, no reasonable re-weighting scheme could transform the near complete survival in the sample already observed, and from this perspective, the main contribution of study IM101841 is the corroborative information on the outcomes in the comparative treatment combinations.

A favourable effect of abatacept vs. ATG when added to a CNI + MTX regimen is also suggested; OS at Day 180 was 98% for abatacept + CNI + MTX vs. 74% for CNI + MTX + ATG. Nevertheless, the same caveats also apply to this comparison. Furthermore, the demonstrated benefit of ATG is particularly in the prevention of cGvHD and the profile is thus somewhat different to abatacept (as currently studied). The short-term analyses provided by the MAH may therefore be insufficient in particular for a comprehensive comparison of these two agents.

Reasons for death in the different study groups have not been clearly summarised in the documentation, and the MAH was requested to provide a tabular summary and discuss relevant differences for the primary objective cohort as well as for the ATG comparison. No tabular summaries for either study were received as part of the MAH's response, and the request is thus reiterated. **OC**

In their response to the 1st RSI, the MAH indicated that Study 841 had been expanded to cover outcomes observed over 1 year post transplant; furthermore, an 8/8 HLA-MUD cohort, consisting of 426 patients (abatacept+CNI/MTX, 71 patients [17%]; CNI/MTX, 355 patients [83%]) had been added using the same methodology as described in the previously submitted CSR for Study 841. The analyses provided in the response include comparison of abatacept+CNI/MTX to 3 different GvHD prophylaxis approaches, CNI/MTX, CNI/MTX+ATG and PT-Cy+Tac+MMF, for two outcomes: OS (the primary endpoint), and RFS (one of the exploratory endpoints).

Similar to Study 311, the newly provided data are considered very useful in principle and could be used to mitigate the initially raised concerns. In particular, the newly available 8/8 MUD cohort is significant in showing a beneficial net effect on OS vs ATG in this group of patients. It should however be noted that no data has been made available concerning GFS, an endpoint that would have more direct applicability in relation to the sought indication. The origin of the 8/8 cohort is also currently not yet clear and it remains to be confirmed whether the abatacept group includes the patients participating in Study 311 (as is the case for the 7/8 cohort).

Overall, as also stated for Study 311, the nature and quality of the information provided in the MAH's response is, in the CHMP's opinion, inadequate for purposes of regulatory decision-making. The same quality standards should apply to all follow-up information that has a significant bearing on final assessment of benefit-risk, and the MO thus covers follow-up data for both studies. **MO**

Additional expert consultation

In light of the pivotal study failing on its pre-specified primary endpoint, efficacy in the sought indication cannot be considered to have been convincingly demonstrated; moreover, the overall relevance of the claimed indication is also not straight-forward. As such, consultation as part of an expert group meeting is recommended. This seems pertinent also in light of an eventual authorisation of the indication setting a potentially important precedent. As substantial new information is expected within the MAH responses to the 2nd RSI, the exact questions would be best formulated upon receipt of MAH responses to the 2nd RSI.

Assessment of paediatric data on clinical efficacy

The number of paediatric patients included in Study 311 was very small, and no definitive conclusions can be made; moreover, the analyses are limited to the Day 180 data only. With due consideration to these limitations, the results seem generally consistent with those in the broader population and are not suggestive of inferior efficacy or detrimental effects among paediatric patients.

The MAH is requested to repeat the analyses by paediatric age group for the long-term data and provide the results, including data on cGvHD, as part of the response to the 2nd RSI. **OC**

It is to be noted that no patients under 6 years of age were enrolled in the study; the proposal to extend the age group down to 2 years and above is thus completely dependent on extrapolation based on pharmacokinetic considerations.

In their response to the 1st RSI, the MAH provided additional discussion and justification supporting the extension of the indication into paediatric patients for whom limited or no clinical data is available. The discussion referenced relevant literature and demonstrated that the treatment protocols for HSCT are generally similar between adults and paediatric patients. Furthermore, based on paediatric data from other indications, there seem to be no age-specific issues in relation to the pharmacodynamic effects of abatacept that would warrant specific concern. Moreover, the effects are generally reversible upon discontinuation of therapy, which is of relevance in light of the short treatment duration proposed for the currently sought indication.

Thus, even when recognising the very limited clinical experience in paediatric patients undergoing HSCT, the extension of the indication into paediatric patients is supported by the relative similarity of HSCT treatment protocols for adults and children, the absence of concerning signals from the use of abatacept in paediatric patients in other indications as well as a review of relevant scientific literature. Although paediatric HSCT patients from 2 to 5 years age have not been treated, the proposed dosing regimen for

this age group is based on a population PK and simulation exercise that targets a dose regimen to achieve exposures that would match exposures in older children, adolescents, and adults.

The extrapolation into all proposed paediatric age groups is thereby overall supported.

4.4.4. Conclusions on the clinical efficacy

In clinical study IM101311, abatacept was studied as an addition to a standard prophylactic GvHD regimen, comprising a combination of a calcineurin inhibitor and methotrexate, in patients with haematological malignancies and receiving an allogeneic haematopoietic stem cell transplant from an 8/8 or 7/8 HLA-matched unrelated donor. The primary endpoint was Grade III-IV aGvHD -free survival at Day 180 post transplant. Secondary endpoints included overall survival and other measures of treatment benefit, and supplementary analyses were provided to cover a longer post-treatment follow-up.

In the 8/8 cohort, the GFS rate at Day 180 was numerically higher with abatacept compared to placebo, but the difference was not statistically significant. Overall survival was also higher with abatacept compared to placebo at Day 180, but the treatment difference appears to decrease over time. The 7/8 cohort was studied in a single arm setting, and GFS and OS results at Day 180 were strikingly positive, exceeding those observed in abatacept-treated patients within the 8/8 cohort. However, due in part to the small sample size, there are reservations regarding the generalisability and external validity of the results in the 7/8 cohort.

The results of the clinical study are supplemented with a RWD registry study (Study 841) in patients with haematological malignancies receiving an allogeneic haematopoietic stem cell transplant from a 7/8 HLA-matched unrelated donor. In this registry study, the addition of abatacept to a combination of a calcineurin inhibitor and methotrexate was associated with higher overall survival at Day 180 post transplant when compared to a control group only receiving a calcineurin inhibitor and methotrexate. A favourable effect of abatacept vs. ATG when added to a CNI + MTX regimen is also suggested. However, the value of these data is limited by the fact that the 7/8 cohort of Study 311, with its inherently very favourable efficacy profile, accounts for over 80% of abatacept-treated patients in Study 841 and is thus a major driver in the analyses. The results of Study 841 can therefore not be used for independent support of results form Study 311. Moreover, the follow-up period of 180 days post transplant may not be sufficient to cover the entire period of interest.

Considering these uncertainties, a favourable efficacy profile to support the claimed indication could not be concluded in the initial assessment, and the MAH was requested to discuss the clinical relevance of the claimed indication in the broader context of an expected benefit in HSCT.

In their response to the RSI, the MAH provided additional justification for their claims and supplemented the application with newly available data from both studies. These new data are considered potentially key to assessment of benefit-risk, but their nature and quality is currently considered inadequate for regulatory decision-making purposes. A formal MO regarding quality and incompleteness of data provided in the response is thereby raised, and a follow-up submission, meeting the same quality standards as applied by the MAH for the initial submission and including complete data for all relevant endpoints, is expected to enable adequate assessment of the new data, and consequently appropriate assessment of benefit-risk. In light of the pivotal study failing on its pre-specified primary endpoint, expert consultation is also recommended to gain additional clinical insight into the overall robustness of the data package and the clinical relevance of observed treatment effects.

Two other MO's raised in the 1st RSI have been resolved. Extrapolation to all proposed age groups is thereby now agreed (pending successful resolution of new MO). Also, at the CHMP's request, the MAH

agreed to amend the wording of the indication to align with the population studied, and the authorised population is now restricted to " … adult and paediatric patients 2 years of age and older **with haematologic malignancies** undergoing haematopoietic stem cell transplantation (HSCT) …".

4.5. Clinical safety

Introduction

Proposed indication

ORENCIA (abatacept) in combination with a CNI and MTX is indicated for the prophylaxis for aGvHD in adult and pediatric patients 2 years of age and older undergoing HSCT from a matched or 1 allele-mismatched unrelated donor.

Proposed dose

Adults

The recommended dose of abatacept for adult patients is 10 mg/kg (maximum dose of 1,000 mg) and should be administered as a 60-minute IV infusion on the day before transplantation (Day -1), followed by a dose on Days 5, 14, and 28 after transplantation.

Pediatric Population

- The recommended dose of abatacept for patients 6 to 17 years of age is the same as for adults, 10 mg/kg (maximum dose of 1,000 mg). Abatacept should be administered on the day before transplantation (Day -1), followed by a dose on Days 5, 14, and 28 after transplantation.
- The recommended dose of abatacept for patients 2 to less than 6 years of age is 15 mg/kg on the day before transplantation (Day -1), followed by 12 mg/kg on Days 5, 14, and 28 after transplantation.
- Abatacept should be administered as a 60-minute intravenous infusion.

The main safety data to support the use of abatacept in patients with haematologic malignancies for the prophylaxis of acute graft-versus-host disease (aGvHD) in unrelated donor (URD) hematopoietic stem cell transplantation (HSCT) are from a phase 2 pivotal study IM101311 (see efficacy section for study details), a randomized, double-blind, placebo-controlled study of abatacept combined with a CNI and MTX in subjects, aged 6 years and older, with high-risk haematologic malignancies who received allogenic HSCT from unrelated donors with HLA-match at no less than seven of eight loci (A, B, C, DRB1).

The primary CSR for Study IM101311 (report date: 21-May-2021) was updated in Addendum 01 (report date: 04-Oct-2022) as follows:

- Replace AE tables and listings that were revised following updates to the coding for the PTs of 306 events. These events were recoded following a request from the FDA (dated 18-August-2021) in which the Agency requested 314 events be recoded. Of the 314 instances noted by the Agency, there were 8 verbatim terms that could not be recoded to a more specific PT.
- The post-hoc analyses limited to the pediatric age group (less than 18 years old) allowed for independent assessment of the utility of abatacept in acute graft versus host prophylaxis by separating the data for this sub-population from the larger primary study population, which included ages 6 and older, which was originally omitted from the primary CSR.

Additional supportive data (occurrence of PTLD) is provided from study IM101841, a retrospective, company sponsored, observational cohort registry study, evaluating patients who received an allogeneic HSCT and who received abatacept in addition to CNI + MTX. The CIBMTR database was used in this study. CIBMTR is a research collaboration between the National Marrow Donor Program/ Be The Match and the Medical College of Wisconsin. CIBMTR collects data on all allogeneic (related and unrelated) HSCTs performed in the US.

To further support the safety evaluation the MAH has provided the following data:

1) A literature review of the safety of abatacept use in stem cell transplantation in clinical and nonclinical studies.

2) A summary of on-treatment AEs beginning with the first dose of a 4-dose regimen (Day 1 [corresponding to the day prior to the calendar date of HSCT], Day 15, Day 29 or 30 and Day 57 or 60) of abatacept up to Day 84 (i.e., up to 28 days after the 4th dose date) from integrated, double-blind, clinical studies with IV abatacept in subjects with RA and JIA.

Study IM101311

For study details, including demographic and disease characteristics, disposition, see the efficacy section.

Patient exposure

Based on a database lock of 06-Nov-2020, 142 of 146 enrolled subjects in the 8/8 MUD cohort were treated with study medication and transplanted (73 received abatacept and 69 received placebo) at 13 sites in the US and 1 site in Canada, and the median duration of therapy was 86.0 days (86.0 days each for abatacept and placebo). In the single-arm 7/8 MMUD cohort, 43 of the 46 enrolled subjects received abatacept at 9 sites in the US, and the median duration of therapy was 86.0 days. The first patient, first visit date was 15-Apr-2013, and the LPLV was 17-Nov-2018. The study is on-going and the long-term duration of the study for each cohort is 5 years post transplantation (DLP Feb-2023).

Safety data from all treated subjects in the abatacept arms (abatacept plus CNI + MTX) and placebo arm (placebo plus CNI + MTX) of study IM101311 are presented in the following populations for analyses:

- 8/8 Matched Unrelated Donor Cohort As Treated Analysis Population: all subjects who received at least one dose of study medication. Analyses using the as treated analysis population grouped the subjects on an as randomized basis unless the subject received the incorrect medication for the entire blinded treatment period. In that case, the subject was analyzed in the treatment arm associated with the incorrect medication they received ("as treated"). This population included subjects who received study medication but did not receive a transplant. *This was the primary population for the safety analyses of the 8/8 MUD cohort.*

- 8/8 MUD Cohort Modified Intent-to-Treat Analysis Population: all randomized and transplanted subjects who received one dose of study medication. This population was used for extent of exposure and demographic analyses. Analyses using the MITT analysis population grouped subjects according to the treatment arm to which they were randomized and treated with at least one dose of study drug. Randomized subjects who were never treated were excluded from all analyses.

- 7/8 Mismatched Unrelated Donors Cohort Treated Analysis Population: all 7/8 MMUD cohort subjects who received at least one dose of abatacept. All treated subjects in the 7/8 MMUD cohort also received a transplant in the study. This population was used for extent of exposure and demographic analyses. *This was the primary population for the safety analyses of the 7/8 MMUD cohort.*

- Immunogenicity Analysis Population: all subjects who received at least one dose of study medication and who had at least 1 immunogenicity result reported after start of study medication.

Extent of exposure to abatacept up to the last dose in the treatment period for 8/8 MUD Cohort and 7/8 Cohort of study IM101311 are presented in Table 66 and Table 67 respectively.

Table 66 ***Extent of Exposure to Study Medication in the Treatment Period: 8/8 MUD Cohort as Treated Analysis Population***

	Number (%) of Subjects		
	Abatacept N = 73	Placebo N = 69	Total N = 142
Number of Infusions			
1	0	1 (1.4)	1 (0.7)
2	2 (2.7)	0	2 (1.4)
3	2 (2.7)	7 (10.1)	9 (6.3)
4	69 (94.5)	61 (88.4)	130 (91.5)
MEAN (SD)	3.9 (0.36)	3.9 (0.46)	3.9 (0.41)
MEDIAN (RANGE)	4.0 (2 - 4)	4.0 (1 - 4)	4.0 (1 - 4)
Days of Exposure			
MEAN DAYS OF EXPOSURE (SD)	85.7 (3.53)	84.8 (5.03)	85.3 (4.33)
MEDIAN (RANGE)	86.0 (64 - 87)	86.0 (57 - 88)	86.0 (57 - 88)

Includes all exposure data up to last dose in Treatment Period Interruptions in therapy were not deducted from calculation of days of exposure. Days of Exposure = [(date of the last infusion in the Treatment Period - date of the first infusion in the Treatment Period +1)+56].

Table 67 ***Extent of Exposure to Study Medication in the Treatment Period: 7/8 Cohort Treated Analysis Population***

	Number (%) of Subjects
	Abatacept N = 43
Number of Infusions	
1	1 (2.3)
2	0
3	0
4	42 (97.7)
MEAN (SD)	3.9 (0.46)
MEDIAN (RANGE)	4.0 (1 - 4)
Days of Exposure	
MEAN DAYS OF EXPOSURE (SD)	85.7 (4.51)
MEDIAN (RANGE)	86.0 (57 - 88)

Includes all exposure data up to last dose in Treatment Period; Interruptions in therapy were not deducted from calculation of days of exposure. Days of Exposure = [(date of the last infusion in the Treatment Period - date of the first infusion in the Treatment Period +1)+56].

The paediatric subpopulation

Age group from 6 to 17 years old: 14 subjects treated with abatacept in the 8/8 MUD cohort and 16 in the 7/8 MMUD cohort were 6-17 years old, resulting in 30 abatacept treated subjects in the 6-17 age group when the 2 cohorts are combined. Thirteen subjects aged between 6 to 17 years were randomized to placebo in the 8/8 MUD cohort.

Age group from 2 to 5 years old: no studies have been submitted with patients from the youngest age group. The MAH is planning, however, to conduct a clinical study to further characterize the safety (and PK) of abatacept in paediatric patients aged 2 to < 6 years for the prophylaxis of aGvHD.

Safety presentations (study IM101311) of AEs, SAEs, AEs leading to discontinuation, other significant AEs, AEs of special interest, and laboratory abnormalities are based on all treated subjects in each

treatment group for the **Day 180 Analysis Period**. Additional safety analyses are presented for the treatment period only.

AEs of special interest included infections, malignancy, autoimmune disorders, and infusion related reactions. Other significant AEs included engraftment related events (neutrophil recovery, platelet recovery, non-engraftment, secondary graft failure, graft rejection); and infections and immune-related events (CMV viremia, CMV invasive disease, PTLD). Assessment of immunogenicity was an exploratory safety endpoint.

Table 68 Collection of Adverse Event Data

Study Timeline	AE Collection Per Protocol	AE Collection based on FDA Recommendations	Additional AEs Retrospectively Collected
Day -1 to Day 100	1) Unexpected non-serious AEs 2) All SAEs	1) Gr 3 to 5 non-serious AEs 2) All SAEs	Expected Gr 3 or higher non-serious AEs
Day 101 to Day 180	1) Unexpected non-serious AEs 2) Unexpected SAEs 3) All fatal events 4) PTLD	1) Gr 3 to 5 non-serious AEs 2) All SAEs	1) Expected Gr 3 or higher non-serious AEs 2) Expected SAEs
Day 181 to Day 365	1) Unexpected non-serious AEs 2) Unexpected SAEs 3) All fatal events 4) PTLD	All SAEs	Expected SAEs

CHMP's comment

Safety data from the two cohorts (8/8 MUD and 7/8 MMUD) of the pivotal study IM101311 are not pooled for this assessment, considering the heterogeneity of these two subpopulations. However, pooled data is presented in the SmPC. Thus, these data should be provided also for the AR in tabulated for pooled and separately for the two cohorts (**OC**).

Adverse events

The overall summary of safety, during the Day 180 analysis period, for the 8/8 MUD and 7/8 MMUD cohorts is presented in Table 69.

Table 69 Summary of Safety Results During the Day 180 Analysis Period – As Treated Population

Summary of Safety Results During the Day 180 Analysis Period - As Treated Population

•	8/8 MUD Cohort		7/8 MMUD Cohort
	Abatacept (N = 73)	**Placebo (N = 69)**	**Abatacept (N = 43)**
AEs with Death as outcome, n (%)	8 (11.0)	16 (23.2)	3 (7.0)
SAEs, n (%)	52 (71.2)	45 (65.2)	29 (67.4)
Drug-related SAEs	20 (27.4)	20 (29.0)	10 (23.3)
Discontinued due to SAEs	0	1 (1.4)	0
Engraftment Related Events, (95% CI)			
Neutrophil recovery up to Day 100	0.98 (0.95, 1.00)	0.98 (0.95, 1.00)	0.95 (0.80, 0.99)
Platelet recovery up to Day 100	0.97 (0.93, 1.00)	0.94 (0.90, 0.99)	0.98 (0.79, 1.00)
Infections and Immune Related Events Cumulative Incidence at Day 180 (95% CI)			
CMV viremia	0.50 (0.40, 0.63)	0.45 (0.35, 0.58)	0.37 (0.23, 0.52)
CMV invasive disease	0.08 (0.04, 0.15)	0.02 (< 0.01, 0.09)	0.00 (NA, NA)
PTLD	0.01 (< 0.01, 0.09)[a]	< 0.01 (< 0.01, < 0.01)	0.05 (< 0.01, 0.14)
Other pre-specified infections	0.33 (0.25, 0.45)	0.31 (0.23, 0.42)	0.49 (0.33, 0.63)
AEs, n (%)	73 (100.0)	69 (100.0)	43 (100.0)
Drug-related AEs	63 (86.3)	62 (89.9)	39 (90.7)
Discontinued due to AEs	2 (2.7)	5 (7.2)	1 (2.3)
AEs Reported in ≥ 5% of Subjects, n (%)	73 (100.0)	69 (100.0)	43 (100)
Adverse Events of Interest, n (%)			
Infections	50 (68.5)	53 (76.8)	30 (69.8)
Malignancy	7 (9.6)	8 (11.6)	2 (4.7)
Autoimmune Disorders	0	2 (2.9)	1 (2.3)
Infusion Reactions			
Peri-infusional AEs	10 (13.7)	11 (15.9)	5 (11.6)
Other 24-hr AEs	69 (94.5)	67 (97.1)	42 (97.7)

01. [a]A second subject was identified as PTLD on study team adjudication post-database lock, and so is not reported in this table.

Common Adverse Events

In the 8/8 MUD cohort, the overall frequencies of any-grade, all causality AEs and drug-related AEs were similar in the abatacept group and the placebo group.

Adverse Events (regardless of causality)

In the 8/8 MUD cohort, any-grade AEs (regardless of causality) were reported in 100% of the treated subjects in both the abatacept and placebo groups (Table 70).

- In the abatacept group the most frequently reported AEs (regardless of causality) were neutrophil count decreased (60 subjects, 82.2%), stomatitis (53 subjects, 72.6%), white blood cell count decreased, and anaemia, (50 subjects each, 68.5%).

- In the placebo group the most frequently reported SAEs were neutrophil count decreased (60 subjects, 87.0%), platelet count decreased (55 subjects, 79.7%), white blood cell count decreased (51 subjects, 73.9%), stomatitis, and febrile neutropenia (49 subjects each, 71.0%).

In the 7/8 MMUD cohort Any-grade AEs (regardless of causality) were reported in 43 (100%) treated subjects.

- The most frequently reported AEs were neutrophil count decreased (33 subjects, 76.7%), white blood cell count decreased and stomatitis (28 subjects each, 65.1%), platelet count decreased (26 subjects, 60.5%), and lymphocyte count decreased (22 subjects, 51.2%).

Table 70 ***Adverse Events (Reported in ≥ 5% of Subjects in Any Treatment Group) During the Day 180 Analysis Period - 8/8 MUD Cohort As Treated Analysis Population***

Adverse Events (Reported in ≥ 5% of Subjects in Any Treatment Group) During the Day 180 Analysis Period - 8/8 MUD Cohort As Treated Analysis Population

PREFERRED TERM (PT) (%)	Abatacept N = 73	Placebo N = 69
TOTAL SUBJECTS WITH AE	73 (100.0)	69 (100.0)
Neutrophil count decreased	60 (82.2)	60 (87.0)
Stomatitis	53 (72.6)	49 (71.0)
White blood cell count decreased	50 (68.5)	51 (73.9)
Platelet count decreased	45 (61.6)	55 (79.7)
Anaemia	50 (68.5)	39 (56.5)
Lymphocyte count decreased	41 (56.2)	47 (68.1)
Febrile neutropenia	38 (52.1)	49 (71.0)
Dehydration	36 (49.3)	30 (43.5)
Hypertension	31 (42.5)	26 (37.7)
Decreased appetite	21 (28.8)	25 (36.2)
Hypokalaemia	20 (27.4)	22 (31.9)
Alanine aminotransferase increased	11 (15.1)	24 (34.8)
Obesity	17 (23.3)	18 (26.1)
Graft versus host disease in gastrointestinal tract	19 (26.0)	13 (18.8)
Hypophosphataemia	16 (21.9)	16 (23.2)
Diarrhoea	16 (21.9)	15 (21.7)
Hyperglycaemia	15 (20.5)	16 (23.2)
Hypotension	13 (17.8)	16 (23.2)
Pyrexia	14 (19.2)	14 (20.3)
Bacteraemia	10 (13.7)	17 (24.6)
Device related infection	14 (19.2)	13 (18.8)
Cytomegalovirus infection reactivation	15 (20.5)	9 (13.0)
Nausea	12 (16.4)	12 (17.4)
Abdominal pain	8 (11.0)	13 (18.8)
Blood bilirubin increased	10 (13.7)	11 (15.9)
Hypermagnesaemia	13 (17.8)	7 (10.1)
Hyponatraemia	11 (15.1)	9 (13.0)
Epistaxis	12 (16.4)	7 (10.1)
Acute kidney injury	11 (15.1)	7 (10.1)
Aspartate aminotransferase increased	7 (9.6)	11 (15.9)
Enterocolitis infectious	6 (8.2)	11 (15.9)
CD4 lymphocytes decreased	10 (13.7)	6 (8.7)
Hyperkalaemia	3 (4.1)	13 (18.8)
Hypoxia	7 (9.6)	9 (13.0)
Pneumonia	9 (12.3)	7 (10.1)
Cytomegalovirus infection	8 (11.0)	6 (8.7)
Graft versus host disease in skin	5 (6.8)	9 (13.0)
Headache	5 (6.8)	8 (11.6)
Respiratory failure	5 (6.8)	8 (11.6)
Chronic kidney disease	8 (11.0)	4 (5.8)
Upper respiratory tract infection	8 (11.0)	4 (5.8)
Urinary tract infection	5 (6.8)	6 (8.7)
Back pain	7 (9.6)	2 (2.9)
Hypertriglyceridaemia	5 (6.8)	4 (5.8)
Hypoalbuminaemia	5 (6.8)	4 (5.8)
Rash maculo-papular	4 (5.5)	5 (7.2)
Acute graft versus host disease in liver	3 (4.1)	5 (7.2)
Acute graft versus host disease in skin	5 (6.8)	3 (4.3)

Adverse Events (Reported in ≥ 5% of Subjects in Any Treatment Group) During the Day 180 Analysis Period - 8/8 MUD Cohort As Treated Analysis Population

PREFERRED TERM (PT) (%)	Abatacept N = 73	Placebo N = 69
Delirium	5 (6.8)	3 (4.3)
Dyspnoea	4 (5.5)	4 (5.8)
Fatigue	3 (4.1)	5 (7.2)
Hypocalcaemia	4 (5.5)	4 (5.8)
Muscular weakness	6 (8.2)	2 (2.9)
Pain	4 (5.5)	4 (5.8)
Weight decreased	1 (1.4)	7 (10.1)
Arthralgia	2 (2.7)	5 (7.2)
Infection	2 (2.7)	5 (7.2)
Infusion related reaction	2 (2.7)	5 (7.2)
Mental status changes	4 (5.5)	3 (4.3)
Peripheral sensory neuropathy	6 (8.2)	1 (1.4)
Sepsis	0	7 (10.1)
Acidosis	5 (6.8)	1 (1.4)
Anxiety	4 (5.5)	2 (2.9)
Blood alkaline phosphatase increased	2 (2.7)	4 (5.8)
Activated partial thromboplastin time prolonged	4 (5.5)	1 (1.4)
Glucose tolerance impaired	1 (1.4)	4 (5.8)
Urine output decreased	4 (5.5)	1 (1.4)
Cardiac arrest	0	4 (5.8)
Encephalopathy	0	4 (5.8)
Forced expiratory volume decreased	4 (5.5)	0
Pulmonary oedema	4 (5.5)	0

01. Note: Includes data from the first dose date up to the Day 180 visit post-transplantation. MedDRA Version 23.1

Related AEs

In the 8/8 MUD cohort, any-grade drug-related AEs were reported in 63 (86.3%) subjects in the abatacept group and 62 (89.9%) subjects in the placebo group (Table 71).

- In the abatacept group the most frequently reported drug-related AEs were lymphocyte count decreased (35 subjects, 47.9%), white blood cell count decreased (21 subjects, 28.8%), anaemia (20 subjects, 27.4%), obesity, and neutrophil count decreased (17 subjects each, 23.3%).

- In the placebo group the most frequently reported AEs were lymphocyte count decreased (32 subjects, 46.4%), obesity (18 subjects, 26.1%), and anaemia, (16 subjects, 23.2%).

In the 7/8 MUD cohort, any-grade drug-related AEs were reported in 39 (90.7%) treated subjects in the 7/8 MMUD cohort. Grade 3, Grade 4, and Grade 5 AEs (all causality) were reported in 18 (41.9%), 20 (46.5%), and 1 (2.3%) subjects, respectively.

- The most frequently reported AEs were lymphocyte count decreased (15 subjects, 34.9%), anaemia and obesity (9 subjects each, 20.9%).

Table 71 ***Drug-related Adverse Events (Reported in ≥ 2% of Subjects in Any Treatment Group) During the Day 180 Analysis Period - 8/8 MUD Cohort As Treated Analysis Population***

Drug-related Adverse Events (Reported in ≥ 2% of Subjects in Any Treatment Group) During the Day 180 Analysis Period - 8/8 MUD Cohort As Treated Analysis Population

PREFERRED TERM (PT) (%)	Abatacept N = 73	Placebo N = 69
TOTAL SUBJECTS WITH AE	63 (86.3)	62 (89.9)
Lymphocyte count decreased	35 (47.9)	32 (46.4)
Anaemia	20 (27.4)	16 (23.2)
Obesity	17 (23.3)	18 (26.1)
White blood cell count decreased	21 (28.8)	14 (20.3)
Neutrophil count decreased	17 (23.3)	10 (14.5)
Cytomegalovirus infection reactivation	12 (16.4)	7 (10.1)
Platelet count decreased	13 (7.8)	6 (8.7)
Cytomegalovirus infection	6 (8.2)	6 (8.7)
Hypertension	8 (11.0)	3 (4.3)
CD4 lymphocytes decreased	7 (9.6)	3 (4.3)
Pneumonia	4 (5.5)	2 (2.9)
Pyrexia	3 (4.1)	3 (4.3)
Acute myeloid leukaemia recurrent	2 (2.7)	3 (4.3)
Blood disorder	2 (2.7)	3 (4.3)
Device related infection	2 (2.7)	3 (4.3)
Enterocolitis infectious	3 (4.1)	2 (2.9)
Febrile neutropenia	2 (2.7)	3 (4.3)
Sepsis	0	5 (7.2)
Urinary tract infection	3 (4.1)	2 (2.9)
Decreased appetite	3 (4.1)	1 (1.4)
Nausea	3 (4.1)	1 (1.4)
Pain	3 (4.1)	1 (1.4)
Upper respiratory tract infection	3 (4.1)	1 (1.4)
Acute lymphocytic leukaemia recurrent	2 (2.7)	1 (1.4)
Anxiety	2 (2.7)	1 (1.4)
Diarrhoea	1 (1.4)	2 (2.9)
Headache	1 (1.4)	2 (2.9)
Hyperglycaemia	2 (2.7)	1 (1.4)
Hypotension	2 (2.7)	1 (1.4)
Infusion related reaction	1 (1.4)	2 (2.9)
Abdominal pain	0	2 (2.9)
Acute lymphocytic leukaemia	2 (2.7)	0
Encephalopathy	0	2 (2.9)
Glucose tolerance impaired	0	2 (2.9)
Insomnia	0	2 (2.9)
Multiple organ dysfunction syndrome	0	2 (2.9)

01. Note: Includes data from the first dose date up to the Day 180 visit post-transplantation. Related is defined as an AE with Possibly, Probably, Definitely Related or Missing relationship to study medication. MedDRA Version 23.1

Deaths/serious adverse event/other significant events

Deaths

In the 8/8 MUD cohort there were 11 (9.5%) abatacept-treated subjects and 16 (23.2%) placebo-treated subjects had AEs with onset date prior to Day 225 after transplantation (the upper limit of the Day 180 visit) and death as the outcome.

The causes of death in the 11 abatacept-treated subjects were hematological malignancy recurrence (n=5), GvHD (n=4), cerebrovascular accident (n=1), and respiratory failure (n=1) that was considered to be due to acute respiratory distress syndrome and pulmonary fibrosis possibly associated with prior bleomycin therapy.

In the placebo group, 16 subjects died due to one or more causes, including hematological malignancy recurrence (n=7), GvHD (n=7), infections (n=5), encephalopathy (n=2), and organ failure (n=2).

Three (3) placebo-treated subjects and 3 abatacept-subjects had an AE with death as outcome with onset within 225 days after transplantation, but the death occurred more than 225 days after transplantation

In the 7/8 MMUD cohort, up to Day 180 visit, 3 (7.0%) abatacept-treated subjects had AEs with outcome of death with onset within 225 days after transplantation. One of these subjects died more than 225 days after transplantation. During the Day 180 analysis period, 2 subjects died due to GvHD.

Narratives for deaths were provided.

CHMP's comment

The number of deaths in abatacept-treated subjects was lower compared to that in placebo group: 11 (9.5%) vs. 16 (23.2%). The main causes of deaths reported in both abatacept- and placebo-treated subjects were recurrence of underlying malignancy and GvHD, which are expected in the type of population under study. Somewhat unexpectedly, considering the known anticipated high-risk profile of this patient cohort, the numbers for deaths in the 7/8 MMUD cohort were clearly lower.

Other Serious Adverse Events

In the 8/8 MUD cohort, the overall frequencies of all-causality SAEs and drug-related SAEs were similar in the abatacept group and the placebo group. This was also the case for SAEs reported up to Day 365.

During the Day 180 analysis period, any-grade all-causality SAEs were reported in 52 (71.2%) subjects in the abatacept group and 45 (65.2%) subjects in the placebo group (**Error! Reference source not found.**5.5.7.).

- In the abatacept group, the most frequently reported SAEs were pyrexia (11 subjects, 15.1%), graft versus host disease in gastrointestinal tract (10 subjects, 13.7%) diarrhoea, hepatobiliary disease, and acute kidney injury (6 subjects each, 8.2%).
- In the placebo group, the most frequently reported SAEs were pyrexia (11 subjects, 15.9%), sepsis and respiratory failure (7 subjects each, 10.1%).

During the Day 180 analysis period, any-grade drug-related SAEs were reported in 20 (27.4%) subjects in the abatacept group and 20 (29.0%) subjects in the placebo group (**Error! Reference source not found.**5.5.7.).

- In the abatacept group the most frequently reported drug-related SAEs were pneumonia, upper respiratory tract infection, recurrent acute myeloid leukaemia, recurrent acute lymphocytic leukaemia, acute lymphocytic leukaemia, and pyrexia (2 subjects each, 2.7%). All other drug-related SAEs occurred in a single subject.
- In the placebo group the most frequently reported drug-related SAEs were sepsis (5 subjects, 7.2%), recurrent acute myeloid leukaemia (3 subjects, 4.3%), diarrhoea, abdominal pain, pyrexia, multiple organ dysfunction syndrome, and encephalopathy (2 subjects each, 2.9%). All other drug-related SAEs occurred in a single subject.

In the 7/8 MMUD cohort, during the Day 180 analysis period, any-grade all-causality SAEs were reported in 29 (67.4%) subjects.

- The most frequently reported SAEs were pyrexia (12 subjects, 27.9%), GvHD in gastrointestinal tract (7 subjects, 16.3%), and pneumonia (5 subjects, 11.6%).

In the 7/8 MMUD cohort, during the Day 180 analysis period, any-grade drug-related SAEs were reported in 10 (23.3%) subjects.

- Drug-related SAEs reported in more than 1 subject included pneumonia, post-transplant lymphoproliferative disorder, and pyrexia, (all 2 subjects each, 4.7%). All other drug-related SAEs occurred in a single subject.

Table 72 ***Serious Adverse Events Reported in ≥ 4% of Subjects in Any Treatment Group During the Day 180 Analysis Period - 8/8 MUD Cohort As Treated Analysis Population***

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 73	Placebo N = 69
TOTAL SUBJECTS WITH SAE	**52 (71.2)**	**45 (65.2)**
Infections and infestations	21 (28.8)	17 (24.6)
Infection	3 (4.1)	4 (5.8)
Sepsis	0	7 (10.1)
Device related infection	4 (5.5)	1 (1.4)
Pneumonia	4 (5.5)	1 (1.4)
Upper respiratory tract infection	3 (4.1)	1 (1.4)
General disorders and administration site conditions	14 (19.2)	18 (26.1)
Pyrexia	11 (15.1)	11 (15.9)
Multiple organ dysfunction syndrome	0	3 (4.3)
Gastrointestinal disorders	15 (20.5)	13 (18.8)
Diarrhoea	6 (8.2)	2 (2.9)
Nausea	4 (5.5)	2 (2.9)
Abdominal pain	1 (1.4)	4 (5.8)
Stomatitis	4 (5.5)	0
Respiratory, thoracic and mediastinal disorders	9 (12.3)	11 (15.9)
Respiratory failure	4 (5.5)	7 (10.1)
Acute respiratory distress syndrome	3 (4.1)	2 (2.9)
Hypoxia	3 (4.1)	2 (2.9)
Dyspnoea	3 (4.1)	1 (1.4)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	9 (12.3)	10 (14.5)
Acute myeloid leukaemia recurrent	3 (4.1)	3 (4.3)
Myelodysplastic syndrome	3 (4.1)	3 (4.3)
Acute lymphocytic leukaemia recurrent	3 (4.1)	2 (2.9)
Nervous system disorders	7 (9.6)	10 (14.5)
Cerebrovascular accident	3 (4.1)	2 (2.9)
Encephalopathy	0	4 (5.8)
Headache	1 (1.4)	3 (4.3)
Blood and lymphatic system disorders	8 (11.0)	8 (11.6)
Febrile neutropenia	4 (5.5)	4 (5.8)
Anaemia	3 (4.1)	0
Metabolism and nutrition disorders	10 (13.7)	5 (7.2)
Dehydration	4 (5.5)	1 (1.4)
Cardiac disorders	4 (5.5)	9 (13.0)
Cardiac arrest	0	4 (5.8)
Vascular disorders	8 (11.0)	5 (7.2)
Hypotension	5 (6.8)	3 (4.3)
Hypertension	3 (4.1)	2 (2.9)
Immune system disorders	11 (15.1)	8 (11.6)
Graft versus host disease in gastrointestinal tract	10 (13.7)	3 (4.3)
Acute graft versus host disease in skin	3 (4.1)	2 (2.9)
Acute graft versus host disease in liver	3 (4.1)	1 (1.4)
Hepatobiliary disorders	1 (1.4)	3 (4.3)
Cholecystitis	0 (0.0)	2 (2.9)
Venocclusive liver disease	1 (1.4)	1 (1.4)

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 73	Placebo N = 69
Psychiatric disorders	6 (8.2)	2 (2.9)
Delirium	3 (4.1)	1 (1.4)
Mental status changes	3 (4.1)	1 (1.4)
Investigations	6 (8.2)	2 (2.9)
Platelet count decreased	3 (4.1)	0
Renal and urinary disorders	6 (8.2)	1 (1.4)
Acute kidney injury	6 (8.2)	1 (1.4)

01. Note: Includes data from the first dose date up to the Day 180 visit post-transplantation.

Table 73 ***Drug-related Serious Adverse Events During the Day 180 Analysis Period - 8/8 MUD Cohort As Treated Analysis Population***

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 73	Placebo N = 69
TOTAL SUBJECTS WITH SAE	**20 (27.4)**	**20 (29.0)**
Infections and infestations	8 (11.0)	6 (8.7)
Sepsis	0	5 (7.2)
Encephalitis	1 (1.4)	1 (1.4)
Pneumonia	2 (2.7)	0
Upper respiratory tract infection	2 (2.7)	0
Arthritis bacterial	0	1 (1.4)
Device related infection	1 (1.4)	0
Enterocolitis infectious	1 (1.4)	0
Epstein-Barr virus infection reactivation	1 (1.4)	0
Eye infection	1 (1.4)	0
Urinary tract infection	1 (1.4)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	5 (6.8)	6 (8.7)
Acute myeloid leukaemia recurrent	2 (2.7)	3 (4.3)
Acute lymphocytic leukaemia recurrent	2 (2.7)	1 (1.4)
Acute lymphocytic leukaemia	2 (2.7)	0
Myelodysplastic syndrome	1 (1.4)	1 (1.4)
Central nervous system leukaemia	0	1 (1.4)
Gastrointestinal disorders	2 (2.7)	8 (11.6)
Diarrhoea	1 (1.4)	2 (2.9)
Abdominal pain	0	2 (2.9)
Nausea	1 (1.4)	1 (1.4)
Enteritis	0	1 (1.4)
Enterocolitis	0	1 (1.4)
Lower gastrointestinal haemorrhage	0	1 (1.4)
General disorders and administration site conditions	3 (4.1)	7 (10.1)
Pyrexia	2 (2.7)	2 (2.9)
Multiple organ dysfunction syndrome	0	2 (2.9)
Adverse event	0	1 (1.4)
Disease recurrence	0	1 (1.4)
Influenza like illness	0	1 (1.4)
Oedema peripheral	0	1 (1.4)
Pain	1 (1.4)	0
Nervous system disorders	1 (1.4)	3 (4.3)
Cerebrovascular accident	1 (1.4)	1 (1.4)
Encephalopathy	0	2 (2.9)
Headache	0	1 (1.4)
Seizure	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	1 (1.4)	2 (2.9)
Acute respiratory distress syndrome	0	1 (1.4)
Dyspnoea	1 (1.4)	0
Hypoxia	1 (1.4)	0
Pleural effusion	1 (1.4)	0
Pulmonary oedema	1 (1.4)	0
Respiratory failure	0	1 (1.4)
Blood and lymphatic system disorders	1 (1.4)	1 (1.4)
Blood disorder	0	1 ()
Bone marrow failure	1 (1.4)	0
Cardiac disorders	0	1 (1.4)
Restrictive cardiomyopathy	0	1 (1.4)
Psychiatric disorders	0	1 (1.4)
Mental status changes	0	1 (1.4)
Vascular disorders	1 (1.4)	0
Hypotension	1 (1.4)	0

01. Note: Includes data from the first dose date up to the Day 180 visit post-transplantation. A related SAE defined as an SAE with Possibly, Probably, Definitely Related or Missing relationship to study medication. MedDRA Version 23.1

Laboratory findings

Haematology

Haemoglobin and Haematocrit

In the 8/8 MUD cohort, mean haemoglobin concentrations were lowest (9.5 to 9.9 g/dL) in both treatment groups during the first 2 weeks post-transplant. Mean concentrations trended upward thereafter, stabilizing in the range of 12.7 to 12.9 g/dL between Days 100 and 180 in the abatacept group and 10.9 to 11.7 g/dL in the placebo groups. By Study Day 365, mean concentrations were 12.6 and 12.4 g/dL in the abatacept and placebo groups, respectively.

In the 7/8 MMUD cohort, the mean haemoglobin concentrations were lowest during the first 2 weeks post-transplant (9.4 to 9.7 g/dL). Mean concentrations trended upward thereafter, stabilizing in the range of 11.3 to 11.4 g/dL between Days 100 and 180. At Days 270 and 365, mean concentrations were 12.3 and 12.4 g/dL, respectively.

Mean haematocrit levels changed in parallel with the corresponding haemoglobin concentrations in both treatment groups.

White blood cell (WBC) counts and neutrophils as a percentage of total WBC counts

In the 8/8 MUD cohort, mean total WBC counts decreased from a baseline mean of 3.32×10^9/L and 2.91×10^9/L in the abatacept and placebo groups, respectively, to nadirs of 0.35×10^9/L and 0.21×10^9/L in the respective groups on Day 5. Mean counts increased progressively thereafter, stabilizing on Days 100 and 180 at 5.22 and 7.28×10^9/L, respectively, in the abatacept group and 5.03 and 6.09×10^9/L in the placebo group. By Day 365, the mean counts had further increased to 7.45 and 6.39×10^9/L in the abatacept and placebo groups, respectively.

Neutrophils decreased from a baseline of 84% and 76% of total WBC count in the abatacept and placebo groups, respectively, to nadirs of 37% and 23% of total WBC count on Day 5. The mean percentage of neutrophils increased progressively thereafter, stabilizing on Days 100 and 180 at 67% and 55%, respectively, in the abatacept group and 63% and 55%, in the placebo group. By Day 365, the mean percentage of neutrophils had remained stable at 58% and 60% in the abatacept and placebo groups, respectively.

In the 7/8 MMUD cohort, mean total WBC counts decreased from 1.93×10^9/L on Day 0 to a nadir of 0.37×10^9/L on Day 5. Mean counts fluctuated upward thereafter, stabilizing on Days 100 and 180 at 5.20×10^9/L and 5.92×10^9/L, respectively. By Days 270 and 365, the mean counts had further increased to 8.59×10^9/L and 7.46×10^9/L, respectively.

Neutrophils decreased from a baseline of 76% of total WBC count to a nadir of 37% of total WBC count on Day 5. The mean percentage of neutrophils increased progressively thereafter, stabilizing on Days 100 and 180 at 67% and 57%, respectively, of total WBC. By Day 365, the mean percentage of neutrophils had remained stable at 59% of total WBC.

Platelet counts

In the 8/8 MUD cohort, on Day 0, mean platelet counts were 113×10^9/L and 126×10^9/L in the abatacept and placebo groups, respectively. Mean counts decreased between Days 5 and 14 to a nadir range of 31 to 56×10^9/L in the abatacept group and 25 to 50×10^9/L in the placebo group. Mean counts increased progressively thereafter between Days 180 and 365, ranging from 139 to 175×10^9/L in the abatacept group and 153 to 174×10^9/L in the placebo group.

In the 7/8 MMUD cohort, mean platelet counts decreased from 97 × 10^9/L on Day 0 to a nadir of 32 to 56 × 10^9/L between Days 5 and 14. Mean counts increased between Days 180 and 365 to a range of 175 to 195 × 10^9/L.

Clinical Chemistry

Hepatic transaminases (serum ALT and AST)

In the 8/8 MUD cohort, on Day 0, mean serum concentrations of ALT and AST were 28 and 24 U/L, respectively, in the abatacept group, and 30 and 22 U/L, respectively, in the placebo group. Thereafter, from Day 5 through Day 365, serum ALT and AST fluctuated in similar ranges in the abatacept and placebo groups: ALT: 31-70 U/L and 33-66 U/L, respectively; AST: 30-50 U/L and 25-44 U/L, respectively.

In the 7/8 MMUD cohort, on Day 0, mean serum concentrations of ALT and AST were 26 and 25 U/L, respectively. Thereafter, from Day 5 through Day 365, ALT and AST levels fluctuated in the ranges of 43 to 92 U/L and 29 to 54 U/L, respectively.

Total bilirubin

In the 8/8 MUD cohort, on Day 0, mean serum total bilirubin concentrations were 11.2 and 14.0 µmol/L (0.65 and 0.82 mg/dL) in the abatacept and placebo groups, respectively. Between Days 5 and 365, mean concentrations were in the range of 10.1 to 23.5 U/L (0.59 to 1.37 mg/dL) in the abatacept group and 10.6 to 18.2 U/L (0.62 to 1.06 mg/dL) in the placebo group.

In the 7/8 MMUD cohort, on Day 0, the mean serum total bilirubin concentration was 11.2 mmol/L (0.7 mg/dL). Between Days 5 and 365, mean concentrations were in the range of 11.3 to 17.4 mmol/L (0.7-1.0 mg/dL).

Renal function (BUN and serum creatinine)

In the 8/8 MUD cohort, on Day 0, BUN concentrations were not available for calculation of mean values. Between Days 5 and 365, mean BUN concentrations remained stable in the range of 5.1 to 6.8 mmol/L (14 to 19 mg/dL) in the abatacept group and 4.9 to 7.6 mmol/L (14 to 21 mg/dL) in the placebo group.

On Day 0, mean serum creatinine concentrations were 91 µmol/L (1.02 mg/dL) and 55 µmol/L (0.62 mg/dL) in the abatacept and placebo groups, respectively. Between Days 5 and 365, mean concentrations remained in the range of 58 to 91 µmol/L (0.66 to 1.02 mg/dL) in the abatacept group, with the exception of an isolated level of 191 µmol/L (2.16 mg/dL) on Day 77 that was associated with an improbably large standard deviation of 827 µmol/L (9.36 mg/dL). Further examination revealed one subject in the abatacept group with an isolated creatinine level of 6,542 µmol/L (74.0 mg/dL), representing a likely erroneous result.

Between Days 5 and 365, mean serum creatinine concentrations remained in the range of 58 to 106 µmol/L (0.66 to 1.20 mg/dL) in the placebo group, with the exception of an isolated level of 306 µmol/L (3.46 mg/dL) on Day 8 that was associated with an improbably large standard deviation of 1,764 µmol/L (20.00 mg/dL).

In the 7/8 MMUD cohort, on Day 0, BUN concentrations were not available for calculation of a mean. Between Days 5 and 365, mean BUN concentrations remained stable in the range of 4.5 to 6.7 mmol/L (13 to 19 mg/dL).

On Day 0, the mean serum creatinine concentration was 58 µmol/L (0.66 mg/dL). Between Days 5 and 365, mean serum creatinine concentrations remained in the range of 57 to 83 µmol/L (0.64 to 0.94 mg/dL), with the exception of 2 isolated levels of 270 and 271 µmol/L (3.05 and 3.07 mg/dL) on Days

21 and 28, respectively. These isolated levels were associated with improbably large standard deviations of 1,283 and 1,269 µmol/L (14.5 and 14.4 mg/dL), respectively.

Serum electrolytes and CO2

In the 8/8 MUD cohort, mean serum concentrations of sodium, potassium, chloride, and CO_2 were available beginning on Day 5, at which time levels were all within conventional reference ranges through the end of the 180-day treatment period, and then to Day 365.

In the 7/8 MMUD cohort, with a single exception, mean serum concentrations of sodium, potassium, chloride, and CO_2 were available beginning on Day 5, at which time levels were all within conventional reference ranges through the end of the 180-day treatment period, and then to Day 365. The mean value for serum potassium at Day 5 (17.5 mmol/L) included one or more data entry errors that could not be resolved by query.

Serum glucose

In the 8/8 MUD cohort, mean serum glucose concentrations were available beginning on Day 5, at which time levels were 6.4 and 6.3 mmol/L (115 and 113 mg/dL) in the abatacept and placebo groups, respectively. Thereafter, mean concentrations remained stable in both groups through the end of the 180-day treatment period (6.3 and 6.5 mmol/L [113 and 117 mg/dL] in the abatacept and placebo groups, respectively), and then to Day 365 (6.2 mmol/L [112 mg/dL] in both groups).

In the 7/8 MMUD cohort, mean serum glucose concentration was available beginning on Day 5, at which time the level was 5.7 mmol/L (103 mg/dL). Thereafter, mean concentrations remained stable through the end of the 180-day treatment period in the range of 6.5 to 7.1 mmol/L (117 to 128 mg/dL). Mean concentrations were 6.7 and 5.6 mmol/L (121 and 101 mg/dL) on Days 270 and 365, respectively.

Serum albumin

In the 8/8 MUD cohort, mean serum albumin concentrations were available beginning on Day 5, at which time levels were 35.0 g/L in both treatment groups. Thereafter, mean concentrations remained stable through the end of the 180-day treatment period (39.4 and 39.6 g/L in the abatacept and placebo groups, respectively), and then to Day 365 (39.3 and 39.0 g/L in the abatacept and placebo groups, respectively).

In the 7/8 MMUD cohort, the mean serum albumin concentration was available beginning on Day 5, at which time the level was 33.3 g/L (3.3 g/dL). Thereafter, the mean concentrations remained stable through the end of the 180-day treatment period in the range of 31.6 to 38.0 g/L (3.2-3.8 g/dL). Mean concentrations were 37.8 and 37.4 g/L (3.8 and 3.7 g/dL) on Days 270 and 365, respectively.

Serum immunoglobulin G (IgG)

In the 8/8 MUD cohort, mean serum IgG concentrations were available beginning on Day 21, at which time levels were 6.0 and 5.6 g/L in the abatacept and placebo groups, respectively. Thereafter, mean concentrations remained stable in the abatacept group through the end of the 180-day treatment period and then to Day 365 (6.4 and 6.0 g/L on Days 180 and 365, respectively). Over the same interval, mean concentrations rose slightly in the placebo group (6.7 and 7.8 g/L on Days 180 and 365, respectively).

In the 7/8 MMUD cohort, Mean serum IgG concentrations were available beginning on Day 21, at which time the level was 9.3 g/L. Thereafter, mean concentrations remained in the range of 5.4 to 8.7 g/L through the end of the 180-day treatment period. Mean concentrations were 7.2 and 7.4 g/L on Days 270 and 365, respectively. The range of variation in concentrations during the treatment period was similar to that of the abatacept and placebo groups in the 8/8 MUD cohort.

Change from Baseline Cytomegalovirus and Epstein-Barr Virus Viral Load Post-transplant

Cytomegalovirus (CMV)

In the 8/8 MUD cohort, baseline CMV viral loads in the abatacept (N = 73) and placebo (N = 69) groups were:

- Detectable (at a titer < 300 copies or international units) in 0 and 3 (4.3%) subjects, respectively;
- Negative in 18 (24.7%) and 11 (15.9%) subjects, respectively; and
- Unknown in 55 (75.3%) and 55 (79.7%) subjects, respectively.

In both abatacept and placebo groups, the majority of the CMV change from negative or unknown at baseline to positive or detectable occurred before Day 100.

In the 7/8 MMUD cohort, among the 43 abatacept-treated subjects of the 7/8 MMUD cohort, 5 (11.6%) subjects had negative CMV viral loads, and CMV viral load was unknown in 38 subjects (88.4%) at baseline. The majority of the CMV change from negative or unknown at baseline to positive or detectable occurred before Day 100.

Epstein-Barr Virus (EBV)

In the 8/8 MUD cohort, baseline EBV viral loads in the abatacept (N = 73) and placebo (N = 69) groups e:

- Positive for EBV DNA in 1 (1.4%) and 0 subjects, respectively;
- Negative in 14 (19.2%) and 15 (21.7%) subjects, respectively; and
- Unknown in 58 (79.5%) and 54 (78.3%) subjects, respectively.

In both abatacept and placebo groups, the majority of subjects whose baseline testing was negative or unknown for EBV DNA were negative by Day 180.

In the 7/8 MMUD cohort, among the 43 abatacept-treated subjects of the 7/8 MMUD cohort, 4 (9.3%) subjects had negative EBV viral loads at baseline, and 39 (90.7%) were unknown. The status of the majority of subjects whose baseline testing was negative or unknown for EBV DNA remained negative by Day 180.

CHMP's comment

Overall, it can be agreed with the MAH that the mean changes from baseline of the laboratory test results were in general modest in size and within expected physiological variation between determinations. The few, larger changes from baseline observed were mainly single occurrences, and were not reflective of progressive deviations or changes.

Immunogenicity

In Study IM101311, an immunogenicity response was detected in both 8/8 MUD and 7/8 MMUD cohorts, only post-treatment. Overall, the immunogenicity incidence and associated antibody titers observed were low. Impact on the PK or safety of abatacept could not be assessed due to the low incidence of immunogenicity.

8/8 MUD cohort Of the 73 immunogenicity evaluable subjects in the abatacept group, 5 (6.8%) subjects were positive for CTLA-4, and possibly Ig, during the off-treatment period; no subjects were positive

during the on-treatment period. Of the 5 positive subjects, 3 were found to have at least 1 positive sample with neutralization activity.

7/8 MMUD cohort Of the 40 immunogenicity evaluable subjects in the abatacept group, 1 (2.4%) subject was positive for CTLA-4, and possibly Ig, in the off-treatment period; no subjects were positive during the on-treatment period. The single subject who had samples with positive antibody responses was found to have at least 1 positive sample with neutralization activity.

CHMP's comment

In Study IM101311, due to the nature of the study sample and treatments (the recipient patients having primarily undergone immunosuppressive treatments and thus conferring a general immunodeficiency), an immunogenicity response was detected (in both 8/8 MUD and 7/8 MMUD cohorts) only post-treatment. Overall, the immunogenicity incidences and associated antibody titers observed were low. Some of the positive samples were found to have neutralising activity. Impact on the PK, efficacy, or safety of abatacept could not be assessed due namely to these low incidences.

Immunisations

CHMP's comment

An important potential risk of Orencia is infections associated to immunization with live vaccines (see RMP). The MAH has not updated the PI text regarding this potential risk (see separate PI). Because of severe immunosuppression and immune reconstitution, according to international guidelines live vaccines are usually contraindicated in the patients treated with allo-HSCT for longer than 24 months, if the patient suffers from chronic GvHD or has immunosuppressive medication ([a]). Thus, the MAH should update the PI texts accordingly with data on immunisations with live vaccines for patients with the currently sought indication of aGvHD prophylaxis.

[a] Reference: *Cordonnier et al., Vaccination of haematopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on infections in leukemia. ECIL 7.*

Adverse Events of Special Interest

Infections

Similar proportions of subjects experienced AEs in the SOC of Infections and Infestations in both treatment groups (abatacept vs placebo) up to Day 180 and up to Day 365, 68.5% vs 76.8% and 71.2% vs 79.7%, respectively. Abatacept use was not associated with increased event intensity of infections compared to placebo, and no subject died due to infections. However, in the placebo group, 5 subjects died due to infections, including 4 events of sepsis. The most frequently (≥ 10%) reported PTs of infections in abatacept-treated subjects were CMV infection reactivation, device related infection (15 subjects each, 20.5%), bacteremia, and pneumonia; and bacteremia in the placebo group (17 subjects, 24.6%). Of the 4 events, both CMV infection reactivation (19.8% vs 13.0) and pneumonia (14.7% vs 10.1%) showed a higher event frequency in abatacept-treated subjects compared to placebo, respectively.

In the 7/8 MMUD cohort, AEs in the SOC of Infections and Infestations were reported in 30 (69.8%) and 31 (72.1%) subjects up to Day 180 and Day 365, respectively. The most frequently reported AEs up to Day 180 were pneumonia (11 subjects, 25.6%), bacteraemia, and cytomegalovirus infection reactivation (8 subjects each, 18.6%).

Table 74 ***Cumulative Incidence of Infection and Immune Related Events up to Database Lock - 8/8 MUD Cohort As Treated Analysis Population***

Event Category	Treatment	N	Time Point	Number of Event of Interest	Number of Competing Event	Number of Censor	Cumulative Incidence (95% CI)
CMV VIREMIA	ABATACEPT	73	DAY 100	39	1	0	0.49 (0.39,0.63)
			DAY 180	39	1	0	0.50 (0.40,0.63)
			DAY 225	39	3	0	0.50 (0.40,0.63)
			DAY 365	39	6	0	0.51 (0.42,0.62)
	PLACEBO	69	DAY 100	29	2	0	0.45 (0.34,0.58)
			DAY 180	30	5	0	0.45 (0.35,0.58)
			DAY 225	30	6	0	0.45 (0.35,0.58)
			DAY 365	31	7	0	0.46 (0.36,0.59)
CMV INVASIVE DISEASE	ABATACEPT	73	DAY 100	5	1	0	0.08 (0.04,0.15)
			DAY 180	5	2	0	0.08 (0.04,0.15)
			DAY 225	7	4	0	0.10 (0.05,0.19)
			DAY 365	9	9	0	0.12 (0.07,0.22)
	PLACEBO	69	DAY 100	2	5	0	0.02 (<0.01,0.09)
			DAY 180	2	11	0	0.02 (<0.01,0.09)
			DAY 225	2	13	0	0.02 (<0.01,0.11)
			DAY 365	2	15	0	0.03 (<0.01,0.11)
POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER	ABATACEPT	73	DAY 100	1	1	0	0.01 (<0.01,0.09)
			DAY 180	1	2	0	0.01 (<0.01,0.09)
			DAY 225	1	5	0	0.01 (<0.01,0.09)
			DAY 365	1	12	0	0.01 (<0.01,0.09)
	PLACEBO	69	DAY 100	0	5	0	<0.01 (<0.01, <0.01)
			DAY 180	0	11	0	<0.01 (<0.01, <0.01)
			DAY 225	0	13	0	<0.01 (<0.01, <0.01)
			DAY 365	0	16	0	<0.01 (<0.01, <0.01)
OTHER PRE-SPECIFIED INFECTIONS	ABATACEPT	73	DAY 100	15	1	0	0.24 (0.17,0.33)
			DAY 180	25	2	0	0.33 (0.25,0.45)
			DAY 225	27	3	0	0.35 (0.27,0.47)
			DAY 365	28	6	0	0.38 (0.30,0.48)
	PLACEBO	69	DAY 100	18	3	0	0.22 (0.14,0.34)
			DAY 180	21	7	0	0.31 (0.23,0.42)
			DAY 225	22	9	0	0.33 (0.23,0.48)
			DAY 365	24	9	0	0.35 (0.26,0.48)

Note: Unstratified Fine and Gray model. Competing event includes death.

Table 75 ***Intensity of Infections Reported during the Post-transplantation Analysis Period - 8/8 MUD Cohort As Treated Analysis Population***

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
Treatment Group: Abatacept N = 73							
TOTAL SUBJECTS WITH AE	0	0	46 (63.0)	4 (5.5)	2 (2.7)	0	52 (71.2)
Infections and infestations	0	0	46 (63.0)	4 (5.5)	2 (2.7)	0	52 (71.2)
Cytomegalovirus infection reactivation	0	0	15 (20.5)	0	0	0	15 (20.5)
Device related infection	0	0	15 (20.5)	0	0	0	15 (20.5)
Bacteraemia	0	0	9 (12.3)	1 (1.4)	0	0	10 (13.7)
Pneumonia	0	0	9 (12.3)	1 (1.4)	0	0	10 (13.7)
Cytomegalovirus infection	0	0	8 (11.0)	0	0	0	8 (11.0)
Upper respiratory tract infection	0	2 (2.7)	6 (8.2)	0	0	0	8 (11.0)
Enterocolitis infectious	0	0	6 (8.2)	0	0	0	6 (8.2)
Urinary tract infection	0	0	4 (5.5)	0	0	1 (1.4)	5 (6.8)
Skin infection	0	0	4 (5.5)	0	0	0	4 (5.5)
Sepsis	0	0	0	1 (1.4)	2 (2.7)	0	3 (4.1)
Cytomegalovirus viraemia	0	0	2 (2.7)	0	0	0	2 (2.7)
Infection	0	0	2 (2.7)	0	0	0	2 (2.7)
Lymph gland infection	0	0	2 (2.7)	0	0	0	2 (2.7)
Anorectal infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Appendicitis	0	0	0	1 (1.4)	0	0	1 (1.4)
BK virus infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Bronchitis	0	0	1 (1.4)	0	0	0	1 (1.4)
Encephalitis	0	0	1 (1.4)	0	0	0	1 (1.4)
Epstein-Barr virus infection reactivation	0	0	1 (1.4)	0	0	0	1 (1.4)
Eye infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Febrile infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Human herpesvirus 6 infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Influenza	0	0	1 (1.4)	0	0	0	1 (1.4)
Kidney infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Lip infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Meningitis	0	0	1 (1.4)	0	0	0	1 (1.4)
Mucosal infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Paronychia	0	0	1 (1.4)	0	0	0	1 (1.4)
Pharyngitis	0	0	1 (1.4)	0	0	0	1 (1.4)
Pleural infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Viraemia	0	0	1 (1.4)	0	0	0	1 (1.4)
Treatment Group: Placebo N = 69							
TOTAL SUBJECTS WITH AE	0	1 (1.4)	42 (60.9)	7 (10.1)	5 (7.2)	0	55 (79.7)
Infections and infestations	0	1 (1.4)	42 (60.9)	7 (10.1)	5 (7.2)	0	55 (79.7)
Bacteraemia	0	0	15 (21.7)	1 (1.4)	1 (1.4)	0	17 (24.6)

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
Device related infection	0	0	14 (20.3)	0	0	0	14 (20.3)
Enterocolitis infectious	0	0	11 (15.9)	0	0	0	11 (15.9)
Sepsis	0	0	0	7 (10.1)	4 (5.8)	0	11 (15.9)
Cytomegalovirus infection reactivation	0	0	9 (13.0)	0	0	0	9 (13.0)
Pneumonia	0	0	8 (11.6)	0	1 (1.4)	0	9 (13.0)
Cytomegalovirus infection	0	0	5 (7.2)	1 (1.4)	0	0	6 (8.7)
Urinary tract infection	0	0	6 (8.7)	0	0	0	6 (8.7)
Infection	0	0	5 (7.2)	0	0	0	5 (7.2)
Upper respiratory tract infection	0	1 (1.4)	3 (4.3)	0	0	0	4 (5.8)
Bacterial infection	0	0	2 (2.9)	0	0	0	2 (2.9)
Febrile infection	0	0	2 (2.9)	0	0	0	2 (2.9)
Sinusitis	0	0	2 (2.9)	0	0	0	2 (2.9)
Skin infection	0	0	2 (2.9)	0	0	0	2 (2.9)
Anorectal infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Arthritis bacterial	0	0	1 (1.4)	0	0	0	1 (1.4)
BK virus infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Conjunctivitis	0	0	1 (1.4)	0	0	0	1 (1.4)
Cytomegalovirus viraemia	0	0	1 (1.4)	0	0	0	1 (1.4)
Encephalitis	0	0	0	1 (1.4)	0	0	1 (1.4)
Enteritis infectious	0	0	1 (1.4)	0	0	0	1 (1.4)
Epstein-Barr viraemia	0	0	1 (1.4)	0	0	0	1 (1.4)
Epstein-Barr virus infection reactivation	0	0	1 (1.4)	0	0	0	1 (1.4)
Eye infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Gastrointestinal infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Incision site cellulitis	0	0	1 (1.4)	0	0	0	1 (1.4)
Lip infection	0	0	1 (1.4)	0	0	0	1 (1.4)
Mucosal infection	0	0	1 (1.4)	0	0	0	1 (1.4)

01. Note: Includes data from the first dose date up to the Day 180 Supplemental Database Lock date. MedDRA Version 23.1

Malignancy

In the 8/8 MUD cohort, during the Day 180 analysis period, similar proportions of subjects experienced AEs in the SOC of Neoplasms benign, malignant, and unspecified (including cysts and polyps) in both treatment groups (abatacept: 9.6% vs placebo: 11.6%). Acute myeloid leukemia recurrent and acute lymphocytic leukemia recurrent were the most frequently reported malignancies in both the abatacept (3 subjects each [4.1%]) and placebo groups (3 subjects [4.3%] and 2 subjects [2.9%], respectively).

In the 7/8 MMUD cohort, during the Day 180 analysis period, 2 (4.7%) subjects experienced AEs in the SOC of Neoplasms benign, malignant, and unspecified (including cysts and polyps). Acute lymphocytic leukemia recurrent was reported in 1 (2.3%) subject, and 1 (2.3%) subject experienced chronic myeloid leukemia and chronic myeloid leukemia recurrent.

Autoimmune Disorders

In the 8/8 MUD cohort, during the Day 180 analysis period, no autoimmune disorders were reported in the abatacept group. In the placebo group, 2 (2.9%) subjects experienced autoimmune disorders: 1 Grade 3 autoimmune disorder (not otherwise specified) and 1 Grade 4 immune thrombocytopenia. No additional autoimmune disorders were reported.

In the 7/8 MMUD cohort, during the Day 180 analysis period, autoimmune disorders were reported for 1 (2.3%) subject with a Grade 4 event of autoimmune hemolytic anemia. By Day 365, 1 (2.3%) additional subject experienced autoimmune hemolytic anemia (Grade 2).

Infusion Reactions

In the 8/8 MUD cohort, during the treatment period, 10 (13.7%) subjects in the abatacept group and 11 (15.9%) subjects in the placebo group reported peri-infusional AEs (pre-specified infusional AEs reported within 24 hours following start of infusion. Nausea was the most frequently reported peri-infusional AE in both the abatacept (7 [9.6%], all Grade 3) and placebo (5 [7.2%], 4 Grade 3 and 1 Grade 4).

In the 7/8 MMUD cohort, during the treatment period, 5 (11.6%) subjects reported peri-infusional AEs. There were 4 Grade 4 events (nausea, vomiting, infusion related reaction, and hypotension) and 1 Grade 2 event of hypersensitivity.

Other Significant Adverse Events

Engraftment Related Events

No subjects in either treatment group demonstrated non-engraftment or graft rejection. One abatacept-treated subject with myelodysplastic syndrome (MDS) in the 8/8 MUD cohort demonstrated secondary graft failure in the setting of potentially persistent MDS. The subject underwent a second transplant with successful engraftment. This rate of secondary graft failure is consistent with published rates with standard GvHD prophylaxis.

8/8 MUD cohort

- The cumulative incidence of neutrophil recovery up to Day 100 was 98% (95% CI: 95.0, 100.0) in both the abatacept and the placebo groups.
- The cumulative incidence of platelet recovery up to Day 100 was 97% (95% CI: 93.0, 100.0) in the abatacept group and 94% (95% CI: 90.0, 99.0) in the placebo group.

7/8 MMUD cohort

- The cumulative incidence of neutrophil recovery up to Day 100 was 95% (95% CI: 80.0, 99.0).

- The cumulative incidence of platelet recovery up to Day 100 was 98% (95% CI: 79.0, 100.0).

Infection and Immune Related Events

CMV/EBV viremia

In the 8/8 MUD cohort, CMV viremia was reported in 47.4% of subjects treated with abatacept and 43.5% of subjects treated with placebo. EBV viremia was reported in 37.9% of subjects treated with abatacept and 29.0% of subjects treated with placebo.

The cumulative incidences of infection and immune-related events at Day 180 and at Day 365 in the abatacept group and the placebo group are as follows:

- CMV viremia at Day 180 and Day 365 (abatacept vs placebo): 50.0% vs 45.0% and 51.0% vs 46.0%, respectively.
- CMV invasive disease at Day 180 and Day 365 (abatacept vs placebo): 8.0% vs 2.0% and 12.0% vs 3.0%, respectively.
- The cumulative incidences of EBV viremia in the abatacept and placebo groups were comparable at Day 180 (33% and 29%, respectively) and Day 365 (36% and 32%, respectively).
- PTLD at Day 180 and Day 365 (abatacept vs placebo): 1.0% vs < 1.0% and 1.0% vs < 1.0%, respectively.
- Other pre-specified infections at Day 180 and Day 365 (abatacept vs placebo): 33.0% vs 31.0% and 38.0% vs 35.0%, respectively.

Five cases of CMV invasive disease were reported in the abatacept group by Day 180. Of these 5 cases, 4 were Grade 3 GI disease (3 non-serious, 1 SAE), and 1 was retinitis (Grade 3, SAE). Two cases of CMV GI disease were reported in the placebo group, both were non-serious, Grade 3 events.

In the 7/8 MMUD cohort, the cumulative incidences of infection and immune-related events at Day 180 and at Day 365 are as follows:

- CMV viremia at Day 180 and Day 365: 37%.
- CMV invasive disease at Day 180 and Day 365: 0.0% and 5.0%, respectively. These rates corresponded to 2 cases of invasive CMV disease involving the GI tract that were reported in 2 subjects, both between Days 181 and 270.
- PTLD at Day 180 and Day 365: 5.0%.
- Other pre-specified infections at Day 180 and Day 365: 49.0% and 51.0%, respectively.

PTLD

Four subjects experienced post-transplantation lymphoproliferative disorder (PTLD) during the study; all of them were pediatric subjects with age < 18 years. The only 2 cases of PTLD in the 8/8 MUD cohort were reported in the abatacept treatment group. Two cases of PTLD were reported in abatacept-treated subjects in the 7/8 MMUD cohort. All of the PTLD events were associated with EBV infection and manifested as lymphadenopathy without extra-nodal organ involvement. The onset day of PTLD varied from Day 49 to Day 89 post-transplant. All of the events resolved with treatment. Three of the 4 subjects were EBV serology positive at baseline; 1 patient had negative baseline EBV serology with donor EBV serology unknown. Three subjects were enrolled from the same study site; acyclovir prophylaxis was discontinued at day 30 post-transplant per the local standard of care. Due to the cluster of the cases,

the study protocol was amended to mandate acyclovir or valacyclovir prophylaxis till Day 180 post-transplant. No additional cases were reported among the 71 subsequently enrolled subjects.

CMV invasive disease

A total of 10 subjects experienced CMV invasive disease up to Day 225 post-transplant, 8 subjects (6.9%) were treated with abatacept and 2 (2.9%) were treated with placebo. All of the events occurred in adults. In the 8 abatacept-treated subjects, all of them were CMV sero-positive at baseline; the event onset day in these subjects varied from Day 42 to Day 218 post-transplant (median = Day 91 post-transplant); most of the CMV diseases involved the GI tract (6 subjects). One event was CMV hepatitis and 1 event was CMV retinitis. The event outcomes were reported in 7 cases, all of which resolved with antiviral therapy.

Safety in special populations

Pediatric subgroup of study IM101311 (Post-hoc Analysis)

The types of AEs reported in the from 6 to 17-year-old population were consistent with those expected in a pediatric patient population with hematologic malignancies undergoing HSCT. Review of those events did not identify any unexpected safety concerns among abatacept-treated pediatric patients.

Fourteen subjects treated with abatacept in the 8/8 MUD cohort and 16 in the 7/8 MMUD cohort were 6-17 years old, resulting in 30 abatacept treated subjects in the 6-17 age group when the 2 cohorts are combined. Thirteen subjects aged between 6 to 17 years were randomized to placebo in the 8/8 MUD cohort. In the abatacept combined group, 100% of subjects reported any-grade, all causality AEs. Drug-related AEs were similar in abatacept-treated subjects <18 years of age (n=30) and subjects ≥18 years of age (n=86).

Common Adverse Events

The most frequently reported AEs in subjects <18 years of age in the combined abatacept group were: stomatitis, 24 (80.0%); neutrophil count decreased, 20 (66.7%); febrile neutropenia, 19 (63.3%); lymphocyte count decreased, 18 (60.0%); platelet count decreased, 17 (56.7%); WBC count decreased and anemia, 16 (53.3%) each; pyrexia 15 (50.0%); and decreased appetite 13 (43.3%).

Serious Adverse Events

In the abatacept combined group, the overall frequencies of SAEs were higher in subjects < 18 years of age (n=30) compared to subjects ≥ 18 years of age (n=86): 93.3% and 61.6%, respectively. This was primarily attributable to the higher rate of pyrexia in the paediatric group.

SAEs reported in more than 2 subjects < 18 years of age were: pyrexia in 15 (50.0%); diarrhoea and sepsis in 4 (13.3%) each; and pneumonia, upper respiratory tract infection, and GvHD in GI tract in 3 (10.0%) each.

Paediatric versus adult subjects treated with abatacept

All 4 PTLD events occurred in subjects < 18 years of age. No new cases were reported following implementation of a protocol amendment mandating use of antiviral prophylaxis with acyclovir or valacyclovir for at least 6 months post-HSCT, indicating that the risk in younger patients may be mitigated in this manner.

Serious adverse events related to acute kidney injury, hepatobiliary disease, and mental status changes were not among those most commonly reported among HSCT recipients < 18 years of age. This may be attributable, at least in part, to the fact that comorbid conditions predisposing to such events, such as

atherosclerotic peripheral vascular and biliary tract disease and essential hypertension are typically associated with older age.

One event was reported in a paediatric patient; a 12-year-old male, who developed a GI infection with CMV on Study Day 309.

All but one of the deaths reported in Study IM101311 up to Day 180 occurred in subjects 18 years of age or older. The only pediatric death was reported in a 13-year-old female recipient of a 7/8 MMUD HSCT; it occurred on Post-transplant Day 84 and was attributed to GvHD.

Safety related to drug-drug interactions and other interaction

No formal DDI studies have been performed for abatacept in subjects with HSCT; however, the current approved product information for abatacept states that concomitant use of abatacept with TNF antagonists or other biologic, RA therapy is not recommended in patients with RA or PsA.

Discontinuation due to adverse events

In the 8/8 MUD cohort, any-grade all-causality AEs leading to discontinuation of study treatment were reported in 2 (2.7%) subjects in the abatacept group and 5 (7.2%) subjects in the placebo group (Table 76).

Adverse events leading to discontinuation of study treatment were reported in 3 (2.6%) abatacept-treated subjects and 5 subjects (7.2%) placebo-treated subjects. Eleven AEs were reported in the 5 placebo-treated subjects that led to the discontinuation of the treatment; these events were febrile infection, urinary tract infection, GvHD in GI tract, aGvHD in skin, GvHD in skin, pyrexia, dehydration, chronic lymphocytic leukemia recurrent, headache, dyspnea, and hypotension. Four AEs were reported in the 3 abatacept-treated subjects that led to discontinuation of the study drug; these events were pneumonia, GvHD in GI tract, delirium, and hypotension. There was no trend detected for the AEs that resulted in abatacept discontinuation.

In the 7/8 MMUD cohort, 1 (2.3%) abatacept-treated subject had AEs (delirium, hypotension) that resulted in discontinuation of study treatment.

Table 76 ***Adverse Events Leading to Discontinuation of Treatment Period - 8/8 MUD Cohort As Treated Analysis Population***

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 73	Placebo N = 69
TOTAL SUBJECTS WITH AE	2 (2.7)	5 (7.2)
Immune system disorders	1 (1.4)	2 (2.9)
Graft versus host disease in gastrointestinal tract	1 (1.4)	1 (1.4)
Acute graft versus host disease in skin	0	1 (1.4)
Graft versus host disease in skin	0	1 (1.4)
Infections and infestations	1 (1.4)	2 (2.9)
Febrile infection	0	1 (1.4)
Pneumonia	1 (1.4)	0
Urinary tract infection	0	1 (1.4)
Gastrointestinal disorders	1 (1.4)	1 (1.4)
Gastrointestinal disorder	1 (1.4)	1 (1.4)
General disorders and administration site conditions	0	1 (1.4)
Pyrexia	0	1 (1.4)
Metabolism and nutrition disorders	0	1 (1.4)
Dehydration	0	1 (1.4)
Neoplasms benign, malignant and unspecified	0	1 (1.4)
Chronic lymphocytic leukaemia recurrent	0	1 (1.4)
Nervous system disorders	0	1 (1.4)
Headache	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	0	1 (1.4)
Dyspnoea	0	1 (1.4)
Vascular disorders	0	1 (1.4)
Hypotension	0	1 (1.4)

CHMP's comment

In the 8/8 MUD cohort, discontinuations due to AEs were overall rare, with a slightly higher incidence in the placebo treatment group 7.2% (n=5) vs. 2.7% (n=2). At PT level discontinuations were mainly single occurrence, and thus no clustering was clearly evident.

Post marketing experience

In the currently sought indication abatacept has not been previously marketed in the EU, thus, as such post-marketing data are not available. However, abatacept has been recently approved for this currently sought indication in several other countries. The MAH was requested to provide a summary on available post-marketing safety data (adults and paediatric patients separately) to substantiate the safety profile of abatacept in this indication. The provided data are, so far, scarce and heterogenous for any firm conclusions.

To date, a large abatacept safety dataset of over a decade in long-term duration, including post-marketing data, exists in other approved indications (see Orencia PI/EPAR for details).

Study IM101841

Title *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 International Blood and Marrow Transplant Research Database.*

Study IM101841 was a retrospective cohort study using data routinely collected into the Center for International Blood and Marrow Transplant Research (CIBMTR) database. CIBMTR collects data on all allogeneic (related and unrelated) hematopoietic stem cell transplantation (HSCTs) performed in the United States (US) and on all HSCTs done with products procured through the C. W. Bill Young Cell Transplantation Program but performed outside of the US. Duration: Study Initiation Date: 10-Oct-2020 Study Completion Date: 15-Feb-2021 Study Period: 01-Jan-2011 to 31-Dec-2018.

Study IM101841 was conducted to evaluate whether HSCT patients with 7/8 HLA-matched unrelated donor treated with CNI + MTX + abatacept without ATG (n=54) would have improved outcomes compared with patients treated with CNI + MTX without ATG (n=162). This study utilized secondary data; therefore, causality assessment at the individual case level was not feasible and expedited reporting of individual AEs to BMS was not required.

Occurrence of PTLD after transplant is a datapoint captured in the CIBMTR database and was chosen as an exploratory safety outcome and was collected up to the first 100 and 180 days after transplant among the subset of patients with available CRF data.

There were no cases of PTLD reported at Day 100 or at Day 180 in the primary objective cohort.

CHMP's comment

Overall, study IM101841 retrospectively analysed patient information recorded in the CIBMTR registry database. This database does not include reports of individual adverse events and causality assessment at the individual case level is not feasible. The occurrence of PTLD after transplant was a datapoint captured in the CIBMTR database and it was chosen as an exploratory safety outcome. There were no cases of PTLD reported at Day 100 or at Day 180 in the primary objective cohort. Due to the exploratory nature of the data, firm conclusion on safety cannot be made. See efficacy section for a request on the follow-up data.

Literature Review

Based on the review of 9 publications of abatacept use for prophylaxis of aGvHD following HSCT, a total of 147 patients received abatacept during HSCT, with treatment duration varying from 28 days to 365 days. The study results relevant to safety, including infusion-related reactions, infections, donor cell engraftment, and disease-free survival/fatality rate, were presented in these publications; based upon those outcomes, abatacept use in HSCT was considered to be well-tolerated; no major safety concern was identified in association with the use of abatacept for prophylaxis of aGvHD in stem cell transplantation.

The publications referenced by the MAH also include efficacy data. However, the MAH has not used these studies to support any efficacy claims, and it is noted that the studies have been conducted in variable patient populations and many of them are uncontrolled. These data have therefore not been further considered or discussed in the efficacy section of this AR.

Safety results in other indications

Safety Summary from Rheumatoid Arthritis Studies

The safety results presented represent on-treatment AE data, from the first dose date up to Day 84, in adult RA subjects who were treated with IV abatacept (n=2367) or placebo (n=1352) and enrolled in the following double-blind placebo-controlled studies that are included in the abatacept-integrated safety database: IM101023, IM101043, IM101031, IM101029, IM101100, IM101101, and IM101102.

The following is a brief summary of safety:

- The overall proportion of AEs was similar for both abatacept (64.5%) and placebo (62.9%) groups.
- Three deaths were reported in the abatacept group. No deaths were reported in the placebo group.
- The overall proportion of SAEs was similar for both abatacept (3.0%) and placebo (3.4%) groups.
- Seventeen subjects (0.72%) in the abatacept group and 9 subjects (0.67%) in the placebo group discontinued due to SAEs.

Safety Summary from Juvenile Idiopathic Arthritis Study IM101033

The safety results presented in this section represent AE data from the first dose date up to Day 84 in all abatacept-treated subjects from the open-label, single-arm, lead-in phase (Period A) of Study IM101033 with IV abatacept in subjects with JIA. There were 190 total subjects treated with abatacept in this study.

The following is a brief summary of safety findings:

- The frequency of overall Aes reported in the JIA population was 65.3%, which was comparable to that reported in the adult RA populations studied (64.5%). Similar to the events reported in the adult RA studies, infections and GI disorders were also the most frequently reported events in the JIA study.
- Five SAEs (2.6%) were reported, 3 of which were skeletal disorders related to underlying disease.
- No deaths were reported.
- No SAEs leading to discontinuation were reported.

4.5.1. Discussion on clinical safety

In support of safety, the MAH has submitted a pivotal phase 2 study IM101311 and as supportive evidence an US Epidemiology Registry study IM101841. The sought indication is

ORENCIA (abatacept) in combination with a CNI and MTX is indicated for the prophylaxis for aGvHD in adult and pediatric patients 2 years of age and older undergoing HSCT from a matched or 1 allele-mismatched unrelated donor.

In addition, the results of a literature review on abatacept safety and aGvHD are presented, and a comparison to previous abatacept safety data in other approved indications (RA and JIA) are also referred to.

Exposure

Based on a database lock of 06-Nov-2020 of study IM101311, 142 of 146 enrolled subjects in the 8/8 MUD cohort were treated with study medication and transplanted (73 received abatacept and 69 received placebo) at 13 sites in the US and 1 site in Canada, and the median duration of therapy was 86.0 days (86.0 days each for abatacept and placebo). In the single-arm 7/8 MMUD cohort, 43 of the 46 enrolled subjects received abatacept at 9 sites in the US, and the median duration of therapy was 86.0 days.

A placebo-controlled comparison arm was not feasible for the 7/8 MMUD HSCT recipient cohort due to concerns over the high predicted rate of severe aGvHD. The comparator arm for 7/8 MMUD cohort was changed to a prespecified control cohort from the CIBMTR registry.

The first patient, first visit date was 15-Apr-2013, and the LPLV was 17-Nov-2018. The long-term duration of the study for each cohort is 5 years post transplantation (DLP Feb-2023).

Fourteen subjects treated with abatacept in the 8/8 MUD cohort and 16 in the 7/8 MMUD cohort were 6-17 years old patients, resulting in 30 abatacept treated paediatric patients, in the 2 cohorts combined. Thirteen subjects aged between 6 to 17 years were randomized to placebo in the 8/8 MUD cohort.

No data on paediatric patients in the proposed youngest age group (from 2 to 5 years old) are available. The MAH is planning, however, to conduct a clinical study to further characterize the safety (and PK) of abatacept in paediatric patients aged 2 to < 6 years for the prophylaxis of aGvHD.

Safety was evaluated by assessment of AE, ADR, SAE, and laboratory parameters, including Aes of special interest, engraftment related events and infections and immune-related events during the D180 period post transplantation. Additional safety data were collected (Aes) prospectively (protocol specified) and retrospectively (FDA requested).

The supportive safety data came from the company sponsored observational registry study IM101841 and comprised the primary objective cohort of patients who were 7/8 HLA-matched and received either: CNI + MTX + abatacept without ATG, n=50; CNI + MTX without ATG, n=150. Safety data was accrued only on one outcome measure, the occurrence of PTLD up to d180. Of note is that patients from the single-arm 7/8 MMUD cohort of the pivotal study are included in these numbers.

Pivotal study IM101311

The main safety data derive from the pivotal *study IM101311*, a phase 2, randomized, double-blind, placebo-controlled study of abatacept combined with a CNI and MTX in subjects, age 6 years and older, with high-risk hematologic malignancies who received allogenic HSCT from unrelated donors with HLA-match at no less than seven of eight loci (A, B, C, DRB1).

Safety in the 8/8 MUD cohort

Overall, the types of AEs, SAE, ADRs, other significant Aes, and laboratory abnormalities reported in this study and namely in this cohort, were consistent with those expected in a population of patients with hematologic malignancies undergoing stem cell transplantation and/or patient on abatacept treatment. Aes leading to discontinuation were rare and did not show clustering. Overall safety profile seems as expected based on the pharmacological mechanism of action of abatacept. However, there were several imbalances of ADRs between the treatment groups identified with abatacept treatment in this new target population and compared to that in the currently approved indications, e.g., mainly a higher incidence of infections. Overall, no clear association between abatacept exposure and safety events was identified (see PK section). The inherent challenges of identifying and distinguishing safety concerns in a patient population with high risk haematologic malignancies undergoing intensive treatments associated with the transplant process are acknowledged. Thus, clarifications are necessary.

Deaths

The number of deaths in abatacept-treated subjects was lower compared to that in placebo group: 8 (11.0%) vs. 16 (23.2%). The main causes of deaths reported in both the placebo- and abatacept-treated subjects were underlying malignancy recurrence and GvHD, which were expected in the population under study. Uncertainties in relation to this outcome are discussed in more detail in the efficacy section. Long-term data also on deaths are also awaited. Somewhat unexpectedly, considering the known anticipated high-risk profile of the 7/8 MMUD cohort patient cohort, the numbers for deaths in this cohort were clearly lower 3 (7.0%).

SAEs

The overall frequencies of all SAEs were similar between abatacept group (69.8%) and placebo group (65.2%). These data did not indicate any clear pattern, type, or increased severity of SAE with abatacept treatment compared to placebo. However, among the most frequently reported SAEs (≥ 5% of subjects),

imbalances (≥ 3% more frequent in abatacept-treated subjects compared to placebo) were observed in the incidence of SAEs of pyrexia (19.8% vs 15.9%), GvHD in GI tract (14.7% vs 4.3%), pneumonia (7.8% vs 1.4%), diarrhoea (6.0% vs 2.9%), and acute kidney injury (6.9% vs 1.4%). These differences were judged not to be related to the study drug. This conclusion was further discussed and justified in detail by the MAH.

Infections

Overall, there was no increase in frequency for AEs of infections with abatacept use compared to placebo (69% vs 76.8%). Further, abatacept use was not associated with increased intensity of infections compared to placebo, and no patient died due to infections. In the placebo group, 5 subjects died due to infections, including 4 events of sepsis. The most frequently (⩾ 10%) reported PTs of infections in abatacept-treated subjects were infection, device related infection, and pneumonia; of the 3 events, only pneumonia showed a higher event frequency in abatacept-treated subjects compared to placebo (14.7% vs 10.1%).

Not unexpectedly, considering the MOA of abatacept and the patient population under study, the incidences of both CMV and EBV viremia and CMV invasive disease were more numerous in the abatacept + CNI + MTX treatment group. All infections resolved with therapy. Infections, including opportunistic infections and namely viral reactivation are already important identified risk for abatacept (see RMP). Due to a higher frequency of CMV invasive disease in abatacept-treated subjects compared to placebo and biological plausibility, there is a possibility that abatacept use could be associated with an increased risk of CMV invasive disease also in this study sample. Infections in aGvHD are addressed in detail in the RMP, with appropriate risk minimisation measures.

However, some concern remained. Namely, symptomatic haemorrhagic cystitis (HC) is a frequent serious complication/AE following allo-HSCT. Although reported incidences vary, it is estimated that from 5 to 40 % of recipients may develop HC. HC is associated with factors such as BK polyomavirus reactivation, age, conditioning regimen, CMV viremia and presence of GVHD and it affects duration of hospitalisation. In addition, HSCT recipient patients are susceptible to invasive fungal infections, which also greatly contribute to morbidity and mortality. On request, these SAE were adequately discussed in detail by the MAH.

Immunisations

Infections associated to immunisation with live vaccines has been identified as an important potential safety concern (see RMP). Revision of the proposed text in the SmPC is requested (OC).

PTLD

All the identified four (3,4%) PTLD events occurred in in abatacept-treated subjects and subjects < 18 years of age and were associated with EBV infection. There is a possibility that abatacept use could be associated with an increased risk of PTLD. The available evidence suggested that the risk could be mitigated by anti-viral prophylaxis for a longer period (e.g., 6 months post-transplant). No new cases were reported following implementation of a protocol amendment mandating use of antiviral prophylaxis with acyclovir or valacyclovir for at least 6 months post-HSCT, indicating, according to the MAH, that the risk in younger patients may be mitigated in this manner. These issues, including viral monitoring, pre-emptive antiviral prophylaxis, and pertinent monitoring of patients, are addressed in detail in the RMP. Routine PhV activities are deemed adequate. In addition, the relevance of the putative finding of a discrepancy in the incidence of PTLD between adults and paediatric patients was discussed in the context of the extrapolation exercise.

Engraftment related AEs

No subjects in either treatment group demonstrated non-engraftment or graft rejection. One abatacept-treated subject with MDS in the 8/8 MUD cohort demonstrated secondary graft failure in the setting of potentially persistent MDS. The subject underwent a second transplant with successful engraftment. It can be agreed that this rate of secondary graft failure is consistent with published rates with standard aGvHD prophylaxis.

Chronic GVHD

Data on cGVHD are presented and discussed in detail in the efficacy section of this AR.

Infusion related reactions

Peri-infusional AEs were reported in 12.9% of total subjects treated with abatacept, which was similar to the placebo rate. The most frequent reactions with abatacept were nausea (6.9%) and infusion related reaction (2.6%). One hypersensitivity reaction was reported in 1 abatacept-treated subject (0.9%). Infusion related reactions are an important identified risk for IV abatacept (see RMP).

Malignancies

Similar proportions of subjects reported AEs in the SOC of Neoplasms benign, malignant, and unspecified (including cysts and polyps) in both treatment groups (abatacept: 9.6% vs placebo: 11.6%). Acute recurrent myeloid leukaemia and recurrent acute lymphocytic leukaemia were the most frequently reported malignancy in both the abatacept [3 subjects each (4.1%)] and placebo groups [3 subjects (4.1%) and 2 subjects (2.9%), respectively], all of which represented relapse of the pre-existing hematological malignancies. Malignancies are identified as important potential risks for abatacept (see RMP).

Autoimmune Symptoms and Disorders

No autoimmune disorders were reported in the abatacept group. In the placebo group, 2 (2.9%) subjects reported autoimmune disorders; 1 Grade 3 autoimmune disorder and 1 Grade 4 event of immune thrombocytopenia. No additional autoimmune disorders were reported in either treatment group up to Day 365. Autoimmune symptoms and disorders are identified as important potential risks for abatacept (see RMP).

Immunogenicity

In Study IM101311, due to the nature of the study sample and treatments (the recipient patients having primarily undergone immunosuppressive treatments and thus conferring a general immunodeficiency), an immunogenicity response was detected only post-treatment. Overall, the immunogenicity incidences and associated antibody titers observed were low. Some of the positive samples were found to have neutralising activity (3/5 in the 8/8 MUD and 1/1 in the 7/8 MMUD cohorts). Impact on the PK, efficacy, or safety of abatacept could not be assessed due namely to the low incidences. Thus, acknowledging the explorative nature of these data, no new immunogenicity information specific to the target patient population arose from these data. Some issues concerning the analytical methods still need to be addressed.

Immunisations

An important potential risk of Orencia is infections associated to immunization with live vaccines (see RMP). The MAH has not updated the PI text regarding this potential risk. Because of severe immunosuppression and immune reconstitution, according to international guidelines live vaccines are usually contraindicated in the patients treated with allo-HSCT for longer than 24 months if the patient suffers from chronic GvHD or has immunosuppressive medication. Thus, the MAH should update the PI

texts accordingly with data on immunisations with live vaccines for patients with the currently sought indication of aGvHD prophylaxis.(see separate PI):

Paediatric patients

In the paediatric subgroup, in the abatacept combined group, all subjects reported ADRs. According to the MAH, drug-related AEs were, overall, similar in abatacept-treated subjects <18 years of age (n=30) and subjects ≥18 years of age (n=86). However, in analysis of the paediatric safety data from the two study cohorts (8/8 MUD and 7/8 MMUD) the data were presented only as pooled/combined. These data should be presented also for the two cohorts separately. This would appear important (even acknowledging the small numbers) considering the heterogeneity of the characteristics and accrued safety (and efficacy) results of the two cohorts. The paediatric safety results were presented and discussed (also in the context of the extrapolation exercise) also separately for the two cohorts.

The existing paediatric data is indeed a subpopulation of the pivotal study population and the accrued results are based on post-hoc analysis. Overall, these data are scarce (8/8 n=16; placebo n=13; 7/8 n=14) and no data are available for the youngest age group of 2- to 5-year-old patients, thus, the MAH proposes an extrapolation exercise. The missing description of the extrapolation concept, plan, or results, as per current guidance (EMA/189724/2018), was submitted with the response to 1st RSI. It was also noted that according to guidance, details of the extrapolation concept and the results of the studies in the extrapolation will be included, after marketing authorisation application, in the European Public Assessment Report (EPAR).

Long-term data

Some of the results of the pivotal study long-term follow-up up to 5-years will be available in February of the current year, 2023 were provided. Considering the novel abatacept target patient population and the limitations of the provided safety data (small numbers, post hoc analysis, lack of a control group), it was considered reasonable for the MAH to provide further long-term data within this extension of indication procedure. This should include data for the longest feasible follow-up period (up to 5 years post-transplant, if available) of the study IM101311. The evolution of the safety database/profile should was called for (also in tabulated form). However, data provided was not of regulatory standard allowing assessment. Thus, further data is requested (see efficacy MO). The MAH should also provide the timelines for submitting these outstanding data. In the initial submission, data from the registry study IM101841 were accrued only up to d180, and it is expected that full d365 data is submitted in the response to the 2nd RSI.

Safety in the 7/8 MMUD cohort (study IM101311)

The safety profile of the patients in the 7/8 MMUD of the pivotal study was mostly similar to that of the 8/8 MUD population, but with also clear differences, to the extent that it could even be seen as more favourable. The number of deaths and malignancies were lower in this cohort. This is somewhat disconcerting as the common understanding is that these patients are anticipated to be at a higher risk of serious adverse events and death. While the overall safety profile of abatacept in the 7/8 MMUD cohort seems to be somewhat more favourable compared to the overall safety of abatacept in the 8/8 MUD cohort, higher SAE frequencies in the Infections and infestations SOC as well as in the Respiratory, thoracic, and mediastinal disorders SOC can be found in the 7/8 MMUD cohort compared to the 8/8 MUD cohort. The same imbalance can be seen for the drug-related SAE frequencies in the Infections and infestations SOC.

However, considering overall the limitations of the data accrued in this 7/8 MMUD cohort (small numbers, no adequate control group, data exploratory in nature) the reasons for this unforeseen finding are not clear and results should be interpreted with caution. This issue is discussed in more detail in the efficacy section.

Product information – Appendix 3

Concerning the attached Appendix 3 (Reasons for non-inclusion of PTs in adverse reactions with abatacept - table in section 4.8 of the SmPC) the MAH is requested to clarify the following: It is understandable that PTs with 'no suspected causal relationship' are not included in SmPC section 4.8 the list of ADRs, as per the definition of an ADR. If all other PTs with 'Reasons for non-inclusion' listed are causally related to the study drug i.e., are by definition ADRs, there would appear no reason for excluding any of the present ADRs from the section 4.8 of the proposed SmPC. The MAH has on request reinstated (in section 4.8) several relevant ARDs that were initially presented for exclusion.

Product information - Tabulated list of adverse reactions

As per guidance, separate ADRs tables are acceptable in exceptional cases where adverse profiles markedly differ depending on the use of the product. For example, it might be the case for a product used for different indications (e.g., an oncology and a non-oncology indication). Since the present population under study (study IM101311) differs from the abatacept treatment populations previously studied, it is acceptable to have two separate ADR-tables in the SmPC section 4.8.

The MAH has compiled as requested a separate comprehensive safety table (which still need revision), consisting of all ADRs identified in the currently sought indications (both 8/8 and 7/8 cohorts and combined), for presentation of these data (in tabulated form) in the clinical AR and ultimately, in the EPAR.

Supportive study IM101841

The study IM101841 retrospectively analysed patient information recorded in the CIBMTR registry database. This database does not include reports of individual adverse events and causality assessment at the individual case level is not feasible. The occurrence of PTLD after transplant was a datapoint captured in the CIBMTR database and it was chosen as an exploratory safety outcome. There were no cases of PTLD reported at Day 100 or at Day 180 in the primary objective cohort. Due to the nature of these data, firm conclusion on safety cannot be made.

Other data

Results from the conducted literature review of abatacept in aGvHD prophylaxis did not identify any significant new safety findings, acknowledging the scarcity (only 9 reference) and the heterogeneity of the available data (benign conditions, high-risk haematologic malignancies, all types of allogenic transplantations, differing abatacept dosing, varied transplant conditioning regimens).

The safety profile of abatacept in the current sought indication was mainly comparable to safety data previously reported in the other approved indications referred to (RA and JIA), as presented by the MAH. Inherent uncertainties of this type of comparative data are well known and due to disease-specific unique pathomechanisms, the acquired safety data are not completely transferable/comparable between these indications.

Overall, on the basis of the provided data, the safety profile of abatacept in combination with CNI and MTX in the sought new indication for the prophylaxis for aGvHD appears encouraging (at least in the placebo controlled 8/8 MUD cohort) and in line with the patient population under study and in general, with the safety profile previously reported for abatacept. Some uncertainties remain, which need clarification (see 2nd RSI and separate PI).

Uncertainties

The overall short-term placebo-controlled safety database is not extensive and derives from one phase 2 RC study. Placebo controlled safety data are available only for the 8/8 MUD cohort. Furthermore, long-term (up to 5-year) data are still partly outstanding. Supportive safety evidence for the sought indication

is limited to one outcome measure (PTLD), is exploratory in nature and comes from an US registry data Some uncertainties still remain, which need clarification (see 2nd RSI and separate PI).

Extrapolation

See efficacy section for details.

Overall, the safety and tolerability of abatacept in combination with CNI and MTX in prophylaxis of aGvHD during unrelated donor HCT appears promising. However, some concerns remain, and final conclusions on safety are pending MAH response to the 2nd RSI.

Assessment of paediatric data on clinical safety

CHMP's comment

Concerning the paediatric population, the existing pivotal paediatric data are based on post-hoc analysis of the subgroup of paediatric patients of the pivotal study IM101311 and are, overall, scarce; no data are available for the youngest age group of 2- to 5-year-old patients, thus, the MAH proposes an extrapolation exercise. However, a description of the extrapolation framework (concept, plan, or results) as per current guidance (EMA/189724/2018), has been submitted.. It should be noted that according to this guidance, details of the extrapolation concept and the results of the studies in the extrapolation will be included, after marketing authorisation application, in the European Public Assessment Report (EPAR).

4.5.2. Conclusions on clinical safety

Overall, on the basis of the provided data, the safety profile of abatacept in combination with CNI and MTX in the sought indication for the prophylaxis for aGvHD appears encouraging (at least for the placebo controlled 8/8 MUD cohort) and in line with the patient population under study and in general, the safety profile previously reported for abatacept. However, some differences were also seen (mainly higher incidences of infections in the abatacept treatment group), which have been discussed acceptably .

From the safety perspective a single multidisciplinary major objection was resolved on the proposed extrapolation of data from the adult population to the paediatric population. Some other concerns on safety remain. Thus, final conclusions on safety are pending MAH response to the 2nd RSI.

4.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines' web-portal. However, this issue should be re-evaluated later during this process.

5. Risk management plan

The MAH submitted an updated RMP version 28.0 with this application for an extension of indication of prophylaxis of acute Graft versus Host Disease (aGvHD). Please see the separate RMP AR. The main proposed RMP changes were the following:

- The MAH has presented epidemiology and target population of the proposed indication, prophylaxis of aGvHD. In the Section Main treatment options for prophylaxis and treatment the MAH does not

mention ATG which is nowadays essential part of the standard protocols for allo-HSCT in EU, aimed for preventions of acute and chronic GvHD. The information should be added to the epidemiologic characteristics of aGvHD.

- The MAH has included the Study IM101311 to the list of clinical studies and provided data of exposure to abatacept in the IM101311 study.
- The MAH has updated the description and definitions of the safety concerns so that they cover the new proposed target population. The MAH has updated the description and definitions of important identified risks, Infections, Infusion related reactions, regarding the patients treated with allo-HSCT.
- The PRAC proposes of adding a new safety concern, Important potential risk: "Chronic GvHD in patients treated with allogeneic hematopoietic stem cell transplantation (HSCT)".
- The MAH should discuss the risk of invasive fungal infections and secondary malignancies in the RMP.
- The MAH should update the guidance for immunization with live vaccines also regarding patients with a history of allo-HSCT as routine RMM and present the guidance also in "Description of routine risk minimization measures by safety concern".
- The MAH does not propose any additional PhV activities in the new target population.
  As mentioned above, the PRAC proposes of including chronic GvHD as an important potential risk. There is a need for further characterizing this safety concern. The MAH should: 1.) discuss which data sets might be available already during the extension of the indication evaluation process which could clarify the issue, which data sets might be available later, and provide sample size estimation; 2.) the MAH should provide plans to clarify treatment results of allo-HSCT conditioned with Orencia at well-established timepoints (cGvHD free survival at 1 y and at 2 y, OS 1 y and 2 y). The treatment results of the allo-HSCT patients should be compared to those of the allo-HSCT treated patients with conditioning regimens containing ATG. 3.) the MAH should conduct a feasibility assessment for a PASS study, which aims to further characterize important potential risk of chronic GvHD.
- The MAH has added guidance to monitor CMV- and EBV-viremia, and to prevent CMV-disease and EBV associated PTLD.
- The current proposed indication is lacking in the list of indications in the Summary of the risk management plan, "The medicine and what it is used for". The MAH should add the proposed indication to the list.
- There were some editorial comments to be revised in the next RMP version.
- Depending on the final RMP safety specification, all relevant sections of the RMP should be updated accordingly.

5.1. Overall conclusion on the RMP

☒ The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information are submitted.

6. Changes to the Product Information

As a result of this variation, sections 4.2, 4.3, 4.4, 4.5., 4,8, and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all proposed changes to the Product Information with CHMP comments. However, due to major remaining uncertainties, comprehensive comments on the SmPC are considered premature at this stage. The MAH should consult the SmPC Guideline for general advice on the nature of data to be included in Section 5.1.

6.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. According to the MAH, an additional consultation with target patient groups on the draft PL has not been conducted for the following reasons:

- Consultation with target patient groups on the PL has been performed at the occasion of the original Marketing Authorization Application of ORENCIA powder for concentrate for solution for infusion for the treatment of Rheumatoid Arthritis (EC Decision received on 21 May 2007).
- The readability of the ORENCIA solution for injection PL has been tested at the occasion of the Extension Application for this second pharmaceutical form and route of administration (EC Decision received on 4 October 2012).
- The new indication that is hereby applied for concerns one same route of administration and has a similar safety profile as the previously approved indications (i.e., key safety messages for the existing and new applied for indication are essentially the same).
- ORENCIA powder for concentrate for solution for infusion is administrated by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL remain unchanged.
- The general design and layout of the proposed PL has not changed compared to the tested ones.
- Overall, the proposed leaflet shares large text sections with the reference one. The modifications now proposed in the PL (i.e., those relevant to the new indication) do not represent major changes.

Therefore, within the scope of the current proposed changes, the MAH does not consider it necessary to conduct another consultation with target patient groups for the PL of ORENCIA (abatacept) for this Type II variation for a new indication.

The justification is found acceptable for reasons provided by the MAH.

7. Benefit-Risk Balance

7.1. Therapeutic Context

7.1.1. Disease or condition

Allogeneic HSCT (aHSCT) is an effective treatment for aggressive haematologic malignancies, often representing the only option for cure. However, some of its benefit, especially in the case of unrelated donor (URD) transplantation, is offset by a high rate of transplant-related mortality (TRM) stemming largely from severe aGvHD and infection. aGvHD occurs when reconstituted 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 GI tract being the most common targets. aGvHD-mediated damage to these vital organs has been associated with increased morbidity and death. Chronic graft-versus-host disease (cGvHD) is also a major complication of HSCT and can lead to debilitating consequences and mortality; it has features resembling autoimmune and other immunologic disorders such as scleroderma, Sjögren's syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency. Whereas cGvHD is often preceded by a history of aGVHD, it can also occur in the absence of antecedent aGvHD.

GvHD is the leading cause (20%) of non-relapse mortality in HSCT recipients. Both aGvHD and cGvHD are common complications of HSCT. aGvHD and cGvHD variants have been classically characterised based upon the time of onset, with aGvHD occurring within the first 100 days post-transplant, and cGvHD occurring thereafter. However, clinical findings, rather than a set time period, have increasingly been used to differentiate between acute and chronic GvHD.

Among the many factors that impact the risk of severe aGvHD, the degree of matching between recipient and donor HLA alleles is the most important variable affecting the incidence and severity of this disease. The preferred transplant donor is a fully HLA-matched sibling; however, only a minority of subjects (<20%) have a fully-matched sibling. Hence, a majority of prospective transplant subjects turn to registries of potential unrelated donors, to screen for matches for the 8 alleles at the HLA -A, -B, and -DRB1 loci. With a fully-matched (8/8) unrelated donor, the risk to subjects is lower than with donors who have even a single HLA mismatch. Subjects with a 7/8 mismatched unrelated donor are at high risk for development of severe aGvHD and consequently, aGvHD-related mortality.

7.1.2. Available therapies and unmet medical need

Current transplant management focuses on prophylactic GvHD regimens aimed to either suppress donor T cell function with immunomodulatory agents or deplete T cells from the donor graft; the target is to balance between maximising the reduction of GvHD and minimising the risk of relapse, fatal infections (especially viral reactivation) as well as delayed engraftment. The backbone of the current standard of care for GvHD prophylaxis is the use of a calcineurin inhibitor (either cyclosporine or tacrolimus) plus methotrexate. In addition, anti-thymocyte globulin has been used for prophylaxis of GvHD in the setting of aHSCT for many years. Other immunomodulatory agents are also being used to augment the basic CNI+MTX GvHD prophylaxis regimen. In addition to abatacept, these agents include mycophenolate mofetil, sirolimus and post-transplant cyclophosphamide (PT-Cy).

Current European consensus recommendations for prophylaxis and management of GvHD focus on allogeneic stem-cell transplantation in adult patients with standard risk haematological malignant disease using an HLA-matched sibling or URD and bone marrow or peripheral blood as stem-cell source. According to the published recommendations, patients undergoing matched related donor or matched URD allogeneic transplant should receive GvHD prophylaxis with a calcineurin inhibitor (tacrolimus or cyclosporine) plus an antimetabolite (methotrexate, or in some cases mycophenolate mofetil) .The guidelines also recommend the use of ATG for preventing GvHD in patients undergoing matched URD allogeneic stem-cell transplantation, as well as in patients undergoing matched related donor allogeneic peripheral blood allogeneic stem-cell transplantation who are at a high risk of GvHD.

The recommendations recognise that there are divergent views concerning paediatric transplantations, mismatched unrelated donor transplantations and haploidentical transplantations, and the recommendations therefore do not cover these situations. It is however mentioned that in children (<18 years), many centres use calcineurin inhibitor as a single agent, and many centres also use rATG in matched unrelated donor aHSCT. Moreover, while not covered in the recommendations, ATG is also very commonly used as part of prophylactic regimens in HLA-mismatched transplantations.

The recommendations also acknowledge that while a high consensus was reached during their development regarding the underlying principles for drug management of GvHD prophylaxis, the level of evidence for each specific recommendation (regarding e.g. timing, dose and duration) is low, mainly because comparative analyses are absent. From a regulatory perspective, it is furthermore noted that in the EU, GvHD prophylaxis is quite variably covered among the authorised indications for the medicinal products included in the recommendations, with cornerstone products such as calcineurin inhibitors,

methotrexate and ATG being authorised primarily through national / decentralised procedures and consequently with variable Product Information.

Considering the limited evidence base, an unmet need for prophylaxis of GvHD can be considered to exist in the majority of HSCT recipients who do not have a fully matched sibling donor, and this unmet need is even greater for the 7/8 MMUD population who are considered to be inherently at higher risk of GvHD. Consequently, additional products with a favourable benefit-risk profile and a well-documented basis for their use would be an important addition to the current treatment armamentarium. From a European perspective, where rATG holds an established position as part of the prophylactic regimen in many instances, it should be borne in mind that abatacept would likely be viewed as an alternative to rATG rather than the two agents being used together, as this combination would very likely lead to profound and excessive immunosuppression.

7.1.3. Main clinical studies

The current variation application is based on results from two partly overlapping studies:

- Study 311 was an investigator-sponsored, multicentre Phase 2 trial with 2 treatment populations: a randomised, double-blind, placebo-controlled cohort for patients receiving HSCT from 8 of 8 HLA-matched donors (N = 73 abatacept, N = 69 placebo), and a single-arm cohort for patients receiving HSCT from 7 of 8 HLA-matched donors (N treated = 42). The primary objective of the study was to assess the impact of abatacept on the incidence of severe aGVHD, when added to a background GvHD prophylactic regimen (CNI + MTX) administered to patients with haematological malignancies receiving an unrelated-donor HSCT.
- Study 841 was a registry study using data routinely collected into the CIBMTR database. The primary objective of the registry study was to compare OS with 180 days of follow-up post-HSCT in 7/8 HLA-matched patients treated with CNI + MTX + abatacept without ATG to those treated with CNI + MTX without ATG. A number of other comparator groups were also included in the study. Notably, the 7/8 MMUD cohort of Study 311 was also included in Study 841 and indeed accounts for over 80% of patients in the "CNI + MTX + abatacept without ATG" group of Study 841. In the MAH's response to the 1st RSI, it was indicated that a new 8/8 cohort has been added into the study; further details are awaited as part of the response to the 2nd RSI.

7.2. Favourable effects

In the 8/8 MUD cohort of Study IM101311, the primary endpoint was severe (Gr III-IV) aGvHD-free survival up to Day 180 post-transplantation. The rate was numerically higher for abatacept compared to placebo, but the treatment difference was not statistically significant at the 0.05 level (89% vs. 77%; HR: 0.54 (95% CI: 0.25, 1.19); p = 0.1223). Consequently, the pre-planned hierarchical analysis also failed for the key secondary endpoint, and all p values can only be considered exploratory.

When analysed with data until Database Lock, the severe (Gr III-IV) GFS rate at Day 365 was 72% for both abatacept and placebo. At database lock, the proportion of subjects with a severe (Gr III-IV) event was 41% for abatacept and 45% for placebo, and the HR estimate for severe (Gr III-IV) GFS for abatacept vs. placebo was 0.80 (0.48, 1.34). Most subjects remain censored even in the analysis until Database Lock.

Results for selected secondary endpoints for the 8/8 MUD cohort of IM101311 were as follows:

- Using unstratified competing risk analysis, the cumulative incidence of severe aGvHD up to Day 180 (key secondary endpoint) for abatacept vs. placebo was 7% for abatacept and 16% for placebo; HR: 0.41 (95% CI 0.14, 1.17); p = 0.0964.
- Moderate-to-severe (Gr II-IV) GFS rate at Day 180 was 50% for abatacept vs. 33% for placebo; HR: 0.55 (95% CI: 0.36, 0.86); p = 0.0069.
- OS rates up to Day 180 were 97% for abatacept and 84% for placebo (HR = 0.33 (95% CI: 0.12, 0.93), stratified log-rank test p = 0.0281).
- OS rates up to Day 365 were 84% for abatacept and 77% for placebo.
- Up to last contact prior to Database Lock, 24 subjects (33%) in the abatacept group and 29 subjects (42%) in the placebo group had died. HR = 0.81 (95% CI: 0.46, 1.42), p = 0.4610.
- When analysed with data until database lock, the disease-free survival rate at Day 365 was 79% for abatacept and 65% for placebo. At database lock, the number and proportion of subjects who had relapsed or died was 29/73 (40%) for abatacept and 31/69 (45%) for placebo; HR = 0.81 (95% CI 0.48, 1.35).
- Using unstratified competing risk analysis (the event of interest being cGhVD and competing risks including death and relapse of underlying malignancy), the cumulative incidence of cGvHD up to Day 365 was 49% for abatacept and 43% for placebo. The HR for cGvHD until database lock was 1.19 (95% CI 0.73, 1.94).

In the 7/8 MMUD cohort of IM101311:

- Severe (Gr III-IV) aGvHD free survival rates up to Day 180 and Day 365 were 98% (95% CI: 85, 100) and 88% (95% CI 74, 95), respectively. At database lock, there were 12/43 subjects (28%) with a severe (Gr III-IV) aGvHD event.
- Cumulative incidence of severe (Gr III-IV) aGvHD up to Day 180 was 2% (95% CI: < 1.0, 11.0).
- The moderate-to-severe (Gr II-IV) GFS rate up to Day 180 was 58% (95% CI: 42, 71).
- OS rates until Day 180 and Day 365 were 98% (95% CI: 85, 100) and 88% (95% CI: 74, 95), respectively. At database lock, 12/43 subjects (27.9%) had died. In this dataset, 31 (72.1%) subjects were on-study and censored at their last contact date.
- Using competing risk analysis, the cumulative incidence of cGvHD up to Day 365 was 63% (95% CI: 46, 76).

In Study IM101841:

- OS at Day 180 post-transplant was statistically significantly higher in the abatacept + CNI + MTX group compared to CNI + MTX only: 98% vs. 75%; HR: 0.07 (95% CI, 0.01, 0.30), p = 0.0028.
- OS at Day 180 was higher for abatacept + CNI + MTX when compared to CNI + MTX + ATG: 98% vs. 74%; HR: 0.08 (95% CI, 0.02, 0.36), p = 0.0060.

7.3. Uncertainties and limitations about favourable effects

Study IM101311 did not meet its pre-specified primary endpoint in the 8/8 cohort: although a numerical difference favouring abatacept was seen, there was no statistically significant advantage for abatacept over placebo in Grade III-IV GFS at Day 180. Consequently, the pre-planned hierarchical analysis also failed on the pre-specified key secondary endpoint (cumulative incidence of severe aGvHD up to Day

180). All other analyses were conducted outside of a Type I error -controlled framework. A nominally significant advantage was seen in overall survival at Day 180, but the differences between treatment groups in both GFS and OS displayed a clearly decreasing trend over time.

Results in the 7/8 cohort of study IM101311 were strikingly positive, and at Day 180, GFS and OS were clearly better than corresponding rates for abatacept-treated subjects in the 8/8 cohort. While OS decreased from 98% at Day 180 to 88% at Day 365, it remained higher than in the abatacept arm of the 8/8 cohort also at Day 365. Considering that 7/8 mismatched subjects are supposed to have inherently higher risk of GvHD than 8/8 matched subjects, the results are unexpected. The rationale or plausibility of these findings have been discussed by the MAH, but given the small sample size, the possibility that random chance may have given results that are better than the eventual outcomes to be expected, on average, in the target population, cannot be excluded.

Based on newly available data from Study 311, OS rates in the 8/8 cohort at 5 years post transplant were 63% for abatacept and 53% for placebo; in the 7/8 cohort, the 5-year OS rate was 72%. However, further details for these results are awaited as part of the MAH's response to the 2nd RSI.

The 7/8 cohort of study IM101311 accounts for over 80% of abatacept-treated patients in study IM101841 and is thus a major driver of the favourable results. Due to the overlapping samples, the concerns regarding the generalisability of results in the 7/8 cohort in study IM101311 extend directly also to study IM101841.

The primary comparison in study IM101841 was between CNI + MTX + abatacept vs. CNI + MTX only. As the European standard of care very routinely includes ATG as part of the prophylactic regimen in 7/8 transplants, patients in the control group are de facto undertreated compared to current European practice.

The duration of follow-up in study IM101841 was limited to 180 days. This may be considered quite short and potentially insufficient for a comprehensive comparison, particularly in light of results over longer follow-ups in study IM101311. This limitation may be particularly relevant for the comparison with ATG, for which the main demonstrated benefit is on prevention of cGvHD, and its effects could consequently be expected to be discernible more gradually over longer periods of follow-up.

In their response to the 1st RSI, the MAH provided update Day 365 data for Study 841, and also indicated that a new 8/8 cohort had been included in the study. Currently available data seems to confirm benefits observed at Day 180 and suggests improved OS for abatacept vs. ATG in 8/8 patients; however, further details for the updated dataset are awaited as part of the MAH's response to the 2nd RSI.

All patients included in the studies had their HSCT between 2011 and 2018. It cannot be excluded that a subsequent evolution of the standard of care in GvHD prophylaxis, with overall improvement in expected outcomes, may make some of the comparisons somewhat outdated compared to the current status. It is nevertheless recognised that the CNI + MTX combination remains a relevant and well established backbone in GvHD prophylaxis per current treatment guidelines.

7.4. Unfavourable effects

1. **Study IM101311,** a phase 2, randomised, double-blind, placebo-controlled study

8/8 MUD cohort (abatacept with CNI + MTX vs. placebo, respectively):

- AEs 73 (100.0%) vs 69 (100.0%)
- discontinuations due to AEs 2 (2.7%) vs 5 (7.2%)
- deaths 8 (11.0%) vs 16 (23.2%).

- SAE 52 (71.2%) vs 45 (65.2%); related SAEs 20 (27.4%) vs 20 (29.0%)
- discontinuations due to SAE 0 vs. 1 (1.4%)
- No engraftment failures
- Neutrophil recovery 98% in both; 97% and 94% experienced platelet recovery
- CMV viremia 50.0% vs 45.0%; CMV invasive disease 8.0% vs 2.0%
- EBV viremia 37.9% vs 29.0 %
- 2 cases of PTLD vs 0
- malignancies 9.6% vs 11.6%

*7/8 MMUD cohort (*abatacept with CNI + MTX) a *single arm cohort of the pivotal study;*

- AEs 43 (100.0%)
- discontinuations due to AEs 1 (2.3%)
- deaths 3 (7.0%)
- SAE 29 (67.4%); related SAE 10 (23.3%)
- Discontinuations due to SAE 0
- No engraftment failures
- Neutrophil recovery 95%; platelet recovery 98%
- CMV viremia was 37%; 2 (4,7%) cases of CMV invasive disease
- 2 cases of PTLD
- 2 (4.7%) malignancies

2. The supportive **study IM101841**, is a retrospective, company sponsored, observational, registry study, in which only a single exploratory safety endpoint, PTLD, was used: no cases of PTLD were seen up to d180.

7.5. Uncertainties and limitations about unfavourable effects

Overall, very limited descriptive safety data in the sought indication are available: only 73 8/8 MUD patients and 43 7/8 MMUD patients have been exposed to abatacept. Further, out of these patients only 30 were paediatric patients (14 in 8/8 and 16 in 7/8 cohorts) and no data are available for the youngest age group from 2- to 5-year-old patients. Extrapolation from the adult data (and from other paediatric indications) is considered a critical part of this paediatric extension of indication, without which assessment of benefit/risk balance is not possible. A framework (concept, plan, and results) as per guidance for the proposed by the MAH paediatric extrapolation exercise was provided.

The provided 5-year LTE safety results were available from February 2023 and considering the limitations of the safety data set (limited numbers, lack of long term results) this further long-term data was provided but were preliminary by nature and not of regulatory standard, allowing assessment and is therefore still pending submission.

In addition, some further clarification is sought on the proposed text for section 4.8 of the SmPC and Appendix 3.

7.6. Effects Table

Table 77 ***Effects table for Orencia in aGvHD prophylaxis (data cut-off: 06 November 2020)***

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Gr III-IV GFS, day 180		%	89 98	77 N/A	HR=0.54 (95% CI 0.25, 1.19), p=0.122 95% CI 85, 100	IM101311, 8/8 7/8
Gr III-IV GFS, day 365		%	72 88	72 N/A	HR @ DBL=0.80 (95% CI 0.48, 1.34) 95% CI 74, 95	IM101311, 8/8 311, 7/8
Gr III-IV aGvHD incidence, day 180		%	7 2%	16 N/A	HR=0.41 (95% CI 0.14, 1.17) 95 % CI <1, 11	IM10311, 8/8 7/8
OS, day 180		%	97 98	84	HR=0.33 (95% CI 0.12, 0.93) 95% CI 85, 100	IM101311, 8/8 7/8
OS, day 365		%	84 88	77 N/A	HR @DBL=0.81 (95% CI 0.46, 1.42) 95% CI 74, 95	IM101311, 8/8 7/8
cGvHD incidence, day 365		%	49 63%	43 N/A	HR @DBL=1.19 (95% CI 0.73, 1.94) 95% CI 46, 76	IM101311, 8/8 7/8
OS @day 180, aba vs. no aba		%	98	75	HR=0.07 (95% CI 0.01, 0.30), p=0.003	IM101841 (includes 7/8 only)
OS @day 180, aba vs. ATG		%	98	74	HR=0.08 (95% CI 0.02, 0.36), p=0.006	IM101841 (includes 7/8 only)
Unfavourable Effects						Study
AEs (all)		n (%)	73 (100.0)	69 (100.0)	(8/8 MUD cohort)	IM101311
AEs related		n (%)	63 (86.3)	62 (89.9)	(8/8 MUD cohort)	IM101311
Infections (all)		n (%)	50 (68.5)	53 (76.8)	(8/8 MUD cohort)	IM101311
CMV viremia		%	47.4	43.5	(8/8 MUD cohort)	IM101311
CMV invasive disease		%	8.0 (6.9)	2.0 (2.9)	(8/8 MUD cohort)	IM101311
EBV viremia		%	37.9	29.0	(8/8 MUD cohort)	IM101311
EBV invasive disease		n (%)	1.0 (1.4)	0	(8/8 MUD cohort)	IM101311
PTLD		n (%)	2	0	(8/8 MUD cohort)	IM101311
GI aGvHD		n (%)	19 (26.0)	13 (18.8)	(8/8 MUD cohort)	IM101311
Deaths		n (%)	11 (9.5)	16 (23.2)	(8/8 MUD cohort)	IM101311
SAE (all)		n (%)	52 (71.2)	45 (65.2)	(8/8 MUD cohort)	IM101311
SAE related		n (%)	20 (27.4)	20 (29.0)	(8/8 MUD cohort)	IM101311
Engraftment failures		n (%)	0	0	(8/8 MUD cohort)	IM101311
Neutrophil recovery		(%)	98	98	(8/8 MUD cohort)	IM101311
Platelet recovery		(%)	97	94	(8/8 MUD cohort)	IM101311
Discontinuation due to AE		n (%)	2 (2.7)	5 (7.2)	(8/8 MUD cohort)	IM101311
Malignancy		n (%)	7 (9.6)	8 (11.6)	(8/8 MUD cohort)	IM101311
Peri-infusional AEs		n (%)	10 (13.7)	11 (15.9)	(8/8 MUD cohort)	IM101311

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Autoimmune Disorders		n (%)	0	2 (2.9)	(8/8 MUD cohort)	IM101311

Abbreviations: aba, abatacept; ADR, adverse drug reaction; AE, adverse event; aGvHD, acute graft versus host disease; ATG, antithymocyte globulin; cGvHD, chronic graft versus host disease; DBL, database lock; GFS, aGvHD-free survival; Gr, grade; HC, haemorrhagic cystitis; LTE, long-term extension study; N/A, not applicable; SAE, serious adverse event; Notes:

7.7. Benefit-risk assessment and discussion

7.7.1. Importance of favourable and unfavourable effects

Acute GvHD is one of the most important complications of allogeneic HSCT and is associated with major post-transplant morbidity and mortality. Moreover, HSCT is a potentially curative treatment for haematological malignancies and other difficult disorders, and a new therapy to improve outcomes would therefore be a major step forward. In this respect, the variation application is agreed to address a significant unmet medical need.

Nevertheless, there are concerns with respect to the strength of the evidence regarding a clinically relevant therapeutic benefit. The MAH is applying for a specific indication of prophylaxis for *acute* GvHD, and the studies provided in support of the proposed indication are set up to support this specific claim, with the primary analyses being limited to 180 days of follow-up post-transplant. While it can be agreed that most instances of acute GvHD are indeed likely to occur within this time frame, it is not clear that a potentially isolated effect on acute GvHD is associated with clinically relevant overall benefit; instead, it could be expected that favourable effects on more global outcomes such as overall survival should also be discernible. Indeed, data based on longer follow-ups (provided as supplementary data by the MAH) would seem to suggest that any favourable effects seen at early stages post-transplant decrease over time, and even currently available overall follow-up may be insufficient to illustrate the complete evolution of treatment effects and associated benefit. In weighing the strength of the evidence, the fact that study IM101311 in fact failed on its pre-specified primary endpoint (severe aGvHD -free survival at Day 180 in the 8/8 cohort) should also not be overlooked.

Results in the 7/8 cohort of study IM101311 are particularly impressive, considering that this population should inherently be at a higher risk of GvHD compared to their 8/8 counterparts. It is therefore somewhat counterintuitive that the results in the 7/8 cohort are even better than among the abatacept-treated patients in the 8/8 cohort.

Study IM101841 was designed to provide additional support for the claimed indication. Unfortunately, due to the overlapping samples in the two studies, the unusually favourable results in the 7/8 cohort of study IM101311 are a major efficacy driver for abatacept also in study IM101841. Moreover, the follow-up in study IM101841 is limited to 180 days which, as stated above, may not be sufficient to cover the whole period of interest post-transplant. This limitation is particularly relevant for contextualising the effect of abatacept in relation to standard of care including ATG, as the main benefit of ATG is on prevention of chronic GvHD.

In their response to the 1st RSI, the MAH informed that data for the full 5-year follow-up from Study 311 had recently become available to the MAH, and graphical outputs for OS and RFS were included in the response. Moreover, the MAH had gained access to 1-year outcomes data for Study 841, and a new 8/8 cohort also had been included in Study 841, with selected data included in the response. These data

seem potentially very relevant to address the initially identified limitations, but it should particularly be noted that data on cGvHD, one of the key determinants of long-term success for HSCT, was not included for either study. To allow an adequate assessment of benefit-risk, comprehensive and appropriately quality assured data and documentation must still be awaited for these updated results; this expectation is reflected in the proposed new MO.

The safety profile of abatacept in combination with CNI and MTX in the sought indication for the prophylaxis for aGvHD appears encouraging and is in line with that of the patient population under study. However, some clarification is still needed. Final conclusions on safety are pending the MAH responses to several additional other concerns.

7.7.2. Balance of benefits and risks

While some encouraging findings were reported in study IM101311, they were initially not considered to provide sufficient demonstration of a clinically relevant overall benefit supporting the use of abatacept as part of a GvHD prophylactic regimen in allogeneic HSCT; in particular, as stated above, the failure of study 311 on its pre-specified primary endpoint cannot be overlooked in the overall assessment. The MAH has very recently gained access to updated data for both studies, and while the available data are potentially very useful, they are currently not adequate to enable a detailed assessment. Upon receipt of adequately updated data, an expert consultation is proposed to gain further insight into the overall robustness of the data package and the clinical relevance of observed treatment benefits.

From the safety perspective, the profile observed in HSCT, together with the available post-marketing experience from other indications, would not seem prohibitive for ultimate determination of a favourable benefit-risk balance.

Final conclusions regarding the balance of benefits and risks are pending the MAH response to the 2nd RSI.

7.7.3. Additional considerations on the benefit-risk balance

In the 1st RSI, an MO was raised regarding the proposed wording of the indication, as the wording would not have restricted use to the study population with haematologic malignancies, but would also have permitted the use of abatacept in allogeneic HSCT for non-malignant diseases. In their response, the MAH agreed to amend the indication accordingly, and the MO is considered solved.

7.8. Conclusions

As a major objection remains, the overall B/R of Orencia in aGvHD prophylaxis is currently negative.

8. Recommended conditions for marketing authorisation and product information in case of a positive opinion

Proposed list of recommendations:

Recommendations pertain to quality, non-clinical (e.g. ERA, PK/PD, PAES if not key to the B/R).**Description of post-authorisation measure(s)**

1. It is recommended that the MAH will provide results of the ABA3-study for CHMP assessment, if/ when available (Final study report expected in 2027):

Study/Key Dates/Study Report	Lead Investigator	Study Design/Duration	Subject Population	Treatment Group/Background Therapy	No. Subjects	Efficacy Endpoints
IM101790 NCT04380740 (also known as ABA3) Phase 2 ISR study Study is ongoing Final study report expected: 2027	Leslie Kean	Multicenter, randomized, double blind, Phase 2 trial for patients receiving HSCT from 7 of 8 or 8 of 8 HLA matched unrelated donors, in which an extended dosing regimen of abatacept, and a short-term dosing regimen and placebo, will be compared in their ability to improve outcomes for patients by reducing rates of both severe acute and severe cGHVD and the overlap syndrome after transplant. In addition, dosing regimen in patients age 2 to < 6 will be studied and the PK characterized to verify the model-predicted dose in that age group / 2 year study	Patients at least 2 years old, have a hematologic malignancy, and have an unrelated bone marrow or peripheral blood stem cell donor who is HLA-matched at no less than 7 of 8 loci	Patients > 6 years old will receive 4 doses of abatacept 10 mg/kg IV (Days -1, +5, +14, +28 +/- 1 day). Three days prior to the fifth dose, patients will be randomly assigned to either Regimen A and receive 4 doses of placebo or Regimen B and receive 4 more doses of abatacept. Patients 2 to <6 years old will receive 4 doses of abatacept 15 mg/kg/dose (Day -1) and 12 mg/kg/dose (Day +5, +14, +28 +/- 1 day). After analysis of Regimen C by the DSMC and study committee, if criteria are met to enroll additional patients aged 2 to <6, patients in this age group will receive the dose described above. Three days prior to the fifth dose, patients will be randomly assigned to either Regimen D and receive 4 doses of placebo or Regimen E and receive 4 more doses of abatacept Background Therapy: standard CNI and MTX-based prophylaxis	160 planned	Primary: Severe (Grade IV) Acute GVHD-Free, Severe Chronic GVHD-Relapse-Free Survival (SGRFS) [Timeframe: 1 post-transplant] Note th this study, chronic GvH includes overlap syndro SGRFS will be modelec time-to-event outcome, as such, failures that oc beyond one year and be study end will be consic in the analysis.