

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125118Orig1s240

Trade Name: ORENCIA

Generic or Proper Name: abatacept

Sponsor: Bristol-Myers Squibb Company

Approval Date: December 15, 2021

Indication: ORENCIA is a selective T cell costimulation modulator indicated for:

- the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA)
- the treatment of patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA)
- the treatment of adult patients with active psoriatic arthritis (PsA)
- the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor

CENTER FOR DRUG EVALUATION AND RESEARCH

125118Orig1s240

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Officer/Employee List	
Multidiscipline Review(s) • Summary Review • Office Director • Cross Discipline Team Leader • Clinical • Non-Clinical • Statistical • Clinical Pharmacology	X
Product Quality Review(s)	
Clinical Microbiology / Virology Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125118Orig1s240

APPROVAL LETTER



BLA 125118/S-240

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Kurt Zhu, PhD
US Regulatory Lead, Global Regulatory and Safety Sciences
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Dr. Zhu:

Please refer to your supplemental biologics license application (sBLA), dated June 23, 2021, received June 23, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for Orencia (abatacept).

This Prior Approval supplemental biologics license application provides for data to support the use of abatacept for the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,¹ that is identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use,) and include the labeling changes proposed in any pending “Changes Being Effectuated” (CBE) supplements.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Orenzia (abatacept) was approved on December 23, 2005, we have become aware through clinical trial data of a serious risk of increased infections requiring further characterization in patients age 2 to less than 6 years old with acute graft versus host disease receiving abatacept 15 mg/kg as a 60-minute intravenous infusion on Day -1, followed by 12 mg/kg on Days 5, 14, and 28 after transplantation. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of infections in patients 2 to less than 6 years of age receiving abatacept and to verify the population PK predicted optimal dosing regimen in this population.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this known serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 4189-1 Conduct a clinical trial to further characterize the known serious risk of infections with abatacept in patients age 2 to less than 6 years and to characterize the pharmacokinetics (PK) of abatacept to verify the population PK predicted optimal dosing regimen of abatacept (15 mg/kg as a 60-minute intravenous infusion on Day -1, followed by 12 mg/kg on Days 5, 14, and 28 after transplantation) in pediatric patients age 2 to less than 6 years for the prophylaxis of acute graft versus host disease, in combination with a calcineurin inhibitor and methotrexate, undergoing hematopoietic stem cell transplantation from a matched or 1 allele-mismatched unrelated donor.

The timetable you submitted on December 9, 2021 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2022
Trial Completion: 06/2026
Final Report Submission: 12/2026

Provide the datasets with the final report.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Submit the protocol(s) to your IND 135013, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

following wording in bold capital letters at the top of the first page of the submission, as appropriate: “**Required Postmarketing Protocol Under 505(o)**”, “**Required Postmarketing Final Report Under 505(o)**”, “**Required Postmarketing Correspondence Under 505(o)**”.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁴

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

⁴ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

If you have any questions, call Suria Yesmin, Senior Regulatory Project Manager, at 301-348-1725.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Division Director
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROMEO A DE CLARO
12/15/2021 10:23:56 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125118Orig1s240

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORENCIA safely and effectively. See full prescribing information for ORENCIA.

ORENCIA (abatacept) for injection, for intravenous use
ORENCIA (abatacept) injection, for subcutaneous use
Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Indications and Usage, Prophylaxis for Acute Graft versus Host Disease (1.4)	12/2021
Dosage and Administration, Dosage in Prophylaxis of Acute Graft versus Host Disease (2.4)	12/2021
Warnings and Precautions, Immunizations (5.4)	12/2021
Warnings and Precautions, Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) Reactivation in aGVHD Prophylaxis after Hematopoietic Stem Cell Transplant (HSCT) (5.7)	12/2021

INDICATIONS AND USAGE

ORENCIA is a selective T cell costimulation modulator indicated for:

- the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). (1.1)
- the treatment of patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA). (1.2)
- the treatment of adult patients with active psoriatic arthritis (PsA). (1.3)
- the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor. (1.4)

Limitations of Use:

Concomitant use of ORENCIA with other immunosuppressives [e.g., biologic disease-modifying antirheumatic drugs (bDMARDs), Janus kinase (JAK) inhibitors] is not recommended (1.5, 5.1).

DOSAGE AND ADMINISTRATION

Intravenous Use for Adult RA (2.1) and Adult PsA (2.3)

- Administer at 0, 2, and 4 weeks, and every 4 weeks thereafter, as a 30-minute infusion

Body Weight of Patient	Dose	Number of Vials
Less than 60 kg	500 mg	2
60 to 100 kg	750 mg	3
More than 100 kg	1,000 mg	4

Subcutaneous Use for Adult RA (2.1)

- Prior to the first subcutaneous dose, may administer an optional loading dose as a single intravenous infusion as per body weight categories above.
- Administer 125 mg by subcutaneous injection once weekly (within a day of the intravenous infusion if infusion given).
- Patients switching from intravenous use to subcutaneous use, administer first subcutaneous dose instead of next scheduled intravenous dose.

Intravenous Use for pJIA in Pediatric Patients ≥6 Years Old (2.2)

- Pediatric patients weighing <75 kg administer 10 mg/kg intravenously and those weighing ≥75 kg administer the adult intravenous dosing regimen (not to exceed a maximum dose of 1,000 mg), as a 30-minute infusion.
- Subsequently administer infusions at 2 and 4 weeks and every 4 weeks thereafter.

Subcutaneous Use for pJIA in Pediatric Patients ≥2 Years Old (2.2)

- Administer subcutaneously without an intravenous loading dose

Body Weight of Pediatric Patient	Dose (once weekly)
10 kg to less than 25 kg	50 mg
25 kg to less than 50 kg	87.5 mg
50 kg or more	125 mg

Subcutaneous Use for Adult PsA (2.3)

- Administer 125 mg by subcutaneous injection once weekly without an intravenous loading dose.

- Patients switching from intravenous use to subcutaneous use, administer first subcutaneous dose instead of next scheduled intravenous dose.

Intravenous Use for prophylaxis of aGVHD (2.4)

- For patients 6 years and older, administer at a 10 mg/kg dose (maximum dose 1,000 mg) as a 60-minute infusion on the day before transplantation, followed by a dose on Day 5, 14, and 28 after transplant (2.4).
- For patients 2 to less than 6 years old, administer a 15 mg/kg dose as a 60-minute infusion on the day before transplantation, followed by a 12 mg/kg dose as a 60-minute infusion on Day 5, 14, and 28 after transplant (2.4).

Preparation and Administration Instructions

- Administer as a 30-minute intravenous infusion for RA, pJIA, and PsA (2.5).
- Administer as a 60-minute intravenous infusion for aGVHD prophylaxis (2.5).
- See the Full Prescribing Information for preparation and administration instructions for intravenous infusion and recommendations for subcutaneous use (2.5, 2.6). Prepare ORENCIA using only the silicone-free disposable syringe (2.5).

DOSAGE FORMS AND STRENGTHS

Intravenous Infusion

- For injection: 250 mg lyophilized powder in a single-dose vial (may use less than full contents of vial or use more than one vial). (3)

Subcutaneous Use

- Injection: 50 mg/0.4 mL, 87.5 mg/0.7 mL, 125 mg/mL solution in single-dose prefilled syringes. (3)
- Injection: 125 mg/mL solution in a single-dose prefilled ClickJect™ autoinjectors. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Concomitant use with a TNF antagonist can increase the risk of infections and serious infections. (5.1)
- Hypersensitivity and anaphylaxis have occurred. (5.2)
- Serious infections reported. Patients with a history of recurrent infections or underlying conditions predisposing to infections may experience more infections. Discontinue if a serious infection develops. (5.3)
- Screen for latent TB infection prior to initiating therapy. Patients testing positive should be treated prior to initiating ORENCIA. (5.3)
- Should screen for viral hepatitis prior to initiating ORENCIA. (5.3)
- Update vaccinations prior to initiating ORENCIA. Live vaccines should not be given concurrently or within 3 months of discontinuation. ORENCIA may blunt the effectiveness of some immunizations. (5.4)
- COPD patients may develop more frequent respiratory adverse events. (5.5)
- Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) reactivation in patients treated for aGVHD prophylaxis. (5.7)

ADVERSE REACTIONS

Most common adverse events (≥10%) in RA are headache, upper respiratory tract infection, nasopharyngitis, and nausea. (6.1)

Most common adverse reactions (≥10%) in prophylaxis of aGVHD are anemia, hypertension, CMV reactivation/CMV infection, pyrexia, pneumonia, epistaxis, CD4 lymphocytes decreased, hypermagnesemia, and acute kidney injury. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- Adult Rheumatoid Arthritis
- Polyarticular Juvenile Idiopathic Arthritis
- Adult Psoriatic Arthritis

- 1.4 Prophylaxis for Acute Graft versus Host Disease
- 1.5 Limitations of Use
- 2 DOSAGE AND ADMINISTRATION
- 2.1 Dosage in Adult Rheumatoid Arthritis

- 2.2 Dosage in Polyarticular Juvenile Idiopathic Arthritis
- 2.3 Dosage in Adult Psoriatic Arthritis
- 2.4 Dosage in Prophylaxis of Acute Graft versus Host Disease in Adults and Pediatric Patients Aged 2 Years and Older
- 2.5 Preparation and Administration Instructions for Intravenous Infusion
- 2.6 Recommendations for Subcutaneous Administration
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Increased Risk of Infection with Concomitant Use of TNF Antagonists, Other Biologic RA/PsA Therapy, or JAK Inhibitors
 - 5.2 Hypersensitivity
 - 5.3 Infections
 - 5.4 Immunizations
 - 5.5 Increased Risk of Adverse Reactions When Used in Patients with Chronic Obstructive Pulmonary Disease (COPD)
 - 5.6 Immunosuppression
 - 5.7 Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) Reactivation in aGVHD Prophylaxis after Hematopoietic Stem Cell Transplant (HSCT)
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
 - 6.2 Immunogenicity

- 6.3 Postmarketing Experience
- 7 DRUG INTERACTIONS**
 - 7.1 Immunosuppressants
 - 7.2 Blood Glucose Testing
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 13.2 Animal Toxicology and/or Pharmacology
- 14 CLINICAL STUDIES**
 - 14.1 Adult Rheumatoid Arthritis
 - 14.2 Polyarticular Juvenile Idiopathic Arthritis
 - 14.3 Adult Psoriatic Arthritis
 - 14.4 Prophylaxis of Acute Graft versus Host Disease
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adult Rheumatoid Arthritis

ORENCIA® is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

1.2 Polyarticular Juvenile Idiopathic Arthritis

ORENCIA is indicated for the treatment of patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis.

1.3 Adult Psoriatic Arthritis

ORENCIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA).

1.4 Prophylaxis for Acute Graft versus Host Disease

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

1.5 Limitations of Use

The concomitant use of ORENCIA with other potent immunosuppressants [e.g., biologic disease-modifying antirheumatic drugs (bDMARDs), Janus kinase (JAK) inhibitors] is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Rheumatoid Arthritis

For adult patients with RA, administer as an intravenous infusion or as a subcutaneous injection. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than JAK inhibitors or bDMARDs (e.g., TNF antagonists).

Intravenous Dosing Regimen

Reconstitute ORENCIA lyophilized powder and administer after dilution [see *Dosage and Administration (2.5)*] as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 1. Following the initial intravenous infusion, administer as an intravenous infusion at 2 and 4 weeks and every 4 weeks thereafter.

Table 1: Dose of ORENCIA for Intravenous Infusion in Adult RA Patients

Body Weight of Adult Patient	Dose	Number of Vials ^a
Less than 60 kg	500 mg	2
60 to 100 kg	750 mg	3
More than 100 kg	1,000 mg	4

^a Each vial provides 250 mg of abatacept for administration.

Subcutaneous Dosing Regimen

Prior to the first subcutaneous dose, may administer an optional loading dose as a single intravenous infusion (as per body weight categories in Table 1). If an intravenous loading dose is used, administer the first subcutaneous injection within one day of the infusion. Administer ORENCIA 125 mg in prefilled syringes or in ORENCIA ClickJect™ autoinjector by subcutaneous injection once weekly [*see Dosage and Administration (2.6)*].

For patients switching from ORENCIA intravenous therapy to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.2 Dosage in Polyarticular Juvenile Idiopathic Arthritis

For patients with polyarticular juvenile idiopathic arthritis (pJIA), may administer ORENCIA as an intravenous infusion (only patients 6 years of age and older) or a subcutaneous injection (only patients 2 years of age and older) [*see Use in Specific Populations (8.4)*]. ORENCIA may be used as monotherapy or concomitantly with methotrexate.

Intravenous Dosing Regimen

Administer ORENCIA as a 30-minute intravenous infusion based on body weight [*see Dosage and Administration (2.5)*]:

- If less than 75 kg, administer a dose of 10 mg/kg.
- If 75 kg or greater, administer as per the recommendations in Table 1 (follow the adult intravenous dosing regimen), not to exceed a maximum dose of 1,000 mg.

Following the initial intravenous infusion, administer infusions at 2 and 4 weeks and every 4 weeks thereafter. Immediately discard any unused portion in the vials.

Subcutaneous Dosing Regimen

Administer ORENCIA for subcutaneous injection, without an intravenous loading dose, utilizing the weight range-based dosing as specified in Table 2 [*see Dosage and Administration (2.6)*]. Subsequently administer once weekly.

Table 2: Dose of ORENCIA for Subcutaneous Administration in Patients 2 Years of Age and Older with JIA

Body Weight of Pediatric Patient	Dose (once weekly)
10 to less than 25 kg	50 mg
25 to less than 50 kg	87.5 mg
50 kg or more	125 mg

PJIA patients may self-inject with ORENCIA or the patient’s caregiver may administer ORENCIA if both the healthcare practitioner and the parent/legal guardian determines it is appropriate. The ability of pediatric patients to self-inject with the autoinjector has not been tested.

2.3 Dosage in Adult Psoriatic Arthritis

For adult patients with psoriatic arthritis, administer as an intravenous infusion or a subcutaneous injection. ORENCIA may be used with or without non-biologic DMARDs.

Intravenous Dosing Regimen

Administer ORENCIA as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 1. Following the initial intravenous administration, administer an intravenous infusion at 2 and 4 weeks and every 4 weeks thereafter.

Subcutaneous Dosing Regimen

Administer 125 mg of ORENCIA subcutaneously once weekly (no intravenous loading dose is needed) [see *Dosage and Administration (2.6)*].

For patients switching from ORENCIA intravenous infusions to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.4 Dosage in Prophylaxis of Acute Graft versus Host Disease in Adults and Pediatric Patients Aged 2 Years and Older

Antiviral Prophylactic Treatment

Before administering ORENCIA, administer recommended antiviral prophylactic treatment for Epstein-Barr Virus (EBV) reactivation, and continue for six months following HSCT. In addition, consider prophylactic antivirals for Cytomegalovirus (CMV) infection/reactivation during treatment and for six months following HSCT [see *Warnings and Precautions (5.7)*].

Intravenous Dosing Regimen

For patients 6 years and older, administer ORENCIA 10 mg/kg (maximum dose of 1,000 mg) as an intravenous infusion over 60 minutes on the day before transplantation (Day -1), followed by administration on Days 5, 14, and 28 after transplantation.

For patients 2 to less than 6 years old, administer ORENCIA 15 mg/kg as an intravenous infusion over 60 minutes on the day before transplantation (Day -1), followed by 12 mg/kg as an intravenous infusion over 60 minutes on Days 5, 14, and 28 after transplantation.

2.5 Preparation and Administration Instructions for Intravenous Infusion

Calculate the ORENCIA dose, the total volume of reconstituted solution required, and the number of ORENCIA vials needed. For a full dose, less than the full contents of one vial or more than one vial may be needed. Using aseptic technique, reconstitute, dilute, and then administer ORENCIA as follows:

Reconstitution

- 1) Use the vial only if the vacuum is present.
- 2) Reconstitute each vial of supplied ORENCIA lyophilized powder (each vial supplies 250 mg of abatacept) with 10 mL of Sterile Water for Injection, USP (direct the stream toward the inside wall of the vial) to obtain a concentration of 25 mg/mL. Use only the provided *silicone-free syringe* with an 18- to 21-gauge needle:
 - a. If the ORENCIA lyophilized powder is accidentally reconstituted using a siliconized syringe, the solution may develop a few translucent particles (discard any solutions prepared using siliconized syringes).
 - b. If the silicone-free disposable syringe is dropped or becomes contaminated, use a new silicone-free disposable syringe. To obtain new silicone-free syringes, contact Bristol-Myers Squibb at 1-800-ORENCIA.
- 3) Gently swirl the vial to minimize foam formation, until the contents are completely dissolved. Do not shake. Avoid prolonged or vigorous agitation.
- 4) Upon complete dissolution of the lyophilized powder, vent the vial with a needle to dissipate any foam that may be present.
- 5) Visually inspect the reconstituted solution (the solution should be clear and colorless to pale yellow). Do not use if opaque particles, discoloration, or other foreign particles are present.
- 6) Repeat steps 2) through 5) if two, three, or four vials are needed for a dose (see Table 1).

Dilution

- 7) Must further dilute the reconstituted ORENCIA solution to 100 mL as follows:
 - a. From a 100 mL infusion bag or bottle of 0.9% Sodium Chloride Injection, USP, withdraw a volume equal to the volume of the reconstituted ORENCIA solution required for the patient's dose.
 - b. Slowly add the reconstituted ORENCIA solution(s) into the infusion bag or bottle using the *silicone-free disposable syringe provided with each vial*.
 - c. Gently mix. Do not shake the bag or bottle. The final concentration of abatacept in the bag or bottle will depend upon the amount of abatacept added, but will be no more than 10 mg/mL. Immediately discard any unused portion in the ORENCIA vial.

Administration

- 8) Prior to administration, visually inspect the ORENCIA diluted solution for particulate matter and discoloration. Discard the diluted solution if any particulate matter or discoloration is observed.
- 9) Using an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (pore size of 0.2 µm to 1.2 µm), administer the entire diluted ORENCIA solution over:
 - 30 minutes for RA, pJIA, and PsA
 - 60 minutes for aGVHD prophylaxis
- 10) Must complete the infusion of the diluted ORENCIA solution within 24 hours of reconstitution of the ORENCIA vials.

Do not infuse ORENCIA concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of ORENCIA with other drugs.

Storage of Diluted ORENCIA Solution

May store the diluted ORENCIA solution at room temperature or refrigerate at 2°C to 8°C (36°F to 46°F) up to 24 hours before use. Discard the diluted solution if not administered within 24 hours.

2.6 Recommendations for Subcutaneous Administration

ORENCIA prefilled syringes and ORENCIA ClickJect autoinjectors are intended for:

- subcutaneous use only and are not intended for intravenous infusion
- use under the guidance of a healthcare practitioner.

After proper training in subcutaneous injection technique, a patient or the patient's caregiver may administer a subcutaneous injection of ORENCIA (ClickJect autoinjector or prefilled syringe) if a healthcare practitioner determines that it is appropriate. Instruct patients and/or caregivers to follow the directions provided in the Instructions for Use for additional details on administration. Specifically instruct them to inject the full amount (which provides the proper dose of ORENCIA), rotate injection sites, and to avoid injections into areas where the skin is tender, bruised, red, or hard.

Visually inspect for particulate matter and discoloration prior to administration. Do not use ORENCIA prefilled syringes or ORENCIA ClickJect autoinjectors exhibiting particulate matter or discoloration. ORENCIA should be clear to slightly opalescent and colorless to pale yellow.

3 DOSAGE FORMS AND STRENGTHS

• Intravenous Infusion

For injection: 250 mg white lyophilized powder in a single-dose vial (one may use less than the full contents of the vial or use more than one vial) [*see Dosage and Administration (2.1, 2.2, 2.3)*].

- Subcutaneous Use

Injection: 50 mg/0.4 mL, 87.5 mg/0.7 mL, and 125 mg/mL of a clear to slightly opalescent, colorless to pale-yellow solution in a single-dose prefilled glass syringe.

Injection: 125 mg/mL of a clear to slightly opalescent, colorless to pale-yellow solution in a single-dose prefilled ClickJect autoinjector.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Infection with Concomitant Use of TNF Antagonists, Other Biologic RA/PsA Therapy, or JAK Inhibitors

In controlled clinical trials in patients with adult RA, patients receiving concomitant intravenous ORENCIA and TNF antagonist therapy experienced more infections (63% vs. 43%) and serious infections (4.4% vs. 0.8%) compared to patients treated with only TNF antagonists [*see Adverse Reactions (6.1)*]. These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonists; therefore, concurrent therapy with ORENCIA and a TNF antagonist is not recommended. While transitioning from TNF antagonist therapy to ORENCIA therapy, patients should be monitored for signs of infection. Additionally, concomitant use of ORENCIA with other biologic RA/PsA therapy or JAK inhibitors is not recommended.

5.2 Hypersensitivity

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis reactions. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients. Of the 190 ORENCIA-treated patients in pJIA clinical trials, there was one case of a hypersensitivity reaction (0.5%) [*see Adverse Reactions (6.1)*].

In postmarketing experience, fatal anaphylaxis following the first infusion of ORENCIA and life-threatening cases of angioedema have been reported. Angioedema has occurred as early as after the first dose of ORENCIA, but also has occurred with subsequent doses. Angioedema reactions have occurred within hours of administration and in some instances had a delayed onset (i.e., days).

Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction. If an anaphylactic or other serious allergic reaction occurs, administration of intravenous or subcutaneous ORENCIA should be stopped immediately with appropriate therapy instituted, and the use of ORENCIA should be permanently discontinued.

5.3 Infections

Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA (serious infections were reported in 3% and 1.9% of RA patients treated with intravenous ORENCIA and placebo, respectively) [see *Adverse Reactions (6.1)*]. Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease, could further predispose them to infection. A higher rate of serious infections has been observed in adult RA patients treated with concurrent TNF antagonists and ORENCIA compared to those treated with ORENCIA alone [see *Warnings and Precautions (5.1)*].

Healthcare providers should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infections, underlying conditions which may predispose them to infections, or chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment with ORENCIA should be monitored closely. Administration of ORENCIA should be discontinued if a patient develops a serious infection.

Prior to initiating ORENCIA, patients should be screened for latent tuberculosis (TB) infection with a tuberculin skin test. ORENCIA has not been studied in patients with a positive TB screen, and the safety of ORENCIA in individuals with latent TB infection is unknown. Patients testing positive in TB screening should be treated by standard medical practice prior to therapy with ORENCIA.

Antirheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed in accordance with published guidelines before starting therapy with ORENCIA. In clinical studies with ORENCIA, patients who screened positive for hepatitis were excluded from study.

5.4 Immunizations

Prior to initiating ORENCIA in pediatric and adult patients, update vaccinations in accordance with current vaccination guidelines. ORENCIA-treated patients may receive current non-live vaccines. Live vaccines should not be given concurrently with ORENCIA or within 3 months after discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ORENCIA. In addition, there are clinical considerations for administering live vaccines to infants who were exposed to ORENCIA while in utero [see *Use in Specific Populations (8.1)*]. Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations.

5.5 Increased Risk of Adverse Reactions When Used in Patients with Chronic Obstructive Pulmonary Disease (COPD)

In Study V, adult COPD patients treated with ORENCIA for RA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. A greater percentage of patients treated with ORENCIA developed a serious adverse event compared to patients treated with placebo (27% vs 6%) [see *Clinical Studies (14.1)* and

Adverse Reactions (6.1)]. Use of ORENCIA in patients with COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status.

5.6 Immunosuppression

The possibility exists for drugs inhibiting T cell activation, including ORENCIA, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses. In clinical trials in patients with adult RA, a higher rate of infections was seen in ORENCIA-treated patients compared to placebo-treated patients [*see Warnings and Precautions (5.3) and Adverse Reactions (6.1)*]. The impact of treatment with ORENCIA on the development and course of malignancies is not fully understood [*see Adverse Reactions (6.1)*]. There have been reports of malignancies, including skin cancer in patients receiving ORENCIA [*see Adverse Reactions (6.4)*]. Periodic skin examinations are recommended for all ORENCIA-treated patients, particularly those with risk factors for skin cancer.

5.7 Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) Reactivation in aGVHD Prophylaxis after Hematopoietic Stem Cell Transplant (HSCT)

Post-Transplant Lymphoproliferative Disorder (PTLD) occurred in patients who received ORENCIA for aGVHD prophylaxis during unrelated HSCT. Of 116 patients who received ORENCIA, 4 patients (3.4%) experienced PTLT. All the PTLT events were associated with Epstein-Barr virus (EBV) infection. Three of the four patients were EBV serology positive at baseline; one patient had negative baseline EBV serology with donor EBV serology unknown. Three of the 4 patients discontinued acyclovir prophylaxis at day 30 post-transplant. The range of time to onset of the events was 49 to 89 days post-transplant. Monitor patients for EBV reactivation in accordance with institutional practices. Provide prophylaxis for EBV infection for 6 months post-transplantation to prevent EBV-associated PTLT [*see Dosage and Administration (2.4)*].

Cytomegalovirus (CMV) invasive disease occurred in patients who received ORENCIA for aGVHD prophylaxis during unrelated HSCT. Of 116 patients who received ORENCIA, 7% experienced CMV invasive diseases up to day 225 post-transplant. All the patients who experienced CMV invasive disease were CMV serology positive at baseline. The median time to onset of the event was 91 days post-transplant. CMV invasive diseases predominantly involved the gastrointestinal tract [*see Adverse Reactions (6.1)*].

Monitor patients for CMV infection/reactivation for 6 months post-transplant regardless of the results of donor and recipient pre-transplant CMV serology. Consider prophylaxis for CMV infection/reactivation [*see Dosage and Administration (2.4)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Increased Risk of Infection with Concomitant Use with TNF Antagonists, Other Biologic RA/PsA Therapy, or JAK Inhibitors [*see Warnings and Precautions (5.1)*]
- Hypersensitivity [*see Warnings and Precautions (5.2)*]

- Infections [see *Warnings and Precautions (5.3)*]
- Increased Risk of Adverse Reactions When Used in Patients with Chronic Obstructive Pulmonary Disease (COPD) [see *Warnings and Precautions (5.5)*]
- Immunosuppression [see *Warnings and Precautions (5.6)*]
- Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) Reactivation in aGVHD Prophylaxis after Hematopoietic Stem Cell Transplant (HSCT) [see *Warnings and Precautions (5.7)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Adverse Reactions in Adult Patients with RA

Adverse Reactions in Adult Patients with RA Treated with Intravenous ORENCIA

The data from placebo-controlled studies described herein reflect exposure to ORENCIA administered intravenously in patients with active RA (1955 patients with ORENCIA, 989 with placebo) (Studies I through VI) [see *Clinical Studies (14.1)*]. The studies had either a double-blind, placebo-controlled period of 6 months (258 patients with ORENCIA, 133 with placebo) or 1 year (1697 patients with ORENCIA, 856 with placebo). A subset of these patients received concomitant biologic DMARD therapy, such as a TNF antagonist (204 patients with ORENCIA, 134 with placebo). The concomitant use of ORENCIA with a TNF antagonist is not recommended [see *Indications and Usage (1.5)*]. The majority of patients in RA clinical studies received one or more of the following concomitant medications with ORENCIA: methotrexate, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, TNF antagonist, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sulfasalazine, and anakinra.

The most serious adverse reactions were serious infections and malignancies. The most commonly reported adverse events (occurring in $\geq 10\%$ of patients treated with ORENCIA) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

The adverse reactions most frequently resulting in clinical intervention (interruption or discontinuation of ORENCIA) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

Most Common Adverse Reactions in Adult Patients with RA Treated with Intravenous ORENCIA

Adverse reactions occurring in 3% or more of patients and at least 1% more frequently in ORENCIA-treated patients (intravenous) during placebo-controlled RA studies are summarized in Table 3.

Table 3: Most Common Adverse Reactions* During Placebo-Controlled RA Studies of Intravenous ORENCIA

	Intravenous ORENCIA (n=1955)^a	Placebo (n=989)^b
Headache	18%	13%
Nasopharyngitis	12%	9%
Dizziness	9%	7%
Cough	8%	7%
Back pain	7%	6%
Hypertension	7%	4%
Dyspepsia	6%	4%
Urinary tract infection	6%	5%
Rash	4%	3%
Pain in extremity	3%	2%

* Occurred in $\geq 3\%$ patients and $>1\%$ more frequently in ORENCIA-treated patients.

^a Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

^b Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

Infections in Adult Patients with RA Treated with Intravenous ORENCIA

In the placebo-controlled trials in patients with RA, infections were reported in 54% of intravenous ORENCIA-treated patients and 48% of placebo-treated patients. The most commonly reported infections (reported in 5%-13% of patients) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in fewer than 5% of patients at a higher frequency ($>0.5\%$) with ORENCIA compared to placebo, were rhinitis, herpes simplex, and pneumonia [see *Warnings and Precautions (5.3)*].

Serious infections were reported in 3% of patients treated with ORENCIA and 1.9% of patients treated with placebo. The most common (0.2%-0.5%) serious infections reported with ORENCIA were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis [see *Warnings and Precautions (5.3)*].

Malignancies in Adult Patients with RA Treated with Intravenous ORENCIA

In the placebo-controlled portions of the clinical trials (1955 patients treated for RA with ORENCIA for a median of 12 months), the overall frequencies of malignancies were similar in the ORENCIA- and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in ORENCIA-treated patients (4 cases, 0.2%) than placebo-treated

patients (0 cases, 0%). In the cumulative intravenous ORENCIA clinical trials in patients with RA (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the National Cancer Institute's Surveillance, Epidemiology, and End Results Database. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers [see *Warnings and Precautions (5.6)*]. The potential role of ORENCIA in the development of malignancies in humans is unknown.

Infusion-Related Reactions and Hypersensitivity Reactions in Adult Patients with RA Treated with Intravenous ORENCIA

Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion) in Studies III, IV, and V [see *Clinical Studies (14.1)*] were more common in the ORENCIA-treated patients than the placebo patients (9% for ORENCIA, 6% for placebo). The most frequently reported events (1%-2%) were dizziness, headache, and hypertension.

Acute infusion-related events that were reported in >0.1% and ≤1% of patients treated with ORENCIA included cardiopulmonary symptoms, such as hypotension, increased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild (68%) to moderate (28%). Fewer than 1% of ORENCIA-treated patients discontinued due to an acute infusion-related event. In controlled trials, 6 ORENCIA-treated patients compared to 2 placebo-treated patients discontinued study treatment due to acute infusion-related events.

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients and generally occurred within 24 hours of ORENCIA infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction [see *Warnings and Precautions (5.2)*].

Adverse Reactions in Patients with COPD Treated for RA with Intravenous ORENCIA

In Study V [see *Clinical Studies (14.1)*], there were 37 and 17 patients with chronic obstructive pulmonary disease (COPD) who were treated for RA with ORENCIA and placebo, respectively. The COPD patients treated with ORENCIA for RA developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in ORENCIA-treated patients compared to placebo-treated patients (43% vs 24%, respectively) including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of ORENCIA-treated patients developed a serious adverse event compared to placebo-treated

patients (27% vs 6%), including COPD exacerbation [3 of 37 patients (8%)] and pneumonia [1 of 37 patients (3%)] [see *Warnings and Precautions (5.5)*].

Adverse Reactions in Methotrexate-Naive Patients with RA Treated with Intravenous ORENCIA

Study VI was an active-controlled clinical trial in methotrexate-naive patients [see *Clinical Studies (14.1)*]. The safety experience in these patients was consistent with the patients in Studies I-V.

Adverse Reactions in Adult Patients with RA Treated with Subcutaneous or Intravenous ORENCIA

The data described below are derived from Study SC-1. Study SC-1 was a randomized, double-blind, double-dummy, non-inferiority study that compared the safety of ORENCIA administered subcutaneously or intravenously in 1457 patients with RA, who received background methotrexate, and experienced an inadequate response to methotrexate (MTX-IR) [see *Clinical Studies (14.1)*]. The adverse reaction profile in patients treated with subcutaneous ORENCIA was similar to the adverse reaction profile in patients treated with intravenous ORENCIA and consistent with intravenous ORENCIA administered in Studies I-VI.

Injection Site Reactions in Adult RA Patients Treated with Subcutaneous ORENCIA

The overall frequency of injection site reactions in Study SC-1 was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous ORENCIA group and the subcutaneous placebo group (given intravenous ORENCIA), respectively [see *Clinical Studies (14.1)*]. All these injection site reactions (including hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

Adverse Reactions in Adult Patients with PsA

Adverse Reactions in Adult Patients with PsA Treated with Intravenous or Subcutaneous ORENCIA

The safety of ORENCIA was evaluated in 594 patients with PsA (341 patients on ORENCIA and 253 patients on placebo), in two randomized, double-blind, placebo-controlled trials [see *Clinical Studies (14.3)*]. Of the 341 patients who received ORENCIA, 128 patients received intravenous ORENCIA (PsA-I) and 213 patients received subcutaneous ORENCIA (PsA-II). The safety profile was comparable between ORENCIA given intravenously in Study PsA-I and ORENCIA given subcutaneously in Study PsA-II and also consistent with the safety profile of ORENCIA in patients with RA [see *Warnings and Precautions (5)*, *Adverse Reactions (6.1)*].

Adverse Reactions in Patients with pJIA

Adverse Reactions in Patients with pJIA Treated with Intravenous ORENCIA

In general, the adverse events in pediatric patients with polyarticular JIA (pJIA) treated with intravenous ORENCIA were similar in frequency and type to those seen in adult patients with RA treated with intravenous ORENCIA [see *Warnings and Precautions (5)* and *Adverse Reactions (6)*].

Study JIA-1 was a three-part study including an open-label extension that assessed the safety of intravenous ORENCIA in 190 pediatric patients, 6 to 17 years of age, with pJIA. Overall frequency of adverse events in the 4-month, lead-in, open-label period of the study was 70%; infections occurred at a frequency of 36% [see *Clinical Studies (14.2)*]. The most common infections were upper respiratory tract infection and nasopharyngitis. The infections resolved without sequelae, and the types of infections were consistent with those commonly seen in outpatient pediatric populations. Other events that occurred at a prevalence of at least 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain.

A total of 6 serious adverse events [acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare (2), and joint wear] were reported during the initial 4 months of treatment with intravenous ORENCIA.

Of the 190 pediatric patients with pJIA treated with intravenous ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). During Periods A, B, and C, acute infusion-related reactions occurred at a frequency of 4%, 2%, and 3%, respectively, and were consistent with the types of events reported in adults.

Upon continued treatment in the open-label extension period, the types of adverse events were similar in frequency and type to those seen in adult patients, except for a single patient diagnosed with multiple sclerosis while on open-label treatment.

Adverse Reactions in Patients with pJIA Treated with Subcutaneous ORENCIA

Study JIA-2 was an open-label study with a 4-month short-term period and a long-term extension period that assessed the safety of subcutaneous ORENCIA in 205 pediatric patients, 2 to 17 years of age with pJIA. The adverse reaction profile in patients with pJIA treated with ORENCIA administered subcutaneously in Study JIA-2 were consistent with the adverse reaction profile in patients with pJIA treated with intravenous Study JIA-1.

There were no reported cases of hypersensitivity reactions. Local injection-site reactions occurred at a frequency of 4.4%.

Adverse Reactions in Patients Undergoing Unrelated-Donor Hematopoietic Stem Cell Transplantation (HSCT) with Intravenous ORENCIA

The data described herein were from one clinical study of ORENCIA (GVHD-1) for aGVHD prophylaxis in patients 6 years and older with hematologic malignancies who were undergoing unrelated HSCT wherein all patients were receiving calcineurin inhibitor and methotrexate as the standard of care for aGVHD prophylaxis [see *Clinical Studies (14.4)*]. Two cohorts were studied at 10 mg/kg (maximum dose of 1,000 mg) as an intravenous infusion over 60 minutes on the day before transplantation (Day -1), followed by administration on Days 5, 14, and 28 after transplantation:

- 1) A single-arm cohort of ORENCIA-treated patients (n=43) who underwent 7 of 8 Human leukocyte antigen (HLA)-matched HSCT from unrelated donors (7 of 8 cohort) and

2) A randomized cohort comprised of ORENCIA-treated patients (n=73) and placebo-treated patients (n=69) who underwent 8 of 8 HLA-matched HSCT from unrelated donors (8 of 8 cohort).

Of the 116 patients who received ORENCIA, 27 (23%) were 6 to less than 17 years of age [see Use in Specific Populations (8.4)].

The safety information from the date of first dose of ORENCIA up to Day 225 post-transplantation from this study is presented below. The incidence of adverse reactions was determined based on pooled data of ORENCIA-treated patients from the 2 study cohorts (n=116).

Serious adverse reactions reported in > 5% of patients who received ORENCIA in combination with a calcineurin inhibitor and methotrexate included pyrexia (20%), pneumonia (8%), acute kidney injury (7%), diarrhea (6%), hypoxia (5%), and nausea (5%).

Permanent discontinuation of ORENCIA due to an adverse reaction occurred in two patients (1.7%) due to one case each of pneumonia and allergic reaction.

The most common ($\geq 10\%$) adverse reactions in the ORENCIA treated patients were anemia, hypertension, CMV reactivation/CMV infection, pyrexia, pneumonia, epistaxis, CD4 lymphocytes decreased, hypermagnesemia, and acute kidney injury.

Table 4 summarizes the frequency of adverse reactions reported in the study of ORENCIA in GVHD-1.

Table 4: Adverse Reactions ($\geq 10\%$) in Patients with aGVHD Who Received ORENCIA with a Difference Between Arms of $>2\%$ Compared to Placebo in GVHD-1

Adverse Reaction	7 of 8 Cohort		8 of 8 Cohort			
	ORENCIA (+CNI and MTX) (N=43)		ORENCIA (+CNI and MTX) (N=73)		Placebo (+CNI and MTX) (N=69)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and Lymphatic System Disorders						
Anemia	56	56	69	69	57	57
CD4 lymphocytes decreased	14	14	14	14	9	9
Vascular Disorders						
Hypertension	49	49	43	43	38	38

Adverse Reaction	7 of 8 Cohort		8 of 8 Cohort			
	ORENCIA (+CNI and MTX) (N=43)		ORENCIA (+CNI and MTX) (N=73)		Placebo (+CNI and MTX) (N=69)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General Disorders and Administrative Site Conditions						
Pyrexia	28	9	19	10	20	4
Infections and Infestations						
CMV Reactivation/CMV Infection	26	26	32	32	22	22
Pneumonia	19	19	12	12	10	9
Respiratory and Mediastinal Disorders						
Epistaxis	12	12	16	16	10	10
Renal and Urinary Disorders						
Acute kidney injury	9	7	15	15	10	10
Metabolism and Nutrition Disorders						
Hypermagnesemia	5	5	18	18	10	10

Clinically relevant adverse reactions in <10% of patients who received ORENCIA in combination with calcineurin inhibitor and methotrexate in Study GVHD-1 included EBV reactivation.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the

observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other abatacept products may be misleading.

Immunogenicity in Adult Patients with RA Treated with Intravenous ORENCIA

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in RA patients for up to 2 years following repeated treatment with intravenous ORENCIA. Thirty-four of 1993 (2%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed. In the subset analysis, 9 of 154 (6%) patients that had discontinued intravenous ORENCIA treatment for over 56 days developed antibodies. Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies in a cell-based luciferase reporter assay. Six of 9 (67%) evaluable patients were shown to possess neutralizing antibodies. However, the development of neutralizing antibodies may be underreported due to lack of assay sensitivity.

No correlation of anti-abatacept antibody development to clinical response or adverse events was observed.

Immunogenicity in Adult RA Patients Treated with Subcutaneous or Intravenous ORENCIA

Study SC-1 compared the immunogenicity to abatacept following subcutaneous or intravenous ORENCIA administration. The overall immunogenicity frequency to abatacept was 1% (8/725) and 2% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with previous experience, and there was no correlation of immunogenicity with effects on pharmacokinetics, safety, or efficacy.

Immunogenicity in Adult RA Patients Treated with Subcutaneous ORENCIA Monotherapy

Study SC-2 was conducted to determine the effect of subcutaneous monotherapy use of ORENCIA on immunogenicity (without an intravenous loading dose) in 100 RA patients, who had not previously received ORENCIA or other CTLA4Ig. Patients in this study received either subcutaneous ORENCIA plus methotrexate (n=51) or subcutaneous ORENCIA monotherapy (n=49). No patients in either group developed anti-abatacept antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

Immunogenicity in Adult RA Patients After Treatment, Withdrawal, and then Restart of Subcutaneous ORENCIA

Study SC-3 was conducted to investigate the immunogenicity in adult RA patients after treatment, withdrawal (three months), and restart of ORENCIA subcutaneous treatment (patients were treated concomitantly with methotrexate). One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous

ORENCIA or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label ORENCIA treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 (0%) patients who continued to receive subcutaneous ORENCIA developed anti-abatacept antibodies compared to 7/73 (10%) of patients who had subcutaneous ORENCIA withdrawn during this period. Half of the patients who received subcutaneous placebo during the withdrawal period received a single intravenous infusion of ORENCIA at the start of period 3 and half received intravenous placebo. At the end of period 3, when all patients again received subcutaneous ORENCIA, the immunogenicity rates were 1/38 (3%) in the group who received subcutaneous ORENCIA throughout, and 2/73 (3%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months compared to those who remained on subcutaneous therapy (these results occurred in those who received or did not receive an intravenous loading dose). The safety observed in this study was consistent with that observed in the other studies.

Immunogenicity in Patients with pJIA Treated with Intravenous ORENCIA

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in patients with pJIA following repeated treatment with intravenous ORENCIA throughout the open-label period. For patients who were withdrawn from therapy for up to 6 months during the double-blind period, the rate of antibody formation to the CTLA-4 portion of the molecule was 41% (22/54), while for those who remained on therapy the rate was 13% (7/54). Twenty of these patients had samples that could be tested for antibodies with neutralizing activity; of these, 8 (40%) patients were shown to possess neutralizing antibodies.

The presence of antibodies was generally transient, and titers were low. The presence of antibodies was not associated with adverse events, changes in efficacy, or an effect on serum concentrations of abatacept. For patients who were withdrawn from ORENCIA during the double-blind period for up to 6 months, no serious acute infusion-related events were observed upon re-initiation of ORENCIA therapy.

Immunogenicity in Patients Treated for Prophylaxis of aGVHD with Intravenous ORENCIA

Immunogenicity was assessed in patients undergoing HSCT. Overall, immunogenicity incidence and associated antibody titers were low from the 4-dose intravenous ORENCIA regimen used in this study. Of the 114 immunogenicity evaluable subjects in the ORENCIA groups, none were positive during the ORENCIA treatment period (Day -1 to Day 28 following transplant). During the off-treatment period (Day 29 and up to Day 180 following transplant); 6 of 91 immunogenicity evaluable subjects (6.6%) were positive for CTLA4 and possibly Ig; 4 of the 6 positive subjects were found to have at least one positive sample with neutralization activity. In this study, immunogenicity positive subjects only had ADA positive samples on Day 180 (off-treatment period) and thus due to the timing of the response, the impact on PK, safety, or efficacy could not be determined.

6.3 Postmarketing Experience

Adverse reactions have been reported during the postapproval use of ORENCIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ORENCIA. Based on the postmarketing experience with ORENCIA, the following adverse reactions have been identified:

- Vasculitis (including cutaneous vasculitis and leukocytoclastic vasculitis)
- New or worsening psoriasis
- Non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma)
- Angioedema reactions [*see Warnings and Precautions (5.2)*]

During postmarketing experience with intravenous ORENCIA, systemic infusion reactions were similar to that seen in the clinical trial experience with intravenous ORENCIA with the exception of one case of fatal anaphylaxis [*see Warnings and Precautions (5.2)*]. Postmarketing reports of systemic injection reactions (e.g., pruritus, throat tightness, dyspnea) have occurred following the use of subcutaneous ORENCIA.

7 DRUG INTERACTIONS

7.1 Immunosuppressants

Concomitant administration of a TNF antagonist with ORENCIA has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone. Concurrent therapy with ORENCIA and TNF antagonists is not recommended [*see Warnings and Precautions (5.1)*].

There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with other biologic RA therapy, such as anakinra, or other biologic PsA therapy, and JAK inhibitors and therefore such use is not recommended. [*see Warnings and Precautions (5.1)*].

7.2 Blood Glucose Testing

Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ). The GDH-PQQ based glucose monitoring systems may react with the maltose present in ORENCIA for intravenous administration, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving intravenous ORENCIA, patients that require blood glucose monitoring should be advised to consider methods that do not react with maltose, such as those based on glucose dehydrogenase nicotinic adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

ORENCIA for subcutaneous administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ORENCIA during pregnancy. Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972.

Risk Summary

The data with ORENCIA use in pregnant women are insufficient to inform on drug-associated risk. However, there are clinical considerations for administering live vaccines to infants who were exposed to ORENCIA while in utero (*see Clinical Considerations*). In reproductive toxicology studies in rats and rabbits, no fetal malformations were observed with intravenous administration of ORENCIA during organogenesis at doses that produced exposures approximately 29 times the exposure at the maximum recommended human dose (MRHD) of 10 mg/kg/month on an AUC basis. However, in a pre- and postnatal development study in rats, ORENCIA altered immune function in female rats at 11 times the MRHD on an AUC basis.

Clinical Considerations

Infants and Administration of Live Vaccines

It is unknown if abatacept can cross the placenta into the fetus when a woman is treated with ORENCIA during pregnancy. Abatacept is an immunomodulatory agent. It is unknown if the immune response of an infant who was exposed in utero to abatacept and subsequently administered a live vaccine is impacted. Risks and benefits should be considered prior to vaccinating such infants [*see Warnings and Precautions (5.4)*].

Data

Human Data

There are no adequate and well-controlled studies of ORENCIA use in pregnant women. The data with ORENCIA use in pregnant women are insufficient to inform on drug-associated risk.

Animal Data

Intravenous administration of abatacept during organogenesis to mice (10, 55, or 300 mg/kg/day), rats (10, 45, or 200 mg/kg/day), and rabbits (10, 45, or 200 mg/kg every 3 days) produced exposures in rats and rabbits that were approximately 29 times the MRHD on an AUC basis (at maternal doses of 200 mg/kg/day in rats and rabbits), and no embryotoxicity or fetal malformations were observed in any species.

In a study of pre- and postnatal development in rats (10, 45, or 200 mg/kg every 3 days from gestation day 6 through lactation day 21), alterations in immune function in female offspring,

consisting of a 9-fold increase in T-cell-dependent antibody response relative to controls on postnatal day (PND) 56 and thyroiditis in a single female pup on PND 112, occurred at approximately 11 times the MRHD on an AUC basis (at a maternal dose of 200 mg/kg). No adverse effects were observed at approximately 3 times the MRHD (a maternal dose of 45 mg/kg). It is not known if immunologic perturbations in rats are relevant indicators of a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept. Exposure to abatacept in the juvenile rat, which may be more representative of the fetal immune system state in the human, resulted in immune system abnormalities including inflammation of the thyroid and pancreas [*see Nonclinical Toxicology (13.2)*].

8.2 Lactation

Risk Summary

There is no information regarding the presence of abatacept in human milk, the effects on the breastfed infant, or the effects on milk production. However, abatacept was present in the milk of lactating rats dosed with abatacept.

8.4 Pediatric Use

Polyarticular Juvenile Idiopathic Arthritis

The safety and effectiveness of ORENCIA for reducing signs and symptoms in patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) have been established (ORENCIA may be used as monotherapy or concomitantly with methotrexate). Use of ORENCIA for this indication is supported by evidence from the following studies:

Intravenous Use: A randomized withdrawal efficacy, safety, and pharmacokinetic study of intravenous ORENCIA in 190 pediatric patients 6 to 17 years of age with pJIA [*see Clinical Pharmacology (12.3) and Clinical Studies (14.2)*]. Given that population pharmacokinetic (PK) analyses (after intravenous ORENCIA administration) showed that clearance of abatacept increased with baseline body weight, intravenous ORENCIA is administered either weight-based or weight ranged based [*see Dosage and Administration (2.2)*]. Intravenous ORENCIA administration has not been studied in patients younger than 6 years of age.

Subcutaneous Use: An open-label PK and safety study of subcutaneous ORENCIA in 205 pediatric patients aged 2 to 17 years old with pJIA, extrapolation of effectiveness of intravenous ORENCIA in patients with pJIA and subcutaneous ORENCIA in patients with RA [*see Clinical Pharmacology (12.3) and Clinical Studies (14.2)*]. Given that population PK analyses (after subcutaneous ORENCIA injection) in pJIA patients showed that there was a trend toward higher clearance of abatacept with increasing body weight, subcutaneous ORENCIA dosage is weight range-based [*see Dosage and Administration (2.2)*].

The safety and effectiveness of ORENCIA use in pJIA in pediatric patients less than two years of age have not been established.

Acute Graft Versus Host Disease Prophylaxis

The safety and effectiveness of ORENCIA for the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in pediatric patients aged 2 years of age and older undergoing HSCT from a matched or 1 allele-mismatched unrelated donor have been established. Use of ORENCIA for this indication is supported by evidence from:

- adequate and well-controlled studies in adults and pediatric patients aged 6 years and older administered a dose of 10 mg/kg intravenously on the day before transplantation followed by a dose of 10 mg/kg intravenously on Days 5, 14, and 28 after transplantation and
- pharmacokinetic modeling and simulations of abatacept exposure in pediatric patients aged 2 to less than 6 years administered a dose of 15 mg/kg intravenously on the day before transplantation followed by a dose of 12 mg/kg intravenously on Days 5, 14, and 28 after transplantation.

Furthermore, the course of disease is sufficiently similar in pediatric patients aged 2 years to less than 6 years to that of patients aged 6 years and older to allow extrapolation of data to younger pediatric patients [see *Clinical Pharmacology (12.3) and Clinical Studies (14.4)*]. No new safety signals were observed in pediatric patients aged 6 years and older in Study GVHD-1.

The safety and effectiveness of ORENCIA for this indication have not been established in pediatric patients less than 2 years of age.

Juvenile Animal Toxicity Data

A juvenile animal study conducted in rats dosed with abatacept from 4 to 94 days of age (prior to immune system maturity) showed an increase in the incidence of infections leading to death at all doses compared with controls. Altered T-cell subsets including increased T-helper cells and reduced T-regulatory cells were observed. In addition, inhibition of T-cell-dependent antibody responses (TDAR) was observed. Upon following these animals into adulthood, lymphocytic inflammation of the thyroid and pancreatic islets was observed. In contrast, studies in adult mice and monkeys have not demonstrated similar findings. As the immune system of the rat is undeveloped in the first few weeks after birth, the relevance of these results to humans is unknown.

8.5 Geriatric Use

Rheumatoid Arthritis

A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA in clinical studies. No overall differences in safety or effectiveness were observed between geriatric patients (patients aged 65 years of age and older) and younger adults, and other reported clinical experience has not identified differences in responses between geriatric patients and younger adults, but greater sensitivity of some geriatric patients cannot be ruled out. The frequency of serious infection and malignancy among ORENCIA-treated patients over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the geriatric population in general, caution should be used when treating geriatric patients.

Acute Graft Versus Host Disease Prophylaxis

Of the 116 patients in Study GVHD-1 who received ORENCIA at a dose of 10 mg/kg for the prophylaxis of aGVHD, 12 (10%) were 65 years of age and older, and 2 (2%) patients were 75 years of age and older [see *Clinical Studies (14.4)*]. Clinical studies of ORENCIA for aGVHD did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

10 OVERDOSAGE

ORENCIA doses up to 50 mg/kg (5 times the maximum recommended dose in patients aged 6 years and older and 3.3 times the maximum recommended dose in patients aged 2 to less than 6 years) have been administered intravenously without apparent toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

11 DESCRIPTION

Abatacept is a selective T cell costimulation modulator. Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons.

ORENCIA (abatacept) for injection is a sterile, white, preservative-free lyophilized powder for reconstitution and dilution prior to intravenous infusion. Following reconstitution of the lyophilized powder with 10 mL of Sterile Water for Injection, USP, the reconstituted solution of ORENCIA is clear, colorless to pale yellow, with a concentration of 25 mg/mL and with a pH range of 7.2 to 7.8. Each single-dose vial of ORENCIA provides 250 mg abatacept, maltose (500 mg), monobasic sodium phosphate (17.2 mg), and sodium chloride (14.6 mg).

ORENCIA (abatacept) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution with a pH range of 6.8 to 7.4 for subcutaneous administration. ORENCIA injection is supplied as a single-dose prefilled syringe or as a single-dose ClickJect autoinjector (see Table 5).

Table 5: Contents of ORENCIA Subcutaneous Injection

Presentation	Active Ingredient Quantity and Volume	Inactive Ingredient Content
ORENCIA injection 50 mg/0.4 mL prefilled syringe	50 mg of abatacept in 0.4 mL of solution	dibasic sodium phosphate anhydrous (0.335 mg) monobasic sodium phosphate monohydrate (0.114 mg) poloxamer 188 (3.2 mg) sucrose (68 mg) qs to 0.4 mL Water for Injection, USP
ORENCIA injection 87.5 mg/0.7 mL prefilled syringe	87.5 mg of abatacept in 0.7 mL of solution	dibasic sodium phosphate anhydrous (0.587 mg) monobasic sodium phosphate monohydrate (0.200 mg) poloxamer 188 (5.6 mg) sucrose (119 mg) qs to 0.7 mL Water for Injection, USP
ORENCIA injection 125 mg/mL prefilled syringe and ClickJect autoinjector	125 mg of abatacept in 1 mL of solution	dibasic sodium phosphate anhydrous (0.838 mg) monobasic sodium phosphate monohydrate (0.286 mg) poloxamer 188 (8 mg) sucrose (170 mg) qs to 1 mL Water for Injection, USP

Unlike the lyophilized formulation for intravenous use, the ORENCIA solutions for subcutaneous administration contain no maltose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abatacept, a selective costimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of RA, pJIA and PsA and are found in the synovium of patients with RA, pJIA and PsA.

In vitro, abatacept decreases T cell proliferation and inhibits the production of the cytokines TNF alpha (TNF α), interferon- γ , and interleukin-2. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production, and reduces antigen specific production of interferon- γ . The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its clinical effects is unknown.

12.2 Pharmacodynamics

In clinical trials with ORENCIA at doses approximating 10 mg/kg, decreases were observed in serum levels of soluble interleukin-2 receptor (sIL-2R), interleukin-6 (IL-6), rheumatoid factor (RF), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP3), and TNF α . The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its clinical effects is unknown.

No formal pharmacodynamic analyses of biologic response markers have been performed in patients exposed to ORENCIA as prophylaxis for aGVHD.

12.3 Pharmacokinetics

Healthy Adults and Adult RA - Intravenous Administration

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions of ORENCIA (see Table 6).

Table 6: Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg ORENCIA Intravenous Infusion(s)

PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses^a) n=14
Peak Concentration (C _{max}) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life (t _{1/2}) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (V _{ss}) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

^a Multiple intravenous infusions of ORENCIA were administered at days 1, 15, 30, and monthly thereafter.

The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. In RA patients, after multiple intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, serum concentration appeared to reach a steady state by day 60 with a mean (range) trough concentration of 24 mcg/mL (1 to 66 mcg/mL). No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients.

Population pharmacokinetic analyses in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect clearance. Concomitant methotrexate, NSAIDs, corticosteroids, and TNF antagonists did not influence abatacept clearance.

No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept.

Adult RA - Subcutaneous Administration

Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) for C_{min} and C_{max} at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration was 79%. Mean estimates for systemic clearance (0.28 mL/h/kg), volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration.

Study SC-2 was conducted to determine the effect of subcutaneous monotherapy use of ORENCIA on immunogenicity (without an intravenous loading dose) in 100 RA patients [see *Adverse Reactions (6.3)*]. In this study, a mean trough concentration of 12.6 mcg/mL was achieved after 2 weeks of dosing.

Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous ORENCIA in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight [see *Dosage and Administration (2.1)*]. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance.

Polyarticular Juvenile Idiopathic Arthritis - Intravenous Administration

In Study JIA-1 among patients 6 to 17 years of age, the mean (range) steady state serum peak and trough concentrations of abatacept were 217 mcg/mL (57 to 700 mcg/mL) and 11.9 mcg/mL (0.15 to 44.6 mcg/mL) [see *Clinical Studies (14.2)*]. Population pharmacokinetic analyses of the serum concentration data showed that clearance of abatacept increased with baseline body weight [see *Dosage and Administration (2.2)*]. The estimated mean (range) clearance of abatacept in the juvenile idiopathic arthritis patients was 0.4 mL/h/kg (0.20 to 1.12 mL/h/kg). After accounting for the effect of body weight, the clearance of abatacept was not related to age and gender. Concomitant methotrexate, corticosteroids, and NSAIDs were also shown not to influence abatacept clearance.

Polyarticular Juvenile Idiopathic Arthritis - Subcutaneous Administration

In Study JIA-2 among patients 2 to 17 years of age, steady state of abatacept was achieved by Day 85 following the weekly body-weight–tiered subcutaneous ORENCIA dosing [see *Clinical Studies (14.2)*]. Comparable trough concentrations across weight tiers and age groups were achieved by the body-weight–tiered subcutaneous dosing regimen. The mean (range) trough concentration of abatacept at Day 113 was 44.4 mcg/mL (13.4 to 88.1 mcg/mL), 46.6 mcg/mL (22.4 to 97.0 mcg/mL), and 38.5 mcg/mL (9.3 to 73.2 mcg/mL) in pediatric JIA patients weighing 10 to <25 kg, 25 to <50 kg, and ≥50 kg, respectively.

Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous ORENCIA in JIA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight [see *Dosage and Administration (2.2)*]. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance.

Adult Psoriatic Arthritis - Intravenous and Subcutaneous Administration

In Study PsA-I, a dose ranging study, intravenous ORENCIA was administered at 3 mg/kg, weight range-based dosing: 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1,000 mg for patients weighing greater than 100 kg, or doses of 30 mg/kg on Days 1 and 15 followed by weight-range-based dosing [see *Clinical Studies (14.3)*]. Following monthly intravenous ORENCIA administration, abatacept showed linear PK over the dose range

in this study. At the weight-range-based dosing (see above), the steady state of abatacept was reached by Day 57 and the geometric mean (CV%) trough concentration (C_{min}) was 24.3 mcg/mL (40.8%) at Day 169. In Study PsA-II following weekly subcutaneous administration of ORENCIA at 125 mg, the steady state of abatacept was reached at Day 57 and the geometric mean (CV%) C_{min} was 25.6 mcg/mL (47.7%) at Day 169.

Consistent with the RA results, population pharmacokinetic analyses for abatacept in PsA patients revealed that there was a trend toward higher clearance (L/h) of abatacept with increasing body weight [see *Dosage and Administration* (2.3)]. In addition, relative to the RA patients with the same body weight, abatacept clearance in PsA patients was approximately 8% lower, resulting in higher abatacept exposures in patients with PsA. This slight difference in exposures, however, is not considered to be clinically meaningful.

Prophylaxis of Acute Graft versus Host Disease – Intravenous Administration

Table 7: Pharmacokinetic Parameters (Mean, Range) in Subjects Undergoing HSCT from a Matched or 1 Allele-Mismatched Unrelated Donor in Study GVHD-1

PK Parameter	7 of 8 Cohort n=42	8 of 8 Cohort n=73
Minimum Concentration (C_{min}) ^a [mcg/mL]	59 (26-112)	43 (25-73)
Peak Concentration (C_{max}) [mcg/mL]	221 (163-292)	172 (107-254)
Terminal half-life ($t_{1/2}$) [days]	20.6 (6-43)	20.8 (12-38)
Systemic clearance (CL) [mL/h/kg]	0.26 (0.15-0.65)	0.32 (0.18-0.56)
Volume of distribution (V_{ss}) [L/kg]	0.13 (0.08-0.27)	0.17 (0.11-0.26)

^a C_{min} observed on Day 5 of the treatment period; n = 18 for the 7/8 Cohort; n = 32 for the 8/8 Cohort.

C_{max} , $t_{1/2}$, CL, and V_{ss} are model predicted after first 10 mg/kg ORENCIA intravenous infusion.

In a study of patients who received ORENCIA for prophylaxis of acute Graft Versus Host Disease (aGVHD) aged 6 years and older, the geometric mean (%CV) trough concentrations (C_{min}) of abatacept on Day 63 after transplant after 4 doses utilizing weight-based dosing of 10 mg/kg (maximum dose of 1,000 mg) administered on the day before transplantation (Day -1), followed by a dose on Day 5, 14, and 28 after transplant, were 22.5 mcg/mL (243.9 %CV) for recipients of 8 of 8 Human leukocyte antigen (HLA)-matched HSCTs from unrelated donors (URD), and 31.1 mcg/mL (114.4 %CV) for recipients of 7 of 8 HLA-matched HSCTs from unrelated donors (URD), respectively.

Population pharmacokinetic analyses in patients with aGVHD demonstrated that 7 of 8 HLA-matched HSCT recipients had 29% lower clearance compared to 8 of 8 HLA-matched HSCT

recipients. Consistent with previous data, increasing body weight was associated with higher clearance of abatacept, while age (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate and calcineurin inhibitors (e.g., cyclosporine and tacrolimus), did not influence abatacept clearance.

Based on population PK modeling and simulation with data from patients aged 6 and older, simulated exposures of abatacept following the first and last dose in pediatric subjects 2 to less than 6 years of age who received 15 mg/kg of ORENCIA via 60-minute intravenous infusion on Day -1, followed by 12 mg/kg via 60-minute intravenous infusion on Day 5, 14, and 28 are comparable to those in pediatric patients 6 to less than 17 years of age and adults patients who received 10 mg/kg via 60-minute intravenous infusion on Day -1, 5, 14, and 28.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a mouse carcinogenicity study, weekly subcutaneous injections of 20, 65, or 200 mg/kg of abatacept administered for up to 84 weeks in males and 88 weeks in females were associated with increases in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females). The mice from this study were infected with murine leukemia virus and mouse mammary tumor virus. These viruses are associated with an increased incidence of lymphomas and mammary gland tumors, respectively, in immunosuppressed mice. The doses used in these studies produced exposures 0.8, 2.0, and 3.0 times higher, respectively, than the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC (area under the time-concentration curve). The relevance of these findings to the clinical use of ORENCIA is unknown.

In a one-year toxicity study in cynomolgus monkeys, abatacept was administered intravenously once weekly at doses up to 50 mg/kg (producing 9 times the MRHD exposure based on AUC). Abatacept was not associated with any significant drug-related toxicity. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in immunosuppressed monkeys within the time frame of this study. The relevance of these findings to the clinical use of ORENCIA is unknown.

No mutagenic potential of abatacept was observed in the *in vitro* bacterial reverse mutation (Ames) or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation assays with or without metabolic activation, and no chromosomal aberrations were observed in human lymphocytes treated with abatacept with or without metabolic activation.

Abatacept had no adverse effects on male or female fertility in rats at doses up to 200 mg/kg every three days (11 times the MRHD exposure based on AUC).

13.2 Animal Toxicology and/or Pharmacology

In studies of adult mice and monkeys, inhibition of TDAR was apparent. However, infection and mortality, altered T-helper cells, and inflammation of thyroid and pancreas were not observed.

14 CLINICAL STUDIES

14.1 Adult Rheumatoid Arthritis

Description of Clinical Studies of Intravenous ORENCIA for the Treatment of Patients with RA

The efficacy and safety of ORENCIA for intravenous administration were assessed in six randomized, double-blind, controlled studies (five placebo-controlled and one active-controlled) in patients ≥ 18 years of age with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Studies I, II, III, IV, and VI required patients to have at least 12 tender and 10 swollen joints at randomization, and Study V did not require any specific number of tender or swollen joints. ORENCIA or placebo treatment was given intravenously at weeks 0, 2, and 4 and then every 4 weeks thereafter in Studies I, II, III, IV, and VI.

- Study I evaluated ORENCIA as monotherapy in 122 patients with active RA who had failed at least one non-biologic DMARD or etanercept.
- In Study II and Study III, the efficacy of ORENCIA were assessed in patients with an inadequate response to MTX and who were continued on their stable dose of MTX.
- In Study IV, the efficacy of ORENCIA was assessed in patients with an inadequate response to a TNF antagonist, with the TNF antagonist discontinued prior to randomization; other DMARDs were permitted.
- Study V primarily assessed safety in patients with active RA requiring additional intervention in spite of current therapy with DMARDs; all DMARDs used at enrollment were continued. Patients in Study V were not excluded for comorbid medical conditions.
- In Study VI, the efficacy and safety of ORENCIA were assessed in methotrexate-naive patients with RA of less than 2 years disease duration. In Study VI, patients previously naive to methotrexate were randomized to receive ORENCIA plus methotrexate or methotrexate plus placebo.

Study I patients were randomized to receive one of three doses of ORENCIA (0.5, 2, or 10 mg/kg) or placebo ending at week 8. Study II patients were randomized to receive ORENCIA 2 or 10 mg/kg or placebo for 12 months. Study III, IV, V, and VI patients were randomized to receive a dose of ORENCIA based on weight range or placebo for 12 months (Studies III, V, and VI) or 6 months (Study IV). The dose of ORENCIA was 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1,000 mg for patients weighing greater than 100 kg.

Description of Clinical Studies of Subcutaneous or Intravenous ORENCIA for the Treatment of Patients with Adult RA

The efficacy of ORENCIA for subcutaneous administration were assessed in Study SC-1, which was a randomized, double-blind, double-dummy, non-inferiority study that compared ORENCIA administered subcutaneously to ORENCIA administered intravenously in 1457 patients with moderate to severely active RA, receiving background methotrexate (MTX), and experiencing an inadequate response to methotrexate (MTX-IR). In Study SC-1, patients were randomized with stratification by body weight (<60 kg, 60 to 100 kg, >100 kg) to receive (1) ORENCIA 125 mg subcutaneous injections weekly, after a single intravenous loading dose of ORENCIA based on body weight or (2) ORENCIA intravenously on Days 1, 15, 29, and every four weeks thereafter. Subjects continued taking their current dose of MTX from the day of randomization.

Clinical Response in Adult RA Patients

The percent of ORENCIA-treated patients achieving ACR 20, 50, and 70 responses and major clinical response in Studies I, III, IV, and VI are shown in Table 8. ORENCIA-treated patients had higher ACR 20, 50, and 70 response rates at 6 months compared to placebo-treated patients. Month 6 ACR response rates in Study II for the 10 mg/kg group were similar to the ORENCIA group in Study III.

In Studies III and IV, improvement in the ACR 20 response rate versus placebo was observed within 15 days in some patients and within 29 days versus MTX in Study VI. In Studies II, III, and VI, ACR response rates were maintained to 12 months in ORENCIA-treated patients. ACR responses were maintained up to three years in the open-label extension of Study II. In Study III, ORENCIA-treated patients experienced greater improvement than placebo-treated patients in morning stiffness.

In Study VI, a greater proportion of patients treated with ORENCIA plus MTX achieved a low level of disease activity as measured by a DAS28-CRP less than 2.6 at 12 months compared to those treated with MTX plus placebo (Table 8). Of patients treated with ORENCIA plus MTX who achieved DAS28-CRP less than 2.6, 54% had no active joints, 17% had one active joint, 7% had two active joints, and 22% had three or more active joints, where an active joint was a joint that was rated as tender or swollen or both.

In Study SC-1, the main outcome measure was ACR 20 at 6 months. The pre-specified non-inferiority margin was a treatment difference of -7.5% . As shown in Table 9, the study demonstrated non-inferiority of ORENCIA administered subcutaneously to intravenous infusions of ORENCIA with respect to ACR 20 responses up to 6 months of treatment. ACR 50 and 70 responses are also shown in Table 8. No major differences in ACR responses were observed between intravenous and subcutaneous treatment groups in subgroups based on weight categories (less than 60 kg, 60 to 100 kg, and more than 100 kg; data not shown).

Table 8: Clinical Responses in Controlled Trials in Patients with RA

	Percent of Patients									
	Intravenous Administration								Subcutaneous or Intravenous Administration	
	Inadequate Response to DMARDs		Inadequate Response to Methotrexate (MTX)		Inadequate Response to TNF Antagonists		MTX-Naive		Inadequate Response to MTX	
	Study I		Study III		Study IV		Study VI		Study SC-1	
Response Rate	ORN ^a n=32	PBO n=32	ORN ^b +MTX n=424	PBO +MTX n=214	ORN ^b + DMARDs n=256	PBO + DMARDs n=133	ORN ^b +MTX n=256	PBO +MTX n=253	ORN ^c SC +MTX n=693	ORN ^c IV +MTX n=678
ACR 20										
Month 3	53%	31%	62% [‡]	37%	46% [‡]	18%	64%* [†]	53%	68%	69%
Month 6	NA	NA	68% [‡]	40%	50% [‡]	20%	75% [†]	62%	76% [§]	76%
Month 12	NA	NA	73% [‡]	40%	NA	NA	76% [‡]	62%	NA	NA
ACR 50										
Month 3	16%	6%	32% [‡]	8%	18% [†]	6%	40% [‡]	23%	33%	39%
Month 6	NA	NA	40% [‡]	17%	20% [‡]	4%	53% [‡]	38%	52%	50%
Month 12	NA	NA	48% [‡]	18%	NA	NA	57% [‡]	42%	NA	NA
ACR 70										
Month 3	6%	0	13% [‡]	3%	6%* [†]	1%	19% [†]	10%	13%	16%
Month 6	NA	NA	20% [‡]	7%	10% [†]	2%	32% [†]	20%	26%	25%
Month 12	NA	NA	29% [‡]	6%	NA	NA	43% [‡]	27%	NA	NA
Major Clinical Response^c	NA	NA	14% [‡]	2%	NA	NA	27% [‡]	12%	NA	NA
DAS28-CRP <2.6^d										
Month 12	NA	NA	NA	NA	NA	NA	41% [‡]	23%	NA	NA

* p<0.05, ORENCIA (ORN) vs placebo (PBO) or MTX.

† p<0.01, ORENCIA vs placebo or MTX.

‡ p<0.001, ORENCIA vs placebo or MTX.

§ 95% CI: -4.2, 4.8 (based on prespecified margin for non-inferiority of -7.5%).

^a 10 mg/kg.

^b Dosing based on weight range [see Dosage and Administration (2.1)].

^c Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period.

^d Refer to text for additional description of remaining joint activity.

^e Per protocol data is presented in table. For ITT; n=736, 721 for SC and IV ORENCIA, respectively.

The results of the components of the ACR response criteria for Studies III, IV, and SC-1 are shown in Table 9 (results at Baseline [BL] and 6 months [6 M]). In ORENCIA-treated patients, greater

improvement was seen in all ACR response criteria components through 6 and 12 months than in placebo-treated patients.

Table 9: Components of ACR Responses at 6 Months in Adult Patients with RA

Component (median)	Intravenous Administration								Subcutaneous or Intravenous Administration			
	Inadequate Response to MTX				Inadequate Response to TNF Antagonists				Inadequate Response to MTX			
	Study III				Study IV				Study SC-1 ^c			
	ORN +MTX n=424		PBO +MTX n=214		ORN +DMARDs n=256		PBO +DMARDs n=133		ORN SC +MTX n=693		ORN IV +MTX n=678	
	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M
Number of tender joints (0-68)	28	7 [‡]	31	14	30	13 [‡]	31	24	27	5	27	6
Number of swollen joints (0-66)	19	5 [‡]	20	11	21	10 [‡]	20	14	18	4	18	3
Pain ^a	67	27 [‡]	70	50	73	43 [†]	74	64	71	25	70	28
Patient global assessment ^a	66	29 [‡]	64	48	71	44 [‡]	73	63	70	26	68	27
Disability index ^b	1.75	1.13 [‡]	1.75	1.38	1.88	1.38 [‡]	2.00	1.75	1.88	1.00	1.75	1.00
Physician global assessment ^a	69	21 [‡]	68	40	71	32 [‡]	69	54	65	16	65	15
CRP (mg/dL)	2.2	0.9 [‡]	2.1	1.8	3.4	1.3 [‡]	2.8	2.3	1.6	0.7	1.8	0.7

[†] p<0.01, ORENCIA (ORN) vs placebo (PBO), based on mean percent change from baseline.

[‡] p<0.001, ORENCIA vs placebo, based on mean percent change from baseline.

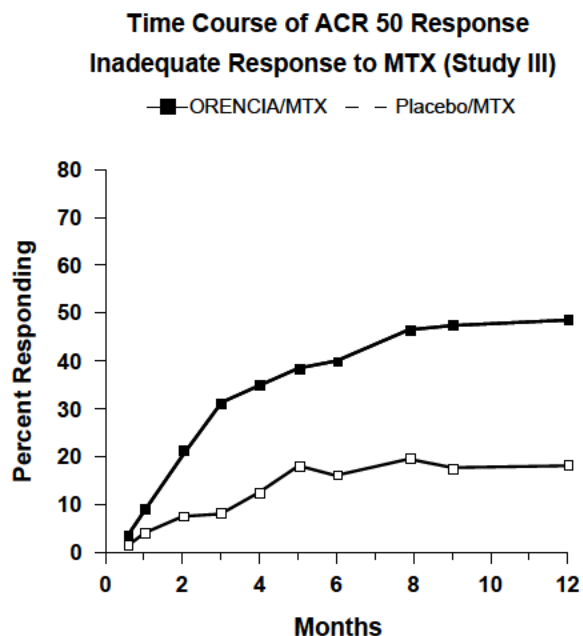
^a Visual analog scale: 0 = best, 100 = worst.

^b Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

^c SC-1 is a non-inferiority study. Per protocol data is presented in table.

The percent of patients achieving the ACR 50 response for Study III by visit is shown in Figure 1. The time course for the ORENCIA group in Study VI was similar to that in Study III.

Figure 1: Percent of Patients Achieving ACR 50 Response by Visit* (Study III)



*The same patients may not have responded at each time point.

The percent of patients achieving the ACR 50 response for Study SC-1 in the ORENCIA subcutaneous (SC) and intravenous (IV) treatment arms at each treatment visit was as follows: Day 15—SC 3%, IV 5%; Day 29—SC 11%, IV 14%; Day 57—SC 24%, IV 30%; Day 85—SC 33%, IV 38%; Day 113—SC 39%, IV 41%; Day 141—SC 46%, IV 47%; Day 169—SC 51%, IV 50%.

Radiographic Response in Adult RA Patients

In Study III and Study VI, structural joint damage was assessed radiographically and expressed as change from baseline in the Genant-modified Total Sharp Score (TSS) and its components, the Erosion Score (ES) and Joint Space Narrowing (JSN) score. ORENCIA/MTX slowed the progression of structural damage compared to placebo/MTX after 12 months of treatment as shown in Table 10.

Table 10: Mean Radiographic Changes in Study III^a and Study VI^b

Parameter	ORENCIA/MTX	Placebo/MTX	Differences	P-value ^d
Study III				
First Year				
TSS	1.07	2.43	1.36	<0.01
ES	0.61	1.47	0.86	<0.01
JSN score	0.46	0.97	0.51	<0.01
Second Year				
TSS	0.48	0.74 ^c	-	-
ES	0.23	0.22 ^c	-	-
JSN score	0.25	0.51 ^c	-	-
Study VI				
First Year				
TSS	0.6	1.1	0.5	0.04

^a Patients with an inadequate response to MTX.

^b MTX-naïve patients.

^c Patients received 1 year of placebo/MTX followed by 1 year of ORENCIA/MTX.

^d Based on a nonparametric ANCOVA model.

In the open-label extension of Study III, 75% of patients initially randomized to ORENCIA/MTX and 65% of patients initially randomized to placebo/MTX were evaluated radiographically at Year 2. As shown in Table 10, progression of structural damage in ORENCIA/MTX-treated patients was further reduced in the second year of treatment.

Following 2 years of treatment with ORENCIA/MTX, 51% of patients had no progression of structural damage as defined by a change in the TSS of zero or less compared with baseline. Fifty-six percent (56%) of ORENCIA/MTX-treated patients had no progression during the first year compared to 45% of placebo/MTX-treated patients. In their second year of treatment with ORENCIA/MTX, more patients had no progression than in the first year (65% vs 56%).

Physical Function Response and Health-Related Outcomes in Adult RA Patients

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). In the HAQ-DI, ORENCIA demonstrated greater improvement from baseline versus placebo in Studies II-V and versus MTX in Study VI. In Study SC-1, improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between subcutaneous and intravenous ORENCIA administration. The results from Studies II and III are shown in Table 11. Similar results were observed in Study V compared to placebo and in Study VI compared to MTX. During the open-label period of Study II, the improvement in physical function has been maintained for up to 3 years.

Table 11: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) in Adult Patients with RA

	Inadequate Response to Methotrexate			
	Study II		Study III	
	ORENCIA ^a +MTX (n=115)	Placebo +MTX (n=119)	ORENCIA ^b +MTX (n=422)	Placebo +MTX (n=212)
HAQ Disability Index				
Baseline (Mean)	0.98 ^c	0.97 ^c	1.69 ^d	1.69 ^d
Mean Improvement Year 1	0.40 ^{c,***}	0.15 ^c	0.66 ^{d,***}	0.37 ^d

*** p<0.001, ORENCIA vs placebo.

^a 10 mg/kg.

^b Dosing based on weight range [see *Dosage and Administration (2.1)*].

^c Modified Health Assessment Questionnaire: 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

^d Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. In these studies, improvement was observed in the ORENCIA group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

14.2 Polyarticular Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis - Intravenous Administration

The safety and efficacy of ORENCIA with intravenous administration were assessed in Study JIA-1, a three-part study including an open-label extension in pediatric patients with polyarticular juvenile idiopathic arthritis (pJIA). Patients 6 to 17 years of age (n=190) with moderately to severely active pJIA who had an inadequate response to one or more DMARDs, such as MTX or TNF antagonists, were treated. Patients had a disease duration of approximately 4 years with moderately to severely active disease at study entry, as determined by baseline counts of active joints (mean, 16) and joints with loss of motion (mean, 16); patients had elevated C-reactive protein (CRP) levels (mean, 3.2 mg/dL) and ESR (mean, 32 mm/h). The patients enrolled had JIA subtypes that at disease onset included oligoarticular (16%), polyarticular (64%; 20% were rheumatoid factor positive), and systemic JIA without systemic manifestations (20%). At study entry, 74% of patients were receiving MTX (mean dose, 13.2 mg/m² per week) and remained on a stable dose of MTX (those not receiving MTX did not initiate MTX treatment during the study).

In Period A (open-label, lead-in), patients received 10 mg/kg (maximum 1,000 mg per dose) intravenously on days 1, 15, 29, and monthly thereafter. Response was assessed utilizing the ACR Pediatric 30 definition of improvement, defined as ≥30% improvement in at least 3 of the 6 JIA core set variables and ≥30% worsening in not more than 1 of the 6 JIA core set variables. Patients

demonstrating an ACR Pedi 30 response at the end of Period A were randomized into the double-blind phase (Period B) and received either ORENCIA or placebo for 6 months or until disease flare. Disease flare was defined as a $\geq 30\%$ worsening in at least 3 of the 6 JIA core set variables with $\geq 30\%$ improvement in not more than 1 of the 6 JIA core set variables; ≥ 2 cm of worsening of the Physician or Parent Global Assessment was necessary if used as 1 of the 3 JIA core set variables used to define flare, and worsening in ≥ 2 joints was necessary if the number of active joints or joints with limitation of motion was used as 1 of the 3 JIA core set variables used to define flare.

At the conclusion of Period A, pediatric ACR 30/50/70 responses were 65%, 50%, and 28%, respectively. Pediatric ACR 30 responses were similar in all subtypes of JIA studied.

During the double-blind randomized withdrawal phase (Period B), ORENCIA-treated patients (intravenous) experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53%); 95% CI of the difference (15%, 52%). The risk of disease flare among patients continuing on intravenous ORENCIA was less than one-third than that for patients withdrawn from intravenous ORENCIA treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]). Among patients who received intravenous ORENCIA throughout the study (Period A, Period B, and the open-label extension Period C), the proportion of pediatric ACR 30/50/70 responders has remained consistent for 1 year.

Polyarticular Juvenile Idiopathic Arthritis - Subcutaneous Administration

ORENCIA for subcutaneous administration without an intravenous loading dose was assessed in Study JIA-2, a 2-period, open-label study that included pediatric patients 2 to 17 years of age (n=205). Patients had active polyarticular disease at the time of the study and had inadequate response to at least one nonbiologic or biologic DMARD. The JIA patient subtypes at study entry included polyarticular (79%; 22% were rheumatoid factor positive), extended and persistent oligoarticular (14%), enthesitis-related arthritis (1%), and systemic JIA without systemic manifestations (2%). Patients had a mean disease duration of 2.5 years with active joints (mean, 11.9), joints with loss of motion (mean, 10.4), and elevated C-reactive protein (CRP) levels (mean, 1.2 mg/dL). At study entry, 80% of patients were receiving MTX and remained on a stable dose of MTX. Patients received weekly open-label ORENCIA subcutaneously by a weight-tiered dosing regimen. The primary objective of the study was evaluation of PK in order to support the extrapolation of efficacy based on exposure to ORENCIA supported by descriptive efficacy [*see Clinical Pharmacology (12.3)*].

JIA ACR 30/50/70 responses assessed at 4 months in the 2- to 17-year-old patients treated with subcutaneous ORENCIA were consistent with the results from intravenous ORENCIA in Study JIA-1.

14.3 Adult Psoriatic Arthritis

The efficacy of ORENCIA was assessed in 594 adult patients (18 years and older) with psoriatic arthritis (PsA), in two randomized, double-blind, placebo-controlled studies (Studies PsA-I and PsA-II). Patients had active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior treatment

with DMARD therapy and had one qualifying psoriatic skin lesion of at least 2 cm in diameter. In PsA-I and PsA-II, 37% and 61% of patients, respectively, were treated with TNF antagonists previously.

During the initial 24-week, double-blind period of Study PsA-I, 170 patients were randomized to receive one of four intravenous treatments on Days 1, 15, 29, and then every 28 days (there was no escape during the 24-week period):

- Placebo
- ORENCIA 3 mg/kg
- ORENCIA 500 mg for patients weighing less than 60 kg, ORENCIA 750 mg for patients weighing 60 to 100 kg, and ORENCIA 1,000 mg for patients weighing greater than 100 kg (weight-range-based dosing), or
- ORENCIA 30 mg/kg on Days 1 and 15 followed by weight range-based ORENCIA dosing (i.e., 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1,000 mg for patients weighing greater than 100 kg).

After the 24-week double blind period in Study PsA-I, patients received open-label intravenous ORENCIA every 28 days.

Patients were allowed to receive stable doses of concomitant MTX, low dose corticosteroids (equivalent to ≤ 10 mg of prednisone) and/or NSAIDs during the trial. At enrollment, approximately 60% of patients were receiving MTX. At baseline, the mean (SD) CRP for ORENCIA IV was 17 mg/L (33.0) and mean number (SD) of tender joints and swollen joints was 22.2 (14.3) and 10.9 (7.6), respectively.

In PsA-II, 424 patients were randomized 1:1 to receive weekly doses of subcutaneous placebo or ORENCIA 125 mg without a loading dose for 24 weeks-in a double-blind manner, followed by open-label subcutaneous ORENCIA 125 mg weekly. Patients were allowed to receive stable doses of concomitant MTX, sulfasalazine, leflunomide, hydroxychloroquine, low dose corticosteroids (equivalent to ≤ 10 mg of prednisone) and/or NSAIDs during the trial. At randomization, 60% of patients were receiving MTX. The baseline disease characteristics included presence of joint erosion on X-rays in 84% (341/407) with a mean (SD) PsA-modified Sharp van der Heijde erosion score (SHS) of 10.8 (24.2), elevated serum C reactive protein (CRP) in 66% [277/421] with a mean (SD) of 14.1 mg/L (25.9), and polyarticular disease in 98% (416/424) of patients with a mean number (SD) of tender joints and swollen joints of 20.2 (13.3) and 11.6 (7.5), respectively. Patients who had not achieved at least a 20% improvement from baseline in their swollen and tender joint counts by Week 16 escaped to open-label subcutaneous ORENCIA 125 mg weekly.

The primary endpoint for both PsA-I and PsA-II was the proportion of patients achieving ACR 20 response at Week 24 (Day 169).

Clinical Response in Adults with PsA

A greater proportion of adult patients with PsA achieved an ACR 20 response after treatment with intravenous ORENCIA (weight-range-based dosing as described above) compared to placebo in

Study PsA-I and a greater proportion of adult patients with PsA achieved an ACR 20 response after treatment with subcutaneous 125 mg compared to placebo in Study PsA-II at Week 24. Responses were seen regardless of prior TNF antagonist treatment and regardless of concomitant non-biologic DMARD treatment. The percent of patients achieving ACR 20, 50, or 70 responses in Studies PsA-I and PsA-II are presented in Table 12 below.

Table 12: Proportion of Patients With ACR Responses at Week 24 in Studies PsA-I and PsA-II^a

	PsA-I		PsA-II	
	ORENCIA Weight-Range- Based Intravenous Dosing ^b	Placebo	ORENCIA 125 mg Subcutaneous	Placebo
	N=40	N=42	N=213	N=211
ACR 20	47.5%*	19.0%	39.4%*	22.3%
ACR 50	25.0%	2.4%	19.2%	12.3%
ACR 70	12.5%	0%	10.3%	6.6%

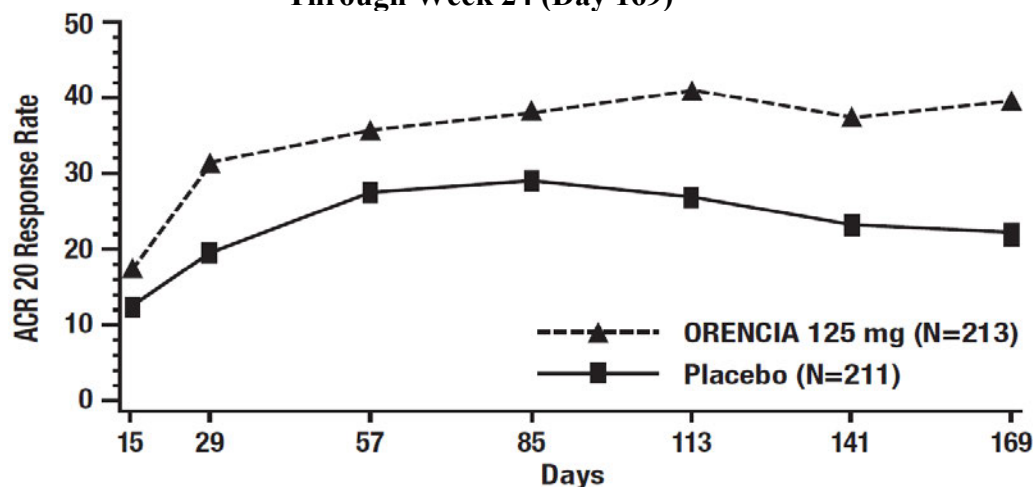
* p<0.05 versus placebo.

^a Patients who had less than 20% improvement in tender or swollen joint counts at Week 16 met escape criteria and were considered non-responders.

^b Weight range-based intravenous dosing: ORENCIA 500 mg for patients weighing less than 60 kg, ORENCIA 750 mg for patients weighing 60 to 100 kg, and ORENCIA 1,000 mg for patients weighing greater than 100 kg.

The percentage of patients in PsA-II achieving ACR 20 response through Week 24 is shown below in Figure 2.

Figure 2: Percent of Patients Achieving ACR 20 Response^a in PsA-II Study Through Week 24 (Day 169)



^a Non-responder imputation for early escape subjects at Day 141 and 169

Results were generally consistent across the ACR components in Study PsA-I and PsA-II.

Improvements in enthesitis and dactylitis were seen with ORENCIA treatment at Week 24 in both PsA-I and PsA-II.

Physical Function Response in Adults with PsA

In study PsA-I, there was a higher proportion of patients with at least a 0.30 decrease from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24, with an estimated difference for ORENCIA weight range-based dosing as described above (45%) vs. placebo (19%) of 26.1 (95% confidence interval: 6.8, 45.5). In study PsA-II, the proportion of patients with at least a 0.35 decrease from baseline in HAQ-DI on ORENCIA was 31%, as compared to 24% on placebo (estimated difference: 7%; 95% confidence interval: -1%, 16%). There was a higher adjusted mean change from baseline in HAQ-DI on ORENCIA (-0.33) vs. placebo (-0.20) at Week 24, with an estimated difference of -0.13 (95% confidence interval: -0.25, -0.01).

14.4 Prophylaxis of Acute Graft versus Host Disease

Study GVHD-1

The efficacy of ORENCIA, in combination with a calcineurin inhibitor (CNI) and methotrexate (MTX), for the prophylaxis of acute graft versus host disease (aGVHD), was evaluated in a multicenter, two cohort clinical study (GVHD-1, NCT01743131) in patients age 6 years and older who underwent hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor (URD). The two cohorts in GVHD-1 included:

- 1) an open-label, single-arm study of 43 patients who underwent a 7 of 8 Human Leukocyte Antigen (HLA)-matched HSCT (7 of 8 cohort); and
- 2) a randomized (1:1), double-blind, placebo-controlled study of patients who underwent an 8 of 8 HLA-matched HSCT who received ORENCIA or placebo in combination with a CNI and MTX (8 of 8 cohort).

In both the 7/8 and 8/8 cohorts, ORENCIA was administered at a dose of 10 mg/kg (1,000 mg maximum dose) as an intravenous infusion over 60 minutes, beginning on the day before transplantation (Day -1), followed by administration on Days 5, 14, and 28 after transplantation. Baseline demographic and clinical characteristics of both the 7 of 8 and 8 of 8 cohorts are outlined below in Table 13.

Table 13: Baseline Demographic and Clinical Characteristics: 7 of 8 and 8 of 8 Cohort Treated Analysis Population in Study GVHD-1

	7 of 8 Cohort	8 of 8 Cohort	
	ORENCIA (+ CNI and MTX) N=43	ORENCIA (+ CNI and MTX) N=73	Placebo (+CNI and MTX) N=69
Age - Median	38	44	40
Age - Range	6-76	6-71	7-74
Gender - Male	27 (63)	41 (56)	37 (54)
White	31 (72)	63 (86)	61 (88)
Black or African American	7 (16)	3 (4.1)	2 (2.9)
Asian	2 (4.7)	4 (6)	2 (2.9)
Hispanic	7 (16)	4 (6)	2 (2.9)
Malignancy type			
Acute Myeloid Leukemia (AML)	15 (35)	30 (41)	22 (32)
Myelodysplastic Syndrome (MDS)	11 (26)	15 (21)	12 (17)
Acute Lymphoblastic Leukemia (ALL)	8 (19)	20 (27)	22 (32)
Acute leukemia or ambiguous lineage	1 (2.3)	0	1 (1.4)
Hodgkin and Non-Hodgkin lymphoma	1 (2.3)	1 (1.4)	1 (1.4)
Acute Lymphoblastic Lymphoma in 2nd or Greater Complete Remission	1 (2.3)	4 (6)	1 (1.4)
Chronic Myelomonocytic leukemia	1 (2.3)	1 (1.4)	4 (6)
Chronic Myelogenous leukemia	4 (9)	1 (1.4)	5 (7)
Not reported	1 (2.3)	1 (1.4)	1 (1.4)
GVHD Prophylaxis			
Cyclosporine	16 (37)	11 (15)	11 (16)
Tacrolimus	27 (63)	62 (85)	58 (84)
Type of Graft			
Bone Marrow	21 (49)	33 (45)	26 (38)
Cytokine Mobilized Peripheral Blood (PBSC)	22 (51)	40 (55)	43 (62)
Conditioning Regimen			
TBI and Chemotherapy	11 (26)	20 (27)	26 (38)
Busulfan and Cyclophosphamide	13 (30)	28 (38)	21 (30)
Busulfan and Fludarabine	8 (19)	7 (10)	2 (2.9)
Melphalan and Fludarabine	11 (26)	18 (25)	20 (29)

Efficacy was established based on overall survival (OS) and grade II-IV aGVHD free survival (GFS) results assessed at Day 180 post-transplantation. ORENCIA + CNI and MTX did not significantly improve grade III-IV GFS versus placebo + CNI and MTX at Day 180 post-transplantation. The efficacy results of the GVHD-1 8 of 8 cohort are shown in Table 14.

Table 14: Efficacy Results in 8 of 8 Cohort in Study GVHD-1 at Day 180 Post-Transplantation

Endpoint	ORENCIA	Placebo
	(+CNI and MTX) n=73	(+CNI and MTX) n=69
Gr III-IV aGVHD Free Survival^a Rate (95% CI)	87% (77%, 93%)	75% (63%, 84%)
Hazard Ratio (95% CI)	0.55 (0.26, 1.18)	
Gr II-IV aGVHD Free Survival^b Rate (95% CI)	50% (38%, 61%)	32% (21%, 43%)
Hazard Ratio (95% CI)	0.54 (0.35, 0.83)	
Overall Survival Rate (95% CI)	97% (89%, 99%)	84% (73%, 91%)
Hazard Ratio (95% CI)	0.33 (0.12, 0.93)	

^a Gr III-IV aGVHD Free Survival was measured from the date of transplantation until the onset of documented Grade III-IV aGVHD, or death by any cause up to Day 180 post-transplantation.

^b Gr II-IV aGVHD Free Survival was measured from the date of transplantation until the onset of documented Grade II-IV aGVHD, or death by any cause up to Day 180 post-transplantation.

In an exploratory analysis of the 7 of 8 cohort of ORENCIA-treated patients (n=43), the rates of Grade III-IV GVHD-free survival, Grade II-IV GVHD-free survival, and overall survival at day 180 post-transplantation were 95% (95% CI 83%, 99%), 53% (95% CI 38%, 67%), and 98% (95% CI 85%, 100%), respectively.

Study GVHD-2

GVHD-2 was a clinical study that used data from the Center for International Blood and Marrow Transplant Research (CIBMTR). The study analyzed outcomes of ORENCIA in combination with a CNI and MTX, versus a CNI and MTX alone, for the prophylaxis of aGVHD, in patients 6 years of age or older who underwent HSCT from a 1 allele-mismatched URD between 2011 and 2018. The ORENCIA + CNI and MTX-treated group (n=54) included 42 patients from GVHD-1, in addition to 12 patients treated with ORENCIA outside of GVHD-1. The comparator group (n=162) was randomly selected in a 3:1 ratio to the ORENCIA-treated group from the CIBMTR registry from patients who had not received ORENCIA during the study period. Analyses used propensity score matching and inverse probability of treatment weighting to help address the impact of selection bias.

Efficacy was based on Overall Survival (OS) at Day 180 post-HSCT. The OS rate at Day 180 in the ORENCIA in combination with CNI and MTX group was 98% (95% CI: 78, 100) and the OS rate at Day 180 in the CNI and MTX group was 75% (95% CI: 67, 82).

16 HOW SUPPLIED/STORAGE AND HANDLING

For Intravenous Infusion

ORENCIA® (abatacept) for injection is a white lyophilized powder for intravenous infusion after reconstitution and dilution. It is supplied as an individually packaged, single-dose vial (one may use less than the full contents of the vial or use more than one vial) with a silicone-free disposable syringe, providing 250 mg of abatacept:

NDC 0003-2187-10: in a clamshell presentation

NDC 0003-2187-13: in a carton presentation

For Subcutaneous Use

ORENCIA® (abatacept) injection and ORENCIA® ClickJect (abatacept) injection are clear to slightly opalescent, colorless to pale yellow solutions for subcutaneous administration.

Prefilled Syringe

ORENCIA (abatacept) injection, 50 mg/0.4 mL, 87.5 mg/0.7 mL, and 125 mg/mL, is supplied as single-dose disposable prefilled glass syringes with BD UltraSafe Passive™ needle guard and flange extenders.

The Type I glass syringe has a coated stopper and fixed stainless steel needle (5 bevel, 29-gauge thin wall, ½-inch needle) covered with a rigid needle shield. The prefilled syringe provides ORENCIA in the following packages:

NDC 0003-2814-11 (50 mg/0.4 mL): pack of 4 syringes with a passive needle safety guard

NDC 0003-2818-11 (87.5 mg/0.7 mL): pack of 4 syringes with a passive needle safety guard

NDC 0003-2188-11 (125 mg/mL): pack of 4 syringes with a passive needle safety guard

ClickJect Autoinjector

ORENCIA (abatacept) ClickJect, 125 mg/mL, is supplied as a single-dose disposable prefilled autoinjector. The Type I glass syringe contained in the autoinjector has a coated stopper and fixed stainless steel needle (5 bevel, 27-gauge special thin wall, ½-inch needle) covered with a rigid needle shield. The autoinjector provides 125 mg of abatacept in 1 mL and is provided in the following package:

NDC 0003-2188-51: pack of 4 autoinjectors

Storage

Refrigerate ORENCIA lyophilized powder supplied in a vial at 2°C to 8°C (36°F to 46°F). Do not

use beyond the expiration date on the vial. Protect the vials from light by storing in the original package until time of use.

Refrigerate ORENCIA solution supplied in a prefilled syringe or ClickJect autoinjector at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date on the prefilled syringe or autoinjector. Protect from light by storing in the original package until time of use. Do not allow the prefilled syringe or autoinjector to freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Increased Risk of Infection with Concomitant Use With Immunosuppressants for RA

Inform patients that the concomitant use with other immunosuppressives (e.g., biologic DMARDs, JAK inhibitors) is not recommended [see *Warnings and Precautions (5.1) and Drug Interactions (7.1)*].

Hypersensitivity

Instruct patients to immediately tell their healthcare professional if they experience symptoms of an allergic reaction on the day of administration or the day after ORENCIA administration [see *Warnings and Precautions (5.2)*].

Infections

Inform patients that serious infections have been reported in patients receiving ORENCIA [see *Warnings and Precautions (5.3)*].

Immunizations

Inform patients that live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation [see *Warnings and Precautions (5.4)*].

Pregnancy

Inform patients that there is a Pregnancy Exposure Registry [see *Use in Specific Populations (8.1)*].

Blood Glucose Testing

Maltose is contained in ORENCIA for intravenous administration and can give falsely elevated blood glucose readings with certain blood glucose monitors on the day of ORENCIA infusion. Advise patients treated with intravenous ORENCIA who are using GDH-PQQ-based monitoring systems for glucose (e.g., diabetics) to consider using other methods for glucose monitoring. This recommendation is not applicable to patients treated with subcutaneous ORENCIA [see *Drug Interactions (7.2)*].

Disposal of Prefilled Syringes and ClickJect Autoinjectors

Advise patients to follow disposal instructions in the Instructions for Use. A puncture-resistant container for disposal of needles and syringes should be used. Instruct patients that they will need to follow their community guidelines for the correct way to dispose of their sharps disposal container. Instruct patients not to recycle their used sharps disposal container.

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
U.S. License Number 1713

PATIENT INFORMATION

**ORENCIA[®] (oh-REN-see-ah)
(abatacept)
for injection, for intravenous use**
**ORENCIA[®] (oh-REN-see-ah)
(abatacept)
injection, for subcutaneous use**

What is ORENCIA?

ORENCIA is a prescription medicine that reduces signs and symptoms in:

- adults with moderate to severe rheumatoid arthritis (RA), including those who have not been helped enough by other medicines for RA. ORENCIA may prevent further damage to your bones and joints and may help your ability to perform daily activities. In adults, ORENCIA may be used alone or with other RA treatments other than tumor necrosis factor (TNF) antagonists.
- people 2 years of age and older with moderate to severe polyarticular juvenile idiopathic arthritis (pJIA). ORENCIA may be used alone or with methotrexate.
- adults with active psoriatic arthritis (PsA). In adults, ORENCIA can be used alone or with other PsA treatments.

ORENCIA is also used for the preventative treatment of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in:

- people 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor.

It is not known if ORENCIA is safe and effective in children less than two years of age for the treatment of pJIA.

It is not known if ORENCIA is safe and effective in children less than two years of age for the preventative treatment of aGVHD.

Before you receive or use ORENCIA, tell your healthcare provider about all of your medical conditions, including if you:

- have any kind of infection even if it is small (such as an open cut or sore), or an infection that is in your whole body (such as the flu). If you have an infection during treatment with ORENCIA, you may have a higher chance for getting serious side effects.
- have an infection that will not go away or an infection that keeps coming back.
- are allergic to abatacept or any of the ingredients in ORENCIA. See the end of this Patient Information leaflet for a complete list of ingredients in ORENCIA.
- have or have had inflammation of your liver due to an infection (viral hepatitis). Your healthcare provider may examine you for hepatitis before treatment with ORENCIA.
- have had a lung infection called tuberculosis (TB), a positive skin test for TB, or you recently have been in close contact with someone who has had TB. Your healthcare provider may examine you for TB or perform a skin test before treatment with ORENCIA. Symptoms of TB may include:
 - a cough that does not go away
 - fever
 - weight loss
 - night sweats
- have a history of Epstein-Barr Virus (EBV) or Cytomegalovirus (CMV) in people receiving ORENCIA for preventative treatment of aGVHD during HSCT from an unrelated donor.
- are scheduled to have surgery.
- recently received a vaccination or are scheduled for a vaccination.
- have a history of a breathing problem called chronic obstructive pulmonary disease (COPD).
- have diabetes and use a blood glucose monitor to check your blood sugar (blood glucose) levels. ORENCIA for intravenous infusion (given through a needle placed in a vein) contains maltose, a type of sugar, that can give false high blood sugar readings with certain types of blood glucose monitors on the day of ORENCIA infusion. Your healthcare provider may tell you to use a different way to monitor your blood sugar levels.

- ORENCIA for subcutaneous injection (injected under the skin) does not contain maltose. You do not need to change your blood sugar monitoring if you are using ORENCIA subcutaneously.
- are pregnant or plan to become pregnant. It is not known if ORENCIA can harm your unborn baby. If you took ORENCIA during pregnancy, talk to your healthcare provider before your baby receives any vaccines.
- There is a registry for pregnant women exposed to ORENCIA. The purpose of this registry is to check the health of the pregnant mother and her child. Women are encouraged to call the registry themselves or ask their healthcare provider to contact the registry for them by calling 1-877-311-8972.
- are breastfeeding or plan to breastfeed. It is not known if ORENCIA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you use ORENCIA.
- Some people treated with ORENCIA have developed skin cancer. Tell your healthcare provider if you have a family or personal history of skin cancer, and if you see any growths or changes in the appearance of your skin during or after your treatment with ORENCIA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ORENCIA may affect the way other medicines work, and other medicines may affect the way ORENCIA works causing serious side effects.

Especially tell your healthcare provider if you take other biologic medicines that may affect your immune system, such as:

- Enbrel® (etanercept)
- Humira® (adalimumab)
- Remicade® (infliximab)
- Kineret® (anakinra)
- Rituxan® (rituximab)
- Simponi® (golimumab)
- Cimzia® (certolizumab pegol)
- Actemra® (tocilizumab)

You may have a higher chance of getting a serious infection if you take ORENCIA with other biologic medicines that may affect your immune system.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new prescription.

How will I receive or use ORENCIA?

For treatment of RA, pJIA or PsA:

- You may receive ORENCIA given by a healthcare provider through a vein in your arm (intravenous infusion). It takes about 30 minutes to give you the full dose of medicine. You will then receive ORENCIA 2 weeks and 4 weeks after the first dose and then every 4 weeks.
- You may also receive ORENCIA as an injection under your skin (subcutaneous). For home use, ORENCIA comes in a prefilled syringe or prefilled ClickJect autoinjector. Your healthcare provider will prescribe the type that is best for you. If your healthcare provider decides that you or a caregiver can give your injections of ORENCIA prefilled syringes or ORENCIA ClickJect autoinjectors at home, you or your caregiver should receive training on the right way to prepare and inject ORENCIA. Do not try to inject ORENCIA until you have been shown the right way to give the injections by your healthcare provider.
- Your healthcare provider will tell you how much ORENCIA to use and when to use it.

See the Instructions for Use at the end of this Patient Information leaflet for instructions about the right way to prepare and give your ORENCIA injections at home.

For preventative treatment of aGVHD:

- You will receive ORENCIA by a healthcare provider through a vein in your arm (intravenous infusion) over 60 minutes on the day before transplantation (Day -1). You will then receive ORENCIA on Days 5, 14, and 28 after transplantation.
- Your healthcare provider may give you antiviral medicines before, during, and after your transplantation to help prevent Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV) infections.

What are the possible side effects of ORENCIA?

ORENCIA can cause serious side effects including:

- infections. ORENCIA can make you more likely to get infections or make the infection that you have get worse. Some people have died from these infections. Call your healthcare provider right away if you have any symptoms of an infection. Symptoms of an infection may include:
 - fever
 - feel very tired
 - have a cough
 - have flu-like symptoms
 - warm, red, or painful skin
- allergic reactions. Allergic reactions can happen to people who are treated with ORENCIA. Call your healthcare provider or go to the emergency room right away if you have any symptoms of an allergic reaction. Symptoms of an allergic reaction may include:
 - hives
 - swollen face, eyelids, lips, or tongue
 - trouble breathing
- **hepatitis B infection in people who carry the virus in their blood.** If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active during treatment with ORENCIA. Your healthcare provider may do a blood test before you start treatment with ORENCIA.
- **vaccinations.** You should not receive ORENCIA with certain types of vaccines (live vaccines). You can receive non-live vaccines, such as pneumococcal and inactivated influenza (flu) vaccines. ORENCIA may also cause some vaccinations to be less effective. Talk with your healthcare provider about your vaccination plans.
- **breathing problems in people with Chronic Obstructive Pulmonary Disease (COPD).** You may get certain respiratory problems more often if you receive ORENCIA and have COPD. Symptoms of respiratory problems include:
 - COPD that becomes worse
 - cough
 - trouble breathing
- **cancer (malignancies).** Certain kinds of cancer have been reported in people using ORENCIA. It is not known if ORENCIA increases your chance of getting certain kinds of cancer.
- **Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) infections.** CMV and EBV infections and return of CMV and EBV (reactivation) have happened in people receiving ORENCIA for preventative treatment of aGVHD during unrelated HSCT. Your healthcare provider will monitor you for 6 months after transplantation and may treat you with medicines to help prevent CMV and EBV infection if needed.

The most common side effects of ORENCIA in people with RA include:

- headache
- upper respiratory tract infection
- sore throat
- nausea

In children and adolescents, other side effects may include:

- diarrhea
- cough
- fever
- abdominal pain

The most common side effects of ORENCIA in prevention of aGVHD include:

- low red blood cell count
- high blood pressure
- CMV infection
- fever
- pneumonia
- nosebleed
- decreased CD4 lymphocytes
- increased levels of magnesium in the blood
- kidney problems

These are not all of the possible side effects of ORENCIA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ORENCIA?

- Store ORENCIA in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Keep ORENCIA in the original package and out of the light.
- Do not freeze ORENCIA.
- Safely throw away medicine that is out of date or no longer needed.

Keep ORENCIA and all medicines out of the reach of children.

General information about the safe and effective use of ORENCIA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ORENCIA for a condition for which it was not prescribed. Do not give ORENCIA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ORENCIA that is written for health professionals.

What are the ingredients in ORENCIA?

Active ingredient: abatacept

Intravenous inactive ingredients: maltose, monobasic sodium phosphate, sodium chloride for administration

Subcutaneous inactive ingredients: sucrose, poloxamer 188, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, water for injection.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA, U.S. License Number 1713

All other trademarks are property of their respective owners.

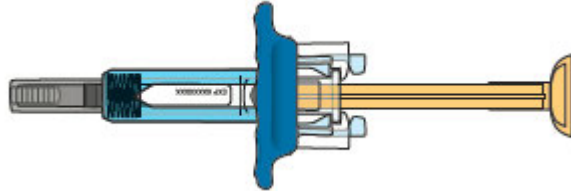
For more information, go to www.ORENCIA.com or call 1-800-ORENCIA.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: December 2021

INSTRUCTIONS FOR USE
ORENCIA® (oh-REN-see-ah)
(abatacept)
Prefilled Syringe with BD UltraSafe Passive™ Needle Guard

**ORENCIA® Prefilled Syringe with
BD UltraSafe Passive™ Needle Guard
(abatacept) Injection**



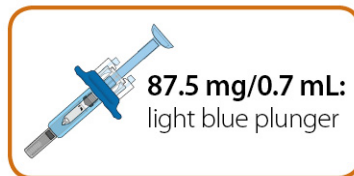
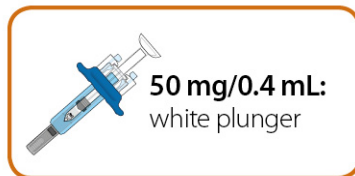
Read these instructions before you start using your ORENCIA Prefilled Syringe and each time you get a refill. There may be new information. Before you use the prefilled syringe for the first time, make sure your healthcare provider shows you the right way to use it and decides that you or a caregiver may be able to give your injections of ORENCIA at home.

Important:

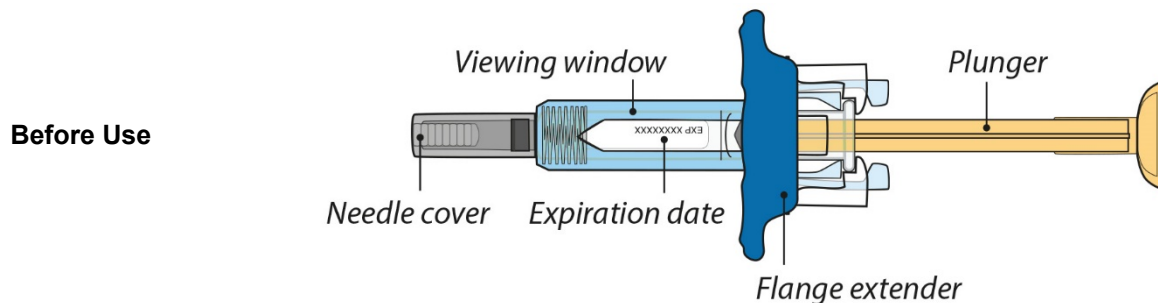
- **Keep the Prefilled Syringe in the refrigerator until ready to use.**
- **Do not freeze.**

Before You Begin: Get to Know Your Prefilled Syringe

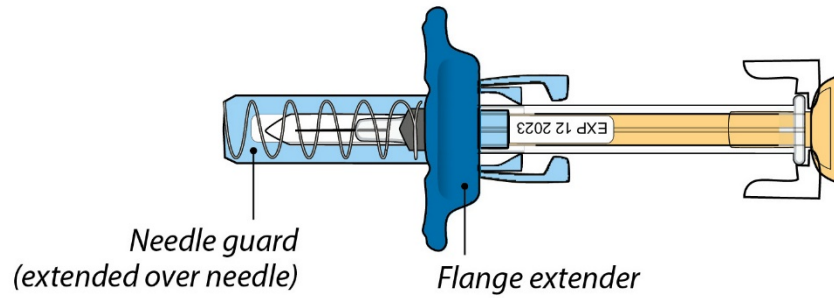
There are **3 types** of prefilled syringes:



The type of prefilled syringe you receive depends on the dose prescribed by your healthcare provider. The 125 mg/mL prefilled syringe is shown below.



After Use



The prefilled syringe has a **flange extender** that makes it easier to hold and inject, and a **needle guard** that automatically covers the needle after a complete injection.



DO NOT remove the needle cover until you are ready to inject.

DO NOT PULL back on the plunger at any time.

DO NOT RECAP the prefilled syringe at any time, as this may damage, bend, or break the needle.

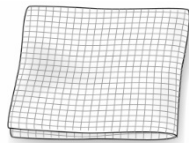
Go to Step 1

Step 1: Preparing for an ORENCIA Injection

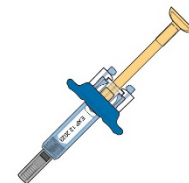
Gather and place supplies for your injection on a clean, flat surface.

Only the prefilled syringe is included in the package:

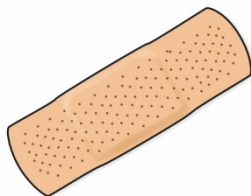
- Alcohol swab



- Prefilled Syringe with UltraSafe Passive Needle Guard



- Adhesive bandage



- Sharps disposal container



- Cotton ball or gauze



Let your Prefilled Syringe warm up.

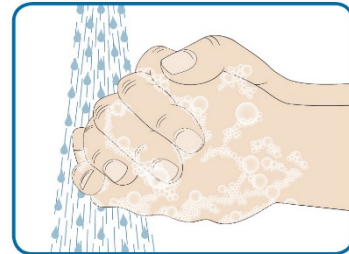
Remove one prefilled syringe from the refrigerator and wait **30 minutes** to allow it to reach room temperature.

- **Do not** speed up the warming process in any way, such as using the microwave or placing the syringe in warm water.
- **Do not** remove the needle cover while allowing the prefilled syringe to reach room temperature.

WAIT



Wash your hands well with soap and water.

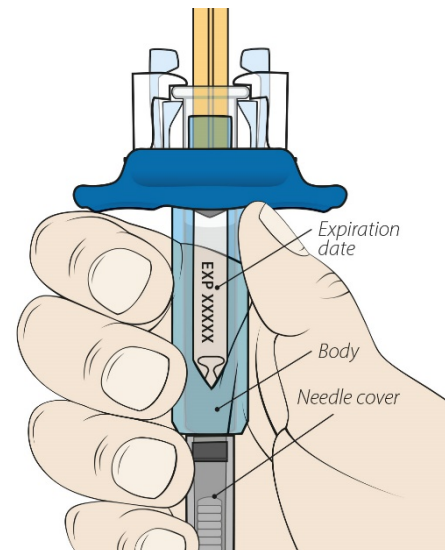


Go to Step 2

Step 2: Examine the Prefilled Syringe

Hold the prefilled syringe by the body with the needle cover pointing down as shown.

- **Check the expiration date** printed on the label. **Do not** use if the expiration date has passed.
- **Check the prefilled syringe for damage.** **Do not** use if it is cracked or broken.



Check the Liquid.

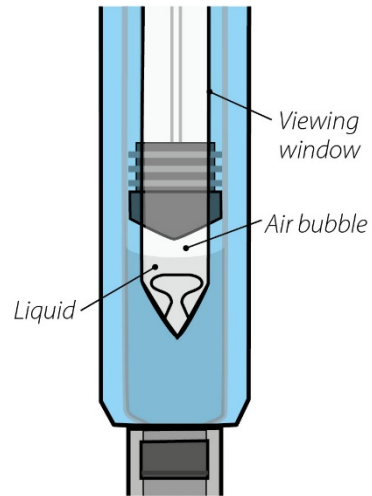
- **Check the liquid** in the prefilled syringe through the viewing window. It should be clear and colorless to pale yellow.

Do not inject if the liquid is **cloudy, discolored, or has particles in it.**

*Note: the 50 mg prefilled syringe is shown.

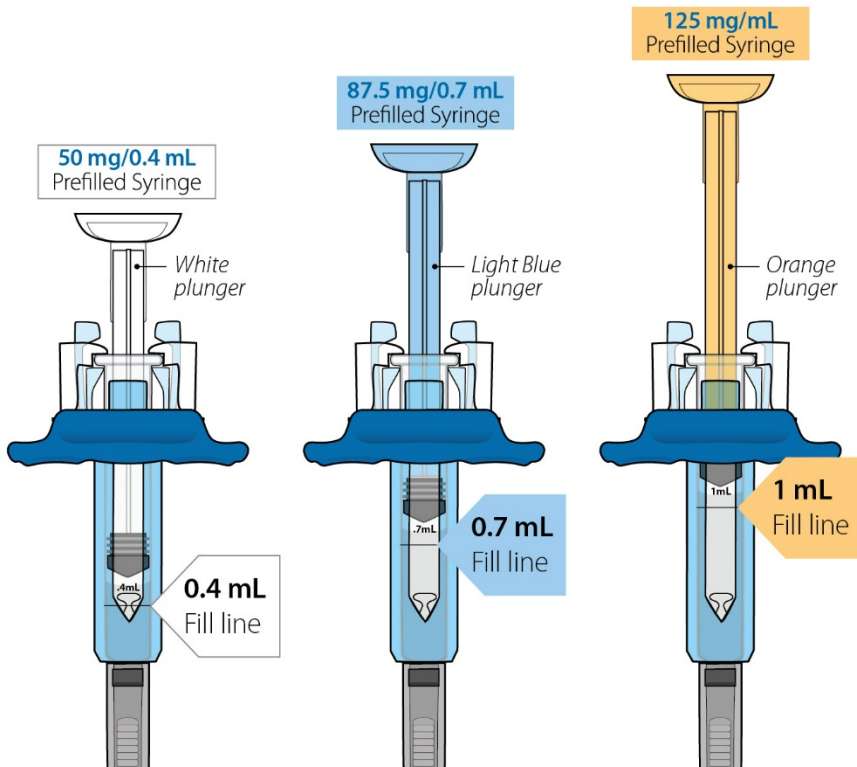
Note: It is normal to see an air bubble. **Do not** attempt to remove it.

Go to Step 3



Step 3: Check the Dose on the Prefilled Syringe

Hold the syringe at eye level. Look closely to make sure that the amount of liquid in the prefilled syringe is **at or just above the fill line** for your prescribed dose:



Do not use if your prefilled syringe does not have the correct amount of liquid. Call your pharmacist immediately.

Go to Step 4

Step 4: Choose and Prepare an Injection Site

Choose your injection site.

Choose your injection site in either the stomach (**abdomen**), front of the **thighs**, or outer area of **upper arm** (only if caregiver administered).

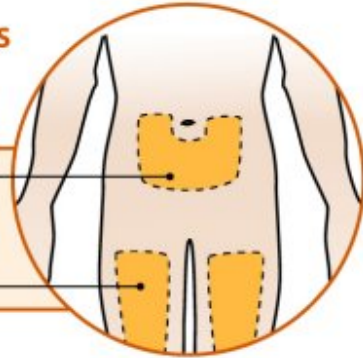
Rotate injection site.

- Each week you can use the same area of your body, but use a different injection site in that area.
- **Do not** inject into an area where the skin is tender, bruised, red, scaly, or hard. **Do not** give the injection in any areas with scars or stretch marks.
- Record the date, time, and site where you inject.

Injection Areas Self-Injection and Caregiver

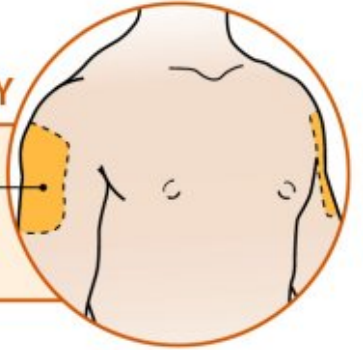
Abdomen,
avoid 2 inches
around navel

Front of thighs



Caregiver ONLY

Outer area of
upper arms



Gently clean injection site.

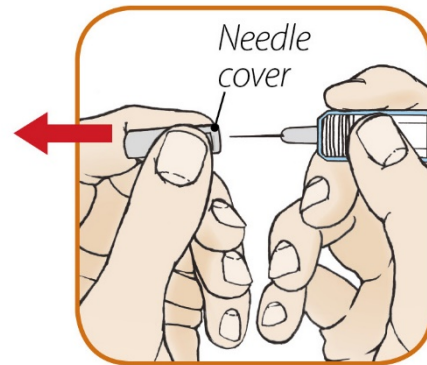
- Wipe the injection site with an alcohol swab and let it air dry.
- **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

Remove the needle cover by holding the body of the prefilled syringe with one hand and pulling the cover straight off with your other hand.

Do not put the needle cover back on the needle after you remove it. Throw away the needle cover in your household trash.

- **Do not** use the prefilled syringe if it is dropped after the needle cover is removed.
- **Do not** use the prefilled syringe if the needle is damaged or bent.

Note: It is normal to see a drop of fluid leaving the needle.

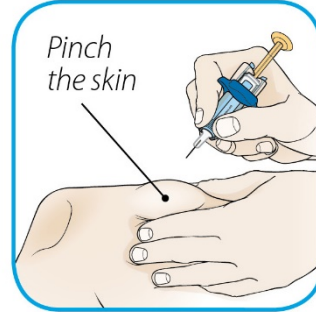


DO NOT RECAP the Prefilled Syringe, as this may damage the needle.

Go to Step 5

Step 5: Inject Your Dose of ORENCIA

Hold the body of the prefilled syringe in your hand using your thumb and index finger. With your other hand, **pinch the area of skin you cleaned**.

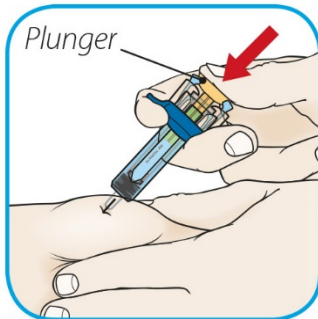


Insert the needle.

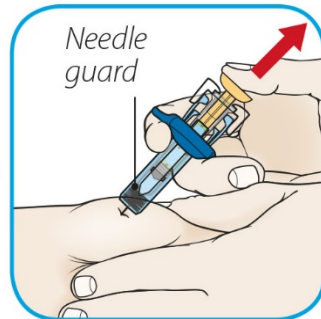
Gently insert the needle into the pinched skin at a 45° angle.



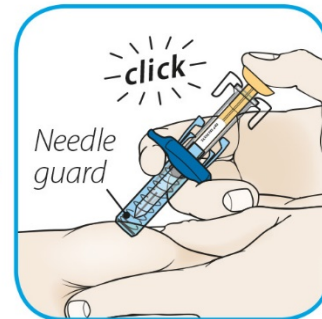
Complete all steps to deliver your full dose of the medicine.



Inject: push the plunger with your thumb as far as it will go.



Release Needle Guard: slowly lift your thumb from the plunger to activate the needle guard.



Confirm: after a complete injection, the needle guard will cover the needle and you may hear a click.

Remove the prefilled syringe and let go of the pinched skin.

Go to Step 6

Step 6: After the Injection

Care of injection site:

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with an adhesive bandage.



Disposing of used Prefilled Syringes:

- Put your used ORENCIA prefilled syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and prefilled syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- **Do not** throw away (dispose of) your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

See **Frequently Asked Questions** for additional disposal information.

If your injection is administered by a caregiver, this person must also be careful handling the syringe to prevent accidental needle stick injury and possibly spreading infection.

Keep ORENCIA prefilled syringes and the disposal container out of the reach of children.



How to store ORENCIA Prefilled Syringe

- Store ORENCIA in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Keep ORENCIA in the original package and out of the light.
- Do not freeze ORENCIA.
- Safely throw away medicine that is out of date or no longer needed.

Go to Next Page

Frequently Asked Questions

Q. Why do I need to allow the prefilled syringe to warm up at room temperature for 30 minutes prior to injecting?

A. This step is primarily for your comfort. Never try to speed up the warming process in any way, like using the microwave or placing the syringe in warm water.

Q. Is it necessary to hold the skin pinch during the entire time I inject the dose?

A. You must pinch the skin during needle insertion however, for your comfort you may release the skin pinch as you deliver the injection.

Q. What if my prefilled syringe appears to be broken or damaged?

A. Do not use the prefilled syringe. Contact your healthcare provider or pharmacist for further instructions.

Q. What if I cannot clearly see the liquid inside the syringe?

A. Look at the syringe closely by holding at eye level and up to the light. You may tilt the syringe slowly to get a better view of the drug fluid. If you still have trouble, contact your healthcare provider or pharmacist for further instructions.

Q. Is it normal to feel a little bit of burning or pain during injection?

- A. You may feel a prick from the needle. Sometimes, the medicine can cause slight irritation near the injection site. Discomfort should be mild to moderate. If you have any side effects, including pain, swelling, or discoloration near the injection site, contact your healthcare provider.

Go to next page

Frequently Asked Questions

Q. How should I dispose of a used prefilled syringe?

- A. Place the used prefilled syringe into an FDA-cleared sharps disposal container. If you do not have one you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use, leak-resistant, and properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and injector pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

Q. How should I keep my prefilled syringes cool while traveling?

- A. Store them in a cool carrier between 36°F to 46°F (2°C to 8°C). Do not freeze them. Keep them in the original carton and protected from light. Your healthcare provider may know about special carrying cases.

Q. Can I take my prefilled syringes on an airplane?

- A. Generally you are allowed to carry your prefilled syringes with you on an airplane. Do not put them in your checked luggage. You should carry your prefilled syringes with you in your travel cooler at a temperature of 36°F to 46°F (2°C to 8°C). Keep your prefilled syringes in the original carton, and with its original preprinted labels and protected from light.

Q. What if my prefilled syringe does not stay cool for an extended period of time? Is it dangerous to use?

- A. Contact 1-800-673-6242 for more information.

Go to Back Cover

If you have questions or concerns about your prefilled syringe, please contact your healthcare provider or call our toll-free help line at 1-800-673-6242.

Bristol-Myers Squibb Company

Princeton, NJ 08543 USA, U.S. License Number 1713

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

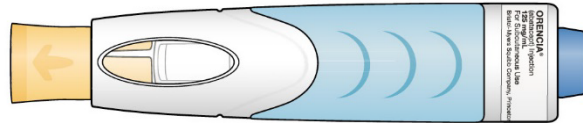
ORENCIA is a registered trademark of Bristol-Myers Squibb Company.

BD UltraSafe Passive™ is a trademark of Becton, Dickinson and Company.

Revised March 2017

INSTRUCTIONS FOR USE
ORENCIA® ClickJect™ (oh-REN-see-ah)
(abatacept)
Prefilled Autoinjector

ORENCIA® ClickJect™
(abatacept) Injection
Prefilled Autoinjector



125 mg/mL, Single-Dose Autoinjector, For Subcutaneous Use Only

Read these instructions before you use the ClickJect Autoinjector and each time you get a refill. There may be new information. Before you use the Autoinjector for the first time, make sure your healthcare provider shows you the right way to use it.

Important:

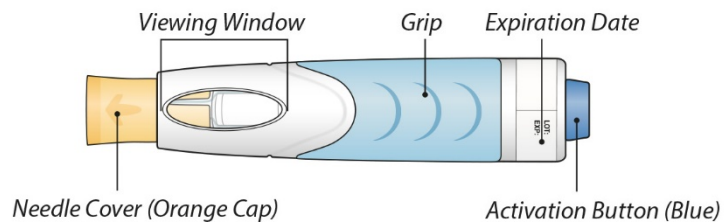
- **Keep the ClickJect Autoinjector in the refrigerator** until ready to use.
- **Do not freeze.**

Before You Begin

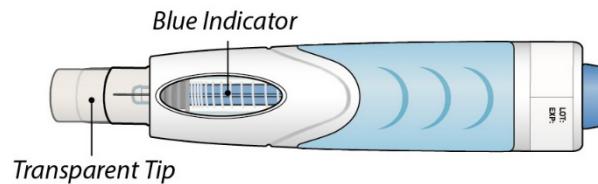
Get to know the ClickJect Autoinjector

- The Autoinjector automatically delivers the medicine. The transparent tip locks over the needle once the injection is complete and the Autoinjector is removed from the skin.
- **Do not remove the orange needle cover until you are ready to inject.**

Before Use

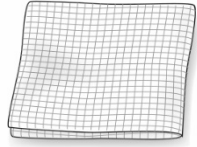


After Use

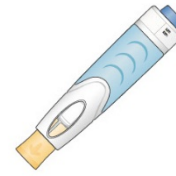


Gather supplies for your injection on a clean, flat surface
(only the ClickJect Autoinjector is included in the package):

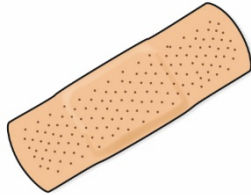
- Alcohol swab



- ClickJect Autoinjector



- Adhesive bandage



- Sharps disposal container



- Cotton ball or gauze



Go to Step 1

Step 1: Prepare Your Autoinjector

Let your ClickJect Autoinjector warm up.

Remove one Autoinjector from the refrigerator and let it rest at room temperature for **30 minutes**.

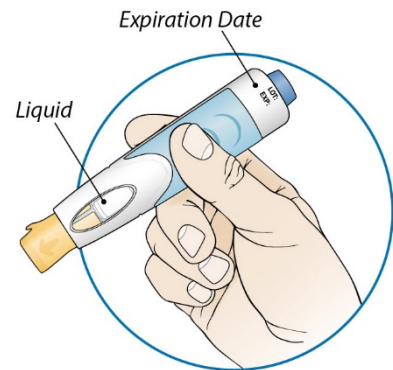
Do not remove the Autoinjector needle cover while allowing it to reach room temperature.



Wash your hands well with soap and water.

Examine the ClickJect Autoinjector:

- **Check expiration date** printed on the label. **Do not** use if past the expiration date.
- **Check the Autoinjector for damage.** **Do not** use if it is cracked or broken.
- **Check the liquid** through the viewing window. It should be clear and colorless to pale yellow. You may see a small air bubble. You do not need to remove it. **Do not inject** if the liquid is cloudy, discolored, or has particles in it.



Go to Step 2

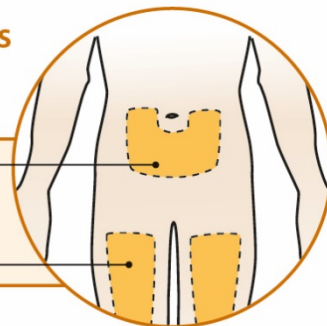
Step 2: Prepare for Injection

Choose your injection site in either the stomach (**abdomen**), front of the **thighs**, or outer area of **upper arm** (only if caregiver administered).

**Injection Areas
Self-Injection
and Caregiver**

*Abdomen,
avoid 2 inches
around navel*

Front of thighs

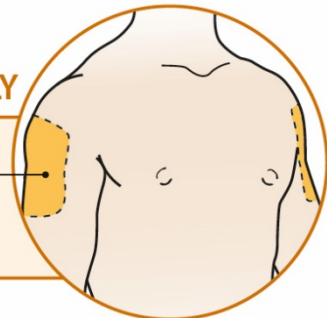


Rotate injection site.

- Each week you can use the same area of your body, but use a different injection site in that area.
- **Do not** inject into an area where the skin is tender, bruised, red, scaly, or hard. **Do not** give the injection in any areas with scars or stretch marks.
- Record the date, time, and site where you inject.

Caregiver ONLY

*Outer area of
upper arms*



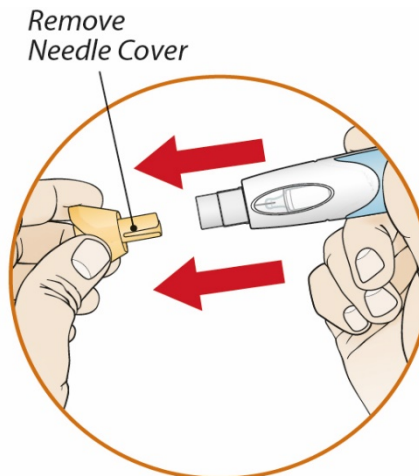
Gently clean injection site:

- Wipe the injection site with an alcohol swab and let it air dry.
- **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

Pull orange needle cover STRAIGHT off.

- **DO NOT RECAP** the Autoinjector.
- Throw away (discard) the needle cover in your household trash.
- **Do not** use the Autoinjector if it is dropped after the needle cover is removed.

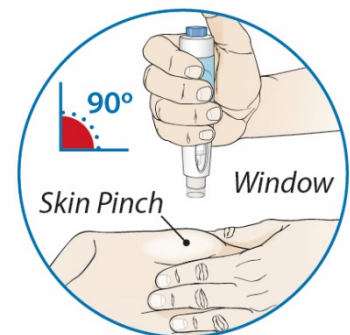
Note: It is normal to see a drop of fluid leaving the needle.



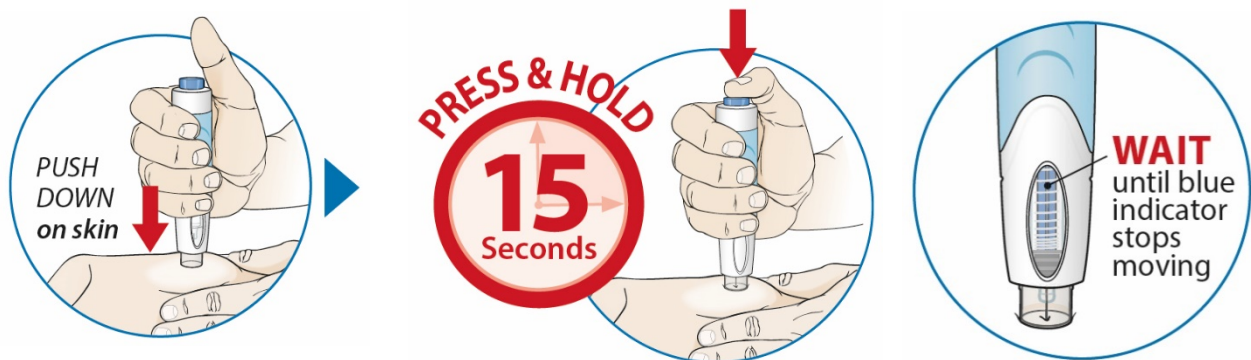
Go to Step 3

Step 3: Inject Your Dose

Position the Autoinjector so you can see the **viewing window** and it is at a 90° angle to the injection site. With your other hand, gently **pinch the cleaned skin**.



Complete all steps to deliver your full dose of medicine:



Push DOWN on the skin to unlock the Autoinjector.

Press button, HOLD for 15 seconds AND watch window.

- You will hear a click as the injection begins.
- To deliver the full dose of medicine, hold the Autoinjector in place for 15 seconds **AND** wait until the blue indicator stops moving in window.

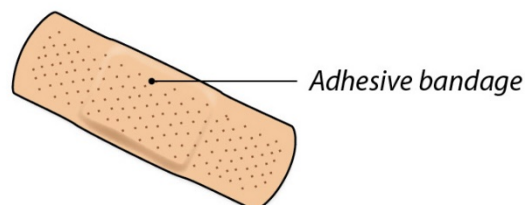
Remove the ClickJect Autoinjector from the injection site by lifting it straight up. After you remove it from your skin, the transparent tip will lock over the needle. Release skin pinch.

Go to Step 4

Step 4: After the Injection

Care of injection site:

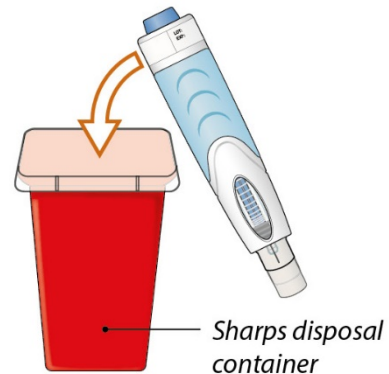
- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with an adhesive bandage.



- Disposing of used ClickJect Autoinjectors:
- Put your used ClickJect Autoinjector in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and prefilled syringes in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

See **Frequently Asked Questions** for additional disposal information.

If your injection is administered by a caregiver, this person must also handle the Autoinjector carefully to prevent accidental needle stick injury and possibly spreading infection.



Keep Autoinjector and the disposal container out of the reach of children.

How to store ORENCIA ClickJect Autoinjector

- Store ORENCIA in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Keep ORENCIA in the original package and out of the light.
- Do not freeze ORENCIA.
- Safely throw away medicine that is out of date or no longer needed.

Continued on next page

Frequently Asked Questions

Q. Why do I need to allow the Autoinjector to warm up at room temperature for 30 minutes prior to injecting?

A. This step is primarily for your comfort. If the medicine is cold, the injection may take longer than 15 seconds. Never try to speed the warming process in any way, like using the microwave or placing the Autoinjector in warm water.

Q. What if I accidentally remove the needle cover (orange cap) before I'm ready to use the Autoinjector?

A. If you remove the cover before you are ready to use the Autoinjector, be careful. Do not try to replace it. Use the Autoinjector as soon as possible. While you prepare for the injection, carefully place the Autoinjector on its side on a clean, flat surface. Be sure to keep the Autoinjector away from children.

Q. What if the Autoinjector appears to be broken or damaged?

A. Do not use the Autoinjector. Contact your healthcare provider or pharmacist for further instructions.

Q. What if the injection was not triggered?

A. Before the injection can be triggered, the device must be unlocked. To unlock, firmly push the Autoinjector down on the skin without touching the button. Once the stop-point is felt, the device is unlocked and can be triggered by pushing the button.

Q. I feel a little bit of burning or pain during injection. Is this normal?

A. When giving an injection, you may feel a prick from the needle. Sometimes, the medicine can cause slight irritation near the injection site. If this occurs, the discomfort should be mild to moderate. If you experience any side effects, including pain, swelling, or discoloration near the injection site, contact your healthcare provider or pharmacist immediately. You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Q. How do I know I received my full dose?

A. Before lifting the Autoinjector from the injection site, check to ensure that the blue indicator has stopped moving. Then, before disposing of the Autoinjector, check the bottom of the transparent viewing window to make sure there is no liquid left inside. If the medicine has not been completely injected, consult your healthcare provider or pharmacist.

Continued on next page

Frequently Asked Questions

Q. How should I dispose of a used Autoinjector?

- A. Place used Autoinjector into an FDA-cleared sharps disposal container right away after use.
- If you do not have one, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use, leak-resistant, and properly labeled to warn of hazardous waste inside the container.
 - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and Autoinjectors. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
 - **Do not** recycle your used sharps disposal container.

Q. How should I keep my Autoinjector cool while traveling?

A. Your healthcare provider or pharmacist may be familiar with special carrying cases for injectable medicines. Store at 36°F to 46°F (2°C to 8°C). Do not freeze. Protect from light.

Q. Can I take my Autoinjector on board an aircraft?

A. Generally, this is allowed. Be sure to pack your Autoinjector in your carry-on, and do not put it in your checked luggage. You should carry it with you in your travel cooler at a temperature of 36°F to 46°F (2°C to 8°C) until you are ready to use it. Airport security procedures and airline policies change from time to time, so it's best to check with airport authorities and the airline for any special rules. Prior to flying, get a letter from your healthcare provider to explain that you are traveling with prescription medicine that uses a device with a needle; if you are carrying a sharps container in your carry-on baggage, notify the screener at the airport.

Q. What if my Autoinjector does not stay cool for an extended period of time? Is it dangerous to use?

A. Contact 1-800-673-6242 for details.

If you have questions or concerns about your Autoinjector, please contact a healthcare provider or call our toll-free help line at 1-800-673-6242.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA, U.S. License Number 1713

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

ORENCIA is a registered trademark and ClickJect is a trademark of Bristol-Myers Squibb Company.

Revised March 2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125118Orig1s240

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Health Canada, Israel’s Ministry of Health (MOH) and Switzerland’s Swissmedic. While the conclusions and recommendations expressed herein reflect FDA’s completed review of the application, the applications may still be under review at the other regulatory agencies. In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA or the other Regulatory Authorities.

Application Type	BLA (Efficacy – new indication)
Application Number(s)	125118 Supplement 240
Priority or Standard	Priority
Submit Date(s)	June 23, 2021
Received Date(s)	June 23, 2021
PDUFA Goal Date	December 23, 2021
Division/Office	Division of Hematologic Malignancies I/OOD
Review Completion Date	December 15, 2021
Established Name	Abatacept
(Proposed) Trade Name	Orencia
Pharmacologic Class	Disease modifying anti-rheumatic drug, T-cell costimulation modulator
Code name	CTLA-4lg
Applicant	Bristol-Myers Squibb Company
Formulation(s)	lyophilized powder; Injection, Solution
Dosing Regimen	Refer to USPI
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	for the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation.....	10
Additional Reviewers of Application	10
Glossary	13
1 Executive Summary	16
1.1. Product Introduction	16
1.2. Conclusions on the Substantial Evidence of Effectiveness	16
1.3. Benefit-Risk Assessment (BRA).....	19
1.4. Patient Experience Data.....	22
2 Therapeutic Context.....	24
2.1. Analysis of Condition	24
2.2. Analysis of Current Treatment Options.....	24
3 Regulatory Background.....	27
3.1. U.S. Regulatory Actions and Marketing History	27
3.2. Summary of Presubmission/Submission Regulatory Activity.....	27
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	29
4.1. Office of Scientific Investigations (OSI)	29
4.2. Product Quality.....	29
4.3. Clinical Microbiology.....	29
4.4. Devices and Companion Diagnostic Issues.....	29
5 Nonclinical Pharmacology/Toxicology	30
6 Clinical Pharmacology	31
6.1. Executive Summary	31
6.2. Summary of Clinical Pharmacology Assessment.....	31
6.2.1. Pharmacology and Clinical Pharmacokinetics.....	32
6.2.2. General Dosing and Therapeutic Individualization	35
6.2.2.1. General Dosing	37
6.2.2.2. Therapeutic Individualization	38
6.2.2.3. Outstanding Issues.....	45
6.3. Comprehensive Clinical Pharmacology Review.....	46
6.3.1. General Pharmacology and Pharmacokinetic Characteristics.....	46
6.3.2. Clinical Pharmacology Questions.....	48
7 Sources of Clinical Data.....	51
7.1. Table of Clinical Studies	51
8 Statistical and Clinical Evaluation	57
8.1. Review of Relevant Individual Trials Used to Support Efficacy	57
8.1.1. Study IM101311	57
8.1.2. Study Results from IM101311	74
8.1.3. Supportive Study - IM101841.....	100
8.1.4. Study Results, IM101841.....	109
8.1.5. Integrated Review of Effectiveness.....	141

8.1.6. Assessment of Efficacy Across Trials	142
8.1.7. Integrated Assessment of Effectiveness.....	142
8.2. Review of Safety.....	150
8.2.1. Safety Review Approach	151
8.2.2. Review of the Safety Database.....	167
8.2.3. Adequacy of Applicant’s Clinical Safety Assessments	173
8.2.4. Safety Results.....	174
8.2.5. Analysis of Submission-Specific Safety Issues.....	199
8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability	199
8.2.7. Safety Analyses by Demographic Subgroups	199
8.2.8. Specific Safety Studies/Clinical Trials	201
8.2.9. Additional Safety Explorations.....	203
8.2.10. Safety in the Postmarket Setting.....	205
8.2.11. Integrated Assessment of Safety	205
SUMMARY AND CONCLUSIONS.....	209
8.3. Statistical Issues.....	209
8.4. Conclusions and Recommendations	209
9 Advisory Committee Meeting and Other External Consultations	211
10 Pediatrics	212
11 Labeling Recommendations	215
12 Risk Evaluation and Mitigation Strategies (REMS)	218
13 Postmarketing Requirements and Commitment.....	219
14 Division Director (DHOT) (NME ONLY)	220
15 Division Director (OCP)	221
16 Division Director (OB)	222
17 Division Director (Clinical)	223
18 Office Director (or designated signatory authority).....	224
19 Appendices	225
19.1. References.....	225
19.2. Financial Disclosure	225
19.3. Nonclinical Pharmacology/Toxicology	226
19.4. OCP Appendices (Technical documents supporting OCP recommendations)	227
19.5. Additional Safety Analyses Conducted by FDA.....	286
19.6. LIST OF REFERENCES.....	286

Table of Tables

Table 1: Summary of Available GVHD Prophylaxis Regimens	26
Table 2: Key Regulatory Milestones and Communications.....	27
Table 3: Summary of Primary and Derived PK Parameters for the Final PPK Model, Stratified by Disease Status and Study IM101311 Cohorts	32
Table 4. Observed Abatacept Concentrations in Study IM101311 Cohort 7/8 and Cohort 8/8 ...	36
Table 5: Listing of Clinical Trials Relevant to this sBLA	51
Table 6: High-Risk Hematologic Malignancies	58
Table 7: Study IM101311 Objectives and Endpoints Based on Investigator Protocol	62
Table 8: Study IM101311 Objectives and Endpoints Based on BMS SAP	65
Table 9: Key Study Level Changes to Study IM101311	71
Table 10: Disposition of Subjects in the 8/8 MUD Cohort - IM101311.....	75
Table 11: Disposition of Subjects in the 7/8 MMUD Cohort - IM101311	75
Table 12: Demographic Characteristics: 8/8 MUD Cohort MITT Analysis Population - IM101311	77
Table 13: Demographic Characteristics - 7/8 MMUD Cohort Treated Analysis Population - IM101311.....	77
Table 14: Key Baseline Disease Characteristics: 8/8 MUD Cohort MITT Analysis Population - IM101311.....	79
Table 15: IM101311 Baseline Disease Characteristics: 7/8 MMUD Cohort Treated Analysis Population -IM101311	81
Table 16: Primary Endpoint Efficacy Results - IM101311	83
Table 17: Comparison of Grade III/IV aGVHD Free Survival (GFS) During the Day 180 Analysis Period:7/8 Cohort As Treated Analysis Population versus Historic Controls - IM101311.....	84
Table 18: Sensitivity Analysis of Grade III-IV GFS at Day 180 in the 8/8 cohort of IM101311 - Unstratified Multivariate Cox Regression Model Adjusted for Baseline Prognostic Factors.....	87
Table 19: Efficacy of Abatacept and Placebo: 8/8 MUD Cohort MITT Analysis Population - IM101311.....	90
Table 20: Efficacy of Abatacept: 7/8 MMUD Cohort Treated Analysis Population - IM101311 ...	90
Table 21: Approximate Number of Eligible Subjects by Treatment Group (Planned) - IM101841	100
Table 22: Sample Size of the Comparison Groups	104
Table 23: Covariate Selection	106
Table 24: Amendments and Updates - IM101841	108
Table 25: Disposition during the Day 180 period, Primary Objective Cohort - IM101841	109
Table 26: Key Demographic Characteristics at Transplant for the Un-Weighted Samples, Primary Objective Cohort - IM101841	111
Table 27: Key Demographic Characteristics at Transplant for the Weighted Samples Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores - IM101841.....	112

Table 28: Disease and Other Characteristics at Transplant: Un-weighted Samples - Primary Objective Cohort - IM101841	113
Table 29: Disease and Other Characteristics at Transplant for the Weighted Samples Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores -IM101841	116
Table 30: Summary of OS During 180 Days of Follow-up Post-Transplant Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores (PS), Primary Objective Cohort - IM101841	121
Table 31: Propensity Score Balance Diagnostic	123
Table 32: Independent Variables of Interest.....	124
Table 33: Other CIs Investigated on the Primary Endpoint of OS at Day 180 - Study IM10184 .	126
Table 34: Analysis of the Effect of Imbalance in Covariates on the Primary Endpoint of OS at Day 180 Post-HSCT on Study IM101841	128
Table 35: 8/8 HLA-matched Subjects Treated with CNI + MTX without ATG for IM101311 participants to IM101311 non-participants.....	129
Table 36: Summary of Degree of Concordance of Variables of Interest between the CIBMTR Database and Study IM101311	130
Table 37: Cause of death to day 180 post-transplantation in Study IM101841 primary endpoint population.....	133
Table 38: Summary of OS During 180 Days of Follow-up Post-transplant Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores (PS) in the Comparator Group with ATG - IM101841	133
Table 39: Summary of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the Tacrolimus Sub-group - IM101841	135
Table 40: Cause of death in Study IM101841 secondary endpoint using comparator arm with ATG.....	137
Table 41: Summary of Grade II-IV GFS and Grade III-IV GFS During 180 Days of Follow-up Post-transplant- IM101841	138
Table 42: Summary of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the PT-Cy Comparator Group - IM101841	139
Table 43: Causes of death in Study IM101841 for the exploratory comparison of Aba + CNI + MTX without ATG versus PT-Cy without ATG	141
Table 44: Summary of change of analysis plan for Study IM101311.....	144
Table 45: Efficacy results for Study IM101311 and Study IM101841	148
Table 46: Summary of Study and Safety Results for Abatacept from the Literature	152
Table 47: Safety Population, Size, and Denominators.....	167
Table 48: Extent of Exposure to Study Medication in the Treatment Period - IM101311	167
Table 49: Summary of Methotrexate Dose Received - IM101311	168
Table 50: Summary of Calcineurin Inhibitor and Sirolimus Levels Over Time: 8/8 Cohort As Treated Analysis Population.....	169
Table 51: Summary of Calcineurin and Sirolimus Inhibitor Levels Over Time: 7/8 Cohort Treated Analysis Population	171

Table 52: Summary of Safety Results During the Day 180 Analysis Period - As Treated Population - IM101311.....	174
Table 53: Summary of extended TESAEs on Study ABA2 through day 225.....	178
Table 54: Intensity of Adverse Events Reported in $\geq 2\%$ of Subjects During the Treatment Period: 8/8 Cohort As Treated Analysis Population	184
Table 55: Intensity of Adverse Events Reported during the Treatment Period: 7/8 Cohort Treated Analysis Population.....	189
Table 56: Frequently Reported Adverse Events (in at Least 10 Percent of Subjects in Any Treatment Group) During the Day 180 Analysis Period	192
Table 57: Proposed Adverse Drug Reaction Table for US Prescribing Information	193
Table 58 FDA tabulated common ($\geq 10\%$ with $>2\%$ difference compared to placebo) extended TEAEs through Day 225 on Study ABA2	194
Table 59: Mean Serum Electrolyte and CO ₂ Concentrations by Treatment Group and Study Day – IM101311	196
Table 60 FDA Common ($\geq 10\%$) Abnormal Laboratory Tabulation through Day 225 on Study ABA2.....	197
Table 61: Serious Adverse Events Reported during the Day 180 Analysis Period by Subgroups	199
Table 62 Most Common Extended TESAEs through Day 225 in Patients <18 years ($>5\%$ incidence) on Study ABA2.....	201
Table 63 Pyrexia Extended TESAe through Day 225 by age and treatment group on Study ABA2	201
Table 64: Summary of Safety Results During the Treatment Period (Up to and including 56 days after the last dose of Abatacept/Placebo) - As Treated Population - IM101311	205
Table 65: Adverse Events Summary during the Post-transplantation Analysis Period -IM101311	206
Table 66 Safety summary of Study ABA2	207
Table 67: Summary of Efficacy Results During the Day 180 Analysis Period in Pediatric Subgroup (< 18 Years)	212
Table 68: Summary of Bioanalytical Method Validation for the Measurement of Serum Concentrations of BMS-188667.....	228
Table 69: Sensitivity and Drug Tolerance of Method (b) (4) for the detection of anti-abatacept antibodies	228
Table 70: Sensitivity and Drug Tolerance of Method (b) (4) for the Detection of neutralizing antibodies to BMS-188667.....	229
Table 71. Summary of Baseline Characteristics in the Population PK Dataset.....	236
Table 72. Applicant Parameter Estimates for the Final Population PK Model	240
Table 73. Summary of Relevant Reviewer Independent Analysis Model Runs.....	248
Table 74. Parameter Estimates for the Reviewer’s Final Model.....	250
Table 75. Summary of Individual Predicted Abatacept Exposure in the Exposure-Response Dataset	252
Table 76. Summary of Individual Predicted Abatacept Exposure According to Age Group in the Exposure-Response Dataset.....	256

Table 77. Summary of Simulated Abatacept Exposure Measures for Last Dose According to Dose Level and Age Group.....	262
Table 78. Summary of Relevant Reviewer Independent Analysis Model Runs.....	263
Table 79. Summary of Baseline Patient Characteristics in the Exposure-Response Dataset	267
Table 80. Summary of Patient Characteristics in the Exposure-Response Dataset Stratified by Minimum Concentration Following Last Dose up to Day 42 After Transplant	268
Table 81. Severe aGFS Events up to Day 180 Assessment Per Cohort and Exposure Quartile ...	272
Table 82. Parameter Estimates of Exposure-Response Efficacy for Time to First Severe aGFS up to Day 180 Assessment (Applicant’s Final Model)	273
Table 83. Parameter Estimates of Exposure-Response Efficacy for Time to First Severe aGFS up to Day 180 Assessment (Reviewer’s Final aGFS Model)	274
Table 84. Parameter Estimates of Exposure-Response Efficacy for Time to First Severe aGFS up to Day 180 Assessment (Reviewer Independent aGFS Model #1)	274
Table 85. Parameter Estimates of Exposure-Response Efficacy for Time to First Severe aGFS up to Day 180 Assessment in Cohort 8/8 Only (Reviewer Independent aGFS Model #2)	275
Table 86. Overall Survival Events up to Day 180 Assessment Per Cohort and Exposure Quartile	278
Table 87. Parameter Estimates of Exposure-Response Efficacy for Overall Survival up to Day 180 Assessment (Applicant’s Full/Final Model).....	278
Table 88. Parameter Estimates of Exposure-Response Efficacy for Time to Overall Survival up to Day 180 Assessment (Reviewer Independent OS Model)	280
Table 89. Exposure-Response Dataset Incidence of Invasive CMV Disease up to Database Lock According to Predicted Maximum Concentration after Last Dose	280
Table 90. Exposure-Response Dataset Incidence of CMV Viremia up to Database Lock According to Predicted Maximum Concentration after Last Dose	281
Table 91. Study IM101311 Adverse Events Reported during the Day 180 Analysis Period	282
Table 92. Exposure-Response Dataset Incidence of Infection during the Day 180 Analysis Period According to Predicted Maximum Concentration after Last Dose	283
Table 93. Incidence of Select Common Treatment Emergent Adverse Events during the Day 180 Analysis Period According to Maximum Concentration after Last Dose Quartile	284
Table 94. Analysis Codes and Output Files	285

Table of Figures

Figure 1: Clinical Relevance of Covariate Effects in Full PPK Model	34
Figure 2. Model-Predicted Exposure Stratified by Cohort in Study IM101311	37
Figure 3. Study IM101311 Observed Abatacept Trough Concentrations at Day 5, Day 14 and Day 28 After Transplant in Pediatric Patients versus Adult Patients	40
Figure 4. Study IM101311 Observed Abatacept Concentrations at Day 35, 42, 63 and 100 After Transplant in Pediatric Patients versus Adult Patients.....	41
Figure 5. Simulated Abatacept Exposure for First Dose According to Dose Level and Age Group	43
Figure 6. Simulated Abatacept Exposure for Last Dose According to Dose Level and Age Group.....	44
Figure 7: Estimated Covariate Effects on the Hazard Ratio of Time to First Severe aGFS (Full Model).....	46
Figure 8: IM101311 Study Schematic.....	57
Figure 9: Kaplan-Meier Plot of Grade III-IV GFS up to Day 180 Visit: 8/8 MUD Cohort MITT Analysis Population - IM101311	85
Figure 10: Grade III-IV GFS in Subsets During the Day 180 Analysis Period: 8/8 MUD Cohort MITT Analysis Population - IM101311	94
Figure 11: Grade II-IV aGVHD Free Survival (GFS) in Subsets During the Day 180 Analysis Period: 8/8 Cohort MITT Analysis Population - IM101311	96
Figure 12: Overall Survival (OS) in Subsets During the Day 180 Analysis Period: 8/8 Cohort MITT Analysis Population - IM101311	98
Figure 13: K-M Plot of OS During 180 Days of Follow-up Post-transplant using Stabilized IPTW with PS in the Primary Objective Cohort - IM101841	121
Figure 14: K-M Plot of OS During 180 Days of Follow-up Post-transplant Using Stabilized Inverse IPTW with Propensity Scores (PS) in the Comparator Group with ATG - IM101841	135
Figure 15: K-M Plot of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the Tacrolimus Sub-group - IM101841	136
Figure 16: K-M Plot of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the PT-Cy Comparator Group - IM101841	140
Figure 17: Model Evaluation of Final PPK Model, by Disease Status.....	231
Figure 18: Model Evaluation of Time to First Severe aGFS (Final Model), by Treatment	233
Figure 19: Model Evaluation of Overall Survival (Final Model), by Treatment	234
Figure 20. Study IM101311 Observed Abatacept Trough Concentrations Versus Nominal Time After Transplant up to Day 28 Predose	238
Figure 21. Study IM101311 Observed Abatacept Concentrations Versus Nominal Time After Transplant Following Day 28 Dose.....	239
Figure 22. Clinical Relevance of Covariate Effects in Sensitivity Analysis PopPK Model.....	241
Figure 23. Goodness-of-Fit Plots for Final Model: Overall.....	242
Figure 24. Goodness-of-Fit Plots for Final Model: Study IM101311 Patients Stratified by Cohort	243
Figure 25. Distribution of Individual Predicted Clearance by Baseline Albumin Concentration.	245

Figure 26. Population PK Dataset Age Versus eGFR.....	246
Figure 27. Study IM101311 Model-Predicted Exposure Stratified by Cohort	252
Figure 28. Study IM101311 Body Weight Versus Age	253
Figure 29. Study IM101311 Model-Predicted Exposure Versus Body Weight by Cohort	254
Figure 30. Study IM101311 Model-Predicted Exposure Versus Body Weight by Age Category.	255
Figure 31. Study IM101311 Model-Predicted Exposure Versus eGFR by Age Category	257
Figure 32. Simulated Abatacept Exposure Measures for First Dose According to Dose Level and Age Group.....	259
Figure 33. Simulated Abatacept Exposure Measures for Last Dose According to Dose Level and Age Group.....	261
Figure 34. Simulated Abatacept Exposure after First Dose from the Updated PopPK Model for Sensitivity Analysis	264
Figure 35. Simulated Abatacept Exposure after Last Dose from the Updated PopPK Model for Sensitivity Analysis	265
Figure 36. Severe aGFS up to Day 180 Assessment Per Cohort and Treatment Arm	270
Figure 37. Cohort 8/8 Severe aGFS up to Day 180 Assessment Per Exposure Quartile	271
Figure 38. Cohort 7/8 Severe aGFS up to Day 180 Assessment Per Exposure Quartile	272
Figure 39. Model Evaluation of Time to First Severe aGFS up to Day 180 Assessment (Applicant’s Final Model) by Placebo and Quartiles of Abatacept Exposure	273
Figure 40. Age Distribution of Exposure-Response Dataset by Relapse Status.....	275
Figure 41. Overall Survival up to Day 180 Assessment Per Cohort and Treatment Arm	276
Figure 42. Cohort 8/8 Overall Survival up to Day 180 Assessment Per Exposure Quartile	277
Figure 43. Cohort 7/8 Overall Survival up to Day 180 Assessment Per Exposure Quartile	277
Figure 44. Model Evaluation of Overall Survival up to Day 180 Assessment (Applicant’s Final Model) by Placebo and Quartiles of Exposure.....	279
Figure 45. Probability of Invasive CMV Disease during the Day 180 Analysis Period by Quartiles of Abatacept Maximum Concentration after Last Dose	281
Figure 46. Probability of CMV Viremia during the Day 180 Analysis Period by Quartiles of Abatacept Maximum Concentration after Last Dose	282

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Suria Yesmin, MS
Office of Clinical Pharmacology Reviewer(s)	Lili Pan, PhD Pharmacometrics: Robyn Konicki, PharmD
Office of Clinical Pharmacology Team Leader(s)	Ruby Leong, PharmD Pharmacometrics: Lian Ma, PhD
Clinical Reviewer	Joseph Wynne, MD, PhD
Clinical Team Leader	Kelly Norsworthy, MD
Statistical Reviewer	Jian (Jay) Zhao, PhD
Statistical Team Leader	Jonathon, Vallejo, PhD
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP
Cross-Disciplinary Team Leader	Kelly Norsworthy, MD
Division Director (OCP)	Brian Booth, MD
Division Director (OB)	Thomas Gwise, PhD
Division Director (OOD)	R. Angelo de Claro, MD

Additional Reviewers of Application

OPDP	Nisha Patel, PharmD, RAC
OCE/RWE & RWDRWD	Donna Rivera, PharmD, MSc.
OSE/DEPI	Aida Kuzucan, PhD, PharmD; Steve Bird, PhD, PharmD
OSE/DMPPDMPP	Susan Redwood, MPH, BSN, RN; Barbara Fuller, RN, MSN, CWOCN
OSIOSI	Anthony Orenca, MD

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

Project Orbis #53 - Health Canada (HC; Canada) Review team	
ROLE	NAME
Director	(b) (6)
Clinical Manager (Clinical Evaluation Division – Radiopharmaceuticals & Hematology)	(b) (6)
Lead Clinical Reviewer	(b) (6)
Biostatistics Reviewer	(b) (6)
Senior Regulatory Affairs Officer / Regulatory Affairs Supervisor	(b) (6) / (b) (6) / (b) (6)
Risk Management Reviewer	(b) (6)
Policy & International Coordination Advisor / Office of Regulatory Intelligence & Risk Mgmt Biologic & Radiopharmaceutical Drugs Directorate	(b) (6) / (b) (6)

Project Orbis # 53 - Swissmedic (Switzerland) Review team	
ROLE	NAME
Clinical Reviewer	(b) (6)
Clinical Peer Reviewer	(b) (6)
Clinical PK Reviewer	(b) (6)
Biostatistics Reviewer	(b) (6)
Biostatistics Reviewer Peer	(b) (6)
Non-Clinical Reviewer	(b) (6)
Risk Management Reviewer	(b) (6)
Regulatory Project Manager	(b) (6)
Project Orbis coordinators	(b) (6) / (b) (6)
Head Clinical Review Unit Oncology	(b) (6)

Project Orbis # 53 – Ministry of Health (MOH; Israel) Review team	
ROLE	NAME
Head of the Drug Registration Department, Pharmaceutical Division	(b) (6)
Regulatory Manager	(b) (6)
Clinical Reviewer (External Scientific Advisory Committee Member: subject to MOH confidentiality & non-disclosure agreements)	(b) (6)
Head of Medical Technologies National Projects and International Regulatory	(b) (6)

Glossary

AC	advisory committee
ADA	anti-drug antibodies
ADME	absorption, distribution, metabolism, excretion
ATG	antithymocyte globulin
AE	adverse event
ALL	acute lymphocytic leukemia
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AUC	area under the concentration-versus-time-curve
BLA	biologics license application
BLQ	below the limit of quantification
BMT	Blood and Marrow Transplant
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BTD	Breakthrough Designation
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
cGVHD	chronic GVHD
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CL	clearance
C _{max}	maximum concentration
CMC	chemistry, manufacturing, and controls
C _{min}	minimum concentration
CMV	Cytomegalovirus
CNI	calcineurin inhibitor
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CO	Clinical overview
CPH	Cox proportional hazards
CR	complete response (CR)
CRF	case report form
CRF	Comprehensive Report Form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTEP	Cancer Therapy Evaluation Program
CTLA4	cytotoxic T cell-associated antigen 4
CV	coefficient of variation
DFS	Disease-free Survival

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

DMARD	disease modifying anti-rheumatic drug
DMC	data monitoring committee
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCTD	electronic common technical document
E-R	Exposure-Response
ETASU	elements to assure safe use
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GFS	GVHD free survival
GI	gastrointestinal
GLP	good laboratory practice
GRMP	good review management practice
aGVHD	acute graft versus-host disease
HLA	human leukocyte antigen
HM	hematological malignancies
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
ICH	International Conference on Harmonization
IgG1	immunoglobulin G1
IND	Investigational New Drug
IPD	Important Protocol Deviations
IPTW	inverse probability of treatment weighting
ISE	integrated summary of effectiveness
ISR	investigator-sponsored research/trial
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
JIA	juvenile idiopathic arthritis
LLOQ	lower limit of quantification
K-M	Kaplan-Meier
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent to treat
MMUD	mismatched unrelated donor
MUD	matched unrelated donor
MTX	methotrexate
NAbs	neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
ODD	Orphan Drug Designation

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PBSC	peripheral blood stem cell
PCR	polymerase chain reaction (
PD	pharmacodynamics
PI	prescribing information
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PPK	population PK
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PsA	psoriatic arthritis
PSUR	Periodic Safety Update report
PT-Cy	post-transplant cyclophosphamide
PTLD	Post-transplant lymphoproliferative disorders
RA	rheumatoid arthritis
REMS	risk evaluation and mitigation strategy
RFS	relapse-free survival
RPD	Relevant Protocol Deviations
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TED	Transplant Essential Data
TRM	transplant-related mortality
URD	unrelated donor
USPI	US Prescribing Information
VC	central volume of distribution
VP	peripheral volume of distribution

1 Executive Summary

1.1. Product Introduction

Trade Name:	Orencia®
Established Name:	Abatacept
Also Known As:	CTLA-4Ig
Therapeutic Class:	Disease modifying anti-rheumatic drug (DMARD), T-cell costimulation modulator
Chemical Class:	Biologic
Pharmacologic Class:	Fusion protein
Mechanism of Action:	Inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28

Abatacept is an intravenously administered T-cell costimulation modulator that was initially approved for the treatment of rheumatoid arthritis in 2005, followed by approvals for juvenile idiopathic arthritis in 2009, and psoriatic arthritis in 2017. The Applicant now submits a supplementary Biologics License Application (sBLA) to support regular approval for prophylaxis of acute graft versus host disease (aGVHD) in patients undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor based on results of the randomized, Phase 2 Study IM101311 and the registry Study IM101841.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval for abatacept “for the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age or older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.” The recommendation is based on compelling evidence of benefit on several secondary endpoints in Study IM101311, including overall survival (OS) and Grade II-IV aGVHD Free Survival (GFS) assessed at Day 180 post-HSCT (despite the lack of a statistically significant benefit in Grade III-IV GFS at Day 180) and findings of improved OS at Day 180 in Study IM101841.

Abatacept was evaluated as aGVHD prophylaxis in subjects 6 years of age and older undergoing HSCT from unrelated donors (URDs) in the investigator-initiated Phase 2 study IM101311 and the clinical registry study IM101841.

Study IM101311 was a multicenter Phase 2 trial with two cohorts: 1) a randomized (1:1), double-blind, placebo-controlled cohort that compared abatacept + calcineurin inhibitor (CNI) + methotrexate (MTX) (n=73) with placebo + CNI + MTX (n=69) in subjects undergoing HSCT from

ORENCIA (abatacept)

an 8/8 human leukocyte antigen (HLA) matched unrelated donor (MUD) and 2) a single-arm cohort that evaluated abatacept + CNI + MTX subjects undergoing HSCT from a 7/8 mismatched unrelated donor (MMUD) (n=43). On the randomized, 8/8 cohort, randomization was stratified by baseline age category (≤ 21 years vs > 21 years). Demographic and disease characteristics of randomized patients had some notable imbalances, as follows (listed as abatacept versus placebo): age ≥ 65 years 10% versus 17%, age ≥ 18 to < 65 years 71% versus 64%, median weight 71.3 versus 76.7 kg, acute myeloid leukemia [AML] 41% versus 32%, CMML 1% versus 6%, CML 1% versus 7%, bone marrow graft 45% versus 38%, peripheral blood graft 55% versus 62%, Bu Cy conditioning 38% versus 30%, Bu Flu 10% versus 3%, and TBI + chemotherapy 27% versus 38%.

The final analysis of the 8/8 cohort of Study IM101311 included a prespecified assessment of Grade III-IV GFS, measured from the date of transplantation to the onset date of documented Grade III-IV aGVHD or death due to any cause up to day 180 post-transplantation, whichever occurred first. Patients randomized to abatacept + CNI + MTX had non-significantly higher Grade III-IV GFS at Day 180 post-transplantation compared to placebo + CNI + MTX (HR 0.55; 95% CI: 0.26-1.18; p-value = 0.12). The similar key secondary endpoint of Grade III-IV GFS cumulative incidence rate at day 180 post-transplantation showed a similar non-significant trend towards benefit on the abatacept + CNI + MTX arm (HR 0.41; 95% CI: 0.14-1.17).

The 8/8 cohort of Study IM101311 included other secondary endpoints of Grade II-IV GFS at day 180 and OS at day 180. Grade II-IV GFS at day 180 in patients randomized to abatacept + CNI + MTX was greater than in patients randomized to placebo + CNI + MTX (HR 0.54; 95% CI: 0.35-0.83). OS to day 180 was also greater in patients randomized to abatacept + CNI + MTX compared to the control arm (HR 0.33; 95% CI: 0.12-0.93). Due to failure of the primary endpoint to meet statistical significance, significant improvement in the secondary endpoints of Grade II-IV GFS or OS could not be declared for abatacept + CNI + MTX. However, these results demonstrate compelling evidence of efficacy for the abatacept + CNI + MTX combination and will be included descriptively in labeling.

The numerical improvement in Grade II-IV GFS to day 180 was consistent across various disease and transplantation subsets (e.g., acute lymphocytic leukemia [ALL] HR 0.67, AML HR 0.84, myelodysplastic syndrome [MDS] HR 0.44; early disease HR 0.81, intermediate disease HR 0.45, advanced disease HR 0.18; bone marrow source HR 0.60, peripheral blood stem cell [PBSC] HR 0.58; TBI + chemotherapy HR 0.82, Bu Cy HR 0.50, Mel Flu 0.48).

Furthermore, the numerical improvement in OS to day 180 was consistent across disease and transplantation subsets (e.g., ALL HR 0.68, AML HR 0.35, MDS HR 0.24; early disease HR 0.58, intermediate disease HR 0.27, advanced disease HR 0.21; bone marrow source HR 0.14, PBSC HR 0.50, TBI + chemotherapy not applicable [no deaths abatacept arm], Bu Cy HR 0.18, Mel Flu 0.74).

Efficacy of abatacept in combination with CNI + MTX was supported by results in the higher-risk 7/8 single-arm cohort of IM101311. While this second cohort was originally designed as a randomized comparison, the control arm was swiftly closed due to a perceived lack of clinical equipoise (only one patient was randomized to placebo). Of the 43 patients enrolled and treated with abatacept + CNI + MTX, Grade III-IV GFS to Day 180 was 95% (95% CI 83-99%), Grade III-IV GFS cumulative incidence rate was 2% (95% CI <1-11%), Grade II-IV GFS to Day 180 was 53% (95% CI 38-67%), and OS was 98% (95% CI 85-100%).

Given the inability to perform a randomized comparison to a placebo control arm in the 7/8 MMUD population, the Applicant conducted Study IM101841, a clinical study using data routinely collected in the Center for International Blood and Marrow Transplant Research (CIBMTR). Eligible patients ages 6 years and older who underwent 7/8 MMUD HSCT treated with CNI + MTX with or without abatacept between 2011 and 2018 were selected from the CIBMTR database. There were 54 patients in the abatacept-treated group, including 42 patients from the 7/8 cohort of Study IM101311. The comparator group (n=162) was randomly selected in a 3:1 ratio to the abatacept-treated group from the CIBMTR registry from patients who had not received abatacept during the study period.

Analyses on Study IM101841 used propensity score matching and inverse probability of treatment weighting (IPTW) to minimize the impact of selection bias in the 2 treatment groups. Nonetheless, the demographic and disease characteristics had notable imbalances, including (abatacept versus comparator; refer to Table 27 and Table 29 for full information): white race 72% versus 83%, black or African American 20% versus 4%; early disease 72% versus 54%, advanced disease 6% versus 22%; HLA matching 9/10 80% versus 95%, HLA matching 8/10 16% versus 3%; year of transplant 2011-2013 2% versus 17%, 2014-2018 98% versus 83%; time from diagnosis to transplant < 6 months 29% versus 40%; HCT-CI 0 19% versus 31%, HCT-CI 1-2 33% versus 21%; mild hepatic comorbidity 43% versus 13%, severe pulmonary comorbidity 5% versus 18%; participation in IM101311 82% versus 0%; and participation in any clinical trial 82% versus 13%.

The primary efficacy analysis of Study IM101841 included a prespecified assessment of OS at 180 days post-transplantation of abatacept + CNI + MTX without anti-thymocyte globulin (ATG) compared to CNI + MTX without ATG. The OS rate at Day 180 in patients treated with abatacept + CNI + MTX without ATG was 98% (95% CI: 78-100%) and the OS rate at Day 180 in patients treated with CNI + MTX without ATG was 75% (95% CI: 67-82%) (HR 0.07; 95% CI: 0.01 – 0.30; p-value = 0.0028). (b) (4)

the point estimates and 95% CIs are appropriate to display descriptively in labeling to demonstrate compelling confirmatory evidence of efficacy for the abatacept + CNI + MTX combination.

1.3. **Benefit-Risk Assessment (BRA)**

Benefit-Risk Summary and Assessment

Abatacept is an intravenously administered T-cell costimulation modulator that was initially approved for the treatment of rheumatoid arthritis, followed by approvals for juvenile idiopathic arthritis and psoriatic arthritis. This supplemental NDA serves to support regular approval for prophylaxis of aGVHD in patients undergoing HSCT from a matched or 1 allele-mismatched unrelated donor.

Acute GVHD occurs in recipients of allogeneic HSCT when reconstituting donor T cells become activated against recipient tissues. Transplant recipients at particularly high risk of aGVHD include those receiving HSCT from URDs with whom they are matched at only 7/8 HLA loci (i.e., “7/8 mismatched” unrelated donor [MMUD] transplants). Existing standard of care therapies for the prophylaxis of aGVHD in patients undergoing HSCT from a matched or 1 allele-mismatched URD are associated with high rates of aGVHD. Thus, this patient population has a significant unmet medical need.

The recommendation for regular approval is based on the efficacy results from a randomized controlled trial evaluating abatacept in combination with a CNI and MTX in patients undergoing HSCT from an 8/8 MUD and a clinical study using data from the CIBMTR evaluating abatacept in combination with a CNI and MTX in patients undergoing HSCT from a MMUD. Study IM101311 was a multicenter Phase 2 trial including 1) a randomized (1:1), double-blind, placebo-controlled cohort that compared abatacept + CNI + MTX (n=73) with placebo + CNI + MTX (n=69) in subjects undergoing HSCT from an 8/8 MUD and 2) a single-arm cohort that evaluated abatacept + CNI + MTX subjects undergoing HSCT from a 7/8 MMUD (n=43). Randomization in the 8/8 cohort was stratified by baseline age category. Patients randomized to abatacept + CNI + MTX had non-significantly higher Grade III-IV GFS at Day 180 post-transplantation (87%; 95% CI, 77% to 93%) compared to placebo + CNI + MTX (75%; 95% CI 63% to 84%) (HR 0.55; 95% CI: 0.26-1.18; p-value = 0.12). Supportive secondary endpoints included improvements in Grade II-IV GFS and OS. Grade II-IV GFS was 50% (95% CI, 38% to 61%) on the abatacept + CNI + MTX arm and 32% (95% CI, 21% to 43%) on the placebo + CNI + MTX arm (HR 0.54; 95% CI, 0.35 to 0.83); OS was 97% (95% CI, 89% to 99%) versus 84% (95% CI, 73% to 91%) (HR 0.33; 95% CI, 0.12 to 0.93), respectively.

Efficacy of abatacept in combination with CNI + MTX was supported by exploratory results in the 7/8 single-arm cohort of IM101311. Rates of Grade III-IV GFS, Grade II-IV GFS, and OS at Day 180 post-transplantation were 95% (95% CI, 83% to 99%), 53% (95% CI, 38% to 67%), and 98%

(95% CI 85% to 100%), respectively.

Study IM101841 was a clinical registry study using data routinely collected in the CIBMTR, including patients ages 6 years and older who underwent 7/8 MMUD HSCT treated with CNI + MTX with (n=162) abatacept. Patients treated with abatacept in combination with CNI and MTX had significantly longer survival compared to those treated with CNI and MTX alone (HR 0.07; 95% CI: 0.01 – 0.30; p-value = 0.0028).

Safety of abatacept in combination with a CNI and MTX was demonstrated on IM101311, as well as on the Study IM101841. Common adverse reactions (≥ 10%) for the combination of abatacept, CNI, and MTX from Study IM101311 were anemia, hypertension, CMV reactivation/CMV infection, pyrexia, pneumonia, epistaxis, CD4 lymphocytes decreased, hypermagnesemia, and acute kidney injury. Frequent serious adverse reactions (≥ 5%) included pyrexia, pneumonia, acute kidney injury, diarrhea, hypoxia, and nausea. Events were managed by supportive care and anti-infectives as indicated. Post-transplant lymphoproliferative disorder was infrequent and can be mitigated by the prophylaxis and monitoring for EBV reactivation stipulated in labeling.

In conclusion, the endpoints used to assess efficacy in the presented studies were Grade II-IV GFS and OS at Day 180 post-transplantation. Grade II-IV GFS at Day 180 was 50% (95% CI, 38% to 61%) on the abatacept + CNI + MTX 8/8 arm of Study IM101311 compared to 32% (95% CI, 21% to 43%) on the placebo + CNI + MTX arm with HR 0.54 (95% CI, 0.35 to 0.83). OS at Day 180 post-transplantation was 97% (95% CI, 89% to 99%) versus 84% (95% CI, 73% to 91%), respectively, with HR 0.33 (95% CI, 0.12 to 0.93). Failure to achieve statistical significance on the primary endpoint of Grade III-IV GFS at Day 180 (87% vs 75%; HR 0.55 [95% CI, 0.26 to 1.18]; p=0.12) was thought to be a consequence of an underpowered study design. Grade II-IV GFS and OS at Day 180 post-transplantation were similar at 53% and 98%, respectively, on the single arm 7/8 cohort of Study IM101311. On Study IM101841, OS at Day 180 post-transplantation was 98% (95% CI, 78 to 100%) in patients undergoing 7/8 MMUD HSCT treated with abatacept + CNI + MTX compared to 75% (95% CI, 67 to 82%) in patients treated with CNI + MTX alone. The totality of the results, including compelling evidence of benefit on several secondary endpoints on Study IM101311 (Grade II-IV GFS and OS at Day 180) and the OS benefit on IM101841 support effectiveness of abatacept + CNI + MTX in adults and pediatric patients undergoing HSCT from a matched or 1 allele-mismatched unrelated donor.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• aGVHD is a fatal disease. • The incidence of aGVHD is increased in patients who undergo HSCT from an unrelated donor.	aGVHD is a fatal disease with an increased incidence in patients undergoing HSCT from an URD.
Current Treatment Options	• Patients undergoing HSCT from an unrelated donor may use standard of care aGVHD prophylaxis regimens with reported rates of Grade II-IV aGVHD at 100 days post-transplantation of 32-53% and Grade II-IV aGVHD at 100 days post-transplantation of 13-21%. OS at 6 months post-transplantation with such regimens ranges from 66-78%. • No therapies are approved for the prophylaxis of aGVHD in patients undergoing HSCT from an unrelated donor.	There is a need for effective therapies to prevent the occurrence of aGVHD in patients undergoing HSCT from an unrelated donor.
Benefit	• In Study IM101311, a randomized (1:1), controlled trial, 73 patients age ≥ 6 years undergoing HSCT from an 8/8 MUD received abatacept in combination with a CNI and MTX and 69 received placebo in combination with a CNI and MTX. The rate of Grade III-IV GFS at day 180 post-HSCT was non-significantly longer with abatacept + CNI + MTX versus placebo + CNI + MTX (HR 0.55; 95% CI: 0.26 – 1.18; p-value = 0.12). On the abatacept + CNI + MTX versus placebo + CNI + MTX arms, rates of Grade II-IV GFS at day 180 post-HSCT were 50% versus 32% with OS at day 180 post-HSCT 97% versus 84%, respectively. • In Study IM101841, a clinical study using CIBMTR registry data, 54 patients age ≥ 6 years who underwent HSCT from a 7/8 MMUD received abatacept + CNI + MTX and 162 received a CNI and MTX alone. The rate of OS at day 180 post-HSCT was significantly longer with abatacept + CNI + MTX versus CNI + MTX alone at 98% (95% CI,	The endpoints of Grade II-IV GFS and OS support effectiveness in patients undergoing HSCT from a matched or 1-allele mismatched unrelated donor. The addition of abatacept to a CNI and MTX shows a non-significant trend towards improvement in Grade III-IV GFS, and clinically meaningful improvements in Grade II-IV GFS and OS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	78 to 100% versus 75% (95% CI, 67 to 82%), respectively.	
<u>Risk and Risk Management</u>	- Common adverse reactions (≥ 10%) for abatacept + CNI + MTX were anemia, hypertension, CMV reactivation/CMV infection, pyrexia, pneumonia, epistaxis, CD4 lymphocytes decreased, hypermagnesemia, and acute kidney injury. - Frequent serious adverse reactions (> 5%) for abatacept + CNI + MTX included pyrexia, pneumonia, acute kidney injury, diarrhea, hypoxia, and nausea. - PTLD associated with EBV infection was an infrequent event.	Adverse reactions can be managed with anti-infectives and transfusions. CMV reactivation/CMV infection and EBV reactivation/PTLD can be mitigated by prophylaxis and monitoring. Risks of abatacept in combination with CNI and MTX can be sufficiently addressed through warnings and precautions in the United States Prescribing Information.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
☐	☐ Patient reported outcome (PRO)	
☐	☐ Observer reported outcome (ObsRO)	
☒	☒ Clinician reported outcome (ClinRO)	Section 8.1.1 Study endpoints (documented GVHD as component of GFS endpoints)

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

☐	☐	Performance outcome (PerfO)	
☐	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
☐	☐	Observational survey studies designed to capture patient experience data	
☐	☐	Natural history studies	
☐	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	☐	Other: (Please specify)	
☐	☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective treatment for aggressive leukemias and other hematological malignancies (HM), 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 acute graft versus-host disease (aGVHD) and infection.^{1,2,3,4,5,6,7} Acute GVHD occurs when reconstituting donor T cells⁸ become activated against recipient tissues.⁹ This activation can result in severe immune-mediated tissue damage to the host, with the skin, liver and gastrointestinal (GI) tract being the most common targets. Acute GVHD-mediated damage to these vital organs has been associated with increased morbidity and death.

GVHD is the leading cause (20%) of nonrelapse mortality in HSCT recipients.^{10,11,12,13} While T cell depletion of the allograft can successfully reduce rates of aGVHD, patients receiving T cell depleted- grafts exhibit profound defects in protective immunity, and often die of infection or relapse of their primary disease.^{14,15,16} This has created an unmet clinical need for a more effective strategy that prevents severe aGVHD while preserving the transplant recipient's protective immune response. Transplant recipients at particularly high risk of aGVHD include those receiving HSCT from URDs with whom they are matched at only 7 of 8 human leukocyte antigen (HLA) loci ("7/8 mismatched" unrelated donor [MMUD] transplants), with the incidence rate of severe (Grade [Gr] III-IV) aGVHD in this population being as high as 40% after HSCT,¹⁷ and transplant associated mortality as high as 45%.³

FDA Assessment

We agree with the Applicant's assessment that aGVHD is a serious complication of potentially curable HSCT. Indeed, the entire infrastructure for unrelated donor matching is due to the need to minimize the risk of aGVHD after transplant. While it is usually possible to find an unrelated donor match for Caucasian patients, finding a match for patients from minority racial or mixed racial backgrounds is challenging due to the unrelated donor registry being heavily skewed to Caucasian donors and due to the increased HLA loci diversity present in certain racial backgrounds, particularly in African Americans. Therefore, drug therapies that improve upon existing aGVHD prophylaxis, especially those that are effective for mismatch unrelated donors are desperately needed to increase the pool of potential donors for this potentially curative therapy.

We would also note that the Applicant correctly points out the three-way balance that is hard to thread with aGVHD preventative therapies. That is that profound untargeted immunosuppression results in lower rates of aGVHD but greatly increases the risk of morbidity and mortality from infections after transplant. Moreover, profound immunosuppression can also inhibit the graft-versus-leukemia effects and lead to higher rates of disease relapse. Therefore, the ideal therapy would block the aGVHD while generally leaving the immune system intact to fight infections and any residual leukemia stem cells.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

There are currently no approved therapies for the prevention of aGVHD. Current transplant

ORENCIA (abatacept)

management focuses on aGVHD prophylaxis, either via suppression of donor T-cell function with immunomodulatory agents or depleting T cells from the donor graft.¹⁸ Allogeneic HSCT recipients frequently develop aGVHD despite treatment with a standard of care prophylactic regimen consisting of a calcineurin inhibitor (CNI)+methotrexate (MTX).¹⁹ While the use of post-transplant cyclophosphamide (PT-Cy)-based GVHD prophylaxis is growing, CNI+MTX based regimens remain the standard to which new strategies are compared, with ongoing studies actively comparing multiple new strategies (including PT-Cy) to CNI+MTX (**Table 1**).

APPEARS THIS WAY ON ORIGINAL



Table 1: Summary of Available GVHD Prophylaxis Regimens

Regimens	Efficacy outcomes (aGVHD): [RR (95% CI) or event rates, % (95% CI)]	Safety outcomes: RR (95% CI) or event rates, % (95% CI)
MTX + CsA vs. CsA alone ²⁰	RR (95% CI): 0.52 (0.39-0.7)	All-cause mortality: 0.84 (0.61, 1.14)
MTX + TAC vs. MTX + CsA ²⁰	RR (95% CI): 0.62 (0.52, 0.75)	All-cause mortality: 1.10 (0.93-1.30) (Ram et al., 2009) Acute renal failure: 1.20 (0.093, 1.39) for MTX+TAC vs. MTX+CsA
MTX + CsA vs. MMF+ CsA vs. MTX + TAC vs. MMF + TAC ²¹	Gr II-IV aGVHD* Gr III-IV aGVHD* % (95% CI)% (95% CI) 32 (22-44)15 (8-25) 53 (45-61)21 (15-28) 37 (32-41)13 (10-17) 47 (41-54) 21 (16-27) * Unrelated donor transplants, Day 100	2-year overall survival* 2-year Non-relapse mortality* % (95% CI)% (95% CI) 40 (28-52)30 (19-42) 45 (37-53)31 (24-39) 47 (42-51)23 (19-27) 41 (35-48)36 (29-42) * Unrelated donor transplants
CsA + MTX + ATG vs. CsA + MTX + PTCy ²²	- 2-yr Gr II-IV: 46% vs. 67%, p=0.008 - 2 yr Gr III-IV: 3% vs. 34%, p=0.003 -Delayed platelet engraftment with PTCy vs. ATG -Similar neutrophil engraftment	- Estimated overall survival at 2 yrs: 58% vs. 60%, p=0.475); -Non-relapse mortality: 24% vs. 22% -Hemorrhagic cystitis: 20% vs. 12.5%, p=0.497 - CMV reactivation: 40% vs. 51%, p=0.191 - EBV reactivation: 5% vs. 0%, p=0.05; - Bacterial or fungal infection: 19 vs. 33%

FDA Assessment:

We agree with the Applicant’s summary of currently used aGVHD prevention strategies. We also note, as the Applicant also pointed out, that no drug regimen is currently FDA approved for this indication. Regimens fall into the issue discussed above, the higher the risk of aGVHD, the more potentially the immune system must be inhibited but at a cost of increased risk of infections and higher rates of primary disease relapse. This has generally limited the use of donors that have not been well matched to patients.

Of note, from reference 21 in the third row of **Table 1** above, the various aGVHD prophylaxis strategies were associated with OS rates at 6 months post-transplantation of 66-78%. This study used data from the CIBMTR including patients with hematologic malignancies who underwent a first reduced intensity allogeneic HSCT between 2000 and 2013.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Abatacept was first approved by the United States (US) Food and Drug Administration (FDA) on 23-Dec-2005 for the treatment of rheumatoid arthritis (RA) in the adult population. Intravenous (IV) abatacept is approved for the treatment of moderate to severe adult RA and psoriatic arthritis (PsA) in the US, the European Union (EU), Japan, Latin America, and other countries. A subcutaneous (SC) formulation of abatacept in a prefilled syringe and autoinjector has been approved for treatment of adult RA and PsA patients in the US, EU, and several other countries. IV abatacept is also approved for juvenile idiopathic arthritis (JIA) in patients aged 6 and above in the US, EU, and other countries; SC abatacept is approved for JIA in patients aged 2 and above in the US and EU.

FDA Assessment:

The FDA agrees with the Applicant's assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Regulatory milestones in **Table 2** refer to (p)IND 135013.

Table 2: Key Regulatory Milestones and Communications

Date	Purpose
25-Jul-2017	Face-to-Face Type B, Pre-IND Meeting: The Sponsor met with the Agency to discuss potential pathways for submission of aGVHD prevention indication with abatacept, based on preliminary results from an ISR, IM101311. The FDA provided feedback on a necessary safety database, the appropriate endpoint for an indication of prevention of GVHD, use of historic controls and the request for potential Breakthrough Designation (BTD)
26-Dec-2017	Granted Orphan Drug Designation (ODD) ODD# DRU-2017-6141
02-Mar-2018	Type C Written Response: Key Items communicated: 1. Lab data to be collected in the IM101311 study. 2. Safety data collection plan 3. Statistical analysis plan (SAP).
28-Jun-2018	Type C Written Response: Key Items communicated: 1. More details and clarifications on Lab data. 2. More details and clarifications on safety data. 3. More details and clarifications on SAP.
17-Jun-2019	Type C meeting: Key Discussion Items: 1. Potential registrational pathway for prevention of severe aGVHD in MMUD HSCT, based on IM101311 study results. 2. BTD for abatacept in GVHD prevention. In a post meeting note, the FDA suggested a prospective-retrospectively designed study of registry data comparing OS with 180 days of follow-up for patients who received prophylactic abatacept to a control group of patients who received standard of care prophylaxis in the aGVHD setting (this became IM101841).
17-Oct-2019	Breakthrough Therapy Designation granted for abatacept for the prevention of moderate to severe aGVHD after URD HSCT.

Table 2: Key Regulatory Milestones and Communications

Date	Purpose
13-Jan-2020	Type B meeting: Key Discussion Items: Design elements of the proposed registry study, IM101841 1. The primary endpoint of the IM101841 should be OS with 180 days of follow-up in the 7/8 cohort. 2. FDA provided detailed input on secondary endpoints, statistical methods, and Study Data Standardization Plan. 3. Confirmation that there is no established pathway for accelerated approval for aGVHD prophylaxis
10-Mar-2020	Submitted the original protocol and SAP for IND-opening study IM101841
09-Apr-2020	FDA Study May Proceed letter for IM101841 provided detailed comments on the study design and SAP.
01-Oct-2020	BMS incorporated all of FDA's comments in the protocol and SAP for IM101841 letter of 09-Apr-2020.
12-Apr-2021	Topline Results from IM101311 and IM101841 shared with FDA/Informed the FDA that the efficacy supplement (sBLA) will be submitted by June 2021. FDA recommended the abatacept for aGVHD prophylaxis application for Project Orbis.

FDA Assessment:

The FDA agrees with the Applicant's assessment.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections for Study IM101311 at clinical sites in Atlanta, GA (Emory University – Winship Cancer Institute) and Seattle, WA (Seattle Children’s Hospital). These sites had the highest accrual. Inspection review of both sites revealed no objectionable conditions, and no Form FDA-483, Inspectional Observations, were issued. The Sponsor-Investigator, Dr. Leslie Kean from Boston Children’s Hospital, was also inspected and no objectionable conditions were noted. Based on these inspection results, the study data derived from the inspected clinical sites were considered reliable in support of the requested indication.

4.2. Product Quality

No changes to the abatacept drug substance or drug product were submitted with this application.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable. No devices or companion diagnostics are needed for this indication.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission

6 Clinical Pharmacology

6.1. Executive Summary

FDA Assessment:

Abatacept is a selective T-cell co-stimulation modulator proposed in combination with a calcineurin inhibitor and methotrexate for prophylaxis of moderate to severe acute graft versus host disease (aGVHD) in patients 2 years of age and older receiving hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor (URD) due to hematologic malignancies (HM). The proposed dosing regimen for patients 6 years of age and older is 10 mg/kg per dose (maximum dose 1000 mg) as a 60-minute IV infusion on the day before transplantation, followed by a 10 mg/kg (maximum dose 1000 mg) dose on Days 5, 14, and 28 after transplant. The proposed dosing regimen for patients 2 to <6 years of age is 15 mg/kg per dose as a 60-minute IV infusion on the day before transplantation, followed by a 12 mg/kg dose on Days 5, 14, and 28 after transplant.

The evidence of efficacy and safety at the proposed dosing regimen for adult and pediatric patients 6 years of age and older is supported by results of the Phase 2 randomized clinical trial (IM101311) and a supportive retrospective cohort study (IM101841). The proposed dosing regimen for pediatric patients aged 2 to <6 years is supported by extrapolation of efficacy from patients aged 6 years and older, exposure-matching based on population PK (PPK) analyses, and safety data in patients with polyarticular juvenile idiopathic arthritis (pJIA) aged 2 to <6 years of age who received subcutaneous (SC) abatacept. Extrapolation of efficacy is acceptable given that the course of aGVHD is similar in ages 2 to <6 years compared to ages 6 years and older. The PPK analyses support a dose regimen of 15 mg/kg on the day before transplantation followed by 12 mg/kg on Days 5, 14, and 28 after transplantation in patients aged 2 to <6 years which is expected to result in similar exposure compared to the 4-dose regimen of 10 mg/kg in patients aged 6 years and older. The proposed dosing regimens are acceptable from a clinical pharmacology perspective.

The Clinical Pharmacology section of this BLA supplement is supported by pharmacokinetics (PK) characterization, PPK and exposure-response (E-R) analyses, and immunogenicity assessment. The key review questions focused on the appropriateness of the 10 mg/kg proposed dosing regimen in patients aged 6 years and older, the appropriateness of the proposed dosing regimen of 15 mg/kg on the day before transplantation followed by 12 mg/kg on Days 5, 14, and 28 after transplantation in patients aged 2 to <6 years, and extrapolation of efficacy to pediatric patients aged 2 to <6 years.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in the submitted efficacy supplement and it is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

Review Issues	Recommendations and Comments
Evidence of effectiveness	A multicenter, Phase 2 trial IM101311 with 2 cohorts provided primary evidence:

Review Issues	Recommendations and Comments
	- A single arm cohort for patients receiving transplants from 7/8 HLA mismatched unrelated donors (MMUD) (“7/8” cohort). - A randomized, double blind, placebo-controlled cohort for patients receiving transplants from 8/8 HLA matched unrelated donors (MUD) (“8/8” cohort).
General Dosing instructions	For patients 6 years of age and older: The recommended dose of abatacept is 10 mg/kg dose (maximum dose 1000 mg) as a 60-minute IV infusion on the day before transplantation, followed by a dose on Day 5, 14, and 28 after transplant. For patients 2 to <6 years of age: The recommended dose of abatacept is 15 mg/kg as a 60-minute IV infusion on the day before transplantation, followed by a 12 mg/kg dose on Days 5, 14, and 28 after transplant.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Body weight is a clinically significant covariate on abatacept PK, i.e., increasing body weight was associated with higher clearance of abatacept. The effect of body weight has been accounted for with the body weight-based dosing regimen. Pediatric patients aged 2 to <6 years of age are expected to have higher abatacept clearance-per-kg compared to patients aged 6 years and older. Pediatric patients aged 2 to <6 years who receive 15 mg/kg IV on the day before transplant followed by 12 mg/kg on Days 5, 14, and 28 after transplant are expected to have similar exposure after first and last dose compared to patients aged 6 years and older who receive 10 mg/kg on the day before transplant followed by a dose on Days 5, 14, and 28 after transplant. No dose modification is needed for specific populations of sex or race. These factors were not found to be clinically significant covariates on abatacept PK.

From a Clinical Pharmacology perspective, there is a need for a post-marketing requirement (PMR) in order to assess the safety risk and verify the PK profile of abatacept in pediatric patients aged 2 to <6 years receiving HSCT from a matched or 1 allele-mismatched URD (refer to Section 13).

6.2. Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

Table 3: Summary of Primary and Derived PK Parameters for the Final PPK Model, Stratified by Disease Status and Study IM101311 Cohorts

Pharmacokinetic Parameter	RA (N = 386)	JIA (N = 184)	HM Cohort 7/8 (N = 42)	HM Cohort 8/8 (N = 73)	Overall (N = 685)
Clearance, Median [L/h]	0.02390	0.01834	0.01663	0.02204	0.02188

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Pharmacokinetic Parameter	RA (N = 386)	JIA (N = 184)	HM Cohort 7/8 (N = 42)	HM Cohort 8/8 (N = 73)	Overall (N = 685)
Min, Max	0.0091, 0.0593	0.0064, 0.0399	0.0070, 0.0406	0.0091, 0.0417	0.0064, 0.0593
Volume at Steady-state, Median [L]	8.807	5.407	9.834	11.655	8.242
Min, Max	4.32, 28.21	1.93, 11.49	2.55, 16.64	3.98, 19.60	1.93, 28.21
Half-life, Median [day]	14.259	10.947	21.129	20.102	14.099
Min, Max	4.49, 54.54	4.47, 21.69	5.66, 42.57	11.60, 38.11	4.47, 54.54

Abbreviations: Max: maximum; Min: minimum; N: number of subjects; SD: standard deviation

Source: 002586\d2pk\tables\rtf\sumstat-pkparam-bydiscoh.rtf

APPEARS THIS WAY ON ORIGINAL

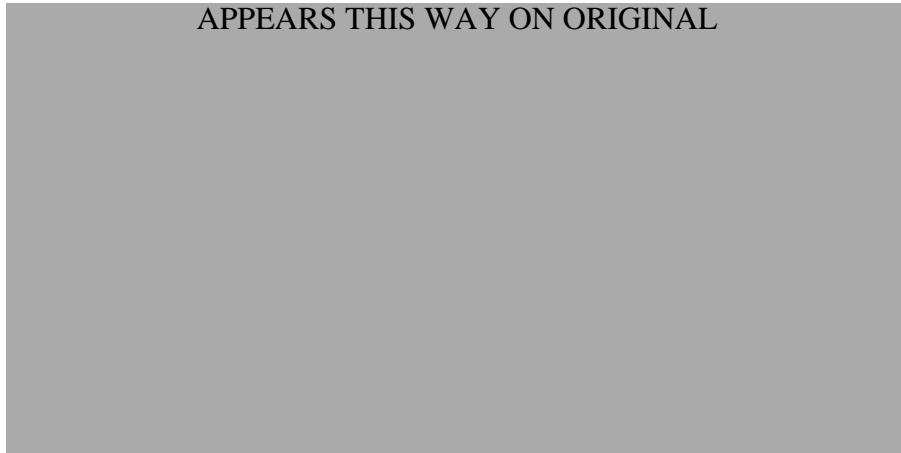
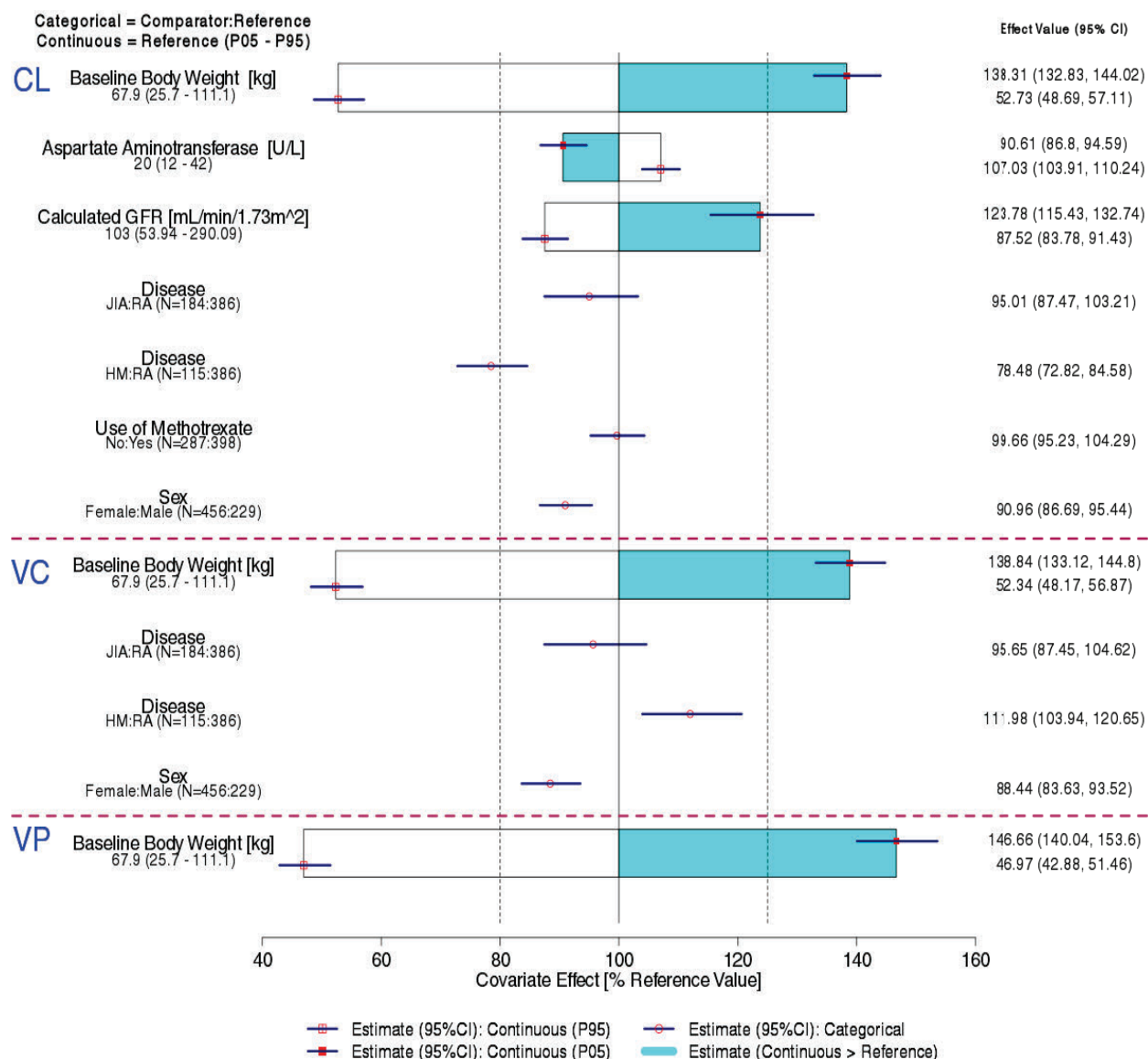


Figure 1: Clinical Relevance of Covariate Effects in Full PPK Model



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 m². 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.

Source: 002586\d2pk\graphs\pnglo\coveff-full-r231157.png

The Applicant's Position:

Pharmacology

Abatacept, a fusion protein consisting of the extracellular domain of cytotoxic T cell-associated antigen 4 (CTLA4) fused to a modified Fc fragment of immunoglobulin G1 (IgG1), is a selective costimulation modulator that inhibits full T cell activation. Abatacept binds to CD80 and CD86 on antigen presenting cells, thereby blocking the interaction with CD28 on T cells that provides a costimulatory signal necessary for full activation of T cells.²³

Clinical Pharmacokinetics

A previously developed population PK (PPK) model using data collected in subjects with RA and subjects with JIA served as the base model, which was re-estimated using the pooled set of GVHD, JIA, and RA data. Overall, the findings of the PPK analysis were consistent with those reported in previous population analyses of abatacept PK in datasets that did not include subjects undergoing URD HSCT due to HM. Although, on average, all exposures in subjects in the 8/8 MUD cohort were approximately 20% lower than in subjects in the 7/8 MMUD cohort, improved survival benefit was demonstrated in both 8/8 MUD and 7/8 MMUD cohorts. In the 8/8 MUD and 7/8 MMUD cohorts, mean Cmin levels achieved or maintained levels of 10 µg/mL or greater during the treatment period and beyond Day 28 up to Day 100 in the PK evaluable population. Steady state exposure of abatacept achieved by Day 63. Steady state Cmin concentrations were 22.5 µg/mL (0.0 to 90.0 µg/mL) and 31.1 µg/mL (0.8 to 75.5 µg/mL) for matched URD and mismatched URD respectively (Table S.8.1 [ADaM Dataset: ADPC] in the IM101311 primary CSR).

In particular, the linear 2-compartment model structure with zero-order IV infusion and first-order elimination used in previous models was able to describe the PK of abatacept in the 3 different sub-populations of subjects (RA, JIA, and HM) (Table 3 and Figure 1). Body weight was a statistically significant covariate with a clinically relevant impact on abatacept exposures.

FDA Assessment:

The FDA generally agrees with the Applicant's characterization of abatacept PK in adult and pediatric patients 6 years of age and older with one exception: the observed PK data does not support the statement that average Cmin levels are ≥10 ug/mL up to Day 100 in both the 8/8 MUD and 7/8 MMUD cohorts.

Observed Cmin levels are summarized for Cohort 7/8 and Cohort 8/8 in **Table 4**. In the 7/8 MMUD cohort, the geometric mean Cmin on Day 100 was 6.4 ug/mL (CV = 769.7%). In the 8/8 MUD cohort, the geometric mean Cmin level on Day 100 was 7.6 ug/mL (CV = 78.3%).

Geometric mean Cmin levels are ≥10 ug/mL up to Day 63 in both the 8/8 MUD and 7/8 MMUD cohorts. The geometric mean (CV%) abatacept concentration was 31.1 ug/mL (114.4%) in the 7/8 cohort and 22.5 ug/mL (243.9%) in the 8/8 cohort on Day 63 after transplant.

Table 4. Observed Abatacept Concentrations in Study IM101311 Cohort 7/8 and Cohort 8/8

	Day 5*	Day 14*	Day 28*	Day 35	Day 42	Day 63	Day 100	
Cohort 7/8	N	18	40	38	33	34	37	
	Median (ug/mL)	54.9	58.6	63.9	111	77.3	38	12.4
	Mean (ug/mL)	59.2	60.2	67.6	114.1	85.9	38.8	13
	Geometric mean (ug/mL) (CV%)	55.5 (38.6%)	57.5 (31.5%)	63.5 (40.6%)	109.2 (32.4%)	77.3 (49%)	31.1 (114.4%)	6.4 (769.7%)
	Geometric mean 95% CI (ug/mL)	46.1 - 66.8	52.1 - 63.5	55.8 - 72.2	97.6 - 122.1	65.7 - 90.9	22.7 - 42.6	3.3 - 12.6
	Range (ug/mL)	26 - 112	27.1 - 109	14.1 - 103	46.3 - 171	20.9 - 304	0.78 - 75.5	0.0046 - 30.9
	Cohort 8/8	N	32	68	68	63	62	64
Median (ug/mL)		43	42.2	47.7	82.1	58.3	25.8	8
Mean (ug/mL)		43.4	45	51.4	86.8	61.8	28.9	9.3
Geometric mean (ug/mL) (CV%)		41.9 (27.4%)	42.5 (34.2%)	46.9 (44.1%)	82.7 (32.4%)	57.6 (39.2%)	22.5 (243.9%)	7.6 (78.3%)
Geometric mean 95% CI (ug/mL)		38 - 46.1	39.2 - 46	42.4 - 51.9	76.3 - 89.5	52.3 - 63.4	16.1 - 31.4	6.4 - 9
Range (ug/mL)		25 - 72.6	20.7 - 122	12.7 - 214	41.1 - 160	27.7 - 141	BLQ - 90	0.57 - 30.6

*Predose concentration.

Patients received 10 mg/kg (maximum dose of 1000mg) via IV infusion over 1 hour on the day before transplant and then on Day 5, Day 14, and Day 28 after transplant. Abatacept LLOQ= 0.001 ug/mL.

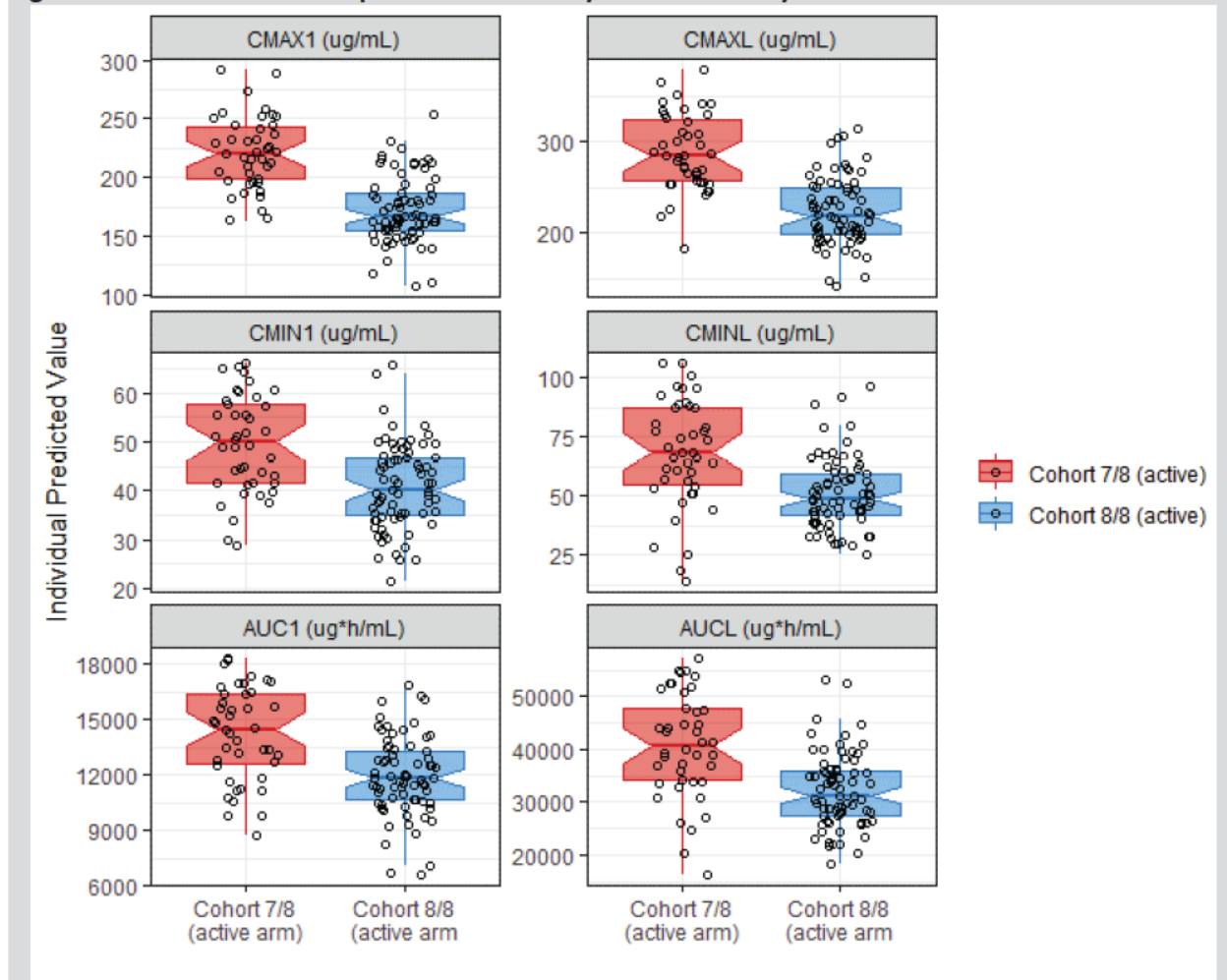
BLQ = below the limit of quantification; CI = confidence interval; CV = coefficient of variation; LLOQ= lower limit of quantification.

Source: Reviewer analysis of Applicant's Study IM101311 PK Concentration Dataset ('adpc.xpt')

The Applicant's final PPK model was adequate for the purpose of predicting abatacept concentration in patients with RA, pJIA, or HM. The model has a tendency to underpredict abatacept concentrations above 300 ug/mL (Appendix 19.4.1-1.2.3) and therefore individual trough concentration may be more accurately predicted as compared to exposure parameters calculated from higher concentrations, such as Cmax.

The PPK analysis identified several patient covariates that were associated with abatacept PK and exposure, as shown in Figure 1 above. Increased individual predicted abatacept clearance (CL) was associated with increased body weight, male sex, lower aspartate aminotransferase (AST), higher estimated glomerular filtration rate (eGFR), RA or pJIA disease status (versus HM), and Cohort 8/8 (versus Cohort 7/8). Increased individual predicted central volume of distribution (Vc) was associated with increased weight, male sex, and HM patients in Cohort 8/8 (versus RA patients, pJIA patients, and HM patients in Cohort 7/8). The effects of body weight, HM cohort, and eGFR were predicted to have significant impact on PK parameters. Median Cmax and Cmin for the first dose in Cohort 7/8 were predicted to be 32.5% higher and 23.1% higher, respectively, compared to Cohort 8/8. Exposure parameters for both cohorts are presented in Figure 2.

Figure 2. Model-Predicted Exposure Stratified by Cohort in Study IM101311



All patients received 10 mg/kg (maximum of 1000 mg) via 1-hour IV infusion on the day before transplant and on Day 5, Day 14, and Day 28 after transplant.

Active arm = abatacept + calcineurin inhibitor + methotrexate; AUC1 = AUC from 0-144 h after start of first dose; AUCL = AUC from 0-360 h after start of last dose (696-1056 h after start of first dose); Cmax1 = maximum concentration between 0-144 h after start of first dose; CmaxL = maximum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); Cmin1 = minimum concentration between 1-144 h after start of first dose; CminL = minimum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CV = coefficient of variation; h = hours.

Source: Figure 30 in Appendix Section 19.4.1-1.4.1 Pharmacometrics Review

6.2.2 General Dosing and Therapeutic Individualization

6.2.2-1 General Dosing

The Applicant's Position:

Rationale for Dosing Regimen Selection in Study IM101311

The abatacept IV dosing regimen for abatacept in combination with standard aGVHD prophylaxis regimen (CNI+MTX) for the Phase 2 study, IM101311, was designed to obtain steady state target trough

ORENCIA (abatacept)

serum concentration of abatacept of at least 10 µg/mL and to provide exposures comparable to those observed in the Phase 2/3 RA and JIA abatacept studies with the approved IV dose regimen. In vitro and in vivo preclinical data suggested a concentration of ≥ 10 µg/mL provided the maximal autoimmunity response (eg, maximal T-cell inhibition as measured by T-cell proliferation and cytokine responses).²⁴

The PK of abatacept in adults with RA and children with JIA is well understood based on experience from multiple studies^{25,26,27} wherein abatacept was dosed at 10 mg/kg (maximum dose of 1000 mg) and was administered on days 1, 15, 29 (1 trial used 30), and every 28 days thereafter. Results from these trials demonstrated that abatacept had a positive benefit-risk profile at the administered dosing regimen of 10 mg/kg dose regimen.

In addition, a Phase 1 trial of abatacept at a dose of 10 mg/kg (maximum dose of 1000 mg) IV abatacept on days -1, 5, 14, and 28 for the treatment of aGVHD showed promising efficacy and safety results.²⁸ The abatacept treated patients demonstrated a low rate of aGVHD, no deaths from infection, no TRM before Day 100, and with 7 of 10 evaluable patients surviving (median follow-up, 16 months). The PK and PD effects of abatacept informed the 10 mg/kg (maximum dose of 1000 mg) IV abatacept dose in randomized Phase 2 trial, ABA2 (IM101311).²⁹

Confirmation of the selected Doses and Regimens

Study IM101311 was conducted using body-weight based dosing for abatacept (10mg/kg with a maximum of 1000 mg) on Days -1, +5, +14, +28. PK results demonstrated that mean Cmin levels achieved or maintained levels of 10 µg/mL or greater during the treatment period and beyond Day 28 up to Day 100 in the PK evaluable population in both the 8/8 MUD and 7/8 MMUD cohorts.

Furthermore, the results from the pharmacometric Analysis (PPK and E-R) support the results of IM101311 and were consistent with previous abatacept pharmacometric analyses in autoimmune indications of RA and JIA.

Improved survival benefit was demonstrated in both the 8/8 MUD and 7/8 MMUD cohorts. In the randomized, double-blind treatment cohort for subjects receiving an 8/8 HLA-matched allogeneic HSCT, there was a numerically lower rate of severe aGVHD in the abatacept-treated patients and subsequent increase in GVHD free survival (GFS) at Day 180 compared to placebo (GFS rate 89% vs. 77%; HR: 0.54 [95% confidence interval (CI): 0.25, 1.19]); see Table 16. In the single arm 7/8 MMUD cohort, the observed GFS rate at Day 180 was 98% (95% CI: 85%, 100%) following the administration of abatacept in combination with a standard GVHD prophylaxis regimen; see Table 20. In addition, results from both 7/8 MMUD and 8/8 MUD cohorts showed an overall benefit in terms of disease-free survival (DFS), TRM, and overall survival (OS).

Collectively, these results support the recommended dosing regimen as appropriate prophylaxis for aGVHD in patients ≥ 6 years of age undergoing URD HSCT and offer a consistent benefit-risk profile in the target population. Findings from the E-R analysis indicate that the benefit-risk profile is not expected to be impacted by abatacept exposure level within the range produced by abatacept 10 mg/kg IV.

FDA Assessment:

For Patients Aged 18 Years and Older:

The FDA agrees with the Applicant's proposed body-weight based dosing regimen of abatacept 10 mg/kg (maximum of 1000 mg) in adult patients on the day before transplant and on Day 5, Day 14,

and Day 28 following transplant, which is supported by clinical data from Study IM101311, as well as PPK and E-R analysis:

- (1) In Study IM101311, the 4-dose regimen of abatacept 10 mg/kg (maximum of 1000 mg) on the day before transplant and on Day 5, Day 14, and Day 28 following transplant was demonstrated to be safe and effective in adult patients for prophylaxis of aGVHD in both 7/8 MMUD and 8/8 MUD cohorts (See Section 8.1.1).
- (2) In the PPK analysis, body weight was found to have a clinically significant association with abatacept PK where higher weight was associated with higher clearance.
- (3) In both 8/8 MUD and 7/8 MMUD cohorts, geometric mean observed C_{min} levels achieved or maintained levels of 10 µg/mL or greater during the treatment period and beyond Day 28 up to Day 63 in the PK evaluable population (see Section 6.2.1). Concentrations above 10 ug/mL were associated with maximal autoimmunity response based on in vitro and in vivo preclinical data.
- (4) Exposure-response relationship of Study IM101311:
 - a. For efficacy: increased abatacept concentration on Day 42 following transplant was associated with improved survival-without-severe-aGVHD up to Day 180 assessment and improved OS up to Day 180 assessment. However, relapse of underlying malignancy was strongly associated with worsened survival-without-severe-aGVHD up to Day 180 assessment and worsened OS up to Day 180 assessment. The effect of relapse appeared stronger than the effect of abatacept concentration on Day 42 (see Appendix Section 19.4.1-2.4).
 - b. For safety: the exploratory E-R safety analysis of Study IM101311 patients identified no clear associations between abatacept exposure and the time to first infection, time to invasive CMV disease, or time to CMV viremia (see Appendix Section 19.4.1-2.5).

For Patients Aged ≥6 Years to <18 Years:

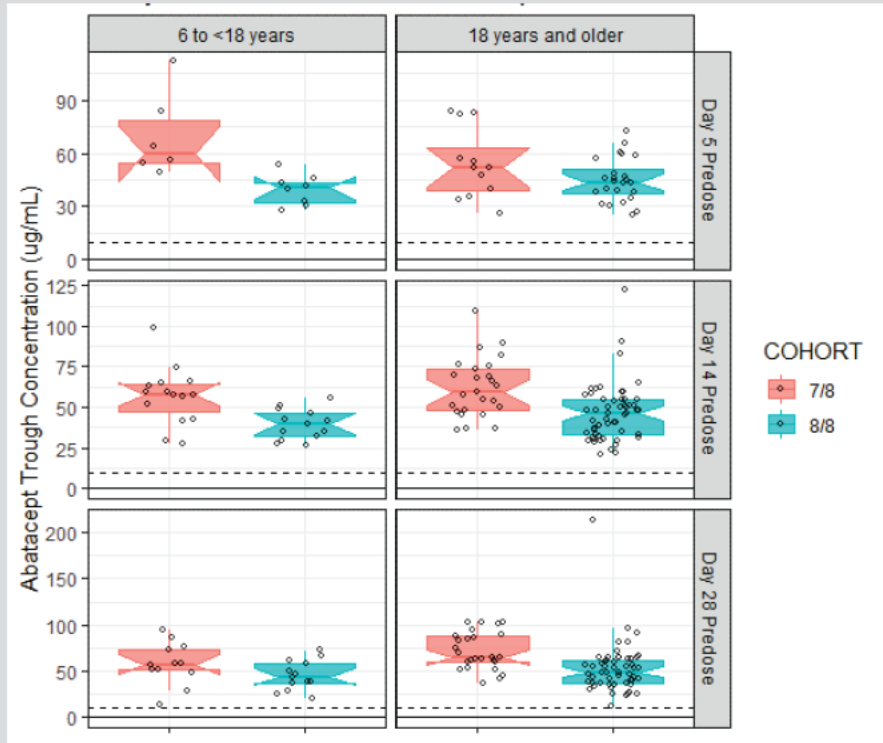
The FDA agrees with the Applicant's proposed dosing regimen of abatacept 10 mg/kg on the day before transplant and on Day 5, Day 14, and Day 28 following transplant in patients aged 6 to <18 years.

The dosing regimen in patients aged 6 to <18 years of age was supported by the clinical experience as well as PPK analysis:

- (1) In Study IM101311, the 4-dose regimen of abatacept 10 mg/kg was demonstrated to be safe and effective in patients aged 6 years and older for prophylaxis of aGVHD in both 7/8 MMUD and 8/8 MUD cohorts.
- (2) Observed PK data from Study IM101311:
 - a. Observed abatacept trough concentration did not significantly differ in pediatric patients aged 6 to <18 years compared to adult patients within each cohort (Figure 3 and Figure 4).
 - b. All individual abatacept trough concentrations up to Day 42 after transplantation were ≥10 ug/mL, and geometric mean concentration after Day 28 remained ≥10 ug/mL until at least Day 63 in both the 7/8 MMUD cohort and 8/8 MUD cohort (see Table 4). The target trough threshold for maximal autoimmunity response was ≥10 ug/mL based on in vitro and in vivo preclinical data.
- (3) PPK analysis:
 - a. Age was not a significant covariate for abatacept PK after accounting for body weight.

- b. Predicted abatacept exposure after last dose did not significantly ($\geq 20\%$) differ in pediatric patients aged 6 to <18 years compared to adult patients (see Appendix Section 19.4.1-1.4.2).
- c. All individual predicted concentrations after Day 28 after transplantation up to Day 42 (last predicted time point) were ≥ 10 ug/mL (see Appendix Section 19.4.1-1.4.2) which was the Applicant's predicted trough threshold for maximal autoimmunity response based on in vitro and in vivo preclinical data.

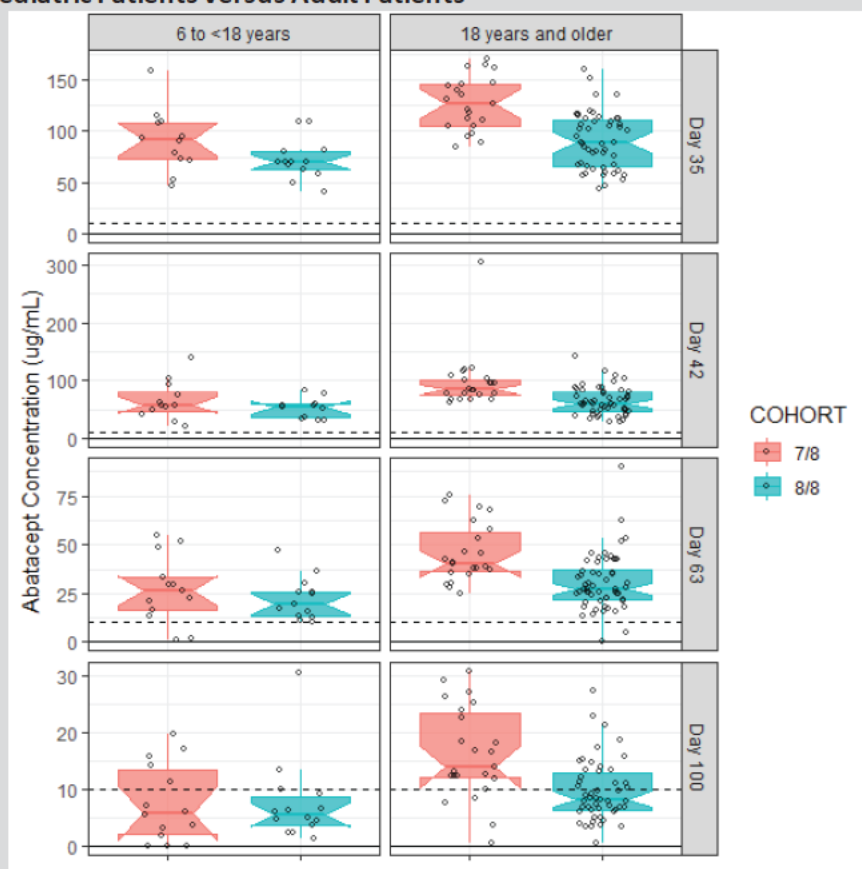
Figure 3. Study IM101311 Observed Abatacept Trough Concentrations at Day 5, Day 14 and Day 28 After Transplant in Pediatric Patients versus Adult Patients



Patients received 10 mg/kg (maximum dose of 1000 mg) via IV infusion over 1 hour on the day before transplant and then on Day 5, Day 14, and Day 28 after transplant. Dashed vertical line = 10 ug/mL. Solid vertical line = LLOQ. BLQ observations displayed as $1/2 * \text{LLOQ}$. Abatacept LLOQ = 0.001 ug/mL. BLQ = below limit of quantification; LLOQ = lower limit of quantification.

Source: Reviewer analysis of Applicant's Study IM101311 PK Concentration Dataset ('adpc.xpt')

Figure 4. Study IM101311 Observed Abatacept Concentrations at Day 35, 42, 63 and 100 After Transplant in Pediatric Patients versus Adult Patients



Patients received 10 mg/kg (maximum dose of 1000 mg) via IV infusion over 1 hour on the day before transplant and then on Day 5, Day 14, and Day 28 after transplant. Dashed vertical line = 10 ug/mL. Solid vertical line = LLOQ. BLQ observations displayed as 1/2*LLOQ. Abatacept LLOQ = 0.001 ug/mL. BLQ = below limit of quantification; LLOQ = lower limit of quantification.

Source: Reviewer analysis of Applicant's Study IM101311 PK Concentration Dataset ('adpc.xpt')

For Pediatric Patients Aged ≥ 2 Years to <6 Years:

The FDA agrees with the Applicant's proposed dosing regimen (see Applicant's "BMS Response to FDA Request dated 05 November 2021" which is dated November 29, 2021) of abatacept 15 mg/kg IV on the day before transplant and 12 mg/kg IV on Day 5, Day 14, and Day 28 following transplant in pediatric patients aged 2 to <6 years.

The dosing regimen in pediatric patients aged 2 to <6 years of age was supported by extrapolation of efficacy from patients aged 6 years or older, PPK modeling and simulation showing similar exposure in patients aged 2 to <6 years compared to those in patients aged 6 years and older, and additional safety data in pediatric patients with pJIA aged 2 to <6 years treated with SC abatacept:

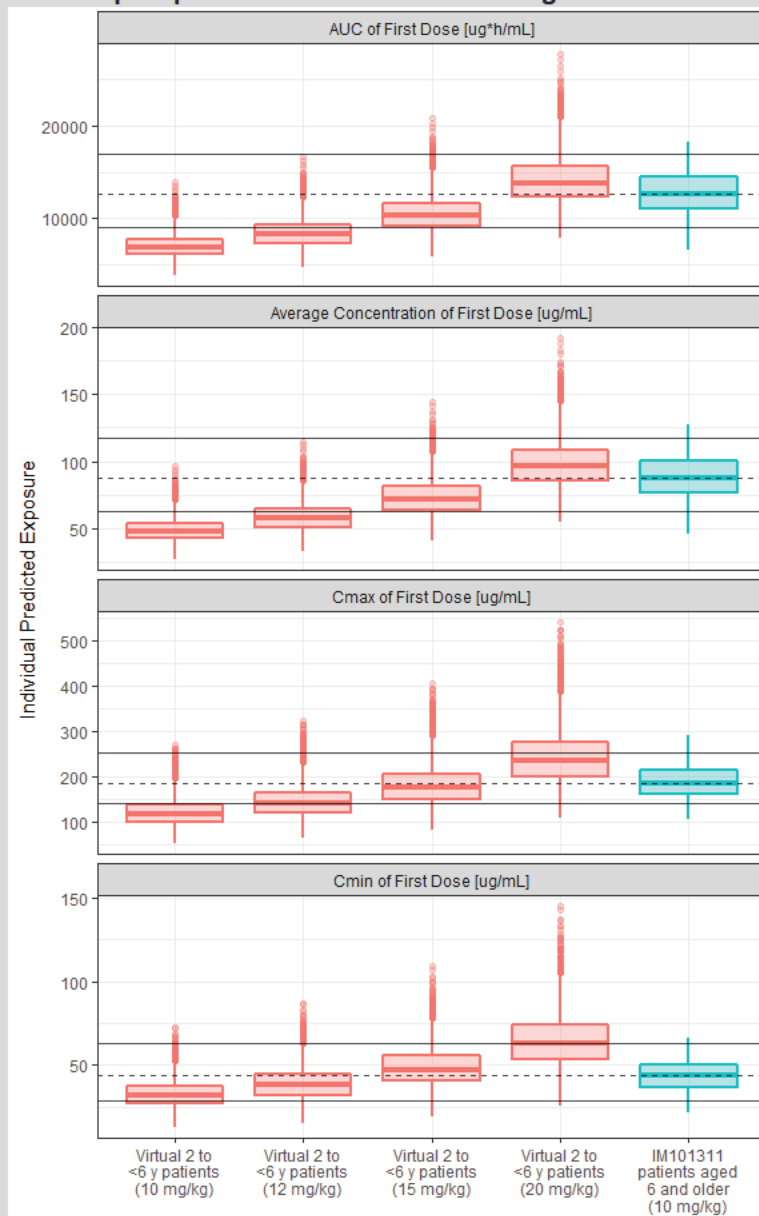
- (1) The course of disease is sufficiently similar in pediatric patients aged 2 to <6 years and patients aged 6 years and older to allow extrapolation of efficacy from patients aged 6 years and older to pediatric patients aged 2 to <6 years when both age groups have similar abatacept exposure.

(2) PPK analysis:

- a. Virtual pediatric patients aged 2 to <6 years were predicted to have higher abatacept clearance-per-kg compared to pediatric and adult patients aged 6 years and older.
- b. For both first dose and last dose, the predicted exposure (C_{min}, C_{max}, and AUC) in virtual pediatric patients aged 2 to <6 years with the proposed dosing regimen was similar to exposure in Study IM101311 patients aged 6 years and older administered a 4-dose regimen of abatacept 10 mg/kg IV (Figure 5 and Figure 6).

- (3) No new safety signals with abatacept were observed in pediatric patients aged 6 to <18 years with HM in Study IM101311 who were administered IV abatacept or in pediatric patients aged 2 to <6 years with pJIA in Study IM101011 who were administered SC abatacept.

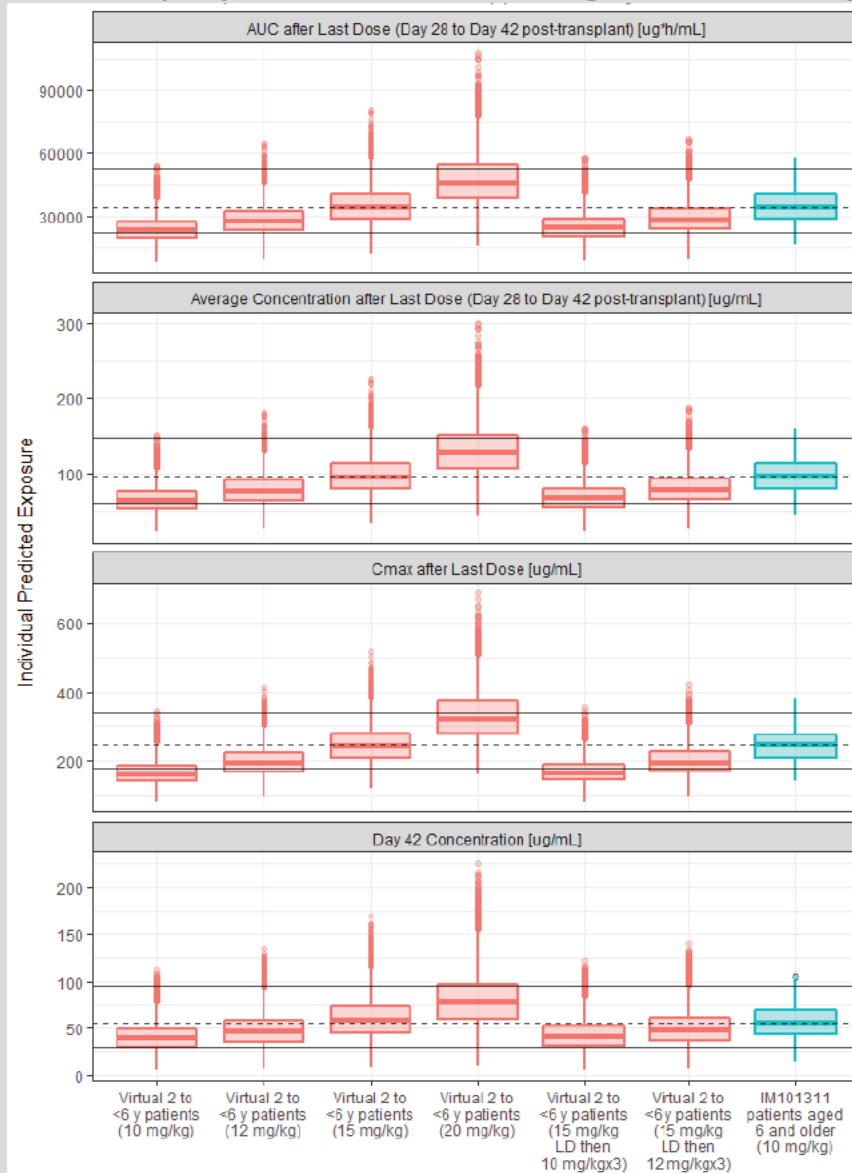
Figure 5. Simulated Abatacept Exposure for First Dose According to Dose Level and Age Group



Study IM101311 patients included 115 patients aged 6 years and older receiving hematopoietic stem cell transplant due to hematologic malignancy. Virtual 2 to <6 year old population contained 10,000 subjects. Boxes are 25th, 50th, and 75th percentiles; whiskers are +/- 1.58x IQR/sqrt(n). Dashed black reference line shows the median of predicted exposure in IM101311 patients following 10 mg/kg. Solid black reference lines show 5th and 95th percentiles of predicted exposure in IM101311 patients following 10 mg/kg. Abatacept was administered on the day before transplant (Day -1) and then Days 5, 14, and 28 after transplant. AUC = area under the concentration-versus-time curve; Cmax = maximum concentration; Cmin = minimum concentration; IQR = interquartile range; y = years.

Source: Figure 35 in Appendix Section 19.4.1-1.5.4 Pharmacometrics Review

Figure 6. Simulated Abatacept Exposure for Last Dose According to Dose Level and Age Group



Study IM101311 patients included 115 patients aged 6 years and older receiving hematopoietic stem cell transplant due to hematologic malignancy. Virtual 2 to <6 year old population contained 10,000 subjects. Boxes are 25th, 50th, and 75th percentiles; whiskers are $\pm 1.58 \times \text{IQR}/\sqrt{n}$. Dashed black reference line shows the median of predicted exposure in IM101311 patients following 10 mg/kg. Solid black reference lines show 5th and 95th percentiles of predicted exposure in IM101311 patients following 10 mg/kg.

Abatacept was administered on the day before transplant (Day -1) and then Days 5, 14, and 28 after transplant. AUC = area under the concentration-versus-time curve; C_{max} = maximum concentration; IQR = interquartile range; LD = loading dose on the day before transplantation (Day -1); y = years.

Source: **Figure 36** in **Appendix Section 19.4.1-1.5.4** Pharmacometrics Review

Clinical Pharmacology recommends approval of abatacept for prevention of aGVHD in URD HSCT in patients aged 2 to <6 years with the proposed abatacept dosing regimen of 15 mg/kg as a 60-minute

intravenous infusion on the day before transplantation, followed by 12 mg/kg on Days 5, 14, and 28 after transplant. This recommendation is based on extrapolation of efficacy from patients aged 6 years and older, PPK modeling and simulation to match abatacept exposures in patients aged 2 to <6 years to that in patients aged 6 years and older receiving 10 mg/kg IV abatacept, and safety data in patients with pJIA aged 2 to <6 years of age who received SC abatacept. The course of disease is sufficiently similar in pediatric patients aged 2 to <6 years and patients aged 6 years and older to allow extrapolation of efficacy from patients aged 6 years and older to pediatric patients aged 2 to <6 years when both age groups have similar abatacept exposure.

6.2.2-2 Therapeutic Individualization

The Applicant's Position:

For abatacept, PPK analyses demonstrated body weight was a predictor of abatacept exposures which is consistent with previous data. As body weight increases, abatacept clearance increase resulting in decrease exposure for a given dose. To that end, the dosing paradigm for abatacept for IV administration (10 mg/kg with a maximum of 1000 mg) was designed according to body weight, in order to achieve therapeutic C_{min} concentrations of 10 µg/mL across all body weights.

FDA Assessment:

The FDA agrees that the 10 mg/kg IV (max of 1000 mg/dose) body weight-based dose on the day before transplant followed by a dose on Day 5, 14, and 28 after transplant is acceptable for adult and pediatric patients aged 6 years and older for prophylaxis of aGVHD with HSCT a matched or 1 allele-mismatched URD due to HM.

FDA agrees with the Applicant's conclusion (see Applicant's "BMS Response to FDA Request dated 05 November 2021" which is dated November 29, 2021) that pediatric patients aged 2 to <6 years are expected to have higher abatacept clearance-per-kg compared to pediatric and adult patients aged 6 years and older. FDA also generally agrees that the Applicant's proposed dosing regimen of 15 mg/kg IV on the day before transplant followed by 12 mg/kg on Days 5, 14, and 28 after transplant is acceptable for pediatric patients aged 2 to <6 years for prophylaxis of aGVHD with HSCT a matched or 1 allele-mismatched URD.

6.2.2-3 Outstanding Issues

The Applicant's Position:

There are no outstanding clinical pharmacology issues or omissions related to this submission.

The FDA's Assessment:

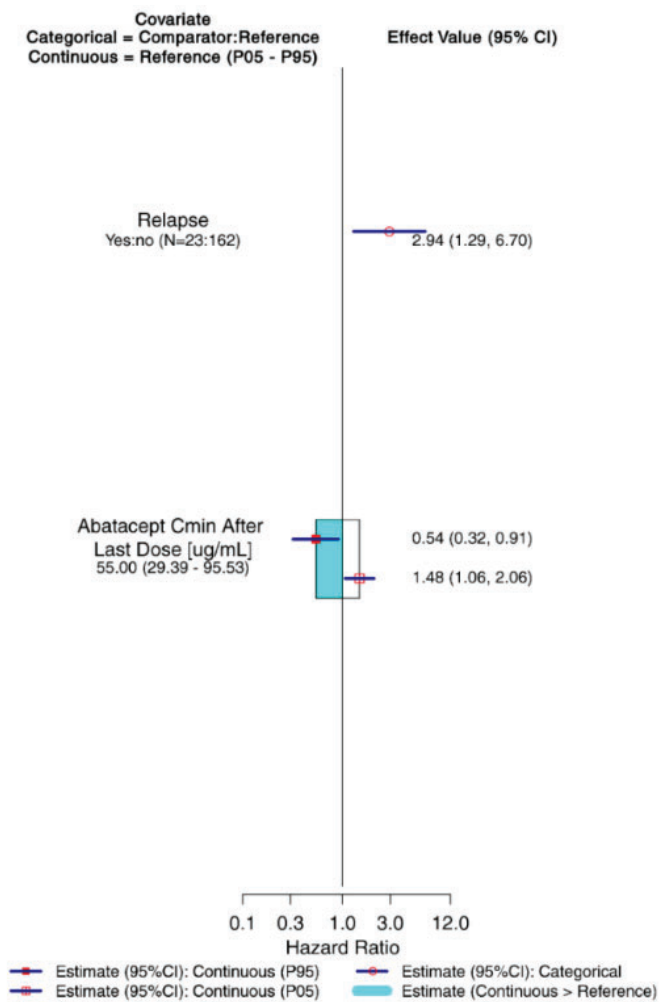
There is no available safety or PK data for IV abatacept in pediatric patients aged 2 to <6 years for prevention of aGVHD with HSCT a matched or 1 allele-mismatched URD. There is a need for a PMR to assess the safety risk and verify the PK profile of abatacept in pediatric patients aged 2 to <6 years for this indication (refer to **Section 13**).

There are no other outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Figure 7: Estimated Covariate Effects on the Hazard Ratio of Time to First Severe aGFS (Full 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.

Source: 002586\d1pkpd-eff\graphs\png\o\R\coveff-full.png

The Applicant's Position:

Abatacept PK and Immunogenicity Methods

The following validated methods were used for the abatacept in IM101311:

- Enzyme-linked immunosorbent assay (ELISA) to quantify abatacept concentrations (PK) in serum samples^{30,31}
- Electrochemiluminescence (ECL) assay to analyze anti-abatacept antibodies (ADAs) in serum and cell-based assay to evaluate neutralizing antibodies (NABs) from CTLA4 specific ADA positive serum samples³²

The performance of the validated bioanalytical methods used in IM101311 demonstrated that the assays were appropriate for the quantification of abatacept PK and the assessment of abatacept ADAs and neutralizing antibodies in the clinical study serum samples. The human serum assays used for the detection of abatacept in the clinical trials supporting the PPK analysis were appropriately cross validated.

Exposure-Response Relationships

In the Cox proportional hazards (CPH) model, abatacept Cmin after the last dose was the most significant predictor of the probability of time to severe aGFS up to Day 180, whereby increasing exposure (higher Cmin) was associated with lower risk (hazard) of severe aGVHD (event). Abatacept Cmin after the last dose and relapse of underlying malignancy were significant predictors of the probability of OS, whereby increasing exposure (higher Cmin) is associated with lower risk (hazard) of death (event) and relapse of underlying malignancy is associated with higher risk (hazard) of death (Figure 7).

In Study IM101311, there was no clear association between abatacept exposure, and the occurrence of infection AEs and the time to invasive cytomegalovirus (CMV) disease or CMV viremia found in subjects receiving URD HSCT after abatacept administration.

Abatacept Immunogenicity in patients with aGVHD

In both the 8/8 MUD and 7/8 MMUD cohorts, abatacept treated subjects had low immunogenicity incidence and associated antibody titers. The incidence of positive antibody response for CTLA4 and possibly Ig, was 6.8% (5 subjects out of 73 evaluable subjects) for the 8/8 MUD cohort and 2.4% (1 subject out of 41 evaluable subjects) for the 7/8 MMUD cohort. In the 8/8 MUD cohort out of 5 positive ADA subjects 3 had at least 1 positive sample with neutralization activity and in the 7/8 MMUD cohort, at least one positive sample from the single positive ADA subject, showed neutralizing activity. (Table S.7.8.1 [ADaM dataset: ADIM] and Table S.7.8.2 [ADaM dataset: ADIM] in the IM101311 primary CSR).

Overall, abatacept immunogenicity did not appear to have an effect on the safety or efficacy of abatacept in combination with standard aGVHD prophylaxis regimen (CNI+MTX) in IM101311. The incidences of ADA occurred during the off treatment period; no subject was positive during the on treatment.

FDA Assessment:

The FDA agrees with the Applicant's position on the validated bioanalytical methods for the quantification of abatacept PK and of exposure-response relationships.

The FDA generally agrees that higher predicted abatacept concentration on Day 42 after transplant was

associated with improved aGFS and OS. However, the FDA disagrees with the Applicant's conclusion that abatacept concentration on Day 42 was the most significant predictor of aGFS. Abatacept concentration on Day 42 and relapse of underlying malignancy were significant predictors of the probability of severe aGFS and the probability of OS up to Day 180 assessment. Increasing concentration on Day 42 was associated with improved severe aGFS and OS, while relapse of underlying malignancy was associated with worse severe aGFS and OS. Relapse status appeared to have a stronger association with both aGFS and OS compared to abatacept concentration. (See **Appendix Section 19.4.1-2.4**)

The FDA generally agrees with the Applicant's position that predicted abatacept concentration on Day 42 after transplant had no clear associations with time to first infection, time to invasive CMV, or time to CMV viremia up to Day 180 assessment. However, as this was an exploratory E-R safety analysis and other safety events were not investigated, the scope of this analysis was limited and the results do not rule out the possibility of E-R safety relationships. (See **Appendix Section 19.4.1-2.5**)

The FDA does not agree with the Applicant's position that abatacept immunogenicity did not appear to have an effect on the safety or efficacy. The impact of immunogenicity on PK, safety, and efficacy could not be determined due to a low number of patients in Study IM101311 with at least one ADA+ sample (6 out of 114 immunogenicity evaluable subjects) and uncertain timing of first ADA+ status. All ADA+ samples were taken between Day 28 and Day 180 following transplant, and it is unclear exactly when ADA first developed in patients with at least one ADA+ sample.

The dose-normalized abatacept concentration from Day 63 onward may be lower in patients with at least one ADA+ sample compared to patients without any ADA+ samples (Figure 5.1.1.6-7 in the "Population Pharmacokinetic and Exposure-Response Analyses of Abatacept in Subjects with Graft Versus Host Disease" report dated 26 March 2020), but the sample size and uncertain timing of first ADA+ status make it difficult to draw conclusions. The PK data do not rule out the possibility of an ADA effect on PK parameters or abatacept exposure.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes, the results of Study IM101311 suggest that 4 doses of abatacept were safe and effective for prophylaxis of aGVHD in patients 6 years of age or older receiving allogeneic HSCT in both 7/8 MMUD and 8/8 MUD recipients. Improved survival benefit was demonstrated in both the 8/8 MUD and 7/8 MMUD cohorts. In the randomized, double-blind treatment cohort for subjects receiving an 8/8 HLA-matched allogeneic HSCT, there was a numerically lower rate of severe aGVHD in the abatacept-treated patients and subsequent increase in GFS at day 180 compared to placebo (GFS rate 89% vs. 77%; HR: 0.54 [95% confidence interval (CI): 0.25, 1.19]). In the single arm 7/8 MMUD cohort, the observed GFS rate at Day 180 was 98% (95% CI: 85%, 100%) following the administration of abatacept in combination with a standard GVHD prophylaxis regimen. In addition, results from both 7/8 MMUD and 8/8 MUD cohorts showed an overall benefit in terms of DFS, TRM, and OS.

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

Collectively, these results support the recommended dosing regimen as appropriate prophylaxis for aGVHD in patients ≥ 6 years of age undergoing URD HSCT and offer a consistent benefit-risk profile in the target population.

FDA Assessment:

The FDA generally agrees with the Applicant's position that the results of Study IM101311 have provided supportive evidence of effectiveness in patients aged 6 years and older. However, as noted in **Section 8.1.2** below, FDA disagrees with the Applicant's assertion that benefit was demonstrated in the 7/8 arm of IM101311 in terms of DFS, TRM, and OS as these results are uninterpretable on a single arm trial. Study IM101841, however, demonstrated an OS benefit to abatacept for patients receiving 7/8 MMUD HSCT. As discussed in **Section 6.2.1**, extrapolation of efficacy from patients aged 6 years and older to patients aged 2 to <6 years is acceptable due to similar disease course between these two age groups.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes, the proposed dosing regimen for abatacept in combination with standard aGVHD prophylaxis regimen CNI+MTX is 10 mg/kg (maximum 1000 mg) in both pediatric and adult patients, to be administered) as a 60-minute IV infusion on the day before transplantation (Day -1), followed by an additional dose each on Days 5, 14, and 28 post-transplant. This regimen is supported by the favorable benefit-risk profile demonstrated in Study IM101311. This regimen was informed by Phase 3 clinical studies conducted in the approved indication in adult subjects with RA, and pediatric subjects with JIA.

In addition, E-R (efficacy and safety) analyses showed that in both 8/8 MUD and 7/8 MMUD HSCT recipients, the serum concentration of abatacept after the last dose, C_{min} , and relapse, were statistically significant predictors of time to OS (see Section 6.3.1). The risk of death decreased with increasing C_{min} after the last dose and increased with a relapse of the underlying malignancy. No other statistically or clinically relevant covariates were identified that significantly influenced the E-R relationship for time to OS in subjects aged ≥ 6 years who received an URD HSCT for treatment of a HM.

No clear association was identified between abatacept exposure and the occurrence of infection-related AEs and time to occurrence of events of invasive CMV disease or CMV viremia, in Study IM101311.

The E-R analysis performed using data from Study IM101311 demonstrated that the benefit-risk profile is not expected to be impacted by the abatacept exposure levels within the range produced by this regimen.

FDA Assessment:

For adult and pediatric patients aged 6 years and older, the FDA generally agrees with the Applicant's proposed 10 mg/kg (maximum 1000 mg) IV dosing regimen of abatacept in combination with CNI+MTX.

For pediatric patients aged 2 to <6 years, the FDA generally agrees with the Applicant's proposed abatacept dosing regimen of 15 mg/kg IV on the day before transplant followed by 12 mg/kg on Days 5, 14, and 28 after transplant in combination with CNI+MTX (see **Section 6.2.2.1**).

6.3.2.3 Is an alternative dosing regimen or management strategy required for any subpopulations based on intrinsic patient factors?

The Applicant's Position:

No, an alternative dosing regimen or management strategy is not required for subpopulation based on the intrinsic patient factors that were evaluated in the PPK analysis; see response to Question 6.3.2.2. The major factor/covariate that was found to influence the PK of abatacept is body weight. Hence, the abatacept dosing paradigm for IV administration is consistent across indications.

FDA Assessment:

The FDA generally agrees with the Applicant's position that no alternative dosing regimen or management strategy is required for subpopulations (other than patients aged 2 to <6 years) based on intrinsic patient factors, given the body weight-based dosing regimen accounts for the higher abatacept clearance associated with higher body weight in patients aged 6 years and older. Although pediatric patients aged 6 to <18 years with lower body weight tend to have lower drug exposure compared to adults based on observed PK data and PPK analysis, the difference was not significant (<20%) (see Section 6.2.2.1).

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

There are no anticipated clinically relevant food-drug or drug-drug interactions associated with abatacept when administered in combination with a standard aGVHD prophylaxis (CNI+MTX) in patients ≥ 6 years of age undergoing URD HSCT. Abatacept is a fusion protein administered IV and SC and does not alter hepatic metabolism via the CYP450 elimination pathways.

FDA Assessment:

The FDA agrees with the Applicant's position that there are no clinically relevant food-drug or drug-drug interactions associated with abatacept administration.

X

X

Primary Reviewer

Team Leader

Lili Pan

Ruby Leong

Robyn Konicki

Lian Ma

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Table 5: Listing of Clinical Trials Relevant to this sBLA

Trial Identity NCT no.	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled/treated	Study Population	No. of Centers and Countries
IM101311 (PBMTC GVH-1201 or ABA2)	NCT01743131	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	<u>8/8 MUD Cohort:</u> Abatacept+CNI+MTX: abatacept 10 mg/kg IV on days -1, +5, +14, +28. ^a Standard GVHD prophylaxis regimen consisting of either cyclosporine (dosed to maintain a pre-dose trough concentration of 100-300 ng/mL) or tacrolimus dosed to maintain a pre-dose trough level of 5-15 ng/mL, administered no later than day-2 (at least 36 hours before transplantation) and MTX dosed at 15 mg/m ² on day 1, and 10 mg/m ² on days 3 and 6 and 11.	<u>8/8 MUD - Primary:</u> To compare severe (Gr III-IV) GFS up to Day 180 post-transplantation between the abatacept + SOC arm and the placebo + SOC arm <u>7/8 MMUD:</u> To evaluate severe (Gr III-IV) GFS up to Day 180 post-transplantation in subjects receiving open-label abatacept+SOC GVHD prophylaxis	<u>Treatment Duration:</u> The period from Day -1 prior to HSCT to Day 28 post-HSCT. <u>Follow Up:</u> To Day 180 (primary endpoint); long-term follow-up for 5 years, thereafter	<u>8/8 MUD Cohort:</u> 146 subjects enrolled and randomized 142 treated with study medication and transplanted (73 with abatacept and 69 with placebo) <u>7/8 MMUD:</u> 46 subjects enrolled; 44 were treated with study medication and transplanted; 43 subjects were treated with abatacept	<u>8/8 MUD Cohort (blinded):</u> a randomized, double blind, placebo-controlled cohort, subjects who received a HSCT from 8/8 MUD <u>7/8 MMUD Cohort (open label):</u> a single arm cohort, for subjects who received a	<u>8/8 MUD Cohort:</u> 14 sites: 13 sites in the US and 1 site in Canada <u>7/8 MUD Cohort:</u> 9 sites in the US

Controlled Studies to Support Efficacy and Safety

Table 5: Listing of Clinical Trials Relevant to this sBLA

Trial Identity NCT no.	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled/ treated	Study Population	No. of Centers and Countries
			<u>Placebo+CNI+MTX:</u> As noted above for CNI+MTX 7/8 MMUD Cohort: Abatacept+CNI+MTX As noted above for CNI+MTX				HSCT from 7/8 MMUD	
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
IM101841 NA		Retrospective cohort study evaluating subjects who received abatacept in addition to SOC aGVHD prophylaxis, compared to subjects receiving SOC aGVHD prophylaxis, using data routinely collected in the CIBMTR database.	Abatacept+CNI+MTX without ATG or CNI+MTX without ATG	Primary: To compare the OS with 180 days of follow-up post-HSCT in subjects treated with abatacept+CNI+MTX without ATG to those treated with CNI+MTX without ATG	Up to 180 days post-transplant No additional follow up data beyond 180 days post-transplant	Abatacept+CNI+MTX without ATG: N=54 CNI+MTX without ATG: N=162	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).	54 centers in the US

Table 5: Listing of Clinical Trials Relevant to this sBLA

Trial Identity NCT no.	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled/treated	Study Population	No. of Centers and Countries
Other studies supporting safety								
IM101033	NCT00095173	A Phase III, Multi-Center, Multi-National, Randomized, Withdrawal Study to Evaluate the Safety and Efficacy of BMS-188667 in Children and Adolescents with Active Polyarticular Juvenile Rheumatoid Arthritis (JRA)	10 mg/kg by IV infusion on Days A1, A15, and A29, and every 28 d thereafter	Efficacy, safety, and PD of abatacept in children and adolescents with JIA/JRA	<u>Period A:</u> Open-label, lead-in phase: 4 m <u>Period B:</u> Double-blind randomized, parallel dosing, placebo-controlled phase: 6 m <u>Period C:</u> Open-label, uncontrolled, extension phase: Up to 5 y in open-lab	Period A = 190 treated Period B = 122 treated <u>-60 on ABA</u> <u>-62 on PBO</u> <u>Period C = 153 treated</u>	Children and adolescent subjects with JIA/JRA	
IM101100	NCT00162266	Randomized, double-blind, placebo-controlled	Parenteral, 2 and 10 mg/kg, Days 1, 15, 29, and monthly thereafter, IV	Efficacy and safety of abatacept vs placebo on background of MTX	Duration: 12 m	339:105 ABA (2 mg/kg), 115 ABA (10 mg/kg) 119 PBO	Adult subjects with active RA and an inadequate response to MTX	
IM101101	NCT00162279	Randomized, double-blind,	Parenteral, 2 mg/kg,	Efficacy and safety of abatacept vs	Duration: 12 m	652:433 ABA 219 PBO	Adult subjects	

Table 5: Listing of Clinical Trials Relevant to this sBLA

Trial Identity NCT no.	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled/treated	Study Population	No. of Centers and Countries
		placebo-controlled	Days 1, 15, 29, and monthly thereafter, IV	placebo on background of ETAN			with active RA and an in-adequate response to ETAN	
IM101102	NCT00048568	Randomized, double-blind, placebo-controlled	Parenteral, Fixed dose, Days 1, 15, 29, and monthly thereafter, IV	Efficacy and safety of abatacept vs placebo on background of MTX	Duration: 12 m	Total: 652 433 ABA 219 PBO	Adult subjects with active RA and an in-adequate response to MTX	
IM101029	NCT00048581	Randomized, double-blind, placebo-controlled	Parenteral, Fixed dose, Days 1, 15, 29, and monthly thereafter, IV	Efficacy and safety of abatacept vs placebo on background of DMARDs	Duration: 6 m	Total: 391 258 ABA 133 PBO	Adult subjects with active RA and an in-adequate response to TNF blockers	
IM101031	NCT00048932	Randomized, double-blind, placebo-controlled	Parenteral, Fixed dose, Days 1, 15, 29, and monthly thereafter, IV	Efficacy and safety of abatacept vs placebo on background DMARDs and/or biologics	Duration: 12 m	Total: 1441 959 ABA 482 PBO	Adult subjects with active RA, with or without co-morbid conditions	

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Table 5: Listing of Clinical Trials Relevant to this sBLA

Trial Identity NCT no.	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled/treated	Study Population	No. of Centers and Countries
IM101023	NCT00122382 NCT00989235	Randomized, double-blind, placebo-controlled	Parenteral, 10 mg/kg (weight-tiered), Days 1, 15, 29, and monthly thereafter, IV	Efficacy and safety of abatacept vs placebo on background of MTX	Duration: 12 m	Total: 509: 256 ABA 253 PBO	Adult, MTX-naive subjects with early erosive RA	

^a Day of transplant was Day 1 of Study; there was no Day 0

The Applicant's Position:

The proposed sBLA is based on data from 2 studies summarized in Table 5:

1. Study IM101311 data (8/8 MUD cohort and 7/8 MMUD cohort) are used to provide evidence of efficacy to support the proposed indication of abatacept added to standard of care prophylaxis of aGVHD in recipients of mismatched, URD HSCT.
2. The sBLA is further supported by Study IM101841, a retrospective cohort study using CIBMTR Registry data from MUD HSCT recipients treated with SOC aGVHD prophylaxis as a comparator group for the single-arm, 7/8 MMUD cohort treated with abatacept+SOC aGVHD prophylaxis, with IPTW and Propensity Scoring to control for potential selection bias inherent to clinical management; 7/8 MMUD HSCT recipients constitute a population with a high unmet medical need and over-representation by patients from minority ethnic groups. The study protocol was developed and reviewed by FDA prior to BMS conducting the pre-specified analyses. It was referred to as prospectively designed retrospective analysis.

FDA Assessment:

FDA agrees with the summary of clinical studies presented in Table 5 above. This review provides detailed analysis of Study IM101311 and Study IM101841.

Study IM101311 is a multicenter, two cohort trial in patients age 6 years or older who underwent HSCT from a matched or 1 allele-mismatched URD. The two cohorts included 1) an open-label, single-arm study of 43 patients who underwent a 7 of 8 HLA-matched HSCT and 2) a randomized (1:1), double-blind, placebo-controlled study of patients who underwent an 8 of 8 HLA-matched HSCT who received abatacept or placebo in combination with a CNI and MTX. This study was initially designed and powered as an investigator-initiated study. However, the submitted data and analyses were conducted per the Applicant's SAP that was discussed with FDA.

Study IM101841 is a clinical study comprised of data collected through the Center For International Blood And Marrow Transplant Research (CIBMTR). The CIBMTR is a prospective observational registry managed by the Medical College of Wisconsin in collaboration with the National Marrow Donor Program through a contract awarded by HHS. CIBMTR represents an international network of transplant centers that submit transplant-related data for patients. The CIBMTR includes data on every allogeneic HSCT performed in the United States. Reporting by transplant centers is required under the Stem Cell Therapeutic and Research Act (Public Law 109-129). Data is collected in accordance with the United States Health Insurance Portability and Accountability Act and the European Union's General Data Protection Regulation. U.S. transplant centers also voluntarily submit autologous transplantation data, and transplant centers worldwide voluntarily submit both autologous and allogeneic transplantation data. CIBMTR continuously collects and audits data at all participating transplant centers, including post transplantation follow-up data for defined outcomes and more detailed data collection on ~25% of registered patients using a regularly reviewed, weighted algorithm. The CIBMTR has a Data Quality Program that includes an Audit Program to evaluate data accuracy, completeness, and implement corrective actions as needed to ensure data quality. The clinical database contains information from more than 585,000 patients.

FDA disagrees with the Applicant's assertion that Study IM101841, was a "...comparator group for the single-arm, 7/8 MMUD cohort treated with abatacept+SOC aGVHD prophylaxis." As

opposed to serving as an external comparator group to Study IM101311, Study IM101841 was conducted as an additional clinical study using CIBMTR registry data to evaluate outcomes in patients who underwent 7/8 MMUD transplantation with or without abatacept in addition to standard CNI and MTX immunosuppression. Detailed assessments of methodology and results are contained in Section 8 of the review below.

Note that per FDA's review, the footnote under Table 5 stating "Day of transplant was Day 1 of Study; there was no Day 0" appears to be incorrect. Per the SAP for Study IM101311, the transplant was conducted on day 0, with first dose day -1. This was also verified in the exposure data file in the submission.

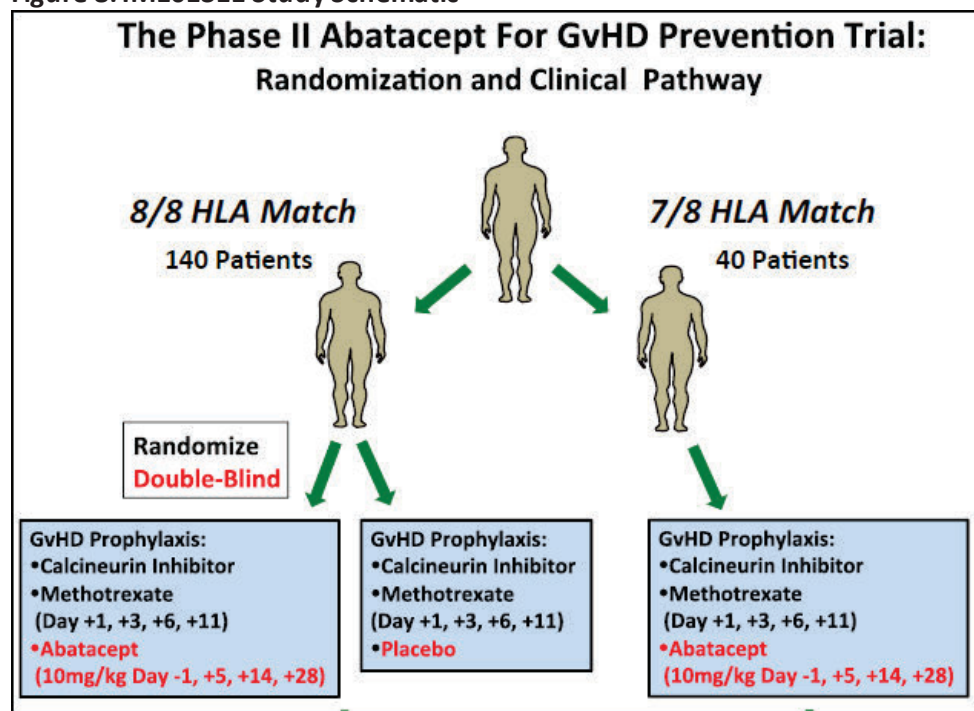
8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study IM101311

Trial Design:

Figure 8: IM101311 Study Schematic



Source: Figure 3.1-1 in IM101311 primary CSR

The Applicant's Description:

IM101311 (also referred to as ABA2 or PBMTG GVH-1201), is a multicenter Phase 2 trial with 2 cohorts:

- A randomized, double-blind, placebo-controlled (8/8 MUD) cohort of subjects who received a HSCT

ORENCIA (abatacept)

from an 8/8 HLA matched, URD, comparing subjects treated with abatacept+SOC aGVHD prophylaxis (CNI+MTX) to those treated with placebo+SOC aGVHD prophylaxis; and

- A single arm (7/8 MMUD) cohort of subjects who received a HSCT from 7/8 HLA-matched, URD (Figure 8). Note that the 7/8 MMUD cohort was initially designed as a randomized, double-blind placebo-controlled cohort. However, after the initiation of the study, based on an emerging consensus among members of the HSCT transplant community that addition of abatacept to a SOC regimen for prophylaxis of aGVHD was therapeutically beneficial, and that it would be unethical to enroll recipients of 7/8 MMUD HSCTs who might be randomized to the placebo arm of the study, given the high risk of TRM associated with treatment with SOC aGVHD prophylaxis. This emerging consensus resulted in Protocol Amendment 04 which eliminated the placebo arm of the study such that all subsequent subjects in the 7/8 MMUD cohort were treated with open-label group, with abatacept+SOC.

Enrollment/Assignment to Treatment: Subjects were enrolled using the REDCap online System and eligibility was confirmed by the study coordinator. After enrollment, subjects in the 8/8 MUD cohort (ie, 8/8 MUD transplants) were randomly assigned 1:1 to the placebo arm (Placebo+CNI+MTX) or to the investigational abatacept arm (abatacept+CNI+MTX) of the study.

Treating physicians chose a conditioning regimen that he or she determined was best suited for the individual patient and the patient’s malignancy from 1 of 4 conditioning approaches (total body irradiation [TBI] based conditioning plus chemotherapy, busulfan and cyclophosphamide [recommended for myeloid malignancies only], melphalan and fludarabine, or busulfan and fludarabine [recommended for myeloid malignancies]). Subjects who had prior autologous HSCT, however, were conditioned with melphalan and fludarabine. At the completion of the conditioning period, subjects received either open-label abatacept in the 7/8 MMUD cohort or the treatment to which they were randomized after enrollment in the 8/8 MUD cohort (abatacept or placebo). All subjects received a CNI (either cyclosporine or tacrolimus) and MTX for GVHD prophylaxis.

Trial Locations: In Study IM101311, 146 8/8 HLA MUD subjects were enrolled and randomized to the blinded arm of the study (8/8 MUD cohort). 142 subjects were treated with study medication and transplanted (73 with abatacept and 69 with placebo) at 13 sites in the US and 1 site in Canada. In the single arm 7/8 MMUD cohort, 43 of the 46 enrolled subjects received abatacept at 9 sites in the US.

Key Inclusion/Exclusion Criteria: The study population included subjects (≥ 6 years and weigh 20 kg) who had high-risk hematologic malignancies as defined below (Table 6), adequate organ function, lacked an HLA-matched related donor, and had an unrelated bone marrow or peripheral blood stem cell donor who was matched at no fewer than 7 of 8 HLA loci (A, B, C, DRB1).

Table 6: High-Risk Hematologic Malignancies

Type of Malignancy	Criteria for enrollment
Acute myeloid leukemia (AML)	Patients with AML in the first CR with intermediate or high risk disease. Patients with AML in first CR with high-risk disease as defined by one of the following abnormalities: Indicators of High-risk Disease are as follows: 1. Flt3/ITD+ 2. Residual marrow disease (≥0.1%) 3. Secondary AML. 4. High-Risk cytogenetic abnormalities

Table 6: High-Risk Hematologic Malignancies

Type of Malignancy	Criteria for enrollment
	5. Other abnormalities associated with higher risk for AML relapse but were not yet incorporated into cooperative group risk classification systems were considered and enrolled with Investigator approval. Patients with a partial first remission, no evidence of extramedullary disease, and an absolute neutrophil count $\geq 1.0 \times 10^9/L$. Patients in 2nd or greater CR or PR.
Myelodysplastic syndrome	Adult patients (≥ 21 years) with secondary disease or de novo disease that meets criteria for intermediate, high or very high-risk disease based on the Revised International Prognostic Scoring System (IPSS-R) ³³
Acute lymphoblastic leukemia (ALL)	Adult patients (≥ 21 years) with ALL, in first or greater CR Pediatric patients (< 21 years) with ALL, must meet one of the criteria listed below and pediatric patients COG ALL trial for newly diagnosed or relapsed disease must meet the criteria for BMT as outlined in that trial 1. In 1st CR with a very high risk for relapse. 2. In 2nd CR with B-lineage disease after a marrow relapse occurring less than 36 months from diagnosis. 3. In 2nd CR with T-lineage disease or Ph+ disease after a marrow relapse occurring at any time. 4. In a 2nd CR with T-lineage disease after an extra-medullary relapse occurring less than 18 months from diagnosis. 5. In 3rd or greater CR after a marrow or extramedullary relapse 6. Other indications for transplant in pediatric patients with ALL must be approved by the Study PI with a note to file reflecting study team discussion and approval.
Patients with acute undifferentiated, biphenotypic, or bilineal leukemia, which is in 1st or greater CR or PR.	
Chronic myelogenous leukemia (CML)	Chronic phase with resistance to tyrosine kinase inhibitors Accelerated phase (development of cytogenetic abnormality in addition to t(9:22), blood blast percentage ≥ 10 , blood basophil percentage ≥ 20 , platelet count $< 100,000 \times 10^9/L$) Blast crisis. 2nd or greater chronic phase.
Acute Lymphoblastic Lymphoma in 2nd or greater complete remission.	
Peripheral T cell lymphoma (PTCL)	In first response (must have at least a PR) • PTCL, unspecified. • Hepatosplenic gamma-delta T cell lymphoma Recurrent PTCL (must be treatment sensitive with at least a partial response). If patient has had a previous autologous transplant, the melphalan and fludarabine conditioning regimen must be utilized.
Chronic myelomonocytic leukemia.	
Atypical (BCR-ABL negative) chronic myelogenous leukemia	

Table 6: High-Risk Hematologic Malignancies

Type of Malignancy	Criteria for enrollment
Hodgkin lymphoma that has recurred or progressed after an autologous BMT	Newly diagnosed or recurrent disease initially refractory to intensive chemotherapy. A partial response or better must be achieved prior to transplantation. Eligibility of newly diagnosed cases must be discussed with the study PI. Disease that has recurred or progressed after an autologous BMT. Salvage chemotherapy must produce a partial response or better.
Non-Hodgkin lymphoma (other than lymphoblastic or peripheral T cell lymphoma)	Newly diagnosed or recurrent disease initially refractory to intensive chemotherapy. A partial response or better must be achieved prior to transplantation. Eligibility of newly diagnosed cases must be discussed with the study PI. Disease that has recurred or progressed after an autologous BMT. Salvage chemotherapy must produce a partial response.

Abbreviations: BMT = Blood and Marrow Transplant; CR = complete remission; PI = principal investigator; PR = partial remission

Source: Section 3.2 in Appendix 1.1 of the IM101311 primary CSR

Dose Selection: See Section 6.2.2

Study Treatments: During the first 28 days post-transplantation all subjects received 1 of the following treatments:

- Placebo plus Standard GVHD prophylaxis (CNI, and short-course MTX)
- Abatacept plus Standard GVHD prophylaxis (CNI and short-course MTX)

Four doses of study medication were administered at a dose of 10 mg/kg during the study on Days -1, +5, +14, and +28.

Dosing Information for Standard GVHD Prophylaxis: Standard GVHD prophylaxis regimen of either cyclosporine dosed to maintain a level of 100-300 ng/ml or tacrolimus dosed to maintain a level of 5-15 ng/ml administered no later than Day -2 (at least 36 hours before transplantation) and MTX dosed at 15 mg/m² on day 1, and 10 mg/m² on days 3 and 6 and 11 based on body weight, administered intravenously.

Placebo: The placebo consisted of 100 ml of 0.9% Sodium Chloride.

Dose modification: Abatacept was required to be withheld for: active serious invasive viral disease, active invasive fungal infections, active opportunistic protozoal and helminthic infections, active opportunistic protozoal and helminthic infections, or imminently life-threatening bacterial infections.

Standard GVHD prophylaxis: The CNI (cyclosporine or tacrolimus) was allowed to be interrupted or dose reduced at the discretion of the treating physician for renal toxicity, poorly controlled hypertension, neurotoxicity, and other serious toxicities. Methotrexate dose modifications were allowed at the discretion of the treating physician.

Guideline for treatment modifications by the treating physician is provided in the IM101311 study protocol.

Schedule of Assessments: Assessments for eligibility, safety, and efficacy were performed during screening, on treatment, and follow-up, based on the Patient Assessments in the protocol. Physical examination, Karnofsky/Lansky score, clinical laboratory including complete blood counts with

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

differential, blood chemistry (creatinine, bilirubin, alkaline phosphatase, ALT, AST, and others), serum IgG, and other routine pre-and post-transplant evaluations were performed according to each site's institutional standards. Routine clinical monitoring for CMV viremia was initiated no later than transplant day +7 and performed at least once a week through at least transplant day 100, and at least every 4 weeks through Day 180. Clinical monitoring by Epstein-Barr virus (EBV) polymerase chain reaction (PCR) was performed in all patients every two weeks between Day +7 and Day 100 and once every four weeks through Day 180. Patients were evaluated for infections on an ongoing basis in accordance with the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures.

Acute and chronic GvHD evaluation was performed at baseline, and weekly through Day 100, and Day 180 post-transplant.³⁴ Acute GVHD was defined according to the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005, section 1) and the 1994 Consensus Conference on Acute GVHD Grading. Chronic GVHD, including overlap syndrome, was assessed according to the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005, section 2) using the NIH consensus criteria.³⁵

Blinding: 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. All participating subjects, their families, all medical providers, and all investigators and study personnel other than those listed above were blinded to treatment assignment. The 7/8 MMUD cohort was not blinded.

Study Conduct: Study IM101311 was conducted as an Investigator-Sponsored research (ISR). This study was conducted in accordance with GCP by qualified investigators using a single protocol to promote consistency across sites. Details on the methods used during study conduct and during analysis and reporting to assure the quality of the data are provided in the protocol.

Measures to minimize bias included aspects of the study design and the use of third parties for critical activities.

FDA Assessment:

FDA agrees with the Applicant's description of the study design.

Study IM101311 was a multicenter phase II trial with 2 cohorts:

8/8 MUD cohort: a randomized, double blind, placebo-controlled cohort for subjects receiving transplants from 8 of 8 HLA matched unrelated donors.

7/8 MMUD cohort: a single arm cohort for subjects receiving transplants from 7 of 8 matched donors.

The staging and grading of aGVHD events used to support the efficacy analyses were reviewed and adjudicated centrally by members of the protocol team. In addition, staging and grading were adjusted by applying an algorithm developed and validated by Weisdorf et al, 2003.

Study Endpoints

The Applicant's Description:

The primary endpoint in the Investigator Protocol of cumulative severe aGVHD incidence rate up to

100 days post-transplant was changed to GFS after a minimum of 180 days post-transplant per FDA guidance on the endpoint to support an indication for prevention of aGVHD. BMS created an independent SAP per FDA guidance; a description of the statistical analyses is provided in the section below on the SAP.

Study IM101311 objectives and endpoints based on Investigator Protocol and BMS SAP are listed in Table 7 and Table 8, respectively.

Endpoints in Study IM101311 Based on BMS SAP

Table 7: Study IM101311 Objectives and Endpoints Based on Investigator Protocol

Objective	Endpoint
Primary To determine the impact that abatacept will make on the incidence of early, severe aGVHD, when it is added to a standard GvHD prophylaxis regimen during unrelated-donor HSCT for patients with hematologic malignancies.	The primary endpoint, as defined in the investigator protocol, was early (before day 100) severe (Grade III-IV) acute GVHD. This endpoint was defined according to the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005, section 1) using the NIH consensus criteria³⁶
Secondary To characterize the impact of abatacept on the post-transplant reconstitution of anti-viral protective immunity.	Engraftment related (a safety endpoint): • Neutrophil recovery: This endpoint was defined as the first of 3 consecutive days following the nadir that the absolute neutrophil count is at least 500/μl. • Platelet recovery: This endpoint was defined as the first day that the platelet count is at least 20 thousand/μl without a transfusion in the preceding 7 days. • Non-engraftment: This endpoint was defined as lack of neutrophil recovery (defined as ANC > 0.5 * 10⁹/L for three consecutive days) by 35 days post-transplant or neutrophil recovery with lack of myeloid donor chimerism. • Secondary graft failure. This endpoint was defined by initial engraftment but subsequent development of an ANC < 0.5 * 10⁹/L for fourteen consecutive days. Transient causes of myelosuppression (infection, drugs, etc) shall be ruled out. • Graft rejection: Defined by initial engraftment (assessed by neutrophil recovery and donor chimerism) with the subsequent loss of donor myeloid chimerism (regardless of whether persistent neutropenia develops). Infection and immune related (a safety endpoint): • CMV Viremia was defined as the occurrence of a positive blood antigen or PCR test prior to Day 180. • CMV invasive disease was defined in accordance with the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005). • Post-transplant lymphoproliferative disorder was defined in accordance with the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005)³⁶ and the 4th edition

Table 7: Study IM101311 Objectives and Endpoints Based on Investigator Protocol

Objective	Endpoint
	of the World Health Organization’s Classification of Tumours of Haematopoietic and Lymphoid Tissues. • Other Infections was defined in accordance with the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005).³⁶ • Immune Reconstitution was assessed by the day 100 CD4+ T cell count and by the reaccumulation of NK cells, B cells, total T cells, and CD8+ T cells as assessed by multicolor flow cytometry. GVHD related • Early onset (before day 100) acute GVHD (including all Grades, and stratified by Grades) was assessed according to the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005, section 1)³⁶ using the NIH consensus criteria.³⁶ • Late onset (after day 100) acute GVHD was assessed according to the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005, section 1) using the NIH consensus criteria.³⁶ • Chronic GVHD, including overlap syndrome, was assessed according to the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005, section 2) using the NIH consensus criteria.³⁶ This assessment will continue through Year 5 post-transplant. • Immune Suppression-Free Survival and Immune Suppression-Free/Disease-Free Survival was assessed at 1 year and will be defined as survival and disease-free survival off of all immunosuppressive agents. • To compare severe (Grade III-IV) aGVHD free survival (GFS) up to Day 180 post-transplantation between the abatacept + standard GVHD prophylaxis and standard GVHD prophylaxis regimen. The aGVHD events in this definition of GFS are the adjudicated Grade (III-IV) aGVHD events. (This is a pre-determined endpoint for the 8/8 cohort and a retrospective endpoint for the 7/8 cohort). • To compare the cumulative incidence of severe (Grade III-IV) aGVHD (based on adjudicated aGVHD events) up to Day 180 post-transplant between the abatacept + standard GVHD prophylaxis and standard GVHD prophylaxis regimen. (This is a pre-determined endpoint for the 8/8 cohort and a retrospective endpoint for the 7/8 cohort). Relapse and Survival • Transplant related mortality was defined as any death occurring in a continuous complete remission. • Relapse of the underlying malignancy. • Disease-free survival was defined as survival without relapse of underlying malignancy. This will be evaluated through Year 5 post-transplant. • Overall-survival was defined as survival with or without relapse of underlying malignancy. This will be evaluated through Year 5 post-transplant.

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

Abbreviations: aGvHD = acute GVHD; HSCT = hematopoietic stem cell transplantation
Source: Appendix 1.1 of the IM101311 primary CSR

APPEARS THIS WAY ON ORIGINAL

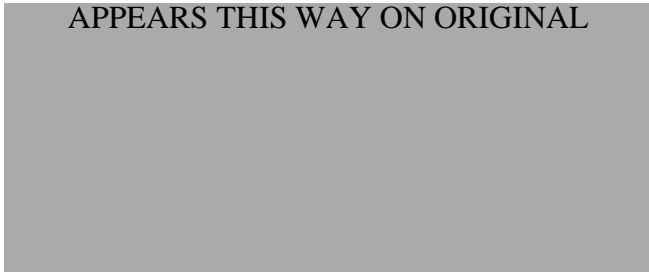


Table 8: Study IM101311 Objectives and Endpoints Based on BMS SAP

Objective	Endpoints	Endpoint Definition
Primary (Efficacy) To compare severe (Gr III-IV) 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 hematologic malignancies. Sensitivity analysis: analysis of severe GFS rate up to Day 180 with censoring at the time of relapse.	Severe (Gr III-IV) GFS up to Day 180	This endpoint is pre-specified in the BMS SAP. 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 is the upper limit of the Day 180 window and used for censoring.
Key Secondary (Efficacy) 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 hematologic malignancies.	Cumulative incidence of severe Gr III-IV aGVHD up to Day 180 post-transplantation	Note that severe aGVHD up to Day 100 post-transplantation is defined as the primary endpoint in the protocol. For the purpose of the analysis plan for this CSR severe aGVHD events up to Day 180 are considered instead of Day 100 post-transplant to align with regulatory expectations. The aGVHD events in this definition of GFS are the adjudicated Gr III-IV aGVHD events.
Other Secondary (Efficacy) To assess OS during the post-transplantation follow-up period	OS	Defined as survival with or without relapse of underlying malignancy
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	Moderate (Gr II-IV) GFS up to Day 180	The aGVHD events in this definition of GFS are the adjudicated Gr II-IV aGVHD events.
To assess DFS during the post-transplantation follow-up period	DFS	Defined as survival without relapse of underlying malignancy.
To assess TRM during the post-transplantation follow-up period	TRM rates	TRM is defined as any death occurring in a continuous complete remission ie, death without relapse of underlying malignancy.
To assess relapse of underlying malignancy during the post-transplantation follow-up period	Relapse rates	Relapse is defined as either morphological or cytogenetic evidence of acute leukemia or MDS consistent with pre transplant feature, or radiologic evidence of lymphoma, documented or not by biopsy.

Table 8: Study IM101311 Objectives and Endpoints Based on BMS SAP

Objective	Endpoints	Endpoint Definition
To assess early onset (occurring on or before Day 100 post-transplantation) (all Grades [Gr I-IV, Gr II-IV and Gr III-IV]) aGVHD	Frequency of early onset (before day 100) aGVHD	Frequency of Early onset (before day 100) aGVHD (all Grades [Gr I-IV, Gr II-IV and Gr III-IV]). Cumulative incidence of early onset severe aGVHD was the primary endpoint specified in the Investigator protocol.
To assess 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.	Frequency of late onset (after day 100) aGVHD	Frequency of Late onset (after day 100) aGVHD (all Grades [Gr I-IV, Gr II-IV and Gr III-IV]), landmark analysis from Day 100 over time during the post-transplantation follow-up period.
To assess chronic GVHD (cGVHD) (Defined using the 2005 NIH Consensus Criteria for cGVHD scoring) during the post-transplantation follow-up period	Frequency of cGVHD	Frequency of cGVHD (including overlap syndrome) over time during the post-transplantation follow-up period. Overlap syndrome is defined as GVHD that has both acute and chronic features.
To assess Immune Suppression-free survival and Immune Suppression-free/Disease-free survival during the post-transplantation follow-up period	Immune Suppression-Free Survival and Immune Suppression-Free/Disease-Free Survival	Defined as survival and disease-free survival off of all immunosuppressive agents.
To assess severe aGVHD free survival (GRFS) during the post-transplantation follow-up to database lock	Severe aGVHD Free-Relapse Free Survival	Severe aGVHD, relapse, and death are events for this endpoint.
Secondary (Safety) To assess the safety of abatacept in combination + standard GVHD prophylaxis and standard GVHD prophylaxis regimen only in URD HSCT for patients with hematologic malignancies by assessment of AEs and laboratory parameters including Engraftment related events and Infections and immune-related events	Engraftment Related events Neutrophil recovery, platelet recovery, non-engraftment, secondary graft failure, graft rejection Infections and Immune-related events CMV viremia, CMV invasive disease, PTLD Immune reconstitution	Neutrophil recovery: defined as the first of 3 consecutive days following the nadir that the absolute neutrophil count is at least 500/ μ l. Platelet recovery: defined as the first day that the platelet count is at least 20 thousand/ μ l without a transfusion in the preceding 7 days. Non-engraftment; Secondary graft failure; Graft rejection The endpoints of secondary graft failure and graft rejection involved clinical evaluation, therefore, cannot purely be derived from the data in the database.
Other safety related outcomes	AEs collected prospectively as outlined	AEs, SAEs, deaths, PTLD

Table 8: Study IM101311 Objectives and Endpoints Based on BMS SAP

Objective	Endpoints	Endpoint Definition
	in the original study protocol • AEs collected retrospectively to align with the FDA request for additional safety data • AEs of special interest • Safety summaries based on laboratory test results	
Exploratory		
To assess pharmacokinetics of abatacept in combination with standard GVHD prophylaxis regimen in URD HSCT for patients with hematological malignancies	Serum concentration of abatacept	
To assess immunogenicity of abatacept in combination with standard GVHD prophylaxis regimen in URD HSCT for patients with hematological malignancies	Positive immunogenicity response up to Day 180.	

Source: Table 3.5.1-1 in the IM101311 Primary CSR

FDA Assessment:

The FDA agrees with the Applicant's description of the study objectives and endpoints in Table 8. The pre-specified primary efficacy endpoint was severe acute GVHD free survival (GFS) up to Day 180 which included all severe (Gr III/IV) acute GVHD events and all cause deaths up to Day 180 post-transplant follow-up for 8/8 MUD cohort.

Of note, the review of efficacy in this BLA application is based on pre-specified objectives and endpoints according to BMS SAP. The primary and key secondary efficacy objectives in Table 8 was for comparison between the abatacept + standard GVHD prophylaxis and standard GVHD prophylaxis regimen based on 8/8 MUD cohort only. The secondary objectives and endpoints in Table 8 applied to both 8/8 MUD cohort and 7/8 MMUD cohort. The efficacy assessment for 7/8 MMUD cohort was considered a secondary objective in Study IM101311.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The pre-specified primary endpoint in the Investigator Protocol was defined as cumulative severe (Grade [Gr] III-IV) aGVHD incidence rate up to 100 days post-transplant. Based on FDA's guidance that the endpoint to support an indication for prevention of aGVHD is GFS with a minimum of 180 days of follow-up, Bristol Myers Squibb (BMS) created an independent SAP, while the 8/8 MUD cohort was still blinded and ongoing.

Considerations for Sample size Power: The sample size of 40 patients in the 7/8 MUD cohort as computed in the protocol was derived for the comparison of the cumulative incidence of Grade III-IV aGVHD by Day 100 to the cumulative incidence of Grade III-IV aGVHD by Day 100 in control subjects from the CIBMTR database. The estimate of cumulative incidence of Grade III-IV aGVHD by Day 100 for the 7/8 matched transplant control group (CNI+MTX for GVHD prophylaxis) was 30%. The Bayesian probability to detect a reduction of 20% in rate of Grade III-IV aGVHD by day 100 with abatacept and 1-sided Bayesian type I error probability of 0.18 using a 1:2 case control matching ratio, and 40 patients in the 7/8 matched group and 80 for the control group was 96%.

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 incidence of cumulative Grade III-IV aGVHD at Day 100 in the standard arm was estimated to be 20% for the patient population be enrolled in this study. In order to detect an absolute reduction of 10% in the incidence of severe GvHD in the investigational cohort, a group size of 70 would be required to achieve at least 80% Bayesian power, using a Bayesian Type I error probability of 0.2. Thus, the total targeted enrollment for the randomized stratum of 8/8 matched transplant recipients was 140 patients.

For the purpose of the pre-planned analysis per the BMSSAP, GFS up to Day 180 was 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 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)

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

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 between the treatment arms, with approximately 81% power when the true hazard ratio (HR) of the abatacept arm relative to control was 0.34. This assumed the median GFS was about 13 months and 38 months in the standard treatment only arm and abatacept arm, respectively, with a follow-up of 6 months (180 Days) post-transplantation.

The **key secondary objective** was to compare the cumulative incidence of adjudicated severe (Gr III-IV) aGVHD up to Day 180 post-transplant between subjects with hematologic malignancies who received the abatacept + standard GVHD prophylaxis regimen and the standard GVHD prophylaxis regimen only, following URD HSCT. Other secondary endpoints included OS, moderate (Gr II-IV) GFS, DFS (also known as relapse-free survival, RFS), and TRM.

Details on the methods used during study conduct and during analysis and reporting to assure the quality of the data are provided in the protocol.

Efficacy Analyses: primary and key secondary endpoints

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 variables.

The primary and key secondary efficacy analyses (defined in Table 8) were performed using the Modified Intent-to-treat (MITT) analysis population; MITT analysis population includes all randomized and transplanted subjects who received at least one dose of study medication. This population was used for all efficacy analyses specified in the SAP. Analyses using the MITT analysis population grouped the subjects according to the treatment arm to which they were randomized. Randomized subjects who were never treated were excluded from all analyses. This is referred to as the treated and transplanted subjects. In the 8/8 MUD cohort, all treated subjects received the treatment to which they were randomized, therefore, efficacy from all subjects were analyzed and presented according to the treatment group assignment. The primary and key secondary analyses were to be repeated using the per-protocol analysis population if more than 10% of subjects in any treatment arm met the criteria for a relevant protocol deviation. All other efficacy analyses were performed using the MITT analysis population, unless otherwise specified.

Time to event analyses up to Day 180 include all events up to Day 225, which is the upper limit of the Day 180 visit interval as defined in the SAP. Censoring for endpoints that include aGVHD was done at the date of the Day 180 aGVHD assessment.

Safety: All safety presentations were based on the As Treated Analysis population and presented by treatment arms. No statistical testing was done for treatment differences with respect to frequencies of AEs or changes in clinical laboratory tests from baseline (last measurement prior to start of study medication). The overall safety analyses were presented separately for the Day 180 Analysis period and the post-transplantation, except otherwise stated.

For all reported AEs, SAEs, serious infections, infections and autoimmune disorders, frequency of subjects experiencing events were presented and a by-subject listings of all AEs were generated. Changes in clinical laboratory test results from baseline were summarized.

Exploratory Endpoints: The incidence of a positive immunogenicity response relative to baseline was summarized for the abatacept and placebo treatment groups through Day 180. The number (and percentage) of subjects with positive samples relative to baseline was summarized and provided by

antibody specificity, and overall results.

Pharmacokinetic analyses were based on determinations of the serum concentrations of abatacept at protocol-specified time points. Tabular presentation of PK variables and descriptive statistics including geometric means and coefficients of variation for C_{min} and C_{max} at Day -1, Day +5, Day +14, and Day +28, by cohort (7/8 MMUD and 8/8 MUD).

FDA Assessment:

The FDA in general agrees with the Applicant's description of the SAP and amendments.

FDA notes that the pre-specified analysis population was the MITT population as opposed to the ITT population. According to the SAP, the MITT population included all randomized and transplanted subjects who received at least one dose of study medication. Subjects who did not receive study medication were excluded from the analyses. Based on the Applicant's data, 4 subjects who were randomized but not treated nor transplanted were excluded from the MITT population.

Reviewer's comment: Note that ICH E9 generally recommends the use of the ITT population the efficacy analyses. ICH E9 notes that in some situations, it may be reasonable to eliminate from the set of all randomized subjects any subject who took no trial medication, particularly when the decision of whether to begin treatment could not be influenced by knowledge of the assigned treatment. In this case, IM101311 was double-blind; note also that all endpoints were defined from the date of transplantation, which is not defined for the subjects excluded in the MITT analysis.

According to protocol, interim analysis for efficacy was planned after the 100th subject enrolled in the 8/8 MUD cohort reached day 100 (50 subjects per group). Based on Bayesian power for detecting a 10% decrease in the incidence of grade III-IV aGVHD rate and the corresponding Bayesian type I error probability, the planned stopping criteria for efficacy was $P(\theta_{\text{placebo}} > \theta_{\text{treat}} \mid \text{data}) > 0.8$. At the time the SAP was finalized, the interim analysis had occurred, and the study was continued to end of enrollment and follow-up of subjects as specified in the protocol.

Of note, the primary endpoint specified in the BMSSAP was Grade III/IV GFS up to Day 180 post-transplantation. The date of transplantation was defined as the study Day 0 and was used to derive the time to event variables for the efficacy analyses. The alpha level of 0.05 in this portion of Assessment Aid provided by the Applicant was at the two-sided level of significance.

Protocol Amendments

The Applicant's Description:

The original protocol for this study was dated 12-May-2012. As of the 06-Nov-2020 database lock, there were a total of 17 global revisions (with 17 global amendments); there were no country specific amendments. Key study level changes to Study IM101311 issued after the original protocol are provided in the table below.

Table 9: Key Study Level Changes to Study IM101311

Document (Amendment) Date of Issue Date of IRB Approval	Key Changes in Study Design	Planned Sample Size	Rationale	Total Subjects Randomized at Time of the Amendment
Original Protocol 12-May-2012 12-Sep-2012 Protocol amendment 12-Dec-2012 01-Jan-2013	NA The main changes to were: (i) increased accrual from 92 to 104 and (ii) revised interim analysis and stopping guidelines.	92 104	Rationale for increased accrual: The first IRB-approved protocol (approved only at the Chair’s institution) facilitated multiple protocol-initiation activities (including grant applications), but underwent a planned revision immediately after approval, including a move to the REDCap database and the changes to accrual discussed here. The changes in accrual were the result of refinements in: Changes in estimates of Grade III-IV aGVHD in the placebo arm. This Protocol amendment altered the Type 1 error used for the study, based on increasing acceptance of a ‘screening Phase 2’ design, as endorsed by Cancer Therapy Evaluation Program (CTEP). The combination of the change in expected effect size and the use of a Type 1 error of 0.2 for sample size calculations, leading to a change in the required accrual from 92 (the original protocol dated 12-May-2012) to 104 (the protocol amendment dated 12-Dec-2012 protocol). Rationale for revised interim analysis and stopping guidelines: In the original protocol, the safety and efficacy analyses were not planned for the same patient accrual milestones (efficacy at 20, 40, and 70 patients, safety at 10, 20, and 35 patients). In the protocol amendment dated 12-Dec-2012, these interim analyses (and linked statistical analyses for stopping guidelines) were refined to dictate that interim analysis would occur after the 10 th , 20 th , 40 th , 70 th subjects, with efficacy assessed after the 20 th , 40 th , and 70 th subjects and safety assessed at all 4 time points.	0 0
Revised Protocol (v.3.3) Protocol amendment <u>10-Dec-2013</u>	The main change was revised interim analysis plan	104	Based on advice from the study’ DSMC, the IM101311 study committee eliminated the interim efficacy analyses that were planned for after enrollment of the 20 th and 40 th subjects. The DSMC provided feedback that, irrespective of the results from this small number of patients, they would not advise stopping the study, and therefore recommended to eliminate the planned interim analyses.	30

71

Version date: January 2020 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table 9: Key Study Level Changes to Study IM101311

Document (Amendment) Date of Issue Date of IRB Approval	Key Changes in Study Design	Planned Sample Size	Rationale	Total Subjects Randomized at Time of the Amendment
10-Apr-2014 Revised Protocol (v.4.0) Protocol amendment 09-Aug-2014 14-Dec-2014	The main changes were: (i) created separate treatment stratum for the 7/8 cohort and (ii) changed GVHD hypothesis	105	The study committee agreed to follow the DSMC suggestion. Rationale for separate treatment stratum for the 7/8 cohort: This revision was based on feedback from treating physicians, and the study committee regarding very slow enrollment for 7/8 HLA-matched subjects. Treating physicians noted that the risk of being randomized to the placebo group was too great, given the increasing knowledge that 7/8 HLA-matched patients did very poorly without adjunctive immunosuppression. Thus, equipoise no longer existed for 7/8 HLA-matched patients; concomitantly, investigators expressed a disinclination to enroll recipients of 7/8 MMUD if they could be randomized to the placebo arm of the study. Because of this, working with the CIBMTR, the IM101311 study committee created a separate, non-randomized 7/8 stratum, that was compared to pre-specified historic controls from the CIBMTR. Rationale for change of GVHD hypothesis: The decision to change the endpoint from Grade III-IV to Grade II-IV aGVHD came after discussions with the IM101311 study committee and the CIBMTR. The team decided that, given the prevailing risks of Grades II-IV aGVHD in both 7/8 and 8/8 HLA-matched patients, that this would be a meaningful endpoint, and, by changing the hypothesis to Grade II-IV aGVHD, the number of patients needed to accrue to the trial remained essentially unchanged, thus helping with the feasibility of the trial. Rationale for increased accrual: This was based on a recommendation by the DSMC to seek statistical advice in determining the feasibility of returning to the original primary endpoint (Grade III-IV aGVHD) by increasing the sample size. Based on the advice from DSMC and based on ongoing discussions with the study committee and the CIBMTR, the IM101311 study committee decided to return to the original primary endpoint, and therefore, increased the sample size accordingly. Rationale for updated GVHD hypothesis: In this amendment, the hypothesis was returned to the original hypothesis of the study. The rationale for returning to the	35
Revised Protocol (v.6) Protocol amendment 08-Oct-2015 09-Jan-2016	The main changes were: (i) increased accrual and (ii) updated GVHD hypothesis.	180		94

72

Version date: January 2020 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table 9: Key Study Level Changes to Study IM101311

Document (Amendment) Date of Issue Date of IRB Approval	Key Changes in Study Design	Planned Sample Size	Rationale	Total Subjects Randomized at Time of the Amendment
Revised Protocol (v.7) Protocol amendment 17-May-2016 06-Jul-2016	The main change was updated eligibility criteria.	180	Grade III-IV aGVHD-based hypothesis was that, while Grade II-IV aGVHD endpoints are clinically meaningful, it is Grade III-IV (severe) aGVHD that causes the most mortality after transplant, and thus, if possible, the study should be powered for this endpoint. Rationale for updated eligibility criteria: Hodgkin’s disease (HD) and Non-Hodgkin’s Lymphoma (NHL) updated criteria. This change was made because it became clear that some treating physicians decided to take HD and NHL patients to an allogeneic transplant without a prior autologous transplant. This amendment allowed patients with germline mutations in RUNX1, GATA2, DDX41 and other genes that predispose patients to developing leukemia without impacting their risks for transplant related complications or secondary solid tumors to be enrolled in Study IM101311. These changes reflect updated information about genetic predisposition to non-hematologic cancers and excessive sensitivity to standard pre-transplant conditioning agents that render some patients ineligible for the IM101311 study ³⁷	126
Revised Protocol (v.9) Protocol amendment 06-Nov-2017 15-Nov-2017	The main change was added secondary endpoints of severe GFS and cumulative incidence of severe aGVHD up to Day 180	180	Rationale for addition of 2 secondary endpoints: At the 25-Jul-2017 Pre-IND meeting, results of the 7/8 MMUD cohort were presented to the FDA. The FDA provided guidance that the endpoint to support an indication for prevention of aGVHD is GFS after a minimum of 180 days of follow-up. The FDA agreed that BMS could create an independent SAP, while the 8/8 MUD cohort was still blinded and ongoing, with GFS up to Day 180 as the pre-specified primary endpoint. The BMS SAP was submitted to the FDA, and the Investigator Protocol was amended to include GFS up to Day 180 as one of the secondary endpoints.	186

Source: Study Protocol (Appendix 1.1 of the IM101311 Primary CSR)

FDA Assessment:

The FDA agrees with the Applicant’s summary of the protocol amendments in Study IM101311.

8.1.2 Study Results from IM101311 Compliance with Good Clinical Practices

The Applicant's Position:

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Council for Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The protocol, amendments, and subject informed consent received appropriate approval by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to initiation of study at the site.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The rights, safety, and well-being of the study subjects were the most important consideration and prevailed over the interests of science and society.

CIBMTR site monitors (unblinded to study assignment) were contracted to perform routine site monitoring visits at regular intervals according to the site monitoring plan (SMP) for the study. Study monitors performed ongoing source data verification to confirm that data entered into the CRF by authorized site personnel were accurate, complete, and verifiable from source documents; the safety and rights of subjects were being protected; and the study was being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

FDA Assessment:

We confirm the Applicant's position.

Financial Disclosure

The Applicant's Position:

Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the IM101311 clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

FDA Assessment:

We confirm the Applicant's position. (b) (6)

(b) (6) She has already received \$45,000 as her (b) (6) and has the potential to receive up to a total of \$201,000. Of note, (b) (6) IM101311 was already fully accrued and the primary endpoint of the trial had been reached. Furthermore, (b) (6) recused herself from the adjudication or review of all safety and efficacy endpoints to avoid potential conflicts of interest. (b) (6)

Patient Disposition

Data:

Table 10: Disposition of Subjects in the 8/8 MUD Cohort - IM101311

	Number of Subjects		
Screening Period			
Enrolled			146
Randomized			146
Abatacept			74
Placebo			72
Randomized, Treated With Study Medication, And Transplanted (A)			142
Abatacept			73
Placebo			69
Post-transplantation Period	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)
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)
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)

(A) MITT population

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

Source (ADaM dataset): Table S.2.1.2.1 (ADSL, Screening period); Table S.2.2.1.1 (ADSL, Post-transplantation period) in the IM101311 primary CSR

Table 11: Disposition of Subjects in the 7/8 MMUD Cohort - IM101311

	Number of Subjects
Screening Period	
Enrolled (A)	46
Enrolled, Treated With Study Medication, And Transplanted	44
Randomized But Not Treated With Study Medication (B)	1
Abatacept	0
Placebo	1
Randomized, Treated With Study Medication, And Transplanted	4
Abatacept	3
Placebo	1
Post-transplantation Period	Abatacept (N = 43)
Number of Subjects Who Discontinued Treatment	8 (18.6)
Reasons for Discontinuation of Treatment	
Relapse	4 (9.3)

Table 11: Disposition of Subjects in the 7/8 MMUD Cohort - IM101311

	Number of Subjects
Refusal of Further Protocol Therapy by Patient/Parent/Guardian	2 (4.7)
Other	2 (4.7)
Number of Subjects Completing Day 180 Visit	43 (100.0)
Number of Subjects Discontinued Study Post Day 180 Visit	6 (14.0)
Death	6 (14.0)

(A) Subjects enrolled after amendment 4: all subjects were assigned to abatacept

(B) Assignment failures

study medication is 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.

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

Source (ADaM dataset): Table S.2.1.2.2 (ADSL, Screening Period); Table S.2.2.1.2 (ADSL, Post-transplantation period) in the IM101311 primary CSR.

The Applicant's Position:

8/8 MUD Cohort MITT Analysis Population: There were 146 subjects enrolled in the 8/8 MUD cohort of the study. Of those, 142 were treated: 73 with abatacept and 69 with placebo. Among the treated 8/8 MUD subjects, 14 (19.2%) subjects in the abatacept group and 18 (26.1%) in placebo group discontinued treatment (Table 10) [Table S.2.1.2.1 [ADaM dataset: ADSL] and Table S.2.2.1.1 [ADaM dataset: ADSL] in the IM101311 Primary CSR. The most frequent reason for discontinuation in both groups was relapse of the underlying malignancy.

7/8 MMUD Cohort Treated Analysis Population: In the 7/8 MMUD cohort of Study IM101311, of the 46 subjects enrolled, 44 were treated with study medication and transplanted; 43 subjects were treated with abatacept (including 3 prior to Amendment 04). One additional subject was randomized to placebo group prior to Amendment 04 (Table 11) in the IM101311 Primary CSR. Among the treated subjects, 8 (18.6%) discontinued treatment; relapse of the underlying malignancy was the most frequent reason for discontinuation.

FDA Assessment:

The FDA agrees with the Applicant's summary of subject disposition. Discontinuation of treatment due to relapse and death prior to the day 180 visit were numerically lower in the abatacept arm compared to the placebo arm in the 8/8 MUD Cohort MITT population. Relapse was the most common reason for discontinuation of study treatment for both 8/8 MUD Cohort and 7/8 MMUD cohort.

The Applicant's summary of subject disposition events was based on data with clinical database lock date November 6, 2020. The first subject first visit date was on 4/15/2013 and the last subject last visit was on 11/17/2018. The 8/8 MUD cohort and 7/8 MMUD cohort had the same enrollment period and duration.

Protocol Violations/Deviations

The Applicant's Position:

Relevant Protocol Deviations (RPDs) are Important Protocol Deviations (IPDs) that could affect the interpretability of key study results, are programmable deviations from the clinical database and are protocol-specific; they are predefined in the SAP (Section 7.2 of Appendix 1.11 in the IM101311 primary

CSR).

No deviations met the criteria for relevant protocol deviations in this study.

FDA Assessment:

We agree with the Applicant’s assessment.

Table of Demographic Characteristics

Data:

Table 12: Demographic Characteristics: 8/8 MUD Cohort MITT Analysis Population - IM101311

	Abatacept N = 73	Placebo N = 69	Total N = 142
AGE (YEARS)			
MEDIAN (Min, Max)	44.0 (6, 71)	40.0 (7, 74)	43.5 (6, 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)
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)
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)

Source (ADaM dataset): Table S.3.1A.1.S (ADSL) in the IM101311 Primary CSR.

Table 13: Demographic Characteristics - 7/8 MMUD Cohort Treated Analysis Population - IM101311

	Abatacept N = 43
AGE (YEARS)	
MEDIAN (Min, Max)	38.0 (6, 76)
AGE GROUP	
<= 21 (PEDIATRIC)	18 (41.9)
> 21 (ADULT)	25 (58.1)
GENDER	
MALE	27 (62.8)
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)

Source (ADaM dataset): Table S.3.1A.2.1 (ADSL) in the IM101311 Primary CSR.

The Applicant’s Position:

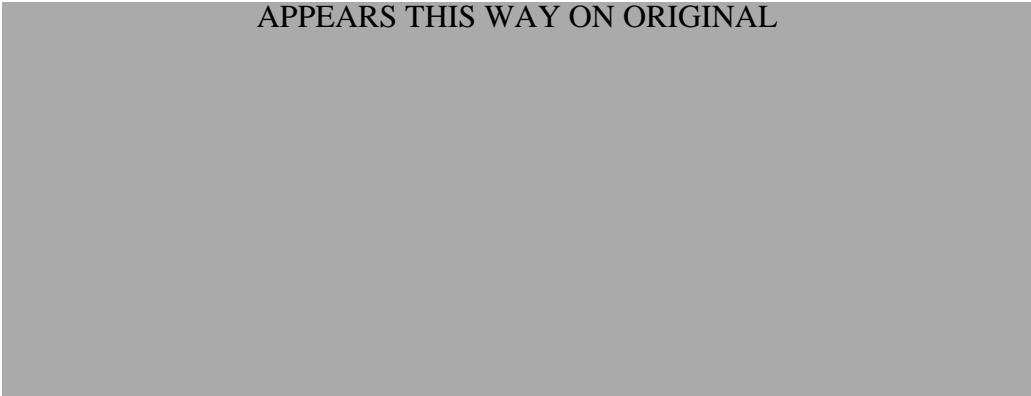
Baseline demographic characteristics for subjects in the 8/8 MUD cohort were balanced between the abatacept and the placebo groups (Table 12). Baseline demographic characteristics for abatacept treated subjects in the 7/8 MMUD cohort are presented in Table 13.

FDA Assessment:

The FDA agrees with the Applicant's summary of demographic characteristics. The majority of the study population in the 8/8 MUD cohort was white (142 subjects, 87%). The 7/8 MMUD population was still majority white subjects (72%) but did have a higher proportion of African Americans (16%) and Hispanic (16%) patients than the 8/8 MUD cohort, 3.5% and 4.2% for African Americans and Hispanic patients, respectively.

On the randomized, 8/8 cohort, randomization was stratified by baseline age category (≤ 21 years vs > 21 years). Demographic characteristics of randomized patients had a few imbalances, including the following (abatacept versus placebo): age ≥ 65 years 10% versus 17%, age ≥ 18 to < 65 years 71% versus 64%, and median weight 71.3 versus 76.7 kg.

APPEARS THIS WAY ON ORIGINAL



NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 14: Key Baseline Disease Characteristics: 8/8 MUD Cohort MITT Analysis Population - IM101311

	Abatacept N = 73	Placebo N = 69	Total N = 142
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 LYMPHOBLASTIC 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)
GMD 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

Table 14: Key Baseline Disease Characteristics: 8/8 MUD Cohort MITT Analysis Population - IM101311

	Abatacept N = 73	Placebo N = 69	Total N = 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 (CMEM)	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)

Source (ADaM dataset): Table S.3.2A.1.5 (ADSL) in the IM101311 Primary CSR.

ORENCIA (abatacept)

Table 15: IM101311 Baseline Disease Characteristics: 7/8 MMUD Cohort Treated Analysis Population - IM101311

	Abatacept N = 43
PRE-TRANSPLANT CMV (PATIENT)	
POSITIVE	28 (65.1)
NEGATIVE	15 (34.9)
PRE-TRANSPLANT CMV (DONOR)	
POSITIVE	20 (46.5)
NEGATIVE	23 (53.5)
PRE-TRANSPLANT EBV (PATIENT)	
POSITIVE	39 (90.7)
NEGATIVE	4 (9.3)
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 LYMPHOBLASTIC 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)
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)

Source (ADaM dataset): Table S.3.2A.2.1(ADSL) in the IM101311 Primary CSR

The Applicant's Position:

In the 8/8 MUD cohort, the most common type of malignancy among subjects was AML (36.6%). The majority of subjects (84.5%) received tacrolimus for GVHD prophylaxis. The most commonly used conditioning regimens were busulfan and cyclophosphamide (34.5%) and total body irradiation and chemotherapy (32.4%); see Table 14.

In the 7/8 MMUD cohort, the most common type of malignancy among subjects was AML (34.9%). The majority of subjects (62.8%) received tacrolimus for prophylaxis of aGVHD. The most commonly used conditioning regimen was busulfan and cyclophosphamide (30.2%); see Table 15.

FDA Assessment:

The FDA agrees with the Applicant's summary of baseline disease characteristics and prior therapies. They generally reflect the expected distribution of high-risk heme malignancies that are indications for URD transplant in the US.

On the randomized, 8/8 cohort, disease characteristics of randomized patients had some notable imbalances, as follows (listed as abatacept versus placebo): AML 41% versus 32%, CMML 1% versus 6%, CML 1% versus 7%, bone marrow graft 45% versus 38%, peripheral blood graft 55% versus 62%, Bu Cy conditioning 38% versus 30%, Bu Flu 10% versus 3%, and TBI + chemotherapy 27% versus 38%.

Treatment Compliance

The Applicant's Position:

A total of 16 study drug (abatacept or placebo) infusions were missed in the 8/8 MUD Cohort of study IM101311 (Appendix 4.2A.1 [ADaM dataset: ADEX] in IM101311 Primary CSR): 4 patients missed a total of 6 infusions in the abatacept group, and 8 patients missed 10 infusions in the placebo group. In the 7/8 MMUD Cohort, 1 patient received only one of the 4 protocol-specified infusions after having experienced an "allergic reaction" related to the first (Day 1) infusion; this patient's last 3 doses were the only ones documented as having been missed due to toxicity per se.

- In the 7/8 matched URD Cohort of study IM101311, of 43 abatacept treated patients, 1 developed an "ALLERGIC REACTION" (not otherwise specified) to the initial (Day 1) infusion and did not receive the remaining 3 protocol-specified doses of abatacept. [Note: This patient was not formally discontinued from assigned therapy in the database and does not appear as a discontinuation due to an adverse event in data report. The remaining 42 patients all received the full (4-dose) course of abatacept; thus, of 172 protocol-specified infusions of abatacept in this study Cohort, 169 (98.3%) were administered.
- In the 8/8 matched URD Cohort, of 73 abatacept treated patients, 69 (94.5%) received all 4 infusions of abatacept. The remaining 4 patients missed a total of 6 infusions (1 or 2 each); of them, each received at least 2 of the 4 protocol-specified infusions. None of the 6 missed infusions were attributed to a prospectively defined infusion-related reaction and none of the 4 patients were discontinued from abatacept for this reason.
 - Subject (b) (6), who received the protocol-specified infusions of abatacept on Days 1, 5, and 14, developed lower gastrointestinal aGVHD on Day 13 and did not receive the Day 28 dose.
 - The remaining 3 patients missed doses on Days 5 and 14, 14 and 28, and 28; the reasons for these missed infusions were not provided.
 - Overall, of (73 X 4) = 292 protocol-specified infusions of abatacept, 286 (97.9%) were administered.
- On the basis of the above analysis, it is concluded that, overall, abatacept infusions were well tolerated and that the small number of missed infusions will not have any substantive impact on the ability to assess the impact of abatacept, when added to a standard of care regimen for aGVHD prophylaxis, on GVHD-related or other outcomes, or the interpretation of overall study results and the conclusions drawn from them.

~~In the 8/8 MUD cohort, 16 infusions were missed in 12 subjects, 8 of whom were placebo treated and~~

~~4 abatacept-treated~~ All subjects in both the abatacept and placebo groups received concomitant medications, including methotrexate (100%) for aGVHD prophylaxis. In both groups, the most frequently used other medications for aGVHD prophylaxis were the calcineurin inhibitors and corticosteroids (Table S.4.16.2.1 [ADaM dataset: ADCM] in IM101311 Primary CSR).

In the 7/8 MMUD cohort, 1 subject missed 3 doses (Appendix 4.2A.2.1 [ADaM dataset: ADCM] in IM101311 Primary CSR). Methotrexate (100%) and tacrolimus (74.4%) were the most frequently used concomitant medications (Table S.4.16.2.2 [ADaM dataset: ADCM] in IM101311 Primary CSR).

FDA Assessment:

We agree with the Applicant’s assessment. Remarkably, most patients received all four planned doses of abatacept on the abatacept treatment arms (69/73 (95%) of 8/8 abatacept-treated patients and 42/43 (98%) of 7/8 abatacept-treated patients received all 4 of the intended doses of study drug). The few reasons for not receiving all planned doses varied without a clear pattern to suggest toxicity or intolerance.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 16: Primary Endpoint Efficacy Results - IM101311

Efficacy Parameters	8/8 MUD Cohort MITT Analysis Population		7/8 MMUD Cohort As Treated Analysis Population	
	Abatacept (N = 73)	Placebo (N = 69)	Abatacept (N = 43)	
Primary Endpoint per BMS SAP^a				
Grade III-IV aGVHD Free Survival (GFS)				
Events, n (%)	10 (13.7)	17 (24.6)	2 (4.7)	
Survival Rate ^b (95% CI)				
Day 100	0.92 (0.83, 0.96)	0.83 (0.71, 0.90)	0.98 (0.85, 1.00)	
Day 180	0.89 (0.79, 0.94)	0.77 (0.65, 0.85)	0.98 (0.85, 1.00)	
HR ^c (95% CI)	0.54 (0.25, 1.19); P = 0.1223 ^d		NA	
Sensitivity analysis^e				
GFS rate up to Day 180	93.0%	80.0%	98%	
HR ^b (95% CI)	0.34 (0.12, 0.96); P-value = 0.0324 ^c		NA	
Primary Endpoint per Investigator protocol	Abatacept (N = 73)	Placebo (N = 69)	Abatacept ^g N = 38	Historic Controls (No-ATG) N = 123
Grade III-IV aGVHD Cumulative Incidence Rate				
Day 100 Cumulative Incidence Rate (95% CI)	0.07 (0.03, 0.15)	0.16 (0.09, 0.28)	0.00 (NA, NA)	0.31 (0.23, 0.39)
HR ^f (95% CI)	0.41 (0.14, 1.17)		NA	

^a 7/8 MMUD Cohort analysis was secondary endpoint per BMS SAP

^b Based on Kaplan-Meier estimates

^c 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.

^d Log-rank test stratified by age group at randomization (≤ 21 years vs > 21 years)

^e Subjects were censored at the time of relapse

^f based on Day 180 Incidence Rate

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

^g Only 38 out of the 43 patients in the 7/8 cohort had at least one No-ATG matched control

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

Source (ADaM dataset): Table S.5.1.1.S (ADSL [MITTFL = Y], ADTTE [PARAMCD = G34FS180]); Table S.5.1B.1.S (ADSL [MITTFL = Y], ADTTE [PARAMCD = G34FS180 or S34FS180]); Table S.5.1.4.S (ADTTE (G34FS180); Table S.5.1.2.1 (ADTTE [PARAMCD = CIGFS180], GFS 7/8 cohort); Table S.5.3.1B.S (ADTTE [PARAMCD = CIGFS180], unstratified cumulative incidence) 8/8 cohort); Table S.5.3.2.4 (ADTTE, cumulative incidence 7/8 cohort matched control) in the IM101311 Primary CSR.

Table 17: Comparison of Grade III/IV aGVHD Free Survival (GFS) During the Day 180 Analysis Period: 7/8 Cohort As Treated Analysis Population versus Historic Controls - IM101311

Endpoints/NoATG	Abatacept n/N (%)	Historic Controls n/N (%)
Grade III-IV GFS Event	10/38 (26.3)	83/126 (65.9)
Day 100 Survival Rate ^a (95% CI)	1.00	0.63 (0.54, 0.70)
Day 180 Survival Rate ^a (95% CI)	1.00	0.55 (0.46, 0.63)
HR ^b (95% CI)	0.26 (0.12, 0.58); P-value = 0.0004	
Gr II-IV GFS Event		
GFS Event	16/38 (42.1%)	87/126 (69.0%)
Day 100 Survival Rate ^a (95% CI)	0.61 (0.43, 0.74)	0.40 (0.32, 0.49)
Day 180 Survival Rate (95% CI)	0.61 (0.43, 0.74)	0.33 (0.25, 0.42)
HR ^b (95% CI)	0.48 (0.27, 0.87); P-value = 0.0127 ^c	
Overall Survival (OS)		
OS (up to Day 180)	1/38 (2.6%)	47/127 (37.0%)
OS (up to DBL)	10/38 (26.3)	75/127 (59.1)
Day 100 Survival Rate ^a (95% CI)	1.00	0.86 (0.78, 0.91)
Day 180 Survival Rate ^a (95% CI)	1.00	0.74 (0.65, 0.81)
HR ^b (95% CI) (up to Day 180)	0.07 (<0.01, 0.48); P-value = 0.0004 ^c	
HR ^b (95% CI) (up to Day DBL)	0.37 (0.17, 0.78); P-value = 0.0070 ^c	

^a Based on Kaplan-Meier estimates

^b Cox proportional hazards model stratified by matched-pairs with treatment as the only covariate. Hazard ratio is Abatacept over historic control

^c Log-Rank test stratified by matched-pairs.

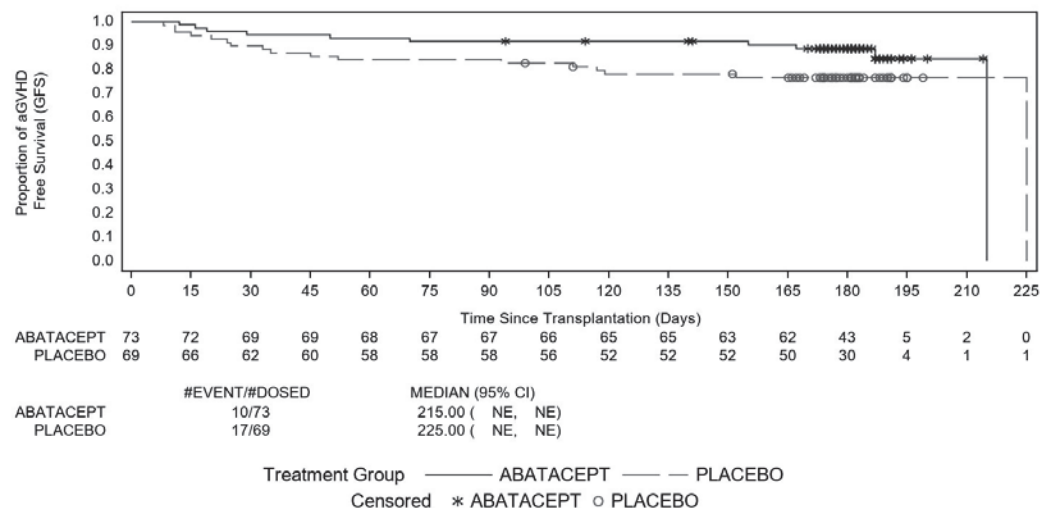
For GFS, n = Number of subjects with GFS event (Grade III/IV aGVHD or death), N = Total number of subjects in the Treatment Group.

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

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

Source (ADaM dataset): Table S.5.7.2.4 (ADTTE [PARAMCD=G34FS180]), Grade III-IV GFS); Table S.5.4.2.4 (ADTTE [PARAMCD=G24FS180]), Grade II-IV GFS); Table S.5.5.2.2.4 (ADTTE [PARAMCD=OS180]) OS up to Day 180); Table S.5.5.2.1.4 (ADTTE [PARAMCD=OS]; OS up to DBL) in the IM101311 primary CSR

Figure 9: Kaplan-Meier Plot of Grade III-IV GFS up to Day 180 Visit: 8/8 MUD Cohort MITT Analysis Population - IM101311



Symbols represent censored observation.

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

NE: Not Estimable.

Source (ADaM dataset): Figure S.5.1.1.S (ADSL [MITTFL = Y], ADTTE [PARAMCD = G34FS180]) in the IM101311 primary CSR

The Applicant’s Position:

The IM101311 clinical trial was designed to examine the impact of abatacept+SOC therapy on the incidence of aGVHD in recipients of HSCTs from 8/8 MUD. In the MITT analysis population of the 8/8 MUD cohort, treatment with abatacept was associated with a higher rate severe aGVHD-free survival (GFS) up to Day 180 post-transplantation, when compared with that of placebo group (Table 16 and Figure 9), although 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-value = 0.1223). Consistent with the primary analysis, in the pre-specified sensitivity analysis wherein subjects were censored at the time of relapse, the rate of severe GFS up to Day 180 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-value = 0.0324).

The pre-specified endpoint of the ISR protocol was defined as the cumulative incidence of severe (Gr III-IV) aGVHD up to 100 days post-transplant (which differed from that specified in the BMSSAP). Day 180 severe GFS was a key secondary endpoint. In the 8/8 MUD cohort, addition of abatacept resulted in a decrease in severe aGVHD rate at Day 100 from 16% in placebo to 7% in subjects receiving abatacept.

In the As Treated Analysis Population of the 7/8 cohort, the addition of abatacept to a CNI and MTX-based prophylactic regimen significantly improved GFS compared to matched controls (Table 17).

FDA Assessment:

FDA adjudicated the GFS results to ensure that the time-to-event analyses were traceable to the reports of clinical events. FDA found that the grading of aGVHD events from reported organ system stages were inline with the FDA calculated grading conducted per the Blood and Marrow Transplant Clinical Trials Network Manual of Procedures (version 2, 2005) using NIH consensus criteria. It is important to note

that use of other grading systems would give slightly different results for grade. However, most of this difference would be in the calling of grade III versus Grade IV and would not have affected the endpoints as currently grouped (i.e. moderate-severe Grade II-IV and severe Grade III/IV).

The FDA did not agree with derivation of event timing for these endpoints. Per the SAP, the primary GFS endpoint was prespecified as the time from transplant until first date of documented severe (Gr III/IV) aGVHD or death due to any cause up to day 180 post-transplant. It was similarly defined for moderate to severe (Gr II/IV) GFS endpoints. The censoring scheme for these endpoints states that the date of documented severe or moderate-severe aGVHD is the event day for the grade III/IV or grade II/IV endpoints, respectively. However, FDA found disagreement with this timing in more than half of the events. FDA discovered that this was due to the algorithm used to calculate these dates with discrepancies caused by three main issues, as follows:

1. The day that an event was called was when any GVHD that was not grade 1 and resolved first occurred. For example, if a patient had grade II aGVHD on day 50 and was found on day 100 to have grade III aGVHD, the algorithm gave the day 50 as the event day for the grade III/IV endpoint, not day 100 when the severity was actually noted to be grade III.
2. Some events were defined as starting when a patient recalled the onset of symptoms, as opposed to when the event was first documented.
3. The co-occurrence of chronic GVHD at the same time as aGVHD, also known as overlap syndrome, was not counted towards aGVHD events. The Applicant's initial analysis treated these overlap cases as non-events for aGVHD endpoints despite patients having cases where the acute component was of moderate or severe grade. The Applicant's SAP noted that overlap syndrome would be captured but did not specify how it would be incorporated or censored for aGVHD events. Events of chronic GVHD occurrence, without any component of aGVHD, were not counted for aGVHD events, which FDA agrees with. However, FDA took issue with not counting the moderate or severe aGVHD component of an overlap syndrome case solely because it contained some features of chronic GVHD. FDA considered the occurrence of the moderate or severe aGVHD to be the more clinically important feature of such overlap cases. Therefore, FDA counted grade II-IV aGVHD that occurred as part of an overlap syndrome toward their respective aGVHD endpoints.

FDA noted these findings to the Applicant so that they could adjust their algorithm and rerun their analyses. While the absolute values changed, the same overall conclusions were reached.

The updated Grade III-IV GFS rates up to Day 180 for the 8/8 cohort were 87% (95% CI: 77%, 93%) in abatacept arm and 75% (95% CI: 63%, 84%) in placebo arm, respectively. The updated HR was 0.55 (95% CI: 0.26, 1.18) and a two-sided stratified log-rank p-value of 0.1215.

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

The primary efficacy endpoint for comparison of abatacept group with placebo group was Grade III-IV acute GVHD free survival (GFS) up to Day 180 stratified by age group at randomization on the MITT population of the 8/8 MUD cohort. The study did not meet its primary objective to show superiority of abatacept group compared to placebo group. The estimated HR was 0.55 (95% CI: 0.26, 1.18) and a two-sided stratified log-rank p-value of 0.1215. The result was not statistically significant when compared to the 0.05 significance level.

According to the BMSSAP, the following sensitivity analyses for the primary endpoint were planned and the numerical results can be reproduced by the statistical reviewer. Note that the analyses presented below were conducted on the original dataset prior to the adjudication process.

According to the BMSSAP, the following sensitivity analyses for the primary endpoint were planned and the numerical results can be reproduced by the statistical reviewer. Note that the analyses presented below were conducted on the original dataset prior to the adjudication process.

1. GFS using unstratified multivariate Cox regression model to estimate the treatment effect with adjustment for the baseline prognostic factors, i.e., gender, age group, ethnicity, disease status, type of transplant received (BM, PBSC, CMBM), Conditioning regimen (TBI, BUS + CYC, MELF + FLUD, BUS + FLUD), Malignancy (ALL, AML, MDS, Other) and GVHD prophylaxis at transplant (tacrolimus, cyclosporine). The results are presented in Table 18.

Table 18: Sensitivity Analysis of Grade III-IV GFS at Day 180 in the 8/8 cohort of IM101311 - Unstratified Multivariate Cox Regression Model Adjusted for Baseline Prognostic Factors

	HR (95% CI)
Treatment [Abatacept vs Placebo (Ref)]	0.46 (0.19, 1.13)
Gender [Male vs Female (Ref)]	0.61 (0.25, 1.49)
Age group [> 21 years vs ≤21 yrs (Ref)]	1.49 (0.37, 6.01)
Ethnicity [not Hispanic vs Hispanic (Ref)]	0.41 (0.04, 3.92)
Disease status	
Intermediate vs Early	0.80 (0.24, 2.68)
Advanced vs Early	5.95 (1.05, 33.76)
Complete Metabolic Response vs Early	NA
Any Disease Status with the Exception of Complete Metabolic Response vs Early	NA
Type of transplant received	
CMBM vs BM	NA
PBSC vs BM	0.90 (0.31, 2.61)
Conditioning regimen	
BUS + CYC vs TBI	1.78 (0.36, 8.92)
MELF + FLUD vs TBI	1.15 (0.28, 4.77)
BUS + FLUD vs TBI	4.36 (0.65, 29.40)
Malignancy	
AML vs ALL	0.30 (0.07, 1.25)
MDS vs ALL	0.08 (0.01, 0.75)

Other vs ALL	0.22 (0.03, 1.39)
GVHD prophylaxis at transplant [Cyclosporine vs Tacrolimus (Ref)]	0.82 (0.20, 3.42)

Source: Generated by statistical reviewer using the adtte.xpt dataset.

2. The primary efficacy analysis was repeated using an unstratified Cox regression model on the MITT population. The estimated HR was of 0.54 (95% CI: 0.25, 1.20).
3. The primary efficacy analysis repeated using stratified Cox regression model on Per-protocol (PP) population. The PP population was defined as MITT population which excludes the subjects with relevant protocol deviations. Based on the analysis data, the MITT population and PP population were identical so the analysis results from these two populations were the same.
4. The primary efficacy analysis was repeated with censoring for relapse. Subjects were censored at the time of relapse which was considered to trigger a start of change in medication. The censoring for relapse further reduced the number of GFS events such that 92% subjects were censored in abatacept group and 81% subjects were censored in placebo group. The estimated HR was of 0.34 (95% CI: 0.12, 0.96).

Per ICH E9 guideline, the FDA conducted ITT analysis as sensitivity analysis for 8/8 cohort. According to study procedure, subject was randomized before having transplantation and the study day 0 was defined as the date of transplantation. However, there were 4 subjects that were randomized but did not receive following transplantation and therefore were removed from primary analysis (MITT population). These subjects were included in the ITT analysis. One subject was randomized to abatacept arm and the other 3 were randomized to placebo arm. These 4 subjects did not report any Gr III-V GFS event, Gr II-V GFS event or death within 180 days after randomization and therefore were censored at Day 225. In the ITT analysis, the time to event was calculated starting from randomization date comparing to the MITT analysis which the time to event was calculated from transplantation date. The Grade III-IV GFS rates up to Day 180 post transplantation based on ITT population were 89% (95% CI = 79%, 94%) in abatacept arm and 78% (95% CI = 66%, 86%) in placebo arm with HR 0.55 (95% CI = 0.25, 1.22). The Grade II-IV GFS rates up to Day 180 post transplantation based on ITT population were 51% (95% CI = 0.39%, 62%) in abatacept arm and 36% (95% CI = 25%, 47%) in placebo arm with HR 0.58 (95% CI = 0.37, 0.90). The OS up to Day 180 post transplantation based on ITT population were 97% (95% CI = 0.90%, 99%) in abatacept arm and 84% (95% CI = 74%, 91%) in placebo arm with HR 0.33 (95% CI = 0.12, 0.94).

Reviewer's comment: Analyses using the ITT population yield similar results to the MITT population in the 8/8 cohort.

The cumulative incidence of severe (Gr III-IV) aGVHD up to 100 days post-transplant, defined as the primary endpoint in the ISR protocol was evaluated as an exploratory analysis. The cumulative incidence of severe aGVHD up to 100 days was assessed using competing risk analysis in which non-aGVHD related death and relapse prior to day 100 without grade 3-4 aGVHD were considered competing risks. The analysis was conducted using Fine and Gray model stratified by age group at randomization. The Day 100 cumulative incident rates for abatacept and placebo were 0.07 (95% CI: 0.03, 0.15) and 0.16 (95%

CI: 0.09, 0.28), respectively. The estimated HR based on Day 180 incidence rate was of 0.41 (95% CI: 0.14, 1.17).

The FDA does not agree with the Applicant's statement about the analysis results for the 7/8 MMUD cohort. In support of a 6/28/2019 meeting with FDA, the Applicant proposed a "historic control" for the 7/8 cohort based on subjects selected from the CIBMTR database. The FDA informed the Applicant that this analysis was not appropriate. First, FDA had concern with the overall adequacy of the matched cohort and the lack of details on the statistical methods. Imbalances in the demographic characteristics and baseline disease characteristics were observed and FDA had concern that the confounding effects from both observed imbalances and other unobserved factors could cause substantial bias. Second, FDA had concern with lack of pre-specification of the analysis, the selection of prognostic factors that might not be the most significant to impact on the primary endpoint, the observed imbalances between study subjects and controls in patient and transplant characteristic, and the lack of granularity in the GVHD data in the CIBMTR database. Lastly, FDA indicated that the lack of positive outcome in the randomized 8/8 cohort detracted from the plausibility of the results of the 7/8 cohort. Therefore, all analysis results for the 7/8 MMUD cohort vs. the "historic control" should be considered exploratory. In addition, the Applicant did not submit the historic control data (comparator) for the 7/8 MMUD cohort to FDA; thus, the results in Table 17 cannot be reproduced by FDA.

Data Quality and Integrity

The Applicant's Position:

Data review and quality control checks were implemented by the IM101311 Study Committee and consisted of site monitoring visits guided by the SMP to review source documents against the eCRF and data validation checks of the eCRF. Any issues or findings were followed up for resolution. Data was declared complete and accurate upon completion of monitoring and query resolution and completion of internal QC of subsets of data conducted by the Sponsor. When the database was declared complete and accurate for the study data through Day +365 post-transplant, the database through the Day +365 time point was locked.

FDA Assessment:

FDA agrees with the data quality and integrity assessment. Moreover, the ongoing COVID-19 pandemic did not affect the result of the trial because the last transplanted patient reached the day 365 milestone in November of 2018, a full year prior to the first reported cases of COVID-19.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 19: Efficacy of Abatacept and Placebo: 8/8 MUD Cohort MITT Analysis Population - IM101311

8/8 MUD Cohort MITT Analysis Population		
Efficacy Parameters	Abatacept (N = 73)	Placebo (N = 69)
Gr III-IV Severe aGVHD - Cumulative Incidence Rate		
Cumulative Incidence Rate (95% CI)		
Day 180 (≤ 21 years of age)	0.05 (0.02, 0.15)	0.12 (0.04, 0.36)
Day 180 (> 21 years of age)	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 ^a	
Gr II-IV aGVHD-Free Survival (GFS)		
Events, n (%)	36 (49.3)	47 (68.1)
Day 180 Survival Rate (95% CI)	0.50 (0.38, 0.61)	0.33 (0.22, 0.44)
HR ^c (95% CI)	0.55 (0.36, 0.86); P-value = 0.0069 ^d	
Overall Survival (OS)		
Deaths, n (%) (Up to Day 180)	5 (6.8)	13 (18.8)
HR ^c (95% CI)	0.33 (0.12, 0.93); P-value = 0.0281 ^d	
Deaths, n (%) (up to last contact prior to DBL)	24 (32.9)	29 (42.0)
Day 180 Survival Rate (95% CI)	0.97 (0.89, 0.99)	0.84 (0.73, 0.91)
Day 365 Survival Rate (95% CI)	0.84 (0.73, 0.90)	0.77 (0.65, 0.85)
Disease-Free Survival (DFS)		
Relapse or Death, n (%)	10 (13.7)	19 (27.5)
HR (95% CI) ^c	0.46 (0.21, 0.99); P-value = 0.0408 ^d	
Day 180 Survival Rate (95% CI)	0.88 (0.78, 0.93)	0.77 (0.65, 0.85)
Transplant Related Mortality (TRM)		
Day 180 Cumulative Incidence Rate (95% CI)	0.01 (< 0.01, 0.06)	0.10 (0.05, 0.22)
HR (95% CI) ^a	0.11 (0.01, 0.87); P-value = 0.0359 ^a	
Chronic GVHD		
Day 180 Cumulative Incidence Rate (95% CI)	0.14 (0.09, 0.23)	0.15 (0.10, 0.24)

^a Wald confidence interval and P-value are presented

^b Based on Kaplan-Meier estimates

^c 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.

^d Log-Rank test stratified by age group at randomization (≤21 years versus > 21 years).

Source (ADaM dataset): Table S.5.1.2.1 (ADTTE [G34FS180]); Table S.5.3.1.S (ADTTE [PARAMCD = CIGFS180], cumulative incidence), Table S.5.4.1.S (ADTTE [PARAMCD = G24FS180], moderate-severe GFS), Table S.5.5.1.1.S (ADTTE [PARAMCD = OS180], OS up to Day 180), Table S.5.5.1.S (ADTTE [PARAMCD = OS], OS up to DBL), Table S.5.9.1.1.S (ADTTE [PARAMCD = DFS180], DFS), Table S.5.10.1.1.S (ADTTE [PARAMCD = TRM180], TRM); Table S.5.14.1.1.S (ADTTE [PARAMCD = CGVHD180], chronic GVHD) in the IM101311 Primary CSR

Table 20: Efficacy of Abatacept: 7/8 MMUD Cohort Treated Analysis Population - IM101311

Efficacy Parameters	Abatacept (N = 43)
Gr III-IV aGVHD-Free Survival (GFS)	
Events, n (%)	2 (4.7)
Day 180 Survival Rate ^a (95% CI)	0.98 (0.85, 1.00)
Gr III-IV Severe aGVHD - Cumulative Incidence Rate	
Day 180 Cumulative Incidence Rate (95% CI) ^b	0.02 (< 0.01, 0.11)
Gr II-IV aGVHD-Free Survival (GFS)	
Events, n (%)	19 (44.2)
Day 180 Survival Rate ^a (95% CI)	0.58 (0.42, 0.71)

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Efficacy Parameters	Abatacept (N = 43)
Overall Survival (OS) (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)
Day 180 Survival Rate ^a (95% CI)	0.98 (0.85, 1.00)
Day 365 Survival Rate ^a (95% CI)	0.88 (0.74, 0.95)
Disease-Free Survival (DFS)	
Relapse or Death, n (%)	5 (11.6)
Day 180 Survival Rate ^a (95% CI)	0.91 (0.77, 0.96)
Transplant Related Mortality (TRM)	
Day 180 Cumulative Incidence Rate (95% CI) ^b	0.02 (< 0.01, 0.11)
Chronic GVHD	
Day 180 Cumulative Incidence Rate (95% CI)	0.21 (0.10, 0.35)

^a Based on Kaplan-Meier estimates

^b Cumulative incidence estimates based on unstratified Gray's model

Source (ADaM dataset): Table S.5.1.2.1 (ADTTE [PARAMCD = CIGFS180], cumulative incidence), Table S.5.4.2.1 (ADTTE [PARAMCD = G24FS180], moderate-severe GFS), Table S.5.5.2.2.1 (ADTTE [PARAMCD = OS180], OS up to Day 180), Table S.5.5.2.1.1 (ADTTE [PARAMCD = OS], OS up to DBL), Table S.5.9.2.2.1 (ADTTE [PARAMCD = DFS180], DFS), Table S.5.10.2.2.1 (ADTTE [PARAMCD = TRM180], TRM), Table S.5.14.2.2.1 (ADTTE [PARAMCD = CGVHD180], Chronic GVHD) in the IM101311 Primary CSR

The Applicant's Position:

Other efficacy outcomes, including cumulative incidence rates of severe aGVHD, rates of moderate to severe GFS, OS, DFS, and TRM, were consistent with the primary endpoint, showing a benefit of abatacept compared to placebo. Except the severe GFS rate and incidence rate of severe aGVHD endpoints, all other endpoints had p values less than 0.05.

In 8/8 MUD cohort MITT subjects (Table 19):

- The cumulative incidence of severe aGVHD up to Day 180 (stratified by age group at randomization) was numerically lower for the abatacept arm compared with the placebo arm: ≤ 21 years: 5% vs. 12%; > 21 years: 7% vs. 17%; HR: 0.41 (95% CI: 0.14, 1.16); P-value = 0.0942.
- The abatacept group had a numerically higher moderate to severe (Gr II-IV) GFS rate at Day 180 compared with the placebo group (50% vs 33%; HR: 0.55 [95% CI: 0.36, 0.86]; P-value = 0.0069).
- The OS HR favored abatacept compared with placebo (up to Day 180 visit); HR = 0.33 (95% CI: 0.12, 0.93), stratified log-rank test P-value = 0.0281. The OS rates were numerically higher for abatacept compared with placebo at 180 days (97% vs 84%) and at 365 days (84% vs 77%).
- The abatacept group had numerically improved efficacy in other secondary efficacy endpoints including such as DFS rate (88% vs. 77%), TRM (1% vs. 10%).
- There was no benefit in reduction of cGVHD in the abatacept group up to Day 180 visit.

In the 7/8 MMUD cohort Treated Analysis Population (Table 20):

- The severe (Gr III-IV) GFS rate up to Day 180 was 98% (95% CI: 85.0, 100.0).
- The cumulative incidence of severe (Gr III-IV) aGVHD up to Day 180 was 2% (95% CI: < 1.0, 11.0).
- The moderate-severe (Gr II-IV) GFS rate up to Day 180 was 58% (95% CI: 42, 71).
- The OS rate at Day 180 and Day 365 was 98% (95% CI: 85, 100) and 88% (95% CI: 74, 95), respectively.
- The DFS rate at Day 180 was 91% (95% CI: 77, 96).
- The rate of cumulative incidence of TRM at Day 180 was 2% (95% CI: < 1, 11).

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

- The rate of cumulative incidence of GVHD at Day 180 was 21%.

FDA Assessment:

The numerical results in Table 19 and Table 20 can be reproduced by the statistical reviewer.

According to BMSSAP, the key secondary endpoint was cumulative incidence of severe aGVHD up to Day 180 post transplantation. The hierarchical testing approach was pre-specified to adjust for multiplicity. The goal was to maintain the overall type I error rate at 5% for the study. However, since the primary endpoint was not met, the key secondary endpoint could not be formally tested. Therefore, the p-value for the key secondary endpoint was nominal.

In addition, the secondary endpoint OS was not included in the statistical testing strategy. The OS endpoint was considered exploratory and corresponding p-value was nominal. Similarly, all other secondary endpoints are considered exploratory without alpha allocation.

The Grade II-IV GFS results for the 8/8 cohort were updated based on FDA clinical adjudication. The updated Grade II-IV GFS rate up to Day 180 was 32% (95% CI: 21%, 43%) in placebo arm and the result in abatacept arm remained the same. The updated HR was 0.54 (95% CI: 0.35, 0.83).

The results for the 7/8 abatacept single arm cohort were also updated based on FDA clinical adjudication. The Grade III-IV GFS and Grade II-IV GFS were updated to 95% (95% CI: 83%, 99%) and 53% (95% CI: 38%, 67%), respectively.

Dose/Dose Response

The Applicant's Position:

E-R analyses support the IM101311 clinical efficacy results. See Section 6.3 for details.

FDA Assessment:

See section 6.3 for FDA discussion.

Durability of Response

The Applicant's Position:

Not applicable. The prophylaxis regimen studied, i.e., 4-dose of abatacept on Days -1, 5, 14 and 28 is designed to reduce acute GVHD incidence rate up to 180 days post-transplant.

FDA Assessment:

FDA agrees.

Persistence of Effect

The Applicant's Position:

The persistence of efficacy of abatacept in preventing severe aGVHD over the study period is supported by the clinically meaningful effects of treatment on GFS that were observed through Day 180 in the pivotal Study IM101311, and OS through Day 180 in Study IM101841. In the IM101311 study, the 4-dose abatacept added to SOC CNI+MTX prophylaxis regimen, was associated with a significantly improved rate of moderate (Gr II-IV) GFS through Day 180 post-transplant in both the 7/8 MMUD and 8/8 MUD cohorts, significantly improved severe (Gr III-IV) GFS through Day 180 in the 7/8 MMUD cohort, and a

ORENCIA (abatacept)

numerically higher rate of severe GFS in the 8/8 MUD cohort. Furthermore, in the IM10311 study, the 4-dose abatacept+CNI+MTX prophylaxis regimen improved OS through Day 180 in both the 7/8 MMUD and 8/8 MUD cohort. See Table 17, Table 19, and Table 20.

FDA Assessment:

The FDA does not agree with the Applicant's assessment regarding persistence of effect.

The primary efficacy endpoint GFS in pivotal Study IM101311 did not demonstrate superiority of the abatacept group compared to the placebo group in the 8/8 MUD cohort. Based on the pre-specified multiplicity control approach, the key secondary endpoint severe (Gr III-IV) GFS through Day 180 could not be formally tested. Furthermore, there was no randomized comparator arm for the 7/8 cohort to make the claim that outcomes were improved on the 7/8 cohort.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Not applicable.

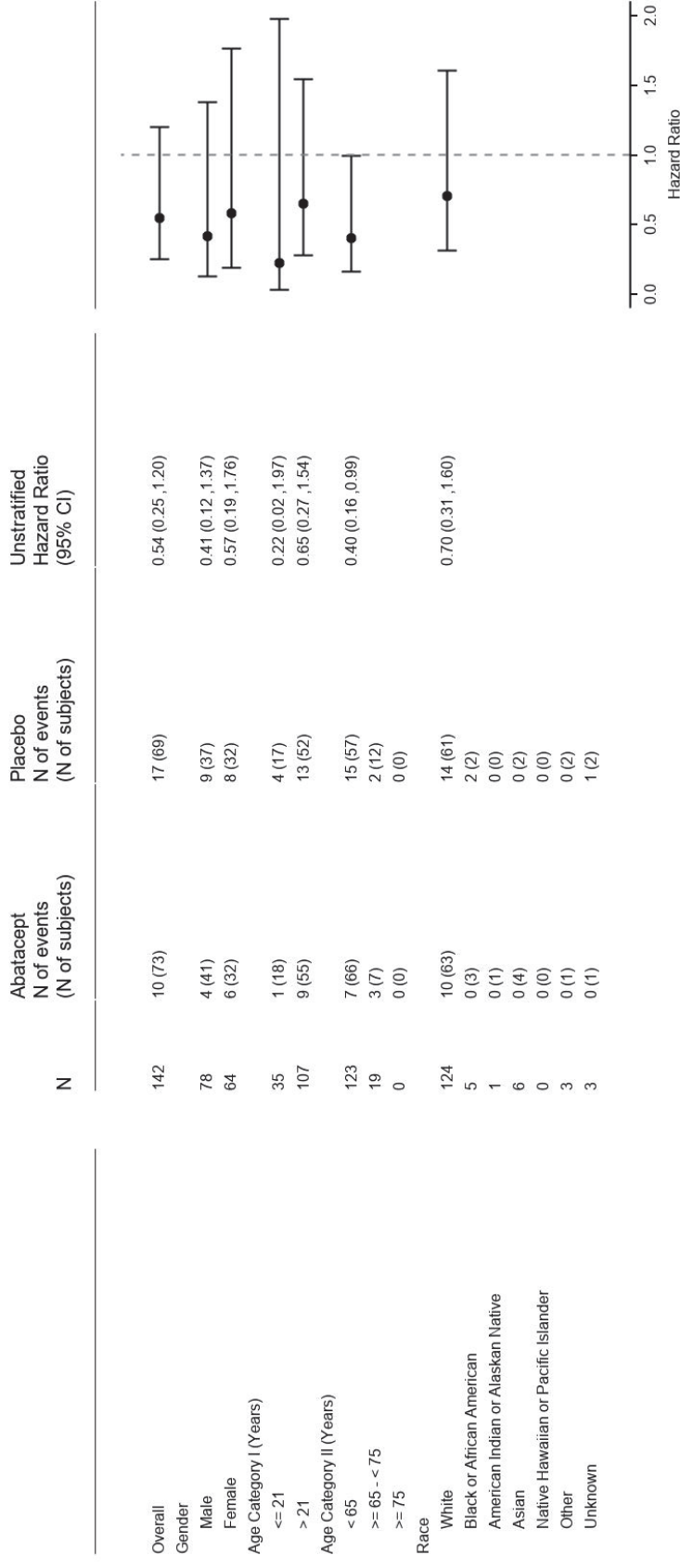
FDA Assessment:

FDA agrees.

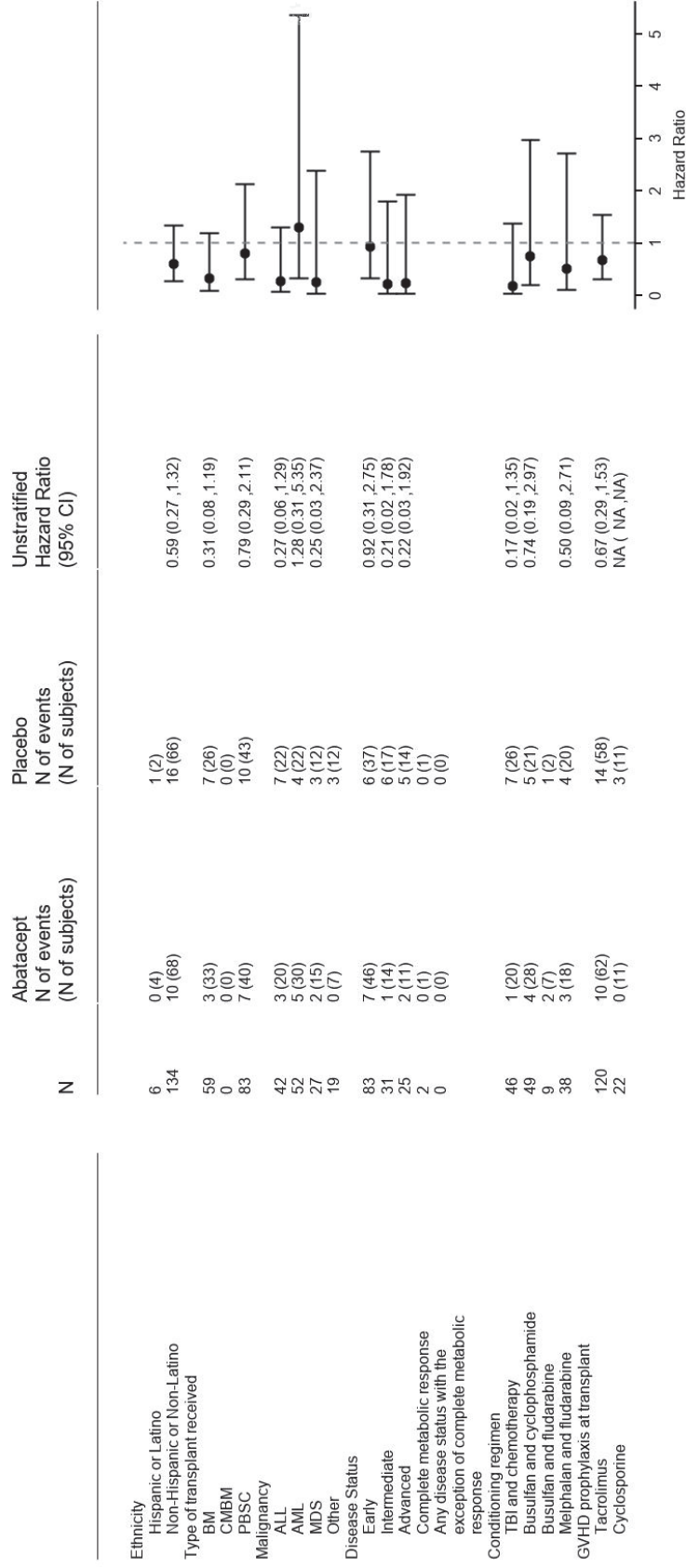
Additional Analyses Conducted on the Individual Trial

Data:

Figure 10: Grade III-IV GFS in Subsets During the Day 180 Analysis Period: 8/8 MUJ Cohort MITT Analysis Population - IM101311

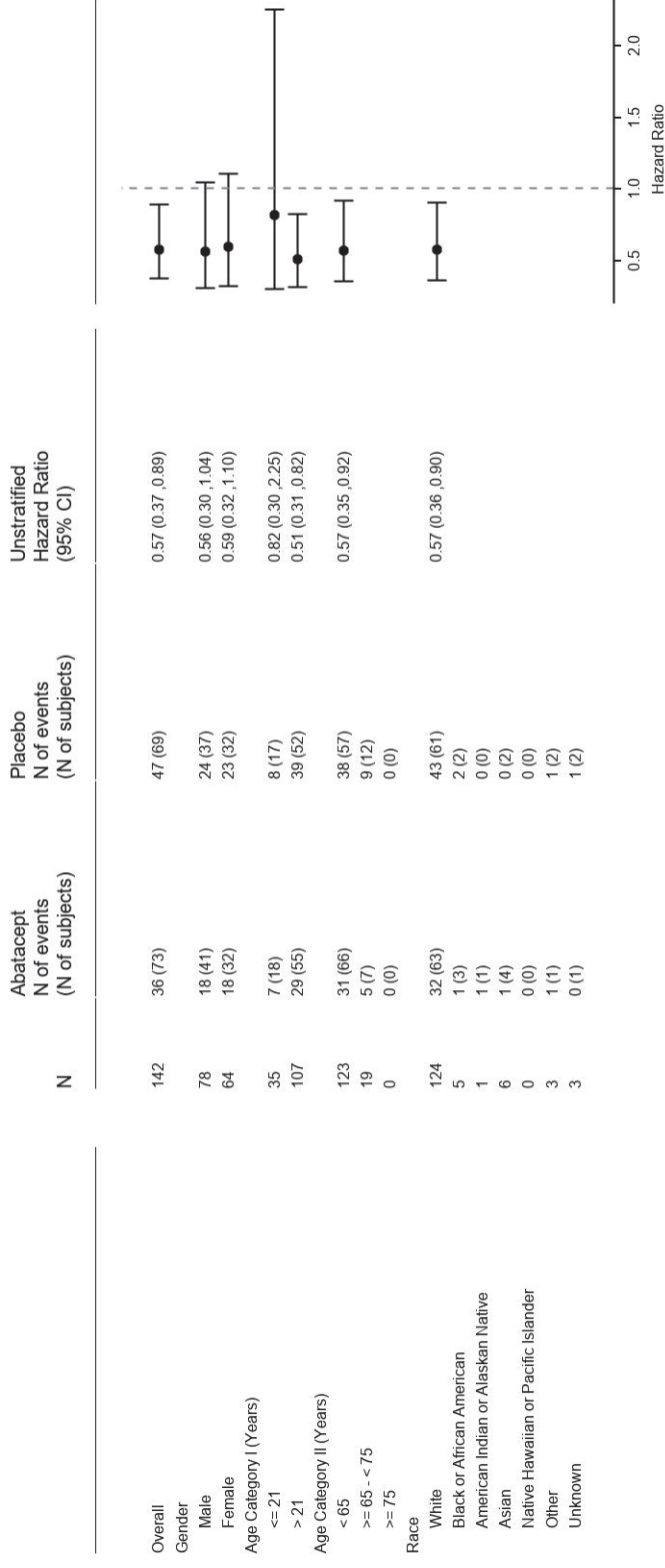


NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)



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). Source (ADaM dataset): Figure S.5.2.S (ADTTE [PARAMCD=G34FS180]) in the IM101311 primary CSR

Figure 11: Grade II-IV aGVHD Free Survival (GFS) in Subsets During the Day 180 Analysis Period: 8/8 Cohort MITT Analysis Population - IM101311



NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

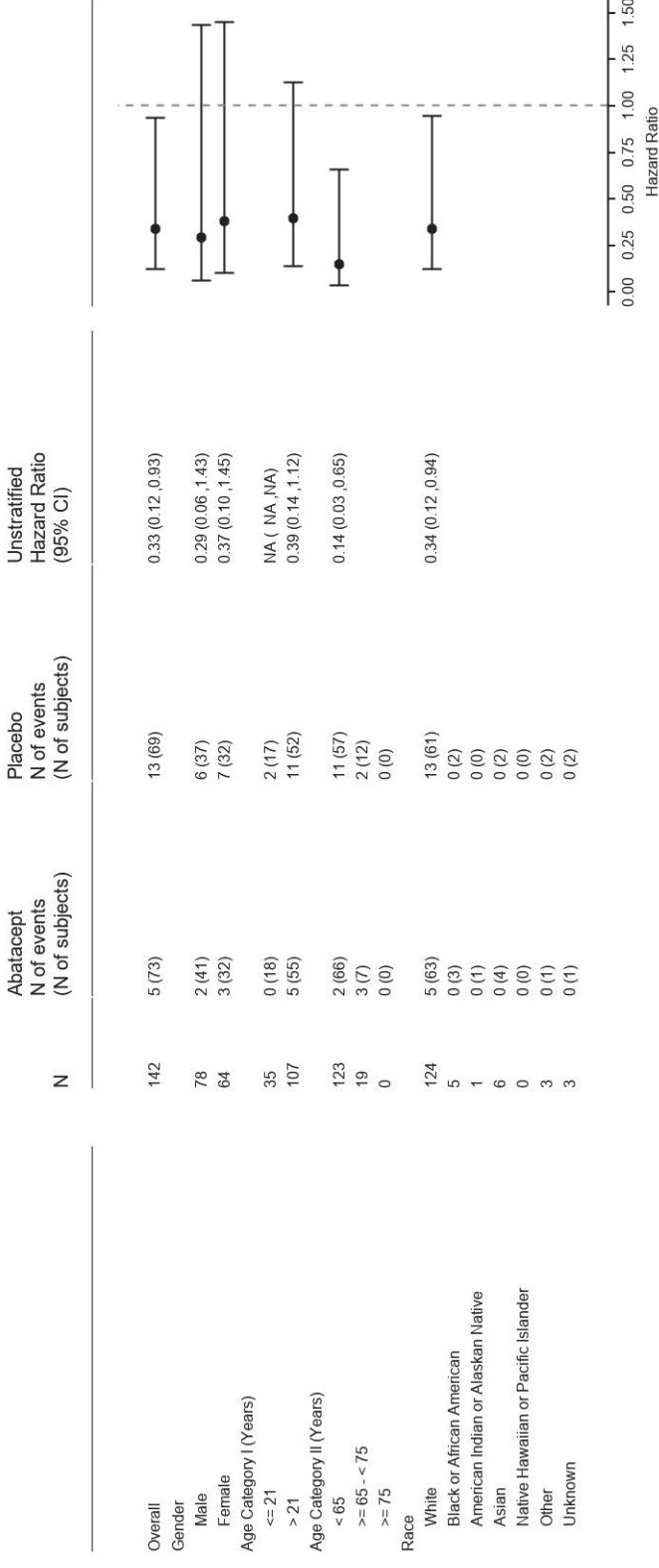
	N	Abatacept N of events (N of subjects)	Placebo N of events (N of subjects)	Unstratified Hazard Ratio (95% CI)
Ethnicity				
Hispanic or Latino	6	0 (4)	2 (2)	0.62 (0.40, 0.96)
Non-Hispanic or Non-Latino	134	36 (68)	45 (66)	
Type of transplant received				
BM	59	12 (33)	14 (26)	0.60 (0.28, 1.29)
CMBM	0	0 (0)	0 (0)	
PBSC	83	24 (40)	33 (43)	0.58 (0.34, 0.99)
Malignancy				
ALL	42	11 (20)	15 (22)	0.67 (0.31, 1.47)
AML	52	17 (30)	14 (22)	0.84 (0.41, 1.74)
MDS	27	6 (15)	8 (12)	0.44 (0.15, 1.27)
Other	19	2 (7)	9 (12)	
Disease Status				
Early	83	28 (46)	24 (37)	0.81 (0.47, 1.39)
Intermediate	31	5 (14)	12 (17)	0.45 (0.16, 1.31)
Advanced	25	3 (11)	11 (14)	0.18 (0.05, 0.65)
Complete metabolic response	2	0 (1)	0 (1)	
Any disease status with the exception of complete metabolic response	0	0 (0)	0 (0)	
Conditioning regimen				
TBI and chemotherapy	46	12 (20)	18 (26)	0.82 (0.40, 1.71)
Busulfan and cyclophosphamide	49	5 (14)	14 (21)	0.50 (0.23, 1.11)
Busulfan and fludarabine	9	3 (7)	1 (2)	
Melfalan and fludarabine	38	9 (16)	14 (20)	0.48 (0.21, 1.13)
GVHD prophylaxis at transplant				
Tacrolimus	120	32 (62)	40 (58)	0.59 (0.37, 0.94)
Cyclosporine	22	4 (11)	7 (11)	0.48 (0.14, 1.65)

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.

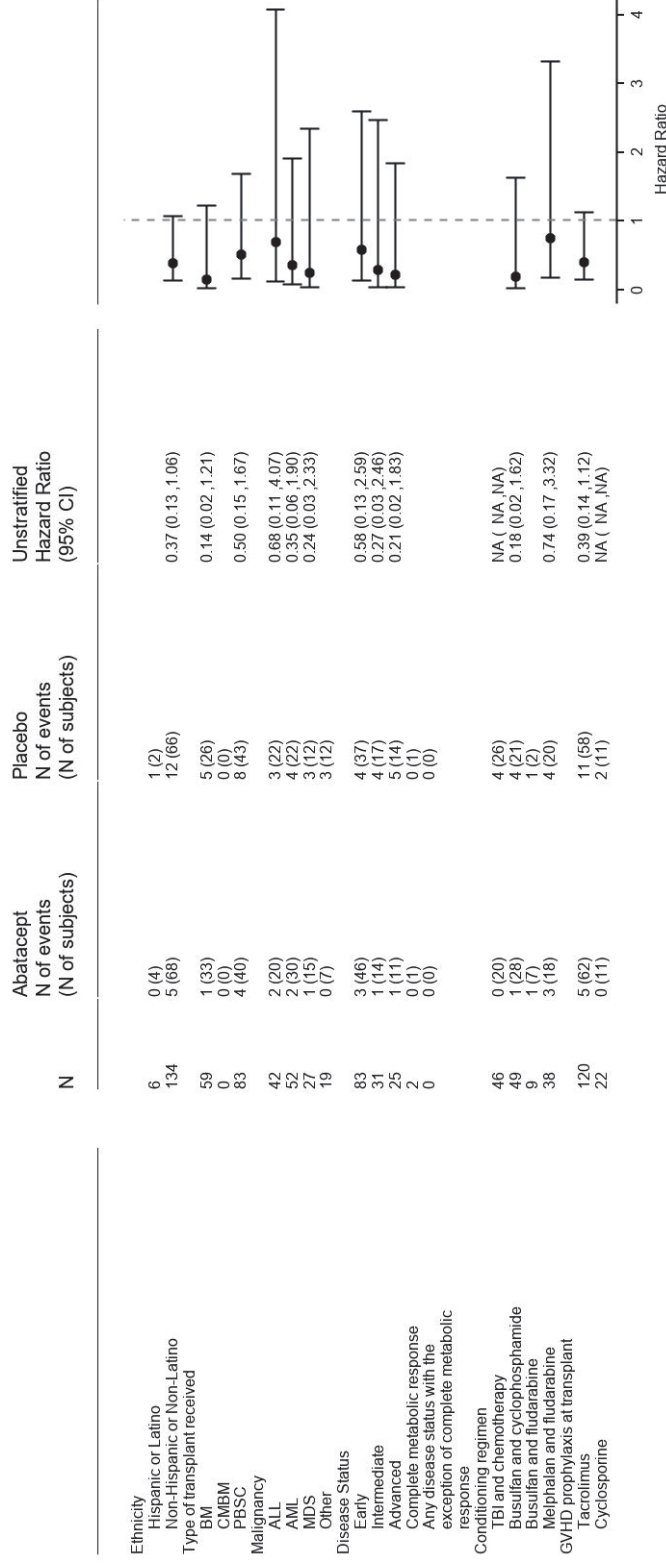
Error bars represent 95% confidence intervals for the hazard ratio. Estimation of Hazard Ratio is Not Applicable (NA).

Program Source: BMS_GBS\Orencia\WYA33451\Biostatistics\Production\Figures\EBR_Plots\rg-ef-forest-24gfs.sas (ADaM dataset: ADTTE [PARAMCD=G24FS180])

Figure 12: Overall Survival (OS) in Subsets During the Day 180 Analysis Period: 8/8 Cohort MITT Analysis Population - IM101311



NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)



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).

Program Source: BMS_GBS\Orencia\WYA33451\Biostatistics\Production\Figures\EBR_Plots\rg-ef-forest-os180.sas (ADaM dataset: ADTTE [PARAMCD=OS180])

ORENCIA (abatacept)

The Applicant's Position:

In subgroup analyses for subjects in the 8/8 MUD cohort, all of the HRs for Grade III/IV and Grade II/IV GFS, as well as OS HRs favored abatacept vs placebo (HR < 1, although the majority of CI included 1), with the exception of AML (Figure 10, Figure 11, and Figure 12).

FDA Assessment:

All subgroup analyses were considered exploratory. However, the numerical improvement in the GFS and OS endpoints at day 180 appeared to be consistent across various demographic and disease/transplantation characteristic subsets. The one exception was AML for the Grade III-IV GFS endpoint (HR 1.28; 95% CI 0.31, 5.35). HRs were < 1 for the AML subgroup for both Grade II-IV GFS and OS.

8.1.3 Supportive Study - IM101841

Study IM101841 was designed after the IM101311 clinical trial resulted in promising clinical outcomes for abatacept+SOC GVHD prophylaxis in 7/8 MMUD subjects and it was agreed that it was unethical to conduct a second RCT in the 7/8 population. With IM101311 clinical data suggesting abatacept as a potential addition to SOC GVHD prophylaxis treatment, Study IM101841 was developed as an epidemiological study to examine outcomes of abatacept+SOC GVHD prophylaxis using the CIBMTR database, and to provide supportive evidence for the effectiveness of this treatment in 7/8 MMUD HSCT recipients.

Trial Design

The study design is provided in Table 21.

Table 21: Approximate Number of Eligible Subjects by Treatment Group (Planned) - 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 (IM101311) Source: Table 4.1.1-1 of Appendix 1.1 of the IM101841 CSR

The Applicant's Description:

Trial Design and treatment arms: Retrospective cohort study evaluating subjects who received abatacept in addition to SOC aGVHD prophylaxis, compared to subjects receiving SOC aGVHD prophylaxis, using data routinely collected into the CIBMTR database. The primary objective cohort included the following treatments:

- Abatacept+CNI+MTX without ATG or
- CNI+MTX without ATG

In the study IM101841 CIBMTR study, there were not specific requirements for dose and schedule of drug exposure.

Study population: Subjects were at least 6 years old and had a BM or PB stem cell donor who was HLA-matched at 7/8 (A, B, C, DRB1) loci. A propensity score was developed to address possible confounding based on established key prognostic factors for this population.

Selection of Study Population: Patients in the CIBMTR database, who received a first allogeneic transplant in the US and fit the inclusion and exclusion criteria, served as the control (non-abatacept-treated) population for this study.

The CIBMTR holds the contract for the Stem Cell Therapeutic Outcomes Database, awarded by the Health Resources and Services Administration of the US Department of Health and Human Services. As the contract holder, the CIBMTR is charged with collecting data on all allogeneic (related and unrelated) HCTs performed in the US. All US transplant centers are required to report data to the CIBMTR; participation of non-US centers is voluntary.

The CIBMTR collects data for approximately 23,000 new transplants annually in the US as well as a continually increasing volume of follow-up data on previously reported recipients and donors. The CIBMTR collects transplant data on two levels, using a Transplant Essential Data (TED) form and a Comprehensive Report Form (CRF). The CIBMTR collects TED data on all patients. TED data are an internationally accepted standard data set that includes hundreds of details about patients' demographics, disease, treatment, response, side effects, and long-term outcomes. Using a regularly reviewed, weighted algorithm, the CIBMTR selects a subset of patients for more detailed CRF data collection.

This study included patients with TED level data in the CIBMTR database with a data cutoff date 07-Sept-2020 who met the inclusion and exclusion criteria of the study population. The inclusion and exclusion criteria of the study population were selected to mimic those of the IM101311 clinical trial.

The eligible patient population consisted of all abatacept patients and approximately 150 patients in each comparator group that fulfilled the following criteria were included in the eligible patient population:

- Patients who underwent first allogeneic transplant in the United States
- Patients with an unrelated donor who are HLA-matched at 7/8 loci (A, B, C, DRB1)
- Patients at least 6 years old with weight at least 20 kg
- Patients with a Karnofsky/Lansky performance score $\geq$ 80%
- Patients whose first allogeneic transplant occurred from 01-Jan-2011 to 31-Dec-2018
- Patients with any of the following diseases: AML, ALL, CML, MDS, HL, 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 regimens: total body irradiation (TBI)/cyclophosphamide (Cy), busulfan (Bu)/Cy, Bu/fludarabine (flu), Flu/Melphalan (MEL)

Patients who met the following criteria were excluded from the study:

- Patients with missing information on ATG (yes/no)
- Patients receiving alemtuzumab (Campath)
- Patients with cord blood grafts

ORENCIA (abatacept)

- Patients with non-MDS myeloproliferative disorders (NOTE: Patients with chronic myelomonocytic leukemia [CMMoL] will be included)
- Patients who did not consent to participate in research
- Patients treated at embargoed centers for research
- Patients treated with abatacept and ATG
- Among non-abatacept treated patients, patients transplanted at centers with abatacept trial patients
- Patients with any of the following missing propensity score variables:
 - Disease status at transplantation (early, intermediate, advanced HL and NHL-chemosensitive)
 - Age
 - Gender (male, female)
 - HSCT graft source (BM, PB)
 - Conditioning intensity (myeloablative, non-myeloablative / reduced intensity)
 - Karnofsky/Lansky Performance Score (80%, 90-100%)
 - CNI type (tacrolimus, CsA) (Only among cohorts including CNI)

Study Procedures and Observations: The CIBMTR[®] is a research collaboration between the NMDP[®]/Be The Match[®] and the Medical College of Wisconsin. CIBMTR holds the contract for the Stem Cell Therapeutic Outcomes Database (SCTOD), awarded by the Health Resources and Services Administration of the US Department of Health and Human Services.

For this study, recipient information at baseline was primarily obtained from the Pre-Transplant Essential Data (TED level) form. HSCT recipient survival was a required data point during follow-up. The instructions on the data collection process related to recipient's survival status was detailed in the CIBMTR Forms Instruction Manual. Additionally, information about aGVHD occurrence, grading, and PTLD was collected for a subset of patients with available CRF-level data in exploratory analyses.

Information on GVHD prophylaxis (abatacept, CNI, MTX, ATG, PT-Cy) was obtained through the standardized data collection form.

Study Endpoints

The Applicant's Description:

Primary endpoint: OS evaluated at 180 days post-transplant of abatacept+CNI+MTX without anti-thymocyte globulin (ATG) compared to CNI+MTX without ATG.

Secondary endpoints: OS evaluated at 180 days post-transplant of abatacept+CNI+MTX without ATG compared to CNI+MTX with ATG and of abatacept+tacrolimus+MTX without ATG compared to tacrolimus+MTX without ATG.

Key exploratory endpoints: Proportions of subjects with Gr II-IV aGVHD and Gr III-IV aGVHD reported at Day 100 and Day 180, relapse-free survival, and subjects treated with abatacept+CNI+MTX without ATG were compared with subjects treated with PT-Cy without ATG.

FDA Assessment:

The FDA generally agrees with the Applicant's description of the study design.

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

Study IM101841 was designed to provide supportive evidence for the effectiveness of abatacept in the 7/8 MMUD cohort because of the single-arm design component of Study IM101311 (with only one patient having received placebo before the comparator arm was dropped). This study was a clinical study evaluating CNI +MTX+abatacept without ATG compared to CNI +MTX without ATG using patient-level data routinely collected in the CIBMTR database between 1/1/2011 to 12/31/2018. CIBMTR includes data from required reporting on every allogeneic HSCT performed in the United States as described in section 7.1.

Of note, abatacept use was not captured in CIBMTR in the same manner as other treatments because it was not selectable as a standard treatment; rather, it was written and subsequently extracted. In an evaluation of the ability of CIBMTR to capture abatacept use, the Applicant randomly selected 9 non-trial participants treated in Study IM101311. No misclassification of abatacept treatment was identified. Thus, misclassification of abatacept users as SOC is not considered likely.

FDA notes that the Applicant only provided eligible subset data from the CIBMTR database based on pre-specified inclusion/exclusion criteria. Thus, without accessing the full CIBMTR database, the FDA statistical reviewer was not able to validate the data extraction process that matched the intended inclusion/exclusion criteria. In addition, the statistical reviewer could not validate the procedure used to randomly select records from the CIBMTR database.

The primary endpoint was OS at 180 days of follow-up post-transplantation. The OS time was defined as the time between the date from allogeneic transplantation to the documented date of death as reported by treating physicians. The date of transplantation was defined as the study Day 0, which was consistent with Day 0 defined in Study IM101311.

The clinical team noted that Study IM101841 was designed to provide a comparison of 7/8 MMUD patients that were treated with either abatacept + CNI + MTX or CNI + MTX. This study was designed using information extracted from the CIBMTR database ensuring that the information for both treatment arms went through the same registry-based data submission process. In addition to inclusion of patients who received abatacept on the 7/8 cohort of Study IM101311, Study IM101841 would also add an additional 12 patients to the 7/8 cohort. However, the addition of these few patients was not expected to significantly alter the overall results of abatacept treatment. The benefit of the proposed approach compared to the previous comparison to historic controls conducted by Dr. Keene and her colleagues was that all data on the patients would be extracted uniformly from CIBMTR, that a comparator group would be randomly sampled from the set of CIBMTR transplant patients that met the inclusion/exclusion criteria, and that propensity score matching and inverse probability of treatment weighting (IPTW) would be used to statistically control for a prespecified list of potential confounding patient/disease attributes.

Statistical Analysis Plan and Amendments

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.

For the 7/8 cohort, survival rates in IM101311 were 100% in patients treated with abatacept and 72.5% in matched controls from CIBMTR database. The number of patients in the CIBMTR database was estimated to be approximately 50 for abatacept+CNI+MTX without ATG and approximately 150 for

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

CNI+MTX without ATG. The actual sample size of the study was similar to the planned study with N=54 for abatacept+CNI+MTX 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 abatacept+CNI+MTX 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.

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 groups.

Table 22: Sample Size of the Comparison Groups

Group	N
CNI+MTX + abatacept without ATG ^{a,b}	54
CNI+MTX without ATG ^a	162
CNI+MTX with ATG ^b	162
Tacrolimus + MTX + abatacept without ATG ^c	33
Tacrolimus + MTX without ATG ^c	99
CsA+MTX + abatacept without ATG ^d	21
CsA+MTX without ATG ^d	21
PT-Cy without ATG ^e	162

Source: Tables S.3.1.1.1, S.3.1.1.2, S.3.1.1.3, S.3.1.1.4, S.3.1.1.5 (ADaM Dataset: ADSL) in the IM101841 Primary CSR

Patients from the CIBMTR database who were included in the analyses were those in the United States who had received a first allogeneic 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 and conditioning regimens 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

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 (among only cohorts including CNI)

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

For this study, recipient information at baseline will be obtained from the TED level form. The instruction on data collection process related to recipient's survival status is detailed in CIBMTR Forms Instruction Manual.

Given the likelihood of model overfitting in the small sample size setting, only the most clinically relevant independent variables were selected for inclusion in the propensity score model.

The IPTW method is an analytical technique aimed to reduce confounding bias. The method estimates the average treatment effect, defined as the average effect of treatment had the entire cohort been treated. All subjects with an estimated propensity score were included in this analysis.

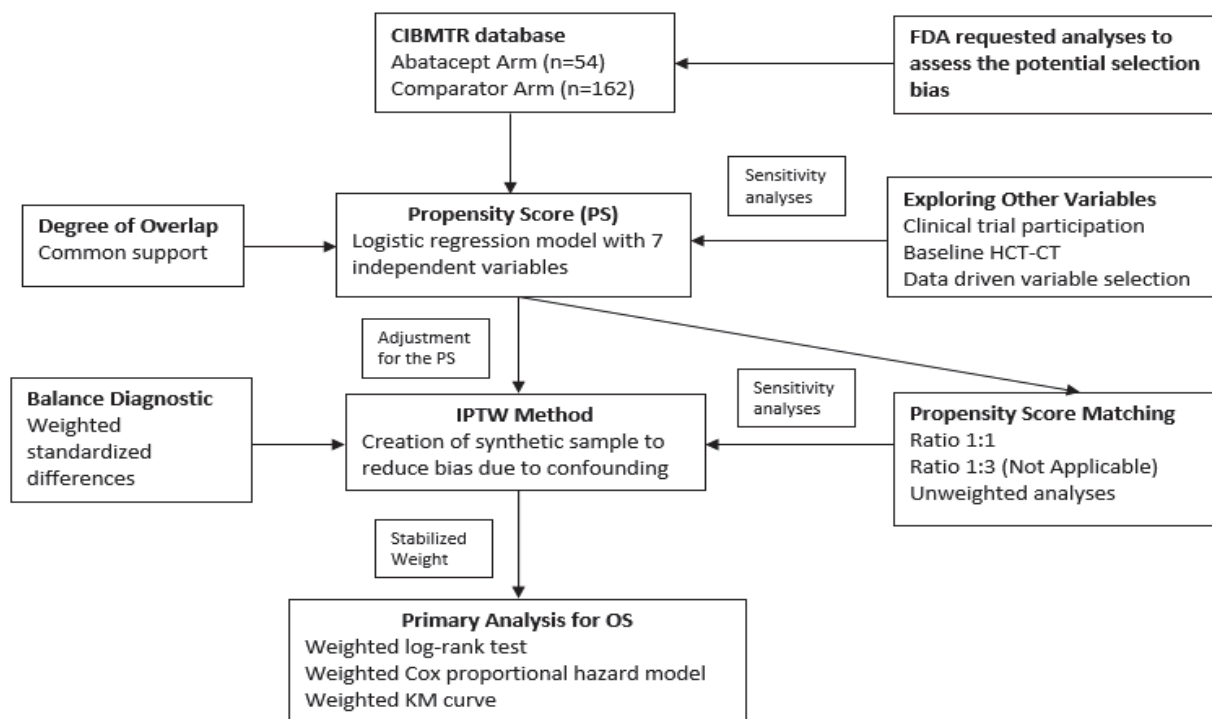
For the primary endpoint, the weighted log-rank test was used to compare OS with 180 days of follow-up post-transplant in subjects receiving a GVHD prophylactic regimen of abatacept+CNI+MTX without ATG, with a standard GVHD prophylactic regimen of CNI+MTX without ATG, using the stabilized inverse of the propensity scores as weights.

FDA Assessment:

The FDA agrees with the Applicant's description of the Statistical Analysis Plan.

In this study, subjects were not randomly assigned treatments and thus it is difficult to determine the degree to which differences in outcomes between treated and control subjects were due to treatment or related baseline variables. Therefore, the Applicant proposed that the IPTW method via a propensity score analysis was used to address potential confounding and bias due to differences between the treatment group in key characteristics at transplantation. The statistical analysis flowchart is presented in Figure 13.

Figure 13: Statistical Analysis Flow Chart for Study IM101841



Source: Generated by the FDA statistical reviewer according to BMS SAP.

According to protocol, the justification for each of the independent covariates in the propensity score model is listed in Table 23. For the covariates without justification in the table; for example, age, gender, Karnofsky/Lansky Performance score, disease, disease status and CNI type, the FDA reviewed and agreed to include these covariates in the propensity model.

Table 23: Covariate Selection

Independent Variable	Included in Propensity Score Model?	Justification
Age at transplantation: continuous	Yes	
Gender: male (M) vs female (F)	Yes	
Karnofsky/Lansky Performance score prior to transplant (%): 80% vs 90-100%	Yes	
Disease: Acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplastic syndromes, Chronic myelogenous leukemia, Hodgkin lymphoma (HL), Non Hodgkin lymphoma (NHL)	Yes	

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Disease Status: Early, intermediate, advanced, HL+NHL Chemosensitive at transplantation	Yes	
Donor age: Continuous	No	All Subjects are unrelated donors and the age for donation is pre-specified for all donors. Given the narrow range of age, this variable is unlikely to cause substantial confounding after adjustment for the other variables in the propensity score model.
Donor-recipient sex match: M/M, M/F, F/M, F/F	No	Donor-recipient sex match, while an important determinant of risk of chronic graft vs host disease (GVHD; exploratory objective), is not a primary predictor of the primary outcome of overall survival.
Donor-recipient Cytomegalovirus (CMV) status match: +/+, +/-, -/+, -/-	No	Donor-recipient CMV status match is not a primary predictor of overall survival at Day 180 in T-cell replete unrelated donor HCT.
Donor-recipient ABO mismatch: matched, minor mismatch, major mismatch, bidirectional mismatch, missing	No	Donor-recipient ABO mismatch is not a primary predictor of overall survival.
HLA matching: Identification of mismatched allele or antigen-level, 8/10 vs 9/10	No	This variable is not relevant as all matchings are currently performed at high resolution.
Conditioning intensity: myeloablative vs nonmyeloablative /reduced intensity	Yes	
Conditioning regimen	No	After adjustment for conditioning intensity, conditioning regimen alone is not expected to be an important predictor of mortality.
Stem cell source: Bone marrow (BM) vs Peripheral blood (PB)	Yes	
Year of transplant: continuous and grouped: 2011-2013 vs 2014-2018 for the controls	No	CIBMTR expects little to no change in mortality during the proposed study period.
Time from diagnosis to transplant, months: median (range)	No	These covariates are accounted for via the inclusion of the Disease Status variable.
Time from diagnosis to transplant, months: < 6, 6-<12, □ 12	No	
Calcineurin inhibitor (CNI) type: tacrolimus vs cyclosporine (CsA)	Yes	
Baseline Hematopoietic Cell Transplantation- Comorbidity Index (HCT-CI)	Yes, in sensitivity analyses	
Participation in the ABA2 clinical trial: yes vs no	No	This variable is not feasible to include in the propensity score model as only patients in the exposure group would have this variable equal to "yes".

Participation in any clinical trial during the study period: yes vs no	Yes, in sensitivity analyses	
Treatment site	No	This variable is not feasible to include in the propensity score model as non-abatacept patients treated at sites with ongoing abatacept trial enrollment were excluded from the study due to concerns of exposure misclassification.

Source: Appendix 5 in the protocol version 2.0.]

Reviewer’s comment: While FDA generally agreed with the covariates selected for the propensity score model, note that this process is limited by the sample size of the analysis (n=54 in the abatacept cohort). Due to the small number of patients in the abatacept arm, it would not be feasible to include more covariates that may also be related to treatment assignment and/or outcome. Indeed, the Applicant removed disease status from the propensity score model in the primary analysis of OS due to quasi-complete separation. Thus, the ability to control for measured confounders is limited by the small sample size of the abatacept group.

Protocol Amendments

The Applicant’s Description:

There was 1 protocol amendment for IM101841. The Revised Protocol 01 included changes in response to comments from the FDA Study May Proceed Letter (Table 24). The planned statistical analyses were updated to better account for unmeasured confounding factors and to establish comparability between the comparison groups. Sensitivity analyses were also included to further analyze the relationship between covariates, treatment assignment, and outcome.

Table 24: Amendments and Updates - IM101841

Document	Date Of Issue	Summary of Change
Revised Protocol 01	23-Jun-2020	- Inclusion Criteria were added to ensure comparability between patient populations and to more closely reflect patients under the regulatory authority of the FDA; Modified the criterion regarding conditioning regimens from an exclusion criterion to an inclusion criterion for improved readability. Added relapse free-survival and post-transplant lymphoproliferative disease as outcomes to be collected. Clarified that that the weighted long-rank test will use a two-sided alpha of 0.05. - Added exploratory objectives regarding patients who were enrolled in the IM101311 clinical trial and patients who were not enrolled in the IM101311 clinical trial (off-label use setting) and regarding relapse-free survival and PTLD. - Added the patient Sampling section. - Added subgroups CNI + MTX + abatacept without ATG among patients treated in the IM101311 clinical trial and CNI + MTX + abatacept without ATG among patients who were not treated in the IM101311 clinical trial (off-label use setting). - Added a list of comorbidities and the overall Hematopoietic Cell Transplant-Comorbidity Index

Table 24: Amendments and Updates - IM101841

Document	Date Of Issue	Summary of Change
		- Added Outcomes and independent variables of interest will be described for those patients excluded due to missing data. - Adjusted the number of eligible patients and added details for the propensity score modeling

Source: Table 5.5-1 in the IM101841 Primary CSR

FDA Assessment:

The FDA agrees with the Applicant’s description of the protocol amendments.

8.1.4 Study Results, IM101841

Compliance with Good Clinical Practices

The Applicant’s Position:

Ongoing data audits were performed at all CIBMTR participating Transplant Centers as part of the CIBMTR’s overall data quality assurance program. The audit compared data in source documents maintained at the Transplant Center with data contained in the CIBMTR outcomes registry. The audits identify errors that otherwise would go undetected by the online validations built into the data entry program. The overall goal of the ongoing audits was to ensure the quality and accuracy of the research database by:

- Ensuring the accuracy (and completeness) of the data reported to the CIBMTR
- Identifying systemic and non-systemic errors
- Requesting corrective action for errors identified during the audit
- Providing training to transplant centers’ data management staff

FDA Assessment:

The CIBMTR is a well-established, internationally recognized source that collects prospectively defined data on every allogeneic transplant recipient in the United States as mandated by law. CIBMTR has established requirements, training, and protocols for data collection, consent, and privacy to ensure data quality along with a defined Audit Program. FDA agrees with the description of this program.

Financial Disclosure

The Applicant’s Position:

Not applicable. IM101841 was an observational study.

FDA Assessment:

We disagree with the Applicant’s position that financial disclosure information is not applicable to this clinical registry study. However, financial disclosures were provided for Study IM101311, which contained the 7/8 single arm cohort comprising approximately 80% of abatacept-treated patients included in this study.

Patient Disposition

Table 25: Disposition during the Day 180 period, Primary Objective Cohort - IM101841

	Abatacept + CNI + MTX without ATG	CNI + MTX without ATG	Total

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

	N=54	N=162	N= 216
Patients completing 180 days of follow-up, n (%)	52 (96.3%)	126 (77.8%)	178 (82.4%)
Patients discontinuing prior to or on Day 180 due to death, n (%)	2 (3.7%)	36 (22.2%)	38 (17.6%)

Source (ADaM dataset): Table S.5.1.1.1 (ADSL [PRIFL = Y]) in the IM101841 primary CSR

The Applicant's Position:

There were 216 patients in the primary objective cohort, consisting of 54 patients treated with abatacept + CNI + MTX without ATG and 162 patients treated with CNI + MTX without ATG. Patients were censored at 181 days post-transplant or at time of last follow-up (death), whichever occurred earlier. The primary objective cohort is summarized in Table 25.

FDA Assessment:

The FDA agrees with the Applicant's summary of patient disposition.

Note that the sample size was not based on statistical assumptions but on the availability of subjects in the CIBMTR database. All subjects received abatacept treatment and met the inclusion and exclusion criteria for the study were included in the study. The placebo group was a subset of the larger population to have a 3:1 ratio in the analysis (1502 subjects met the inclusion criteria for the analysis of the 7/8 cohort according to the SAP). The FDA requested the Applicant to provide the full dataset to evaluate the robustness of sample selection and adequacy of propensity score data variables. However, the Applicant did not have access to the full CIBMTR database for the 7/8 and 8/8 cohorts. Therefore, the FDA was not able to perform further investigations on the full 1502 subjects.

Protocol Violations/Deviations

The Applicant's Position:

Modification to the propensity model

In the CIBMTR data collection, "disease status at transplant" variable contains responses relevant to two different disease status concepts. One set of response (early, intermediate, advanced) is relevant to patients with AML, ALL, CML, and MDS. The other set of responses (chemosensitive) is relevant to patients with NHL and HL.

During the development of the propensity scores, the logistic regression model with all the study covariables resulted in the following error messages: "quasi-complete separation of data points" and "collinearity". The covariate 'disease status' contributed to the quasi-complete separation warning, and along with 'disease type' caused the multicollinearity warning. Additional evaluation revealed the abatacept treated patients did not have all the responses specific to NHL and HL (chemosensitive) categories for the covariable "disease status at transplant".

The reasons for these warnings are that none of the chemo-resistant patients belonged to the cases group, and the disease status categories were distinct for HL and NHL disease (chemo-sensitive, chemo-resistant) versus other diseases (early, intermediate, and advanced). Therefore, disease status was removed from the logistic regression model to compute the propensity scores. In order to account for the effect of "disease status" at transplant, the subsequent marginal HR for OS and the corresponding 2-sided 95% CI was estimated in a weighted Cox proportional hazards model with treatment and disease status at transplantation as covariates in a sensitivity analysis of the primary analysis, which included treatment only as the covariate.

Inclusion of two abatacept treated patients with Karnofsky/Lansky Performance Score of 70% as recorded in the CIBMTR database but as 80% in the IM101311 Study.

In the study protocol, a Karnofsky/Lansky Performance Score of 80% or higher was required as one of the study inclusion criteria. Two patients treated with abatacept in IM101311 had a performance score of 80%. In the CIBMTR data set, their corresponding performance scores were recorded as 70%. In light of the small sample size in the abatacept treated patient group, these 2 patients were included based on their performance scores reported in IM101311.

FDA Assessment:

The described modifications to the propensity model prompted extensive research and evaluation of the disease status variable to evaluate the role of potential bias, including confounding by disease severity. While there is known clinical relevance for the CIBMTR disease status variable (Horowitz et al, 1999), the use in the context of this particular study is challenging to harmonize across disease states for interpretability in a clinically meaningful way. Differences in comparability of characteristics between arms were present, and additional sensitivity analyses were conducted to further evaluate the impact of discrepancies within this variable.

From a clinical perspective, the CIBMTR disease status variable is a construct of the database. While they are defined for each heme malignancy based on clinically used disease status descriptions (e.g. CR1, CR2, refractory disease), the task of collapsing these categories to a single variable that uniformly represents the risk of disease relapse across malignancies is challenging. Broadly, worsening disease status has been shown to predict worse outcome. However, the absolute impact of the disease status on outcomes is a function of age and disease type.

To address the loss of this prespecified factor from the propensity model, the Applicant included disease status as a covariate with treatment in the Cox proportional hazard model as discussed below. Moreover, in response to FDA informational request, the Applicant conducted a sensitivity analysis that excluded the 14 lymphoma patients (3/54 abatacept+CNI+MTX, 11/162 CNI+MTX) from the primary analysis. With their removal, the original propensity model converged, and the OS results were essentially unchanged.

Demographic Characteristics

Table 26: Key Demographic Characteristics at Transplant for the Un-Weighted Samples, Primary Objective Cohort - IM101841

	CNI+MTX+Aba without ATG (N = 54)	CNI+MTX without ATG (N = 162)	Total (N = 216)
Age (years)			
Median (Min, Max)	36.5 (6, 76)	51.0 (10, 74)	49.0 (6, 76)
Gender (%)			
Male	36 (66.7)	87 (53.7)	123 (56.9)
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)

Table 26: Key Demographic Characteristics at Transplant for the Un-Weighted Samples, Primary Objective Cohort - IM101841

	CNI+MTX+Aba without ATG (N = 54)	CNI+MTX without ATG (N = 162)	Total (N = 216)
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)

Source (ADaM dataset): Table S.3.1.1.1 (ADSL [PRIFL=Y]) in the IM101841 primary CSR

Table 27: Key Demographic Characteristics at Transplant for the Weighted Samples Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores - IM101841

	CNI+ MTX + Aba without ATG N = 54	CNI+MTX without ATG N = 162	Total N = 216
AGE (YEARS)			
MEDIAN (Min, Max)	51.0 (6, 76)	49.0 (10, 74)	49.0 (6, 76)
GENDER (%)			
MALE	33.4 (62.1)	95.5 (59.1)	128.9 (59.9)
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)
Stabilized Weight Range^a	0.3 - 4.6	0.8 - 4.8	

^a Patients with Stabilized weight <= 10 included in all analyses.

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.

Source (ADaM dataset): Table S.3.1.2.1 and Table S.5.1A.1 (ADSL) in the IM101841 primary CSR

The Applicant's Position:

The un-weighted and weighted samples for the demographic characteristics at baseline for the primary objective cohort are presented in Table 26 and Table 27, respectively.

These tables include 3 of the proposed 8 covariates in the propensity score model: age, gender, and Karnofsky/Lansky performance score (collapsed).

The weighted samples for age, gender and the performance score, showed smaller differences between the two groups, abatacept+CNI+MTX without ATG and CNI+MTX without ATG, as compared to the unweighted characteristics (Table 27).

FDA Assessment:

The FDA agrees with the Applicant's description of the demographic characteristics.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 28: Disease and Other Characteristics at Transplant: Un-weighted Samples - Primary Objective Cohort- IM101841				
	CNL + MIX + Aba without ATG N = 54	CNL + MIX without ATG N = 162	Total N = 216	
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/MEN 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				
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 (IED 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 (%)				

Table 28: Disease and Other Characteristics at Transplant: Un-weighted Samples - Primary Objective Cohort - IM101841			
	CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162	Total N = 216
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 + ETIPOSIDE	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, GROUPED (%)			
2011-2013	2 (3.7)	24 (14.8)	26 (12.0)
2014-2018	52 (96.3)	138 (85.2)	190 (88.0)
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)

Table 28: Disease and Other Characteristics at Transplant: Un-weighted Samples - Primary Objective Cohort - IM101841

	CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162	Total N = 216
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)

Table 28: Disease and Other Characteristics at Transplant: Un-weighted Samples - Primary Objective Cohort - IM101841			
	CNI + MTX + Aba without ATG N = 54	CNI + MTX without ATG N = 162	Total N = 216
YES	42 (77.8)	23 (14.2)	65 (30.1)

Source (ADaM dataset): Table S.3.2.1.1 (ADSL) in the IM101841 CSR

Table 29: Disease and Other Characteristics at Transplant for the Weighted Samples Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores -IM101841

	CNI/MTX + Aba without ATG N = 54	CNI/MTX without ATG N = 162	Total N = 216
DISEASE, COLLAPSED (%)			
AML	24.6 (45.6)	74.4 (46.1)	99.0 (46.0)
ALL	7.9 (14.6)	29.3 (18.2)	37.2 (17.3)
MDS OR MDS/MEN UNCLASSIFIABLE	13.2 (24.4)	34.2 (21.2)	47.4 (22.0)
CML OR CNL	4.3 (8.1)	12.8 (8.0)	17.2 (8.0)
HL-HNL	3.9 (7.3)	10.7 (6.6)	14.6 (6.8)
DISEASE STATUS (%)			
EARLY	38.7 (71.8)	87.4 (54.1)	126.0 (58.5)
INTERMEDIATE	8.2 (15.3)	27.9 (17.3)	36.1 (16.8)
ADVANCED	3.1 (5.7)	35.6 (22.0)	38.6 (17.9)
CHEMO-SENSITIVE	3.9 (7.3)	6.5 (4.1)	10.5 (4.9)
CHEMO-RESISTANT	0	4.1 (2.5)	4.1 (1.9)
DONOR AGE			
MEDIAN (MIN-MAX)	27.9 (18.4 - 52.6)	29.8 (19.4 - 53.5)	28.9 (18.4 - 53.5)
DONOR-RECIPIENT SEX MATCH (%)			
MALE/MALE	18.0 (33.4)	62.1 (38.4)	80.0 (37.2)
MALE/FEMALE	12.9 (24.0)	35.0 (21.7)	48.0 (22.3)
FEMALE/MALE	15.5 (28.7)	33.4 (20.7)	48.9 (22.7)
FEMALE/FEMALE	7.5 (13.9)	30.9 (19.2)	38.4 (17.9)
DONOR-RECIPIENT CYTOMEGALOVIRUS (CMV) STATUS MATCH (%)			
+/+	22.0 (40.8)	47.4 (29.4)	69.4 (32.2)
+/-	6.7 (12.4)	25.7 (15.9)	32.4 (15.0)
-/+	16.0 (29.7)	45.3 (28.1)	61.3 (28.5)
-/-	9.2 (17.0)	42.2 (26.2)	51.4 (23.9)
NOT REPORTED	0	0.9 (0.5)	0.9 (0.4)
DONOR-RECIPIENT ABO MISMATCH (%)			
MATCHED	4.9 (9.0)	20.3 (12.6)	25.1 (11.7)
MINOR MISMATCH	5.4 (10.1)	12.2 (7.6)	17.7 (8.2)
MAJOR MISMATCH	6.0 (11.1)	10.2 (6.3)	16.1 (7.5)
BI-DIRECTIONAL	1.1 (2.1)	3.6 (2.2)	4.7 (2.2)
NOT COLLECTED (TIED TRACK)	31.9 (59.2)	112.4 (69.6)	144.4 (67.0)
NOT REPORTED	4.6 (8.5)	2.8 (1.7)	7.4 (3.4)
HLA MATCHING (%)			

Table 29: Disease and Other Characteristics at Transplant for the Weighted Samples Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores-IM101841

	CNI-FIX		CNI-FIX		Total N = 216
	+ Aba N = 54	without ATG N = 162	+ Aba N = 54	without ATG N = 162	
9/10	43.3 (80.4)	153.4 (95.0)	43.3 (80.4)	153.4 (95.0)	196.7 (91.4)
8/10	8.5 (15.8)	5.3 (3.3)	8.5 (15.8)	5.3 (3.3)	13.8 (6.4)
NOT REPORTED	2.0 (3.8)	2.8 (1.7)	2.0 (3.8)	2.8 (1.7)	4.8 (2.2)
CONDITIONING REGIMEN (%)					
TBI + CY +- OTHERS	9.3 (17.2)	44.9 (27.8)	9.3 (17.2)	44.9 (27.8)	54.2 (25.2)
BU + CY +- OTHERS	15.2 (28.2)	37.0 (22.9)	15.2 (28.2)	37.0 (22.9)	52.2 (24.2)
BU + FLU +- OTHERS	7.5 (13.9)	60.2 (37.3)	7.5 (13.9)	60.2 (37.3)	67.7 (31.4)
FLU + MEL +- OTHERS	19.9 (36.9)	19.3 (11.9)	19.9 (36.9)	19.3 (11.9)	39.1 (18.2)
TBI + ETOPOSIDE	2.1 (3.8)	0	2.1 (3.8)	0	2.1 (1.0)
CONDITIONING INTENSITY (%)					
MYELOABLATIVE	38.2 (70.8)	110.6 (68.5)	38.2 (70.8)	110.6 (68.5)	148.8 (69.1)
REDUCED INTENSITY OR NON-MYELOABLATIVE	15.7 (29.2)	50.9 (31.5)	15.7 (29.2)	50.9 (31.5)	66.6 (30.9)
STEM CELL SOURCE (%)					
BONE MARROW	15.9 (29.5)	50.2 (31.1)	15.9 (29.5)	50.2 (31.1)	66.0 (30.7)
PERIPHERAL BLOOD	38.0 (70.5)	111.3 (68.9)	38.0 (70.5)	111.3 (68.9)	149.3 (69.3)
YEAR OF TRANSPLANT, GROUPED (%)					
2011-2013	1.1 (2.0)	27.5 (17.0)	1.1 (2.0)	27.5 (17.0)	28.6 (13.3)
2014-2018	52.8 (98.0)	134.0 (83.0)	52.8 (98.0)	134.0 (83.0)	186.8 (86.7)
TIME FROM DIAGNOSIS TO TRANSPLANT, MONTHS, GROUPED (%)					
<6	15.7 (29.2)	64.4 (39.9)	15.7 (29.2)	64.4 (39.9)	80.1 (37.2)
6-<12	16.0 (29.6)	44.9 (27.8)	16.0 (29.6)	44.9 (27.8)	60.9 (28.3)
>=12	22.2 (41.2)	52.2 (32.3)	22.2 (41.2)	52.2 (32.3)	74.4 (34.5)
CNI TYPE (%)					
TAC	46.7 (85.7)	140.6 (87.1)	46.7 (85.7)	140.6 (87.1)	187.3 (87.0)
CSA	7.2 (13.3)	20.8 (12.9)	7.2 (13.3)	20.8 (12.9)	28.0 (13.0)
HCT-CI (%)					
0	10.1 (18.8)	49.4 (30.6)	10.1 (18.8)	49.4 (30.6)	59.5 (27.6)
1-2	17.5 (32.5)	33.9 (21.0)	17.5 (32.5)	33.9 (21.0)	51.4 (23.9)
>=3	26.3 (48.7)	78.2 (48.4)	26.3 (48.7)	78.2 (48.4)	104.4 (48.5)
ARRHYTHMIA (%)					
NO	51.9 (96.3)	157.0 (97.3)	51.9 (96.3)	157.0 (97.3)	208.9 (97.0)
YES	2.0 (3.7)	4.4 (2.7)	2.0 (3.7)	4.4 (2.7)	6.4 (3.0)
CARDIAC COMORBIDITY (%)					
NO	53.9 (100.0)	146.2 (90.5)	53.9 (100.0)	146.2 (90.5)	200.1 (92.9)
YES	0	15.3 (9.5)	0	15.3 (9.5)	15.3 (7.1)
CEREBROVASCULAR DISEASE (%)					
NO	48.2 (89.4)	160.6 (99.5)	48.2 (89.4)	160.6 (99.5)	208.8 (97.0)
YES	5.7 (10.6)	0.8 (0.5)	5.7 (10.6)	0.8 (0.5)	6.5 (3.0)
DIABETES (%)					
NO	48.7 (90.3)	148.5 (91.9)	48.7 (90.3)	148.5 (91.9)	197.1 (91.5)
YES	5.2 (9.7)	13.0 (8.1)	5.2 (9.7)	13.0 (8.1)	18.2 (8.5)
HEART VALVE DISEASE (%)					

Table 29: Disease and Other Characteristics at Transplant for the Weighted Samples Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores-IM101841

	CNI-FMIX		CNI-FMIX		Total N = 216
	+ Aba N = 54	without ATG N = 162	+ Aba N = 54	without ATG N = 162	
NO	53.4 (99.2)	158.8 (98.3)	53.4 (99.2)	158.8 (98.6)	212.2 (98.6)
YES	0.5 (0.8)	2.7 (1.7)	0.5 (0.8)	2.7 (1.7)	3.1 (1.4)
MILD HEPATIC COMORBIDITY (%)					
NO	30.6 (56.9)	139.3 (86.3)	30.6 (56.9)	139.3 (86.3)	170.0 (78.9)
YES	23.2 (43.1)	21.2 (13.1)	23.2 (43.1)	21.2 (13.1)	44.4 (20.6)
NOT REPORTED	0	1.0 (0.6)	0	1.0 (0.6)	1.0 (0.5)
MODERATE/SEVERE HEPATIC COMORBIDITY (%)					
NO	53.6 (99.4)	156.2 (96.7)	53.6 (99.4)	156.2 (96.7)	209.7 (97.4)
YES	0.3 (0.6)	4.3 (2.7)	0.3 (0.6)	4.3 (2.7)	4.7 (2.2)
NOT REPORTED	0	1.0 (0.6)	0	1.0 (0.6)	1.0 (0.5)
INFECTIOUS (%)					
NO	51.0 (94.7)	153.3 (95.0)	51.0 (94.7)	153.3 (95.0)	204.3 (94.9)
YES	2.9 (5.3)	8.2 (5.0)	2.9 (5.3)	8.2 (5.0)	11.0 (5.1)
INFLAMMATORY BOWEL DISEASE (%)					
NO	53.9 (100.0)	160.6 (99.5)	53.9 (100.0)	160.6 (99.5)	214.5 (99.6)
YES	0	0.9 (0.5)	0	0.9 (0.5)	0.9 (0.4)
OBESITY (%)					
NO	46.0 (85.4)	138.7 (85.9)	46.0 (85.4)	138.7 (85.9)	184.8 (85.8)
YES	7.8 (14.6)	22.7 (14.1)	7.8 (14.6)	22.7 (14.1)	30.6 (14.2)
PEPTIC ULCER (%)					
NO	53.9 (100.0)	160.5 (99.4)	53.9 (100.0)	160.5 (99.4)	214.3 (99.5)
YES	0	1.0 (0.6)	0	1.0 (0.6)	1.0 (0.5)
PSYCHIATRIC DISTURBANCE (%)					
NO	44.1 (81.8)	132.9 (82.3)	44.1 (81.8)	132.9 (82.3)	177.0 (82.2)
YES	9.8 (18.2)	28.6 (17.7)	9.8 (18.2)	28.6 (17.7)	38.4 (17.8)
MODERATE PULMONARY COMORBIDITY (%)					
NO	41.4 (76.8)	112.5 (69.7)	41.4 (76.8)	112.5 (69.7)	153.9 (71.5)
YES	12.5 (23.2)	49.0 (30.3)	12.5 (23.2)	49.0 (30.3)	61.5 (28.5)
SEVERE PULMONARY COMORBIDITY (%)					
NO	51.0 (94.6)	132.8 (82.3)	51.0 (94.6)	132.8 (82.3)	183.8 (85.4)
YES	2.9 (5.4)	28.6 (17.7)	2.9 (5.4)	28.6 (17.7)	31.5 (14.6)
MODERATE/SEVERE RENAL COMORBIDITY (%)					
NO	53.9 (100.0)	157.8 (97.7)	53.9 (100.0)	157.8 (97.7)	211.7 (98.3)
YES	0	2.7 (1.7)	0	2.7 (1.7)	2.7 (1.2)
NOT REPORTED	0	1.0 (0.6)	0	1.0 (0.6)	1.0 (0.5)
RHEUMATOLOGIC COMORBIDITY (%)					
NO	52.8 (97.9)	161.5 (100.0)	52.8 (97.9)	161.5 (100.0)	214.2 (99.5)
YES	1.1 (2.1)	0	1.1 (2.1)	0	1.1 (0.5)
PRIOR SOLID TUMOR (%)					
NO	44.0 (81.6)	138.4 (85.7)	44.0 (81.6)	138.4 (85.7)	182.4 (84.7)
YES	9.9 (18.4)	23.1 (14.3)	9.9 (18.4)	23.1 (14.3)	33.0 (15.3)
PARTICIPATION IN THE ABA2 TRIAL (%)					

Table 29: Disease and Other Characteristics at Transplant for the Weighted Samples Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores-IM101841

	CNI+MTX		Total N = 216
	+ Aba without ATG N = 54	without ATG N = 162	
NO	9.5 (17.6)	161.5 (100.0)	171.0 (79.4)
YES	44.4 (82.4)	0	44.4 (20.6)
PARTICIPATION IN ANY CLINICAL TRIAL (%)			
NO	9.5 (17.6)	140.1 (86.8)	149.6 (69.5)
YES	44.4 (82.4)	21.4 (13.2)	65.8 (30.5)
Stabilized Weight Range ^a	0.3 – 4.6	0.8 – 4.8	

Stabilized weight < = 10 included in all analyses.

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.

Source (ADaM dataset): Table S.3.2.2.1 and Table S.5.1A.1 (ADSL) in the IM101841 Primary CSR

The Applicant’s Position:

The un-weighted and weighted samples for the disease and other characteristics at baseline for the primary objective cohort are presented in Table 28 and Table 29, respectively. These tables include the remaining 5 of the proposed 8 covariates in the propensity score model: disease (collapsed), HSCT graft source (stem cell source), conditioning intensity, CNI type and disease status (not included in model as noted previously). For the disease and other characteristics at transplant, the weighted samples for the covariates in the propensity model generally showed smaller differences between the two groups, abatacept + CNI + MT without ATG group and CNI + MTX without ATG group, as compared to the unweighted characteristics.

FDA Assessment:

The FDA agrees with the Applicant’s description of the disease and other baseline characteristics. The IPTW method via propensity score improved balancing between abatacept + CNI + MTX without ATG group and CNI + MTX without ATG group for covariates disease (collapsed), stem cell source (HSCT graft source), conditioning intensity, and CNI type. However, other disease and baseline covariates not included in the propensity score model still indicated some imbalance between groups. Specifically, differences remained in the baseline disease status after weighting (early disease, 71.8% abatacept group vs. 54.1% in standard of care [SOC]), and trial participation (82.4% abatacept patients were enrolled in a clinical trial while 13.2% of SOC patients were enrolled in any trial). However, transplant patients have highly monitored care which reduces concern about potential bias. Other differences remained in conditioning regimen, year of transplant (transplant outcomes have improved over time), HCT-CI, and individual comorbidities (cardiac, cerebrovascular, hepatic, pulmonary).

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

We note that the HCT-CI is a clinical comorbidity risk score developed to predict a patient's risk of non-relapse mortality (NRM) after transplant (Sorrer et al. 2005). It incorporates 17 different categories of comorbidity to determine the risk of NRM. The imbalance that is noted above would be expected to increase the risk of NRM in the abatacept treated patients since the abatacept had a slightly higher proportion of patients that scored 1-2 than the comparison group. However, the Division of Epidemiology provided a detailed review of comparability concerns and concluded that the differences in SOC with abatacept patients treated in later follow-up years, as well as differences in trial participation and in baseline disease status could result in the potential for time related bias and residual confounding, respectively, and impact on benefit could not be ruled out.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance: Not applicable

Concomitant Medications: Concomitant therapy for comorbid diseases or other reasons were not available.

Rescue medication: Not applicable.

FDA Assessment:

Not applicable for this study.

Efficacy Results – Primary Endpoint

Data:

Table 30: Summary of OS During 180 Days of Follow-up Post-Transplant Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores (PS), Primary Objective Cohort - IM101841

	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)
Survival Rate At Day 180 (95% CI) (A)	0.98 (0.78, 1.00)	0.75 (0.67, 0.82)
P-value From Log-Rank Test (A)	0.0028	
Hazard Ratio vs. Comparator Group (95% CI)(B)	0.07 (0.01, 0.30)	

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.

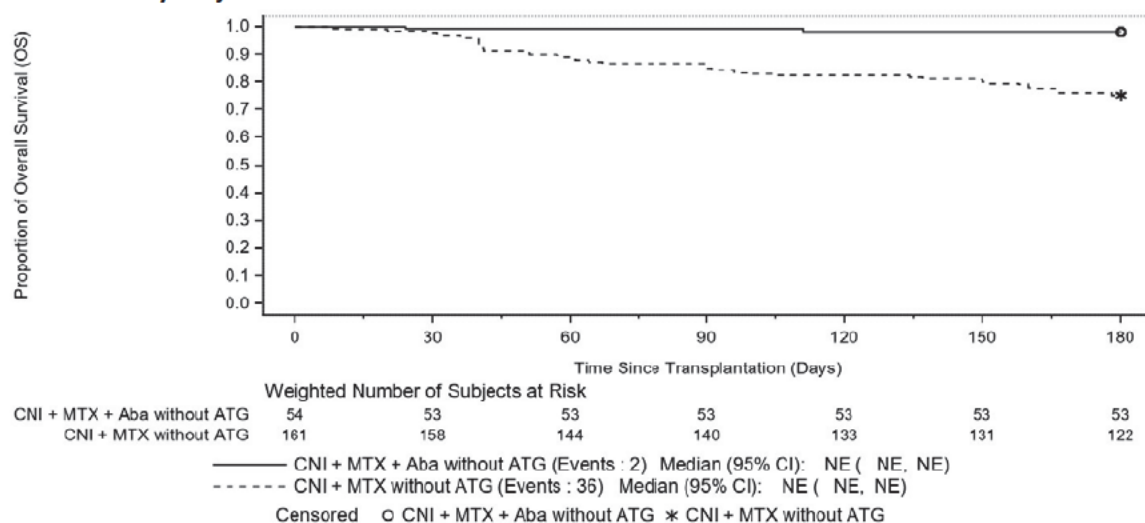
(B) Marginal hazard ratio based on weighted Cox proportional hazards model with treatment and disease status as covariates using a robust variance estimator that accounts for the sample weights. Ties are handled using the Breslow method.

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.

Source (ADaM dataset): Table S.5.1.1 (ADSL, ADTTE [PRIFL=Y and PARAMCD=OS]) in the IM101841 CSR.

Figure 14: K-M Plot of OS During 180 Days of Follow-up Post-transplant using Stabilized IPTW with PS in the Primary Objective Cohort - IM101841



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

Based on weighted Kaplan-Meier method. Symbols represent censored observation.

OS time is defined as the time between the date of transplant to the date of death.

Subjects are censored at 181 days post-transplant or at time of last follow-up, whichever is earlier.

NE: Not Estimable

Source (ADaM dataset): Figure S.5.1.1 (ADTTE [PRIFL=Y and PARAMCD=OS]) in the IM101841 CSR

The Applicant's Position:

Primary Endpoint

In the primary objective cohort, OS rate at 180 days after transplant was significantly higher in patients receiving abatacept+CNI+MTX without ATG compared to patients receiving CNI+MTX without ATG (Table 38). The addition of abatacept to the standard of care therapy showed a protective benefit compared to the comparator group. OS shows separation beginning at approximately Day 30 and continuing through Day 180 (Figure 14).

FDA Assessment:

The FDA agrees with the Applicant's description of the primary endpoint.

The primary efficacy result presented in Table 30 above can be reproduced by the statistical reviewer. The marginal hazard ratio (HR) for OS and the corresponding 2-sided 95% confidence interval (CI) were estimated based on a weighted Cox proportional hazards model adjusted for treatment and disease status using a robust variance estimator that accounted for the sample weights. The OS rate at Day 180 was 98% in the CNI + MTX + abatacept without ATG group and 75% in the CNI + MTX without ATG group. The estimated marginal HR was of 0.07 (95% CI: 0.01, 0.30) with a two-sided log-rank p-value of 0.0028. The result was statistically significant when compared to the 0.05 significance level. Therefore, the study met its primary objective.

Of note, the planned primary efficacy analysis included treatment as the only covariate in the weighted Cox proportional hazards model. However, since the planned covariate "disease status" caused quasi-complete separation warning and the multicollinearity warning in logistic regression model when computing the propensity scores, this covariate was removed from propensity score model and adjusted along with treatment in weighted Cox proportional hazards model for primary efficacy analysis. More details are in the "Modification to the propensity model" section. The estimated marginal HR adjusted for treatment only was of 0.06 (95% CI: 0.01, 0.27) which indicated consistent result with the primary analysis.

Common support analysis

The common support analysis was conducted to assess the degree of overlap on the propensity scores across treatment and comparator groups. Subjects with propensity scores outside the region of common support were excluded from primary analysis. The region of common support is defined as the overlap in the range of propensity scores across treatment and comparator groups. Adequate number of subjects from treated group and comparator group with similar propensity scores warrants the assessment of treatment effect. The lower bound of the common support region is the larger of the minimum propensity scores for the two groups, and the upper bound is the smaller of the maximum propensity scores for the two groups. The Applicant used extended common support region which extended the upper and lower bound by 0.25x (pooled estimate of standard deviation). In this sensitivity analysis, 3 subjects in the CNI + MTX + abatacept group were removed from primary efficacy analysis due to the propensity scores out of the upper bound of common support region. Based on Applicant's results, the OS rate at Day 180 was 98% in the CNI + MTX + abatacept without ATG group and 75% in the CNI + MTX without ATG group. The estimated marginal HR was of 0.07 (95% CI: 0.01, 0.31).

Propensity score balance diagnostic

The standardized differences (Treated - Control) of the covariates included in the propensity scores with and without weighting are summarized in Table 31. All propensity score variables with weighted standardized differences (absolute) were less than the prespecified level of 0.25 which indicated that weight method improved the balance of propensity scores.

Table 31: Propensity Score Balance Diagnostic

Covariates in The Propensity Score Model	Standardized Difference	Weighted Standardized Difference
Age	-0.60709	0.05902
Gender	-0.26716	0.05902
Disease: AML	0.26373	0.01059
Disease: ALL	-0.12021	0.08605
Disease: MDS or MDS/MPN Unclassifiable	-0.06066	-0.08019
Disease: CML or CNL	-0.25654	-0.00448
Disease: HL+NHL	0.05132	-0.02797
HSCT Graft Source	0.64315	-0.03438
Conditioning Intensity	0.21893	0.05202
Karnofsky/Lansky Performance Score	-0.10767	-0.02574
CNI type: tacrolimus vs. CsA	0.87519	0.01085

Source: Generated by statistical reviewer

Sensitivity analyses

The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. Among the limitation of propensity score methods is that it is based on the known or measured covariates but not on the potentially unmeasured confounders. The following sensitivity analyses were conducted to identify confounding factors not originally specified in the model.

Clinical trial participation

The propensity scores were reassessed by including covariate of participation in any clinical trial in the propensity score model to account for the possibility that subjects who participated in clinical trials may be a healthier subset of subjects receiving abatacept overall. Based on the Applicant's unweighted results, subjects participated in any clinical trial was 77.8% in the CNI + MTX + abatacept without ATG group and 14.2 % in the CNI + MTX without ATG group. The OS rate at Day 180 was 98% in the CNI + MTX + abatacept without ATG group and 79% in the CNI + MTX without ATG group. The estimated marginal HR was of 0.09 (95% CI: 0.02, 0.44). In addition, 77.8% of subjects in the CNI + MTX + abatacept without ATG group participated in Study IM101311 and there were no subjects in CNI + MTX without ATG group who participated in Study IM101311.

Baseline Hematopoietic Cell Transplantation-Comorbidity Index (HCTCI)

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

To account for the limitations of the clinical trial indicator, the Applicant included a sensitivity analysis adjusting for comorbidity index (HCT-CI) in the propensity score model which would more directly account for confounding by underlying health status. Based on Applicant’s results, the OS rate at Day 180 was 98% in the CNI + MTX + abatacept without ATG group and 75% in the CNI + MTX without ATG group. The estimated marginal HR was of 0.07 (95% CI: 0.01, 0.31).

Data Driven Variable Selection

All the independent variables of interest in Table 32 were considered for inclusion in the propensity score model using the LASSO selection method. Age, donor age and participation in any clinical trial were selected for propensity score model. Based on Applicant’s results, the OS rate at Day 180 was 97% in the CNI + MTX + abatacept without ATG group and 79% in the CNI + MTX without ATG group. The estimated marginal HR was of 0.12 (95% CI: 0.02, 0.79).

Table 32: Independent Variables of Interest

Category	Variables
Demographics	Age at transplantation, Gender, Karnofsky/Lansky Performance score prior to transplant (%), Race/ethnicity
Disease-related	Disease, Disease status
Donor-related	Donor age, Donor-recipient sex match, Donor-recipient Cytomegalovirus (CMV) status match, Donor-recipient ABO mismatch, HLA matching
Transplant-related	Conditioning regimen, Conditioning intensity, Stem cell source, Year of transplant: continuous and grouped, Time from diagnosis to transplant, Time from diagnosis to transplant, CNI type
Comorbidities	HCT-CI, Arrhythmia, Cardiac comorbidity, Cerebrovascular disease, Diabetes, Heart valve disease, Mild hepatic comorbidity, Moderate/severe hepatic comorbidity, Infection, Inflammatory bowel disease, Obesity, Peptic ulcer, Psychiatric disturbance, Moderate pulmonary comorbidity, Severe pulmonary comorbidity, Moderate/severe renal comorbidity, Rheumatologic comorbidity, Prior solid tumor
Other	Participation in the ABA2 clinical trial, Participation in any clinical trial during the study period

Source: Section 3.4.3 in the protocol version 2.0

Supplementary Analyses Using Propensity Scores Based Matching (no alpha allocation)

Primary Endpoint Results Using Matching 1:1

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

According to the BMSSAP, propensity score matching was conducted as an additional analysis for the primary objective. In contrast to the IPTW approach, only subjects that can be matched to abatacept-treated subjects were included in this analysis. Due to this restriction in included subjects, the propensity score matching approach estimates the average effect of treatment in the treated population (ATT), or the effect of treatment among subjects that actually received the treatment.

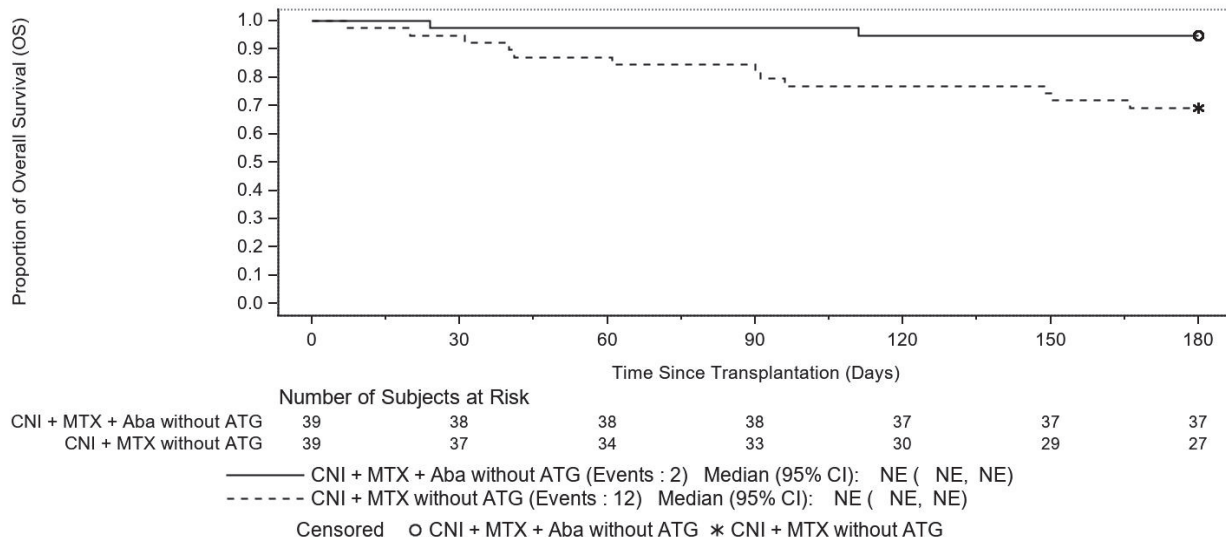
Subjects in the CNI + MTX + abatacept without ATG group were matched 1:1 to subjects in the CNI + MTX without ATG with the smallest absolute difference in the logit of their propensity score (greedy nearest neighbor matching). A caliper width of 20% of the standard deviation of the logit of the propensity score was used. Abatacept subjects were randomly ordered and then matched without replacement. In the case of ties, subjects were randomly matched. Abatacept subjects without a matched comparator were excluded from the subsequent analysis.

The unweighted Cox proportional hazards model with a cluster term for each matched pair was used to estimate the marginal HR for OS and the corresponding 2-sided 95% CI with treatment as the only covariate based on the matched sets. The unweighted Kaplan-Meier method was used to estimate OS rates at 180 days associated 95% CIs.

Based on Applicant's results, using a propensity score based on 1:1 matching ratio, the total sample size reduced from 216 to 78. There were 39 subjects in the CNI + MTX + abatacept without ATG group matched 1:1 to subjects in the CNI + MTX without ATG group. The OS rate at Day 180 was 95% in the CNI + MTX + abatacept without ATG group and 69% in the CNI + MTX without ATG group. The estimated marginal HR was of 0.15 (95% CI: 0.04, 0.53). The results demonstrated consistency with the primary efficacy results using stabilized IPTW with propensity scores. The OS KM curve based on 1:1 Matching is presented in Figure 15.

Figure 15: K-M Plot of Overall Survival (OS) During 180 Days of Follow-up Post-transplant Using Propensity Scores Based 1:1 Matching: Primary Objective Cohort

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)



Source: the Applicant's figure S.5.4.1

Primary Endpoint Results Using Matching 1:3

In the second matching analysis, matching subjects in the CNI + MTX + abatacept without ATG group in a 1:3 ratio to subjects in the CNI + MTX without ATG group was planned in BMS SAP. Abatacept-treated subjects with less than 3 matched comparators would be excluded from the subsequent analysis to maintain the fixed 3:1 ratio. However, based on Applicant's results, there were more than 20% of abatacept subjects could not be matched to 3 comparator controls, therefore, this analysis was not conducted according to BMSSAP.

Additional analyses

Confidence Intervals

The FDA had concern regarding the accuracy of the confidence interval for HR in the primary analysis based on indirect comparison using IPTW method via propensity score approach and rare event rate. The current confidence interval was based on Wald test with the robust variance estimator, which was suspected to under-cover the 95% nominal rate. Therefore, the FDA statistical reviewer further investigated the alternative CIs. The results are presented in Table 33.

Table 33: Other CIs Investigated on the Primary Endpoint of OS at Day 180 - Study IM10184

	HR (95% CI)
IPW Analysis (Primary)	0.06 (0.01, 0.27)
IPW Analysis (naïve variance estimator)	0.06 (0.01, 0.48)
PS Matching (1:1 ratio)	0.15 (0.04, 0.54)
Bayesian Analysis	0.13 (0.02, 0.46)
Bootstrap Method*	0.06 (6.0E-8, 0.23)

*The CI from bootstrap method was based on 1000 bootstrap samples by drawing random samples with replacement from each treatment group.

Unmeasured confounding

The FDA conducted the following sensitivity analyses to further investigate potential concerns specifically related to unmeasured confounding present with observational data in the absence of randomization.

Sensitivity analysis based on E-value

According to VanderWeele, T. J., and P. Ding. 2017, the E-value is the minimum strength of association, on the risk ratio scale (could be converted to HR), that an unmeasured confounder would need to have on both the treatment and outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates. The higher the E-value, the stronger the confounder associations must be to explain away the effect.

In Study IM101841, the E-value of upper bound of 95% CI for the HR was 4.3. This may be interpreted to mean that an unmeasured confounder that was associated with both the treatment and the outcome by a HR of 4.3-fold each, above and beyond the measured confounders that were known, could overturn the significance of the primary analysis. All known clinically relevant potential confounders were included as covariates. Note that the E-value is the point at which the strength of association between the confounder and treatment is identical to that between the confounder and the outcome. Thus, confounders with weaker associations with the treatment than a 4.3 HR could overturn the result if the association between the treatment and outcome were commensurately higher than a 4.3 HR, or vice versa. While there is no well-established gold standard to measure the magnitude of unmeasured confounder, VanderWeele, T. J., and P. Ding, 2017. VanderWeele, T. J., and P. Ding, 2017 suggest that E-values of 2 or 3 are relatively “large” and unlikely to be observed in practice.

Sensitivity analysis based on Rosenbaum’s approach

According to Gastwirth J, Krieger A, Rosenbaum P. Dual, 1998, Rosenbaum’s approach was used to assess the unmeasured confounding issue on the primary endpoint based on full propensity score matching method. This approach finds the thresholds of the association between the unmeasured confounder and the treatment and/or between the unmeasured confounder and the outcome that would make statistical inference insignificant.

The 1:1 matched analysis provided by the Applicant resulted in 39 pairs. In 10 of these pairs, the subject in the control group died but the abatacept group subject did not; there were no pairs in which the abatacept group subject died and the control group subject died. Regarding death by Day 180 as a binary outcome, this would result in a gamma value of $\Gamma=2.25$. When these outcomes are regarded as time-to-event and thus the analysis is stratified by time, the gamma value is $\Gamma=1.60$.

Because the 1:1 matched analysis removed many subjects from the analysis set, the sensitivity analysis was repeated using full matching. Full matching resulted in a matched analysis set containing N=213 subjects. Using this analysis set, Rosenbaum’s bound gamma was $\Gamma=1.67$ when death by Day 180 was treated as a binary outcome and $\Gamma=1.57$ when death by Day 180 was treated as a time-to-event outcome.

ORENCIA (abatacept)

Note that these values are smaller than the E-value, though Rosenbaum's gamma is on a different scale (odds ratio). Rosenbaum's gamma is conservative in the sense that the unmeasured confounder is assumed to have unbounded influence on the outcome; see for instance Rosenbaum, Paul R, 2002. Similar to the E-value, there is no commonly accepted magnitude for Rosenbaum's bound.

Reviewer's comment: Like other standard statistical analyses, analyses of unmeasured confounding generally increase in power when 1) the magnitude of treatment effect is increased and/or 2) the sample size is increased. In this case, there is a ceiling on the magnitude of the treatment effect, since the observed 180-day survival rate was 75% in the control group. Furthermore, the sample size was limited by the number of 7/8 HLA-matched patients treated with abatacept.

Covariate Imbalance

Residual imbalance was observed in the key baseline covariates even after weighting and matching, which is important to further evaluate in observational data. The FDA statistical reviewer conducted sensitivity analysis to include covariates in the survival model along with treatment. The results are presented in Table 34. The following covariates were included due to noted imbalances on disease status, conditioning regimen, clinical trial participation, year of transplant (grouped as 2011-2014 vs. 2014-2018). Race was also one of the considerable variables but removed from the analysis due to the unstable estimate caused by small sample size at some levels. Based on further analysis, it appeared that accounting for this imbalance by including conditioning regimen, clinical trial participation and year of transplant as covariates did not change the significance of the primary result. Further analysis of disease status was conducted (refer to FDA assessment for primary efficacy analysis above for more information).

Table 34: Analysis of the Effect of Imbalance in Covariates on the Primary Endpoint of OS at Day 180 Post-HSCT on Study IM101841

Term	HR (95% CI)	Nominal P-value
Abatacept vs. Control	0.14 (0.02, 0.77)	0.0238
Disease status: Early or Chemo-sensitive vs. Advanced or Chemo-resistant	0.38 (0.18, 0.78)	0.0089
Disease status: Intermediate vs. Advanced or Chemo-resistant	0.43 (0.16, 1.18)	0.1006
Conditioning regimen: Reduced intensity or Non-myeloablative vs. Myeloablative	0.47 (0.22, 1.03)	0.0598
Clinical trial participation: Yes VS. No	0.72 (0.23, 2.24)	0.5769

Year of transplant: 2014-2018 VS. 2011-2014	0.86 (0.35, 2.13)	0.7509

Source: FDA analysis of adtte.xpt for study IM101841

The following analyses were requested by FDA to assess the potential selection bias:

1. *“To assess measurement bias, we recommend a methods study be conducted. This study should include all patients enrolled in the IM101311 study (7/8 and 8/8 matched patients), with stratified analyses by 7/8 and 8/8 HLA matching. All study variables (i.e., baseline covariates, independent variables, exposure, outcomes, etc.) should be compared between the clinical trial and the CIBMTR database among the patients enrolled in IM101311 who have variables collected both in ABA2 and the CIBMTR database. This will result in a direct evaluation of measurement error within the CIBMTR. Please consider stratifying by other factors (e.g., treatment site or groups of treatment sites) to inform the best final study design, in terms of minimizing this bias, for your final study.”*

The Applicant assessed following outcomes in 8/8 HLA-matched subjects treated with CNI+MTX without ATG for IM101311 participants to IM101311 non-participants:

- OS with 180 days of follow-up post-HSCT
- Grade II-IV aGVHD-free survival up to the first 100 and 180 days
- Grade III-IV aGVHD-free survival up to the first 100 and 180 days
- Relapse-free survival up to the first 100 and 180 days of follow-up
- Incidence of PTLD at the first 100 and 180 days of follow-up

The analyses were based on the same selection methodology, definition of study variables, and analysis method (same propensity score model via IPTW method) in Study IM101841 mentioned in section 8.1.4 in this Assessment Aid. The study results are in Table 35.

Table 35: 8/8 HLA-matched Subjects Treated with CNI + MTX without ATG for IM101311 participants to IM101311 non-participants

	IM101311 participants N=67	IM101311 non-participants N=315
OS During 180 Days of Follow-up Post-transplant		
Proportion with Event, n/m (%)	10/67 (14.9)	61/315 (19.4)
Survival Rate at Day 180 (95% CI)	0.86 (0.71, 0.94)	0.81 (0.77, 0.85)
Hazard Ratio vs. Comparator Group (95% CI) *	0.71 (0.32, 1.57)	

* 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.

Source: the Applicant’s Table 8.5.1.2-1, Table 8.5.1.3-1, Table 8.5.1.3-3, Table 8.5.1.4-1

Reviewer’s comment: The outcome of OS at Day 180 demonstrated the consistency between participants and non-participants of Study IM101311. Results were similar for other endpoints (e.g., GFS) as well. However, given that GVHD is not captured with sufficient granularity in CIBMTR for FDA reviewer adjudication, these endpoints are not reported here.

There were no cases of PTLD reported in 8/8 HLA-matched subjects in this analysis.

2. *“To assess measurement bias, we recommend a methods study be conducted. This study should include all patients enrolled in the ABA2 study (7/8 and 8/8 matched patients), with stratified analyses by 7/8 and 8/8 HLA matching. All study variables (i.e., baseline covariates, independent variables, exposure, outcomes, etc.) should be compared between the clinical trial and the CIBMTR database among the patients enrolled in ABA2 who have variables collected both in ABA2 and the CIBMTR database. This will result in a direct evaluation of measurement error within the CIBMTR. Please consider stratifying by other factors (e.g., treatment site or groups of treatment sites) to inform the best final study design, in terms of minimizing this bias, for your final study.”*

The Applicant assessed the degree of concordance of the study outcomes, GVHD prophylaxis treatments, and independent variables of interest between the CIBMTR database and Study IM101311 for all subjects enrolled in Study IM101311. The summary is provided in Table 36.

Table 36: Summary of Degree of Concordance of Variables of Interest between the CIBMTR Database and Study IM101311

	7/8 Cohort		8/8 Cohort	
	Agreement	~5-10% discrepancy	Agreement	~5-10% discrepancy
Outcome	OS	- Gr III-IV aGVHD or Death up to Day 180 (7%) - PTLD up to Day 100 (60%) - PTLD up to Day 180 (60%)	OS (1 patient reported “no” in the CIBMTR database and “yes” in IM101311.)	- Gr II-IV aGVHD or Death up to Day 100 (8%) - Gr II-IV aGVHD or Death up to Day 180 (7%) - Gr III-IV aGVHD or Death up to Day 100 (8%) - Gr III-IV aGVHD or Death up to Day 180 (7%) - Relapse or Death up to Day 180 (6%) - PTLD up to Day 100 (67%) - PTLD up to Day 180 (67%)
Baseline Covariates (Categorical variables)	Treatment, gender, conditioning regimen, stem cell source, or year of transplant	- Performance Score 80% (7%) - Performance Score 90-100% (10%) - Disease (7%)	Treatment, gender, conditioning regimen, or year of transplant	- Performance Score 70% (5%) - Performance Score 80% (7%) - Performance Score 90-100% (9%) - CMV (6%)

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

		Donor-recipient ABO Mismatch (60%)		Donor-recipient ABO Mismatch (61%)
Baseline Covariates (Continuous variables)	Age (ICC, nearly 100%)		Age (ICC, nearly 100%)	

Source: Generated by statistical reviewer based on the Applicant’s Table S.5.17.1.1, Table S.5.17.1.3, Table S.5.17.2.1 and Table S.5.17.2.3 in the IM101841 primary CSR

Among 7/8 matched subjects, there were no discrepancies on treatment, gender, conditioning regimen, stem cell source, or year of transplant. Some discrepancies were noticed on remaining baseline characteristics, general agreement on OS. The ICC for continuous variable age was nearly 100%.

Among 8/8 matched subjects, there were no discrepancies on treatment, gender, conditioning regimen, or year of transplant. Some discrepancies were noticed on remaining baseline characteristics, some discrepancies on outcome variables. The ICC for continuous variable age was nearly 100%.

A clinical question that was posed during the review of the primary endpoint was how well the endpoint of OS relates to the prophylaxis of aGVHD. The clinical team looked at this in two ways. First was to look for differences in aGVHD occurrence in the first 180 days. This was not picked as the primary endpoint for Study IM101841 since this data is not uniformly collected in a granular format for all patients in the CIBMTR database. Time to event data for aGVHD occurrence is available for a non-random subset of patients that have supplemental CRF data forms submitted. However, all patients are required to have TED forms submitted and the occurrence of aGVHD by the day 100 and the day 180 time point are a component of those forms. Figure 16 below shows the contingency tables for grade II-IV aGVHD, grade II-IV aGVHD or death, grade III-IV aGVHD, and grade III-IV aGVHD or death all tallied at day 180. Of note, these are not weighted by propensity score and represent a basic look at the rates of reported aGVHD by day 180 in these two groups of patients. Refer to Table 41 for the Applicant’s analysis of aGVHD events using time to aGVHD data and propensity score weighting. However, note that this analysis only includes patients with CRF data available. Interestingly, while the rate of grade II-IV aGVHD was essentially the same (43.4% vs 43.2%, Aba+CNI+MTX without ATG vs CNI+MTX without ATG), the rate of severe aGVHD was lower in the abatacept treated patients (10.2% vs 19.1%, (Aba+CNI+MTX without ATG vs CNI+MTX without ATG). Since death from other causes is a competing risk to developing aGVHD during this time period, contingency tables with aGVHD or death by day 180 are also shown. The addition of death to the endpoint by day 180 shows some separation between comparison arms (44.4% vs 53.7%, Aba+CNI+MTX without ATG vs CNI+MTX without ATG) for grade II-IV aGVHD or death by day 180 and (11.1% vs 33.3%, Aba+CNI+MTX without ATG vs CNI+MTX without ATG) for the rate of grade III-IV aGVHD or death by day 180.

Figure 16: Analysis of aGVHD events by day 180 in study IM101841

Source: FDA analysis of adsl.xpt for study IM101841

The second approach the review team took was to obtain the cause of death for the patients in Study

Contingency Table				
Overall - Gr2-4 aGVHD 180D FU				
Count	N	Y	Total	
Total %				
Col %				
Row %				
CNI + MTX + Aba without ATG	30 13.95 24.59 56.60	23 10.70 24.73 43.40	53 24.65	
CNI + MTX without ATG	92 42.79 75.41 56.79	70 32.56 75.27 43.21	162 75.35	
Total	122 56.74	93 43.26	215	

Contingency Table				
Gr2-4 aGVHD or Death 180D FU				
Count	N	Y	Total	
Total %				
Col %				
Row %				
CNI + MTX + Aba without ATG	30 13.89 28.57 55.56	24 11.11 21.62 44.44	54 25.00	
CNI + MTX without ATG	75 34.72 71.43 46.30	87 40.28 78.38 53.70	162 75.00	
Total	105 48.61	111 51.39	216	

Contingency Table				
Overall - Gr3-4 aGVHD 180D FU				
Count	N	Y	Total	
Total %				
Col %				
Row %				
CNI + MTX + Aba without ATG	44 20.85 25.14 89.80	5 2.37 13.89 10.20	49 23.22	
CNI + MTX without ATG	131 62.09 74.86 80.86	31 14.69 86.11 19.14	162 76.78	
Total	175 82.94	36 17.06	211	

Contingency Table				
Gr3-4 aGVHD or Death 180D FU				
Count	N	Y	Total	
Total %				
Col %				
Row %				
CNI + MTX + Aba without ATG	48 22.22 30.77 88.89	6 2.78 10.00 11.11	54 25.00	
CNI + MTX without ATG	108 50.00 69.23 66.67	54 25.00 90.00 33.33	162 75.00	
Total	156 72.22	60 27.78	216	

IM101841 and compare them between treatment arms. As can be seen in Table 37 below, the most frequent cause of death by day 180 in the CNI+MTX without ATG group was due to GVHD whereas no patients in the abatacept+CNI+MTX without ATG died of GVHD by day 180. One issue that was discussed above was the impact of an imbalance in advanced disease patients in the comparator arm as it might cause an increased rate of primary disease relapse and relapse related death as a confounding risk in the OS analysis. This was investigated with several methods above. As an additional approach, if we remove from consideration patients that have relapsed from the cause of death tabulations, we still see that GVHD is the most frequent etiology of death in the CNI+MTX without ATG group. This is important since patients that have relapsed usually have their ongoing immunosuppression (CNI) stopped and/or given donor lymphocyte infusions in attempt to induce a graft-versus-leukemia effect to treat the relapse of the primary disease. These actions can greatly increase the risk of developing aGVHD in these patients.

Therefore, censoring relapsed patients from this analysis that have relapsed lessens this potential confounding on aGVHD death events.

Table 37: Cause of death to day 180 post-transplantation in Study IM101841 primary endpoint population

Cause of Death	All patients		Without relapsed patients	
	Abatacept+CNI+MTX (n=54)	CNI+MTX (n=162)	Abatacept+CNI+MTX (n=49)	CNI+MTX (n=137)
GVHD	0 (0%)	10 (6%)	0 (0%)	9 (7%)
Primary disease	1 (2%)	9 (6%)	1 (2%)	1 (1%)
Organ failure	1 (2%)	7 (4%)	1 (2%)	7 (5%)
Infection	0 (0%)	6 (4%)	0 (0%)	5 (4%)
Graft failure	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Idiopathic pneumonia	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Other cause	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Vascular	0 (0%)	1 (1%)	0 (0%)	1 (1%)

Source: FDA analysis of adsl.xpt for study IM101841 merged with cause of death by subject ID supplied by Applicant IR response on 10/8/2021.

Data Quality and Integrity

The Applicant’s Position:

Research conducted by CIBMTR was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The rights, safety, and well-being of the study subjects were the most important consideration and prevailed over the interests of science and society.

FDA Assessment:

We agree with the data quality and integrity assessment. As noted above, CIBMTR continuously collects and audits data at all participating transplant centers, including post-transplant follow up data for defined outcomes and more detailed data collection on ~25% of registered patients using a regularly reviewed, weighted algorithm. The CIBMTR has a Data Quality Program that includes an Audit Program to evaluate data accuracy, completeness, and implement corrective actions as needed to ensure data quality.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 38: Summary of OS During 180 Days of Follow-up Post-transplant Using Stabilized Inverse Probability of Treatment Weighting (IPTW) with Propensity Scores (PS) in the Comparator Group with ATG - IM101841

	CNI+MTX+ Aba without ATG N=54	CNI+MTX with ATG N=162

ORENCIA (abatacept)

Proportion With Event, n/m (%)	2/54 (3.7)	41/162 (25.3)
Survival Rate At Day 180 (95% CI) (A)	0.98 (0.76, 1.00)	0.74 (0.65, 0.80)
P-value From Log-Rank Test (A)	0.0060	
Hazard Ratio vs. Comparator Group (95% CI) (B)	0.08 (0.02, 0.36)	

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 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.

Source (ADaM dataset): Table S.5.1.5 (ADSL, ADTTE) in the IM101841 Primary CSR

Table 39: Summary of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the Tacrolimus Sub-group - IM101841

	Tacrolimus+MTX+ Aba without ATG N=33	Tacrolimus+MTX without ATG N=99
Proportion With Event, n/m (%)	0/ 33	29/ 99 (29.3)
Survival Rate At Day 180 (95% CI) (A)	1.00	0.72 (0.62, 0.80)
P-value From Log-Rank Test (A)		0.0043
Hazard Ratio vs. Comparator Group (95% CI)(B)		0.00 (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.

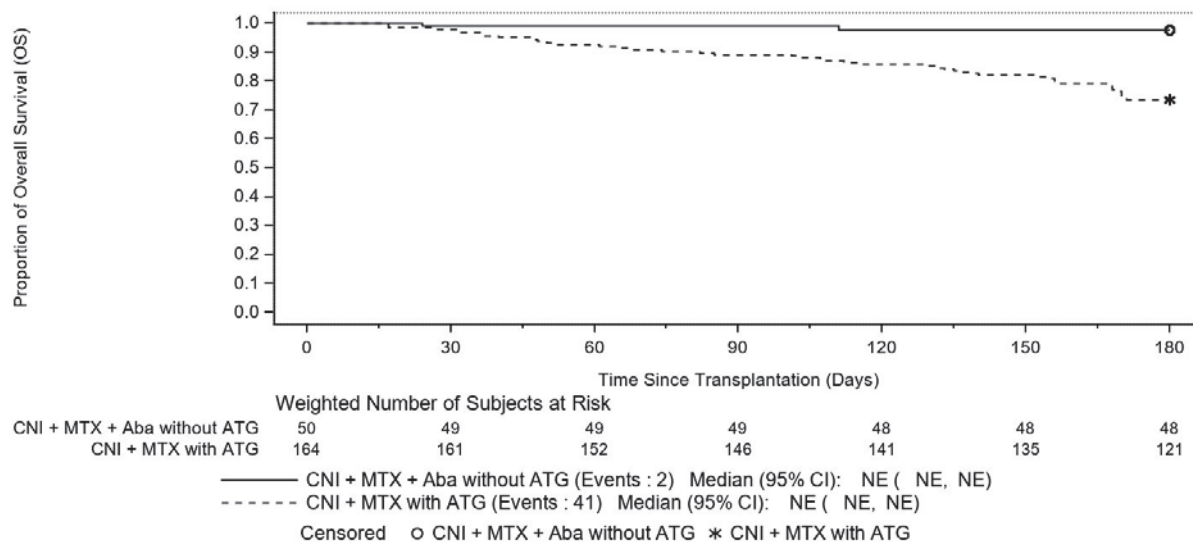
(B) Marginal hazard ratio based on weighted Cox proportional hazards model with treatment and disease status as covariates using a robust variance estimator that accounts for the sample weights. Ties are handled using the Breslow method.

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.

Source (ADaM dataset): Table S.5.1.6 (ADSL, ADTTE) in the IM101841 Primary CSR

Figure 17: K-M Plot of OS During 180 Days of Follow-up Post-transplant Using Stabilized Inverse IPTW with Propensity Scores (PS) in the Comparator Group with ATG - IM101841



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

Based on weighted Kaplan-Meier method. Symbols represent censored observation.

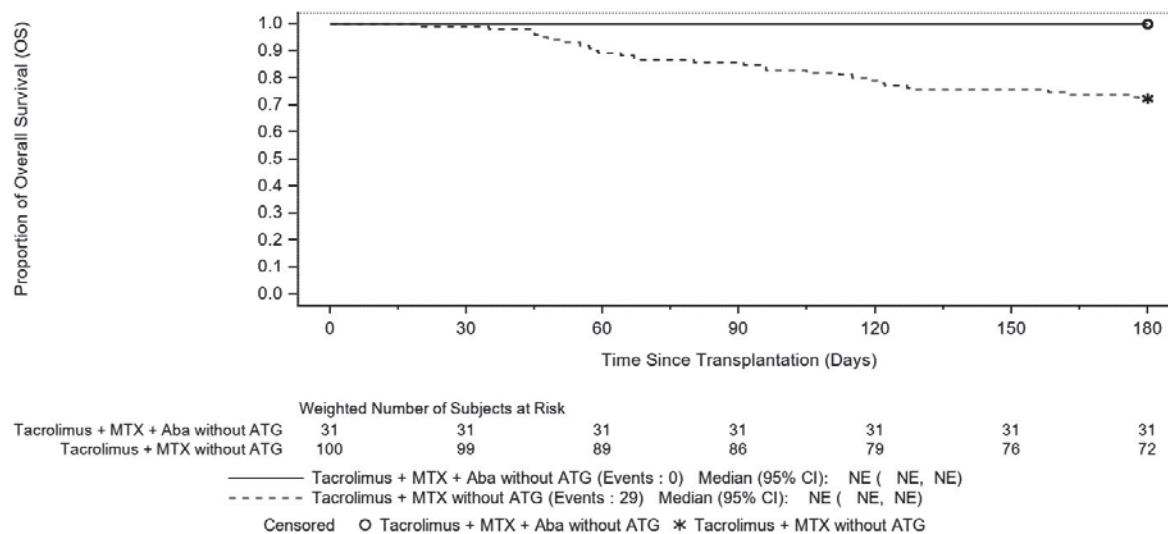
OS time is defined as the time between the date of transplant to the date of death.

Subjects are censored at 181 days post-transplant or at time of last follow-up, whichever is earlier.

NE: Not Estimable

Source (ADaM dataset): Figure S.5.1.5 (ADTTE [SECFL=Y and PARAMCD=OS]) in the IM101841 Primary CSR

Figure 18: K-M Plot of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the Tacrolimus Sub-group - IM101841



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

Source (ADaM dataset): Figure S.5.1.6 (ADTTE [TACFL=Y and PARAMCD=OS]) in the IM101841 Primary CSR

The Applicant’s Position:

Overall Survival - Comparator Group CNI+MTX with ATG:

In the first secondary analysis population, the OS rate through 180 days was significantly higher (Log rank P value = 0.0060; Survival rate at Day 180: 98% vs 74%; HR: 0.08 [95% CI, 0.02, 0.36]) in subjects who received abatacept+CNI+MTX without ATG than in subjects who received CNI+MTX with ATG (Figure 15). The abatacept+CNI+MTX without ATG regimen had a significant protective effect compared to CNI+MTX with ATG.

Overall Survival in the Tacrolimus Sub-group

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

FDA Assessment:

The FDA agrees with the Applicant’s description of the secondary efficacy results.

A hierarchical testing strategy was used for testing secondary endpoint of the OS rate during 180 days of follow-up post-transplant was compared between the CNI+MTX+ Aba without ATG group and CNI+MTX with ATG group. Since the primary efficacy endpoint met its objective, the p-value for this secondary endpoint was interpretable.

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Note that due to the small sample size in the tacrolimus subgroup, no formal statistical tests were included for this analysis population. Therefore, the p-value for the tacrolimus subgroup analysis is nominal only. Furthermore, the hazard ratio is not applicable for this endpoint since no events were reported in the tacrolimus+MTX+ aba without ATG group.

Reviewer’s comment: Note that the primary comparison in Study IM101841 provides indirect evidence of the contribution of effect of abatacept to the combination abatacept+CNI+MTX. The secondary objectives of Study IM101841 provide indirect evidence of efficacy and safety of this combination vs. various commonly-used regimens.

FDA notes that the some of these secondary endpoints represent comparisons of the core abatacept treated group of patients (n=54) from the CIBMTR with a completely different set of alternatively treated transplant patients. It is notable that the abatacept+CNI+MTX without ATG versus the CNI+MTX+with ATG showed a similar OS benefit as the primary endpoint comparison. For this comparison, another sample of 162 patients were randomly selected from CIBMTR that met inclusion/exclusion and were treated with CNI+MTX with ATG during the inclusion time period. Another propensity score and IPTW was then determined for this new comparison with overall results of OS again showing a benefit to abatacept treatment. FDA also analyzed the cause of death for this group with and without patients that have relapsed (Table 40).

Table 40: Cause of death in Study IM101841 secondary endpoint using comparator arm with ATG

Cause of Death	All patients		Without relapsed patients	
	CNI + MTX + Aba without ATG (N=54)	CNI + MTX with ATG (n=162)	CNI + MTX + Aba without ATG (n=49)	CNI + MTX with ATG (n=133)
Infection	0 (0%)	12 (7%)	0 (0%)	12 (9%)
Primary disease	1 (2%)	12 (7%)	1 (2%)	0 (0%)
GVHD	0 (0%)	6 (4%)	0 (0%)	4 (3%)
Organ failure	1 (2%)	3 (2%)	1 (2%)	2 (2%)
ARDS	0 (0%)	2 (1%)	0 (0%)	2 (2%)
Hemorrhage	0 (0%)	2 (1%)	0 (0%)	2 (2%)
Other cause	0 (0%)	2 (1%)	0 (0%)	2 (2%)
Graft failure	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Secondary malignancy	0 (0%)	1 (1%)	0 (0%)	0 (0%)

Source: FDA analysis of adsl.xpt for study IM101841 merged with cause of death by subject ID supplied by Applicant IR response on 10/8/2021.

It is notable that the most frequent causes of death in the ATG treated group were infection and relapse of primary disease as the most frequent followed by GVHD. This is somewhat expected given the previous studies with ATG in that high nonspecific removal of T cells by ATG does reduce the incidence

ORENCIA (abatacept)

of aGVHD and cGVHD but has not shown an OS benefit thought to be due to the high rate of infection seen in such profoundly immunosuppressed patients. It is also notable that ATG patients had a high rate of primary disease relapse. While it is unlikely that abatacept is directly affecting relapse of primary disease, it has been speculated that too much post-transplant immunosuppression will dampen any graft-versus-leukemia effect of the transplant and thereby reduce its potential benefit. Lastly, it is also important to note that even though ATG has been shown to reduce aGVHD that 4% of patients in the ATG treated groups still ultimately developed aGVHD severe enough to be the cause of death within the first 180 days. This secondary endpoint also demonstrated the OS benefit of abatacept treatment against another randomly selected cohort of patients from CIBMTR and perhaps offers a more clinically relevant comparison of aGVHD prophylaxis regimens.

Dose/Dose Response

The Applicant’s Position:

Not applicable.

FDA Assessment:

Not applicable.

Durability of Response

The Applicant’s Position:

Not applicable.

FDA Assessment:

Not applicable.

Persistence of Effect

The Applicant’s Position:

The persistence of efficacy of abatacept in preventing severe aGVHD is supported by the clinically meaningful effects of treatment on GFS through Day 180 in the pivotal Study IM101311 and OS through Day 180 in Study IM101841. The 4-dose abatacept prophylaxis regimen greatly and significantly improved Day 180 OS in 7/8 MMUD subjects.

FDA Assessment:

FDA considers OS at day 180 to be appropriate to convey durability of response with regard to prophylaxis of aGVHD.

Efficacy Results – Key Exploratory endpoints

Data:

Table 41: Summary of Grade II-IV GFS and Grade III-IV GFS During 180 Days of Follow-up Post-transplant- IM101841

	CNI+MTX+ ABA without ATG N=54	CNI+MTX without ATG N=162
Grade II-IV GFS		
Proportion With Event, n/m (%)	7/ 20 (35.0)	33/ 51 (64.7)
Survival Rate At Day 180 (95% CI) (A)	0.65 (0.40, 0.82)	0.35 (0.23, 0.48)

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Hazard Ratio vs. Comparator Group (95% CI)(B)	0.44 (0.19, 0.99)	
Grade III-IV GFS		
Proportion With Event, n/m (%)	0/ 20	20/ 51 (39.2)
Survival Rate At Day 180 (95% CI) (A)	1.00	0.61
Hazard Ratio vs. Comparator Group (95% CI)(B)	0.00 (NA)	
Relapse-free Survival		
Proportion With Event, n/m (%)	7/ 54 (13.0)	51/ 162 (31.5)
Survival Rate At Day 180 (95% CI) (A)	0.87 (0.75, 0.94)	0.69 (0.61, 0.75)
Hazard Ratio vs. Comparator Group (95% CI)(B)	0.37 (0.17, 0.81)	

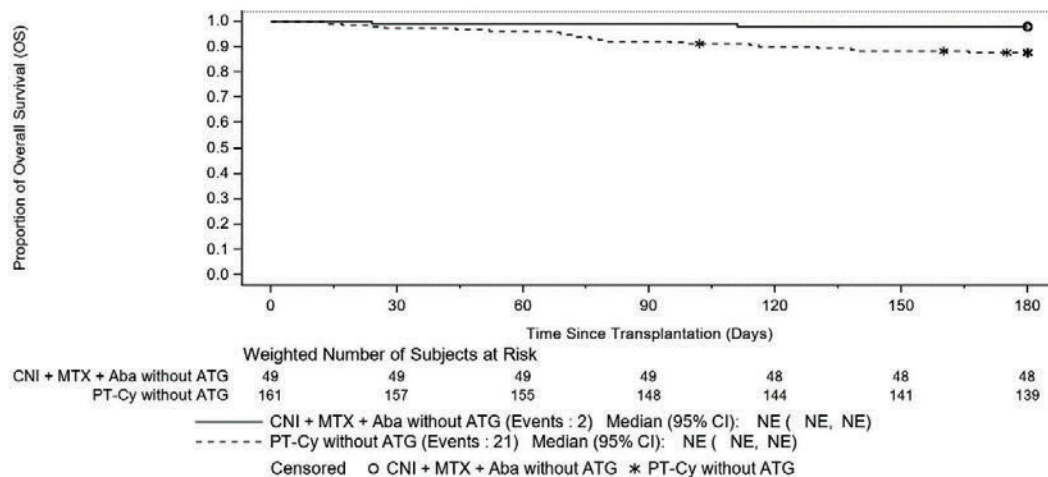
n = Number of subjects who died of any cause, m = Number of subjects in the analysis
 Propensity scores obtained from a logistic regression model including gender, disease, age, HSCT graft source, conditioning intensity, performance score, and CNI type as covariates
 (A) Based on weighted Kaplan-Meier method.
 (B) Marginal hazard ratio based on weighted Cox proportional hazards model with treatment 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.
 Source (ADaM dataset): Table S.5.8.1 and Table S.5.8.2 (ADTTE); Table S.5.11 (ADTTE) in the IM101841 Primary CSR

Table 42: Summary of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the PT-Cy Comparator Group - IM101841

	CNI+MTX+ Aba without ATG N=54	PT-Cy without ATG N=162
Proportion With Event, n/m (%)	2/53 (3.8)	21/162 (13.0)
Survival Rate At Day 180 (95% CI) (A)	0.98 (0.77, 1.00)	0.88 (0.81, 0.92)
P-value From Log-Rank Test (A)	0.1097	
Hazard Ratio vs. Comparator Group (95% CI)(B)	0.15 (0.03, 0.67)	

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, and performance score 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
 One (n=1) subject in the Abatacept group excluded from analysis due to stabilized weight >10.
 Source (ADaM dataset): Table S.5.1.8 (ADSL, ADTTE) in the IM101841 Primary CSR

Figure 19: K-M Plot of OS During 180 Days of Follow-up Post-transplant Using Stabilized IPTW with Propensity Scores in the PT-Cy Comparator Group - IM101841



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

Based on weighted Kaplan-Meier method. Symbols represent censored observation.

OS time is defined as the time between the date of transplant to the date of death.

Subjects are censored at 181 days post-transplant or at time of last follow-up, whichever is earlier.

NE: Not Estimable

Source (ADaM dataset): Figure S.5.1.8 (ADTTE [PTCY=Y and PARAMCD=OS]) in the IM101841 CSR,

The Applicant’s Position:

Primary Objective Cohort: Grade II-IV aGVHD-free Survival, Grade III-IV aGVHD-free Survival and Relapse-free Survival

For all of the three endpoints, the survival rates at Day 180 were higher in the CNI + MTX + abatacept without ATG group compared to the CNI + MTX without ATG group.

Comparison of subjects treated with abatacept+CNI+MTX without ATG to PT-Cy without ATG: The K-M curves showed a small degree of separation in OS favoring abatacept+CNI+MTX without ATG compared to PT-Cy without ATG (Figure 17; survival rate at Day 180: 98% vs 88%). In addition, the HR was 0.15 (95% CI: 0.03, 0.67). This shows a protective effect in patients receiving abatacept+CNI+MTX without ATG compared to those receiving PT-Cy without ATG. However, the difference between the two treatment groups was not significant based on the log rank test (P-value=0.1097).

FDA Assessment:

The exploratory endpoints were not included in the testing order; therefore, all p-values were nominal, and must be interpreted as such.

From a clinical perspective, PT-Cy is an increasingly common regimen for aGVHD prophylaxis in patients at high risk for aGVHD. While this exploratory endpoint did not reach statistical significance, it was encouraging that abatacept treatment showed similar results to PT-Cy. Again, analysis of the cause of death comparison for these two groups showed that three most frequent causes of death in the PT-Cy group were primary disease, infection, and GVHD (Table 43).

Table 43: Causes of death in Study IM101841 for the exploratory comparison of Aba + CNI + MTX without ATG versus PT-Cy without ATG

	All patients		Without relapsed patients	
	CNI + MTX + Aba without ATG (n=54)	PT-Cy without ATG (n=162)	CNI + MTX + Aba without ATG (n=49)	PT-Cy without ATG (n=137)
Primary disease	1 (2%)	8 (5%)	1 (2%)	1 (1%)
Infection	0 (0%)	5 (3%)	0 (0%)	5 (4%)
GVHD	0 (0%)	3 (2%)	0 (0%)	3 (2%)
Organ failure	1 (2%)	2 (1%)	1 (2%)	2 (1%)
ARDS	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Hemorrhage	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Not reported	0 (0%)	1 (1%)	0 (0%)	1 (1%)

Source: FDA analysis of adsl.xpt for study IM101841 merged with cause of death by subject ID supplied by Applicant IR response on 10/8/2021.

Reviewer’s comment: As GVHD and relapse were not captured with sufficient granularity for adjudication by FDA, the exploratory analyses presented above should not be considered in the overall assessment of efficacy of abatacept in the 7/8 HLA-matched population.

Additional Analyses Conducted on the Individual Trial

The Applicant’s Position: Not applicable

8.1.5 Integrated Review of Effectiveness

The Applicant’s Position:

Randomized trial IM101311 provided the pivotal data for effectiveness of abatacept+CNI+MTX aGVHD prophylaxis regimen. In IM101311, 2 different cohorts of patients undergoing HSCT for treatment of a HM received a graft from an URD with whom they were either matched at 7 of 8 (7/8 MMUD cohort) or 8 of 8 (8/8 MUD cohort) HLA loci. In the randomized double-blind 8/8 MUD cohort, abatacept+CNI+MTX was compared to Placebo+CNI+MTX. In the single arm 7/8 MMUD cohort, abatacept+CNI+MTX was compared to a CIBMTR historic comparator group of patients treated with CNI+MTX.

Retrospective observational study IM101841 provided supportive/confirmatory effectiveness data. Study IM101841 examined outcomes of abatacept+SOC GVHD prophylaxis in HSCT subjects receiving a graft from a 7/8 MMUD with those treated with SOC therapy alone.

FDA Assessment:

As the Applicant notes, pivotal data for the indication of prophylaxis of aGVHD is based on the results of the 8/8 MUD cohort of Study IM101311 that compared abatacept treatment in a randomized double blinded design and found that GFS was numerically improved for the severe Grade III/IV GFS to day 180 and for moderate/severe Grade II/IV GFS to day 180, with the point estimate and confidence interval of

the hazard ratio for the latter being less than 1. Analysis of OS results up to day 180 also showed numerical improvement with abatacept treatment, again with the point estimate and confidence interval of the OS hazard ratio being less than 1.

The single arm 7/8 MMUD cohort in Study IM101311 was considered exploratory. In addition, the Applicant did not submit the “historic control” data (comparator) for the 7/8 MMUD cohort in Study IM101311 to FDA, and therefore, FDA was not able to conduct the review on this comparison.

Study IM101841, a second clinical study using data from the CIBMTR, assessed OS through 180 Days for the abatacept + CNI + MTX group versus the CNI + MTX group in patients undergoing 7/8 MMUD HSCT and demonstrated significant improvement. The GFS endpoints, which were considered as the direct measurement of GVHD prophylaxis, were not designed for collection in the CIBMTR database.

8.1.6 Assessment of Efficacy Across Trials

The Applicant’s Position:

Efficacy results from studies IM101311 and the IM101841 study are not directly compared because of differences in study design and statistical methodology, ie, IM101311 is a randomized clinical trial, and its analyses are not weighted, while IM101841 is an observational study and used IPTW to deal with possible confounding and bias due to differences between the treatment groups based on known key prognostic factors. Nevertheless, both studies showed that the addition of abatacept to the SOC aGVHD prophylaxis resulted in significantly improved OS rates.

FDA Assessment:

FDA does not agree with the Applicant’s statement about the “significantly” improved OS rate in Study IM101311. The secondary endpoint OS was not included in the statistical testing strategy, and therefore, considered exploratory. IM101841 was a clinical study that incorporated data from CIBMTR in the evaluation of aGVHD prophylaxis using OS assessed at 6 months after transplantation.

While not able to be formally tested, from a clinical perspective, the OS survival curves and OS HR with a point estimate and CI less than 1 on the 8/8 cohort of Study 101311 were compelling for a drug effect, especially considering numerical improvement on numerous clinical endpoints. Furthermore, Study IM101841 showed a significantly improved survival rate at 6 months post-HSCT for abatacept + CNI + MTX compared to CNI + MTX alone in patients undergoing HSCT from a 7/8 MMUD, despite the caveats of its design noted above and below.

8.1.7 Integrated Assessment of Effectiveness

The Applicant’s Position:

Data from IM101311 demonstrated a favorable benefit-risk profile for abatacept compared to placebo for the prophylaxis of moderate to severe aGVHD in URD HSCT in patients 6 years of age or older. Abatacept treatment improved severe (Gr III-IV) GFS up to 180 days in the 8/8 cohort (89%) compared to the placebo cohort (77%). The improvement was not statistically significant at the 0.05 level (P-value = 0.1223). However, in the 8/8 MUD cohort, the addition of abatacept to a SOC aGVHD prophylactic regimen was associated with a significant increase in the percentage of MUD HSCT recipients who met the more commonly used endpoint of moderate to severe (Gr II-IV) GFS (50% vs 33%; HR: 0.55, P-value = 0.0069), as well as that of OS 97% vs. 84%; HR: 0.33, P-value = 0.0281). When the abatacept treated subjects in the 7/8 MMUD cohort were compared to CIBMTR controls, severe (Gr III-IV) GFS rates up to Day 180 were 100% vs 55% (HR: 0.08, P-value <0.0001); Table 17. Similar

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

improvements were observed in both 7/8 MMUD and 8/8 MUD cohorts in terms of other efficacy outcomes, including cumulative incidence rates of severe aGVHD, DFS, and TRM.

To further evaluate the treatment effect observed in IM101311, Study IM101841 was conducted using patient information recorded in the CIBMTR database with similar inclusion and exclusion criteria, but a larger sample size. To address potential confounding and bias due to differences between the treatment groups in key demographic and disease characteristics of the transplant recipients selected for study participation, IPTW, as computed from the propensity scores, was used in the primary analysis. Propensity score matching was used as a supplemental analytical approach for the primary objective cohort. Study IM101841 demonstrated that 7/8 HLA-matched patients treated with abatacept+CNI+MTX without ATG had a large and significant improvement in OS at Day 180 compared to patients treated with CNI+MTX, both with and without ATG. Similar improvements in OS were also observed in several subgroup analyses. Patients treated with abatacept+CNI+MTX without ATG also showed an improvement in OS at Day 180 compared to patients treated with PT-Cy without ATG

Overall, the available clinical data suggest that the addition of abatacept to a standard of care regimen of a calcineurin inhibitor and methotrexate for prophylaxis of severe aGVHD represents an important and clinically meaningful advance in the care and survival probability of recipients of HSCT from unmatched donors. Data presented in this document substantiate the clinical benefit of abatacept for the prophylaxis of moderate to severe aGVHD in URD HSCT in patients 6 years of age or older.

FDA Assessment:

The FDA does not agree with the Applicant's promotional language about the efficacy results of Study IM101311. The Gr II-IV GFS and OS endpoints for the 8/8 MUD cohort were not included in the testing order; therefore, these endpoints were considered exploratory and corresponding p-values were nominal. The 7/8 MMUD cohort was evaluated as single arm cohort and results were considered exploratory with nominal p-values. The cumulative incidence rates of severe aGVHD, DFS, and TRM in both 7/8 MMUD and 8/8 MUD cohorts were considered exploratory. No formal conclusions could be drawn based on these results.

In addition, though Study IM101841 met its primary objective to show improvement of OS through Day 180 for abatacept compared to SOC, the number of events and HR estimate were quite small which may not represent the true treatment effect. Also, clinical benefit in GFS in Study IM101841 could not be reliably measured since the granular details on the occurrence of GVHD events, necessary for FDA to perform proper adjudication of the GFS endpoints, are not collected routinely in the CIBMTR database.

The clinical development program for prophylaxis of aGVHD included two studies:

- Study IM101311, a randomized, double-blind, placebo-controlled (8/8 MUD) cohort of subjects who received a HSCT from an 8/8 HLA matched, URD, comparing subjects treated with abatacept+SOC aGVHD prophylaxis (CNI+MTX) to those treated with placebo + SOC aGVHD prophylaxis; and a single arm (7/8 MMUD) cohort of subjects who received a HSCT from 7/8 HLA-matched, URD.
- Study IM101841, a clinical study using registry data routinely collected in the CIBMTR database between January 1st 2011 to December 31st 2018 was designed to support the evidence for the effectiveness of abatacept based on the primary outcome of 180-day OS after HSCT among

patients who received abatacept with CNI plus MTX versus receipt of CNI plus MTX alone for aGVHD prophylaxis.

Study IM101311

The 8/8 HLA matched cohort of Study IM101311 was considered an adequate and well-controlled randomized cohort from a regulatory perspective. Due to an inability to randomize subjects to a control arm of CNI + MTX, the 7/8 MMUD cohort was a single-arm cohort, and therefore, the time-to-event endpoints were not interpretable.

The study was originally an investigator-sponsored trial to study the utility of adding abatacept to standard aGVHD prophylaxis regimen in subjects undergoing unrelated allogeneic hematopoietic cell transplantation (HCT) for the treatment of high-risk hematologic malignancies. BMS intended to submit the results of the double-blind stratum (8/8 cohort) and the single arm stratum (7/8 cohort) to support the regulatory approval of the proposed indication above. To support the indication and align with the recommendations in FDA guidance, the primary endpoint in the investigator protocol of cumulative severe aGVHD incidence rate up to 100 days post-transplant was changed to GFS up to 180 days post-transplant in the middle of the trial. Some other changes included statistical methods, Type I error control, statistical power and secondary endpoints. The planned sample size was not changed. All changes were specified in the BMS SAP. The change of analysis plan is summarized in Table 44. Of note, changing the primary endpoint in the middle of the trial without changing the sample size may limit the statistical power to test the treatment effect. Also, the sample size 140 is considered small to detect a large treatment effect (HR of 0.34).

Table 44: Summary of change of analysis plan for Study IM101311

	Investigator Protocol	BMS SAP
Primary Endpoint	Cumulative incidence of Gr III/IV aGVHD event up to Day 100 post transplantation	Grade III-IV GFS up to Day 180
Statistical Method	Bayesian method	Stratified log-rank test on mITT population
Type I Error (2-sided)	0.20	0.05
Power	80% Assumption: placebo 0.2, absolute reduction 0.1, claim efficacy if $P(\theta_1 > \theta_2 \mid \text{data}) > 0.8$	81% Assumption: 28 Severe aGVHD events, HR=0.34
Interim Analyses	Conduct based on Bayesian stopping rule after 100th subject enrolled	Conducted based on Bayesian stopping rule after 100th subject enrolled

Secondary Endpoints	Cumulative incidence curve of anti-viral protective immunity, all grades of early and late aGVHD, overlap syndrome, chronic GVHD, transplant-related mortality (TRM), disease free survival (DFS), immunosuppression-free survival, immunosuppressive-free/relapse-free survival, relapse, OS	Key Secondary: Cumulative incidence of Grade III-IV severe aGVHD Other Secondary: Grade II-IV GFS, OS, DFS, TRM, cGVHD
Planned Sample Size	140	140 (Actual 142)

Study IM101841

In the investigator protocol IM101311, matching with control group drawn from the CIBMTR registry for 7/8 matched cohort was initially planned. However, a detailed analysis plan for 7/8 matched cohort in the investigator protocol was not provided to FDA for review. In June 2019, BMS met with FDA to discuss the analysis results of Study IM101311 for subjects in the 7/8 cohort who were treated with abatacept and compared to a pre-specified historic control group extracted from the CIBMTR database. However, the analysis was conducted prior to FDA’s input and data for the historic control group were not submitted to FDA for review. FDA had concerns with this approach; more detailed information about the regulatory background can be found in section 8.1.4.

In the investigator protocol IM101311, matching with control group drawn from the CIBMTR registry for 7/8 matched cohort was initially planned. However, a detailed analysis plan for 7/8 matched cohort in the investigator protocol was not provided to FDA for review. In June 2019, BMS met with FDA to discuss the analysis results of Study IM101311 for subjects in the 7/8 cohort who were treated with abatacept and compared to a pre-specified historical control group extracted from the CIBMTR database. However, the analysis was conducted prior to FDA’s input and data for the historical control group were not submitted to FDA for review. FDA had concerns with this approach; more detailed information about the regulatory background can be found in section 8.1.4.

In November 2019, BMS provided an analysis plan for Study IM101841 to obtain feedback from FDA on this study. Based on FDA’s feedback for the design of Study IM101841, BMS updated the SAP.

Limitations of Study IM101841:

1. Unmeasured Confounding

Study IM101841 was not randomized; therefore, the treatment effect may be confounded because of differences between comparator arms with respect to related baseline factors. The confounding effects from both observed imbalances and other unobserved factors could cause substantial bias. The Applicant proposed to use the inverse probability of treatment weighting (IPTW) method via a propensity score analysis to address potential confounding and bias due to differences between the treatment group in key characteristics at transplantation. However, in general, unmeasured confounding remains a potential concern for a non-randomized study that cannot be excluded. Additional sensitivity analyses did yield results similar to the initial primary

results, however, suggesting that moderate to strong bias would have to be present to overturn the result.

2. Database Design

The CIBMTR database was designed primarily for research purposes. The design includes completeness of capture of all US HSCT patients and associated overall survival outcomes which increases confidence in the generalizability of findings to the indicated population. CIBMTR also has well-established protocols for data collection, quality, and auditing. However, based on the design of this study, there is potential for a higher proportion of missing data for data fields where reporting was optional. For example, abatacept dosing was limited in subjects identified through the “other GVHD prophylaxis” free text data field compared to structured information collected on CN1 and MTX dosing patterns. The duration of exposure was also not captured. More importantly, the aGVHD-free survival endpoints which were considered as the direct measurement of GVHD prophylaxis were not able to be adequately collected with sufficient granularity in the CIBMTR database. Instead, OS, which is generally considered a secondary endpoint for treatments for GVHD (not necessarily related to anti-GVHD efficacy), was used as the primary endpoint in Study IM101841. The issue was raised regarding whether differences in OS between groups would reflect predominantly drug efficacy on GVHD or whether other factors (e.g. baseline characteristics or clinical care) might affect OS, in the absence of randomization.

3. Misclassification

While misclassification of abatacept recipients could have been a concern, it was not considered likely based on specific study practices and analyses conducted to evaluate the potential for exposure misclassification. Specifically, there was a potential for misclassification of exposure status since abatacept treatment information was from the free text data field. The exposure substudy found no evidence of exposure misclassification. In addition, the comparator subjects who were treated at sites participating in Study IM101311 were excluded to reduce this potential issue. While this practice limited the chance of misclassification of exposure status, it also eliminated the ability to assess site specific or geographic effects in the study. Outcome misclassification was not considered to be a concern based on analyses comparing outcomes between CIBMTR and IM101311.

4. Sample Size

The sample size of the subjects exposed to abatacept was considered small and OS events were rare, and therefore the statistical tests may be potentially under-powered. Note that the sample size was not based on statistical assumptions but on the availability of treated patients in the CIBMTR database.

5. Selection Bias

In the IM101841 study after weighting, 82.4% of abatacept treated patients participated in the IM101311 trial whereas only 13.2% of SOC patients participated in any clinical trial. It was possible that patients who received abatacept through participating in clinical trials were a healthier subset of subjects or received more closely monitored care resulting in improved

outcomes, especially because the differences in the trial participation variable were present after matching. In addition, there was potential variation in the way centers reported clinical trial participation, which could underestimate the proportion of patients participating in trials. However, the clinical care setting for receipt of HSCT is very highly monitored and clinically requires patients have adequate health status to be transplant eligible, which lessens the concern for the impact of this particular clinical setting.

6. Confounding and Covariate Imbalance

Residual imbalance was observed between the abatacept treated and SOC treated groups for the key baseline clinical characteristics even after weighting and matching: disease status, conditioning regimen, clinical trial participation, year of transplant (grouped as 2011-2014 vs. 2014-2018) and race. Of note the differences in disease severity were of concern due to potential confounding by severity; however, upon clinical review this was noted to confer a risk of relapse (an alternative risk of OS event) that varies by age and disease type. This potential was addressed in several sensitivity analyses above including adding disease status as a covariate in the Cox proportional hazard ratio when disease status could not be included in the propensity score, analysis of the subset of patients that did not include those few with lymphoma (which allowed convergence of the propensity score model with the disease status included), and analysis of cause of death +/- the removal of patients that have relapsed within day 180 post-transplant. All of these still showed significant OS difference between groups or that a major cause of death in the control patients was due to GVHD. Moreover, clinical trial participation was further evaluated as a covariate in sensitivity analysis and the treatment effect was still found to be significant. There was general agreement as mentioned by DEPI that there were “multiple sensitivity analysis indicating robust overall survival benefits” Refer to section 8.1.4 for more detailed information.

7. Statistical design and Methodology

Given the limitations of small sample size and inherent biases and confounding present in observational data, the use of IPTW method for propensity score was considered the most viable approach to assess the primary endpoint. However, IPTW yields a population which is difficult to interpret and retains subjects that would otherwise be discarded in a matching analysis. In general, analyses utilizing propensity scores presume that the posited propensity score model is correct and that there are no unmeasured confounders. These are strong assumptions which may not be met in practice.

Of note, FDA previously recommended use of CIBTMR to expand the population. However, most subjects on IM101841 were enrolled in IM101311 (this was not known at time of FDA’s advice). This ultimately resulted in duplication. By design, the Applicant had potential knowledge of effect with use of the early external control; however, if all transplant subjects were reported to CIBMTR and controls were randomly selected, potential bias introduced to create an artificial result may be limited.

In general, early knowledge of treatment effect has the potential to inflate Type I error when this knowledge impacts early discontinuation of a trial. In this case, 1) the external control was

planned in the initial investigator protocol and 2) all data for the 7/8 were to be collected regardless of result (i.e. single-arm design with no early stopping planned).

Patient Population

The population of patients enrolled in study IM101311 reflected the general population of patients that underwent HSCT for high-risk heme malignancies aged 6 and up during the time period of trial enrollment. This reflects two important factors. The first is the age of occurrence of the respective heme malignancies. This is reflected in the higher proportion of ALL patients in the pediatric aged patients versus higher proportion of myeloid malignancies (MDS and AML) in the older patients. The second aspect is the appropriateness of transplant for the patient. One recent trend over the last decade, that was not quite reflected in the trial population, is the increased use of transplant for patients over 65. While Studies IM101311 and IM101841 both had patients over this age, their proportion was comparable to those seen at the beginning of the last decade rather than those seen at the end of the decade.

Efficacy endpoints

The efficacy results for Study IM101311 and Study IM101841 are presented in Table 45.

The 8/8 MUD cohort in Study IM101311 did not meet its primary objective. The results of secondary endpoints OS and Grade II-IV GFS indicated the strong treatment effect. However, these results were considered exploratory without alpha allocation. All time-to-event endpoints in 7/8 MMUD single-arm cohort were not interpretable.

Study IM101841 met its primary objective demonstrating a favorable OS rate at Day 180 for abatacept compared to SOC in 7/8 MMUD subjects. The OS indicated the similar trend compared to the result in Study IM101311. The index date for OS was the date of transplantation which was considered reasonable and consistent with Study IM101311. Some review issues on the quantification of the treatment effect are worth mentioning:

1. Confidence interval appeared to be under coverage when using Wald test compared to other methods. The Bayesian CI and matching-based CI appeared to be reasonable CIs.
2. HR estimate may lack stability and robustness given the rare event rate in the treatment arm. This was due to nature of disease history, study population, and limitation of using CIBMTR database.

Refer to section 8.1.4 for more detailed information.

Table 45: Efficacy results for Study IM101311 and Study IM101841

	Study IM101311		Study IM101841
	RCT Cohort	Single Arm Cohort	
Population	URD HLA-matched at <u>8/8</u>	URD HLA-matched at <u>7/8</u>	URD HLA-matched at <u>7/8</u>
Primary outcome	Grade III-IV acute GFS up to Day 180	Grade III-IV acute GFS up to Day 180	OS at 180 days after HSCT
Grade III-IV GFS to day 180	87% abatacept versus 75% placebo HR 0.55 (95% CI: 0.26, 1.18) p-value: 0.1215	98% (95% CI: 85, 100)	N/A
OS to day 180	97% abatacept versus 84% placebo, HR 0.34 (95% CI: 0.12, 0.94)	98% (95% CI: 85, 100)	98% abatacept versus 75% control HR 0.07 (95% CI: 0.01, 0.30) p-value: 0.0028
Grade II-IV GFS to day 180	50% abatacept versus 32% placebo, HR 0.54 (95% CI: 0.35, 0.83)	58% (95% CI: 42, 71)	N/A

Source: FDA Analysis

Subgroups:

Treatment effect of abatacept appeared to be consistent across subgroups in both Study IM101311 and Study IM101841 in which strong conclusions were precluded under limited sample size in each of the subgroups.

Recommendations for drug labelling

1.  (b) (4)
2. 

- a)
 - b)
 - c)
 - d)
 - e)
- (b) (4)

Dose/Dose Response

Only one dose regimen was tested in Study IM101311. The dose was based on initial PK studies from ABA1 that showed the regimen/dosing followed in Study IM101311 could achieve adequate target occupancy early in the post-transplant period (Koura et al. 2013). See section 6 of this review for a full discussion.

A modified dose for pediatric patients aged 2 to <6 was proposed by the Applicant in response to FDA's suggested exploration of this age group. This modified dosing was based on population PK models but has not yet been evaluated in patients. See section 6 for discussion.

Extrapolation to Pediatric Patients

Study IM101311 included 30 patients aged 6 to <18 that were treated with abatacept between the 8/8 and 7/8 cohorts. Efficacy and safety for pediatric patients is based on the results from these patients. During the FDA review of this application, we discussed extrapolation of these results to include patients age 2 to <6. Extrapolation of efficacy is based on the biology of aGVHD for patients 2 to <6 being the same as those 6 and older. Safe use of abatacept for patients aged 2 to <6 has been demonstrated as part of the abatacept approval for polyarticular juvenile idiopathic arthritis, albeit with a different dosing regimen and administration route.

Overall, FDA notes that in Study IM101311, abatacept + CNI + MTX did not significantly improve the primary endpoint of Grade III-IV GFS at Day 180 post-transplantation compared to placebo + CNI + MTX in patients undergoing 8/8 MUD transplantation. As noted above, however, the observed Grade II-IV GFS and OS results at Day 180 were numerically higher on the treatment arm, with some supportive data in corresponding exploratory single-arm results for these endpoints in the 7/8 MMUD cohort. Furthermore, an OS benefit at Day 180 post-transplantation was demonstrated on the registry Study IM101841 for patients who underwent 7/8 MMUD HSCT. Taken together, the improvement in Grade II-IV GFS and OS at Day 180 post-HSCT may be considered to be clinical benefit.

8.2. Review of Safety

The Applicant's Position:

In IM101311, the safety events reported were consistent with those expected in a population of patients with hematologic malignancies undergoing stem cell transplantation; review of those events did not identify any unexpected safety concerns among abatacept-treated patients.

No major safety concern was identified in review of literature in association with the use of abatacept for prophylaxis of GVHD in stem cell transplantation. Based on the evaluation of the safety data after the first 4 doses of abatacept up to Day 84 from the pooled RA studies and the JIA study, abatacept is considered to have been well-tolerated, with no major safety concerns identified.

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

In IM101841, the safety was assessed by summarizing the occurrence of PTLD 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 (Table 8.4.1.4-1 [ADaM dataset: ADSL: [PRIFL=Y, PTL100FL and PTL180FL=Y] in the IM101841 Primary CSR).

No further safety analyses were performed using the data from the CIBMTR database.

FDA Assessment:

The FDA agrees with the Applicant's approach to safety data. Abatacept has been approved for the treatment of rheumatologic conditions since 2005 and now had over 16 years of post-approval monitoring. It has been generally well tolerated with some expected safety issues of infectious risk, which are present with all known immunosuppressive medications. For the indication of aGVHD prophylaxis, the Applicant has supplied AE data from Study IM101311. The challenge to assessing the safety of abatacept in the context of stem cell transplantation is the high rate of expected AE from the transplantation process. Fortunately, Study IM101311ABA2 contains an 8/8 unrelated donor cohort where patients were randomized to either abatacept or placebo treatment. These data were extremely important for determining which AEs rose above the background rate induced by the transplant process. To further aid in the assessment of infrequent safety events, the Applicant has included a literature review of abatacept use for aGVHD prophylaxis which largely agrees with the other sources of safety information.

8.2.1 Safety Review Approach

The Applicant's Position:

1. Abatacept+CNI+MTX safety data are from Study IM101311, a Phase 2 trial evaluating the addition of abatacept to a standard of care regimen (CNI+MTX) for the prophylaxis of severe aGVHD in subjects with high-risk hematologic malignancies who received HSCT from unrelated donors. All safety presentations were based on the As Treated Analysis population; AEs presented in the safety summaries for the Day 180 analysis period include all AEs with onset date up to Day 225, which is the upper limit of the Day 180 visit window for analysis as defined in the SAP. Since the baseline demographic characteristics, the therapies for aGVHD prophylaxis, and the AE pattern were comparable between abatacept-treated subjects enrolled in 8/8 MUD cohort and 7/8 MMUD cohort, the AEs reported in abatacept-treated subjects from both cohorts (N = 116) are pooled and compared with that reported in placebo group (N = 69)
2. Upon request from the FDA, BMS conducted a literature review of the safety of abatacept use in stem cell transplantation in clinical and nonclinical studies, and generated a summary of on treatment adverse events (AEs) occurring within the first 4 doses (Day -1, 15, 28 and 56) of abatacept up to Day 84 (ie, up to 28 days of follow-up from the planned 4th dose date) from integrated double-blind clinical trials with IV abatacept in patients with RA and JIA.

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
³⁸Sonali Chaudhury, et al. Abatacept for GVHD Prophylaxis after Hematopoietic Cell Transplantation (HCT) for Pediatric Sickle Cell Disease (SCD): A Sickle Cell Transplant Advocacy and Research Alliance (STAR) Trial. Abstracts / Biol Blood Marrow Transplant 26 (2020) S8-S74.	Background: Patients with severe SCD experience organ damage, poor quality of life and premature mortality. HCT is curative in SCD. Adolescent patients with SCD receiving matched related donors (MRD) HCT and patients with SCD receiving matched unrelated donor (MUD) HCT, remain at highest risk for GVHD and resulting morbidity and mortality. Building on the encouraging experience with abatacept for GVHD prophylaxis in URD HCT for hematologic malignancies, we launched an early phase, multicenter trial through the STAR of abatacept in pediatric SCD patients at high risk for GVHD. Methods: Patients with severe SCD were eligible if they were receiving a MRD HCT and either they or their donor were at least 10 years or if they were receiving a MUD HCT. Twenty-five patients have been enrolled to date with 23 patients completing conditioning and HCT. All patients received reduced intensity conditioning (RIC) with distal alemtuzumab, fludarabine, thiotepa and melphalan and marrow grafts. Four doses of abatacept (10 mg/kg/dose IV on days -1, +5, +14, +28) were added to standard GVHD prophylaxis using tacrolimus and methotrexate. Abatacept dosing was extended to eight doses for the last 11 patients (+60, +90, +120, +150). Tacrolimus was tapered at day 180 if no GHVD was present. The median age at HCT was 11 (3-21 years); 13 received a MRD HCT and 10 a MUD HCT. Results: All patients engrafted with neutrophils at a median of 21 days (range 13-26) and platelets at a median of 23 days (13-55). As of 10/1/2019, median follow up is 804 days (range 46 - 1139). The mean myeloid and T-cell chimerisms at one (n=17) and two years (n=10) were 97.9 +/-4.9 and 94.2 +/-10.0 and 96.6 +/-8.9 and 97.5 +/-4.3, respectively. Three evaluable patients at 2 years did not have chimerism studies	In this single arm study, a total of 23 subjects were enrolled. 1) All patients engrafted. 2) There were 4 cases of EBV viremia (1 PTLD) and 6 cases of CMV viremia (1 disease). 3) One patient experienced non-infectiousencephalopathy of unclear etiology. 4) The overall and sickle cell free survival at 2 years post HCT in evaluable patients (N=13) were 100% and 100%, respectively. Infections of EBV and CMV were reported in this study, but no patients died from the viral infections. The incidences of EBV viremia, EBV-PTLD, CMV viremia, and CMV disease were 17.4% (4/23), 4.3% (1/23), 26.2% (6/23), and 4.3% (1/23), respectively, which were within the published incidence range of CMV or EBV infection in the setting of allogeneic stem cell transplantation.^{39,40,41,42,43} The study results suggested that abatacept use in GVHD prophylaxis was safe.

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
⁴⁴Ruby Khoury, et al. Abatacept Decreases the Rate of Acute and Chronic GVHD in Children with Sickle Cell Disease Undergoing Matched Sibling Transplants. Abstracts / Biol Blood Marrow Transplant 26 (2020) S96-S255.	sent. There have been 4 cases of EBV viremia (1 PTLD) and 6 cases of CMV viremia (1 disease). Grades 3-4 acute GVHD was seen in one patient and chronic/overlap in 5 patients with two patients currently receiving systemic immune suppression. There have been no cerebral hemorrhages, but one patient developed non-infectious encephalopathy of unclear etiology. The overall and sickle cell free survival at 2 years post HCT in evaluable patients (N=13) is 100% and 100%, respectively. Conclusion: The preliminary results in first 23 patients enrolled to date suggest that incorporating abatacept into GVHD prophylaxis is a safe and efficacious approach to improving outcomes in HCT for pediatric SCD. Introduction: Study the role of abatacept on the incidence of GVHD in patients with sickle cell disease (SCD) undergoing allogeneic hematopoietic stem cell transplant (HSCT). Methods: Conducted a retrospective chart review of patients who received an allogeneic HSCT for SCD at Cincinnati Children’s Hospital Medical Center and compared various transplant characteristics between patients with and without abatacept for acute GVHD prophylaxis. Results: Sixteen patients were transplanted for SCD at our center. Nine patients received a calcineurin inhibitor, methotrexate and abatacept at 10 mg/kg intravenously on days -1, +5, +14 and +28 while 7 patients received a calcineurin inhibitor with methotrexate and methylprednisolone for acute GVHD prophylaxis. No abatacept infusion related adverse effects were observed. Neutrophil engraftment was comparable at a median of 12.5 days (range 11-21) in patients without abatacept versus 13 days (range 12-16 days) in the abatacept cohort. Incidence of Grade 2-4 GVHD was 0/9 in the abatacept cohort versus 3/7 patients in the no-abatacept cohort. Two of the 3 acute GVHD	In this retrospective study, the efficacy and safety of abatacept use in prevention of aGVHD in children with SCD undergoing fully matched sibling transplants were presented; the data were compared between patients with abatacept (9 patients) and without abatacept (7 patients receiving methylprednisolone instead). 1) None of the abatacept recipients had infusion-related reactions. 2) The viral reactivation between 2 groups were comparable: 8/9 in the abatacept cohort vs 6/7 in the cohort without abatacept. No patient in either group had viral disease. 3) One patient in the abatacept cohort had secondary graft loss and was successfully re-transplanted with a graft from the same donor and conditioning regimen; there was no graft loss in the no-abatacept cohort. 4) The disease-free survival was 100% in both groups at last follow up of 1925 days.

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
patients in the no-abatacept cohort had visceral involvement. One patient in the abatacept cohort had mild chronic GVHD compared to 3 patients in the no-abatacept cohort with mild (n=1) and moderate (n=2) chronic GVHD. Six patients in the no-abatacept cohort had viral reactivation compared to 8/9 patients in the abatacept cohort. No patient in either cohort had viral disease. One patient in the abatacept cohort had secondary graft loss and was transplanted again with the same donor and conditioning regimen successfully. There was no graft loss in patients who did not receive abatacept. The disease-free survival was 100% in both groups at last follow up of 1925 days (range 837-8164 days) in the no-abatacept group and 770 days (range 112-1634 days) after HSCT in the abatacept cohort. Conclusions: Abatacept is well tolerated and decreases the incidence of acute and chronic GVHD in children with SCD undergoing fully matched sibling transplants. Larger studies are needed to definitively determine the impact of abatacept in GVHD prophylaxis in the matched sibling donor setting.	The viral reactivation rate was high in both the abatacept and no abatacept cohorts (89% and 86%, respectively); the abstract did not specify the number of patients who experienced CMV or EBV reactivation; also, no patient had clinically manifest viral disease. One patient in the abatacept cohort experienced secondary graft failure, but recovered following a second stem cell transplant; the possible causes for the event of graft failure could not be assessed due to the limited amount of information in the abstract. The study results suggest that abatacept was well tolerated.	
⁴⁵Amit Patel et al. Elimination of acute GVHD with three doses of abatacept prophylaxis combined with post-transplant cyclophosphamide after myeloablative treosulfan-based conditioning in the HLA identical sibling and unrelated (10-12/12) peripheral blood stem cell donor setting: Improved safety and efficacy compared to alemtuzumab prophylaxis. Blood, (November 2019) Vol. 134, Supp. Supplement 1. Abstract.	Background: Acute GVHD remains a major cause of treatment failure post allogeneic stem cell transplantation (HSCT). CD28-CD80/CD86 axis T cell co-stimulation blockade with CTLA4-Ig using abatacept (AB) is an emerging acute GVHD prophylaxis strategy. After myeloablative conditioning (MAC), together with methotrexate and calcineurin inhibition, four doses of AB commencing day (d)-1 is being investigated in the unrelated HLA 7/8 and 8/8 mismatched/matched donor settings, mostly in children. It is unknown if AB can be de-escalated in adults to three doses for HLA matched sibling (SIB) or unrelated 10-12/12 donors (MUD), or combined with post-transplant cyclophosphamide (PT-CY) GVHD prophylaxis, or combined with treosulfan (Treo)-based MAC, which are other emerging	In this study, 15 patients received abatacept as part of a treatment regimen for prophylaxis of GVHD after MAC; and 24 patients received alemtuzumab for GVHD prophylaxis after reduced intensity conditioning (RIC). The key observations were: 1) No infusion reactions in the abatacept group; 2) A numerically, but not clinically significantly slower time to engraftment in the abatacept group relative to the RIC alemtuzumab group, which was expected for MAC in abatacept recipients; no graft failure in the abatacept group; 3) No cases of mixed donor chimerism, or requirement for a donor lymphocyte infusion in

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
	transplant strategies. We investigated the safety and efficacy of this combination, and compared outcomes to a standard anti-CD52 directed IgG1 alemtuzumab (CH) prophylaxis regimen in a reduced intensity conditioning (RIC). Methods: We report a single center consecutive cohort study using peripheral blood stem cells from SIB or HLA 10-12/12 MUDs, for HSCT in adults with blood cancer indications. One group received AB GvHD prophylaxis while the other group received CH. During 2018-2019, the AB cohort received MAC with IV fludarabine 150 mg/m², IV TREO 42 mg/m², and 2 Gy total body irradiation (TBI). GvHD prophylaxis comprised three doses of IV AB 10 mg/kg on d+5, +14, and +28. This was combined with IV PT-CY 50 mg/kg on d+3 and +4, IV tacrolimus 0.03 mg/kg/d infusion from d+5, and IV mycophenolate mofetil 15 mg/kg tds from d+53. The MAC AB cohort was compared to a RIC CH cohort, chosen to be biased against AB. During 2017-2018 the CH cohort received RIC with IV fludarabine 150 mg/m² and IV melphalan 140 mg/m². GvHD prophylaxis comprised IV CH 10 mg on d-7 to d-3, and IV ciclosporin 1.5 mg/kg bd from d-1. Results: A total of 39 patients were included in this study, with 15 consecutive patients in the AB group. The major cancer indications were acute leukaemia and myelodysplastic syndrome (MDS). The AB and CH groups were largely balanced. There were no AB related infusion reactions. As expected for MAC, the AB group had a numerically but not clinically significantly slower time to engraftment relative to the RIC CH group. There was no AB group graft failure. Remarkably, the AB group did not experience acute GvHD compared to the CH group by d100 (P=0.03) and d180 (P<0.01). In contrast, by d100, 29% in the CH group experienced acute GvHD after a median of 59 days post HSCT.	the abatacept group. 4) A lower frequency of CMV reactivation in the abatacept group compared to the alemtuzumab group: 67% vs 93%, respectively. 5) No cancer relapses were observed by d180 in the abatacept group, vs 8% of those in the alemtuzumab group. 6) Mortality at d180 was similar between the 2 groups: 20% in abatacept group and 21% in alemtuzumab group. The causes of death were not provided in the abstract. Abatacept was well-tolerated in this study and appeared to be safer than the control group. No major safety concern was identified.

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
	No AB group patients experienced mixed donor chimerism (P<0.01), nor required a DLI (P<0.01) compared to the CH group, where all had <99% T cell or whole blood values at d100. Consequently, 45% of the CH cohort without acute GvHD were treated with DLI, with all patients experiencing acute GvHD at a median of 39 days post DLI. Other secondary outcomes were similar. The AB group experienced a CMV reactivation rate of 67% in IgG seropositive patients. Unfortunately, 93% of CMV IgG positive patients in the CH group experienced CMV reactivation. No relapses were observed by d180 in the AB group, whereas in the CH group, 8% of patients experienced relapse. Mortality at d180 was 20% in the MAC AB group, and 21% in the RIC CH group. Conclusions: Acute GvHD prophylaxis with only three doses of AB and PT-CY post TREO-based MAC appears to be safe and efficacious in the SIB and MUD settings, in a highly co-morbid adult blood cancer population. This AB approach seems favourable compared to CH despite RIC, where acute GvHD without DLI or post DLI remains significant.	
⁴⁶Alexander Ngwube, et al. Abatacept is effective as GVHD prophylaxis after unrelated donor stem cell transplantation (URD SCT) for children with severe sickle cell disease. Blood Adv (2020) 4 (16): 3894–3899.	Introduction: We report results of a phase 1 multicenter stem cell transplantation (SCT) trial from HLA-matched (n = 7) or one-antigen-mismatched (n = 7) unrelated donors (URD) using bone marrow or cord blood as stem cell source, following reduced-intensity conditioning (RIC) in severe sickle cell disease (SCD). Methods: Fourteen SCD patients, age 7 to 21 years underwent URD SCT; 7 patients received 8/8 HLA-matched bone marrow, 5 received 7/8 matched bone marrow and 2 received 5/6 matched cord blood. RIC included hydroxyurea, distal alemtuzumab, fludarabine, and melphalan. Thiotepa (8 mg/kg) was added to the regimen for mismatched bone marrow and cord blood products. GVHD prophylaxis included	In this single arm study, a total of 14 patients enrolled. 1) One patient had secondary graft rejection concomitant with CMV reactivation; all other patients engrafted. 2) One patient developed posterior reversible encephalopathy syndrome (PRES) that was self-limiting. 3) Prior to day 180 posttransplant, asymptomatic CMV reactivation was detected in 8 patients; asymptomatic EBV reactivation was detected in 2 patients. 4) The 2-year probability of OS and DFS was 100% and 92.9%, respectively. 5) The most frequent organ toxicity noted was renal

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
	tacrolimus and short-course methotrexate (bone marrow) or mycophenolate mofetil (cord blood). Abatacept (10 mg/kg) was administered intravenously on days -1, +5, +14, +28 in 5 patients (3 bone marrow recipients and 2 cord blood recipients) in this study. Abatacept administration was extended to 8 doses (days -1, +5, +14, +28, +100, +180, +270 and +365) in 9 bone marrow transplants to evaluate the possible benefit of extended use on chronic GVHD (cGVHD). Results: At a median follow up of 1.6 years (range, 1-5.5 years), 13 of 14 recipients had stable donor engraftment. One patient with cytomegalovirus (CMV) reactivation had secondary graft rejection on day +30. This patient subsequently rejected another URD graft following myeloablative conditioning and received a haploidentical transplant with donor engraftment at early follow-up. The 2-year probability of OS and DFS was 100% and 92.9%, respectively. The median time to neutrophil and platelet (>50 x 103/μL) engraftment was 14 days (range, 10-24 days) and 19.5 days (range, 16-39 days), respectively. All engrafted patients had >95% donor chimerism at their last evaluation. The incidence of Grade II to IV aGVHD at day +100 was 28.6%. Three patients developed Grade 2 aGVHD involving the skin, and were treated with topical therapy. One developed Grade 4 GVHD of the gut, and required systemic therapy until resolution. Systemic immune suppression wean was commenced 9 to 12 months post-SCT successfully per protocol. Only 1 of 9 patients who received URD bone marrow and abatacept doses beyond day +100 developed extensive cGVHD affecting the lung; that patient continues systemic immune suppression. One patient developed PRES that was self-limiting, in contrast to 34% reported previously with URD SCT. Abatacept did not hinder donor engraftment. T-cell	dysfunction (n = 3), which resolved with weaning calcineurin inhibitors. The infection rates of EBV and CMV were 14.2% and 57%, respectively, which were consistent with those in the published literature; none of these infected patients had clinical manifestation of viral disease. One patient had secondary graft rejection that could be associated with CMV infection. All the infections responded to treatment. One patient (7.1%) experienced PRES, an event frequency lower than that observed in a previous study (34%) of the same population without abatacept use (patients were receiving methylprednisolone instead).⁴⁷ Abatacept was well-tolerated in this study.

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
⁴⁸Divya Koura et al. In Vivo T Cell Costimulation Blockade with Abatacept for Acute Graft-versus-Host Disease Prevention: A First-in-Disease Trial. Biol Blood Marrow Transplant 19 (2013) 1638e1649.	subsets gradually recovered after day +100 to the normal range by 1 year. The pace of immune reconstitution was robust after 6 months despite the use of abatacept. Asymptomatic CMV reactivation, noted in 8 patients prior to day +180, responded to antiviral therapy and was concomitant with graft rejection in 1 patient. EBV replication noted in 2 patient was asymptomatic; one was treated with 2 doses of rituximab and the other received no treatment. EBV replication subsided in both without symptoms. Additional infections in single patients included adenovirus viremia, BK viremia, influenza, Salmonella enteritis, line infection with Fusarium, and methicillin-resistant Staphylococcus aureus; all responded to treatment. The most frequent organ toxicity noted was renal dysfunction (n = 3), which resolved with weaning calcineurin inhibitors. One patient developed pure red aplasia that was treated with immunoglobulin, bortezomib, and prednisolone, with resolution. One patient required cholecystectomy for cholelithiasis. No patient had SCD-related symptoms post-SCT. Conclusions: Our preliminary results suggest that this RIC regimen combined with abatacept-inclusive GVHD prophylaxis protects against transplant complications that contribute to morbidity/mortality after URD SCT. These results support further study of URD SCT in clinical trial settings.	In this single arm study, 10 patients were treated with abatacept. The key observations were: 1) No infusion reactions. 2) All patients engrafted with donor cells. 3) Four patients developed fever and neutropenia. 4) Four patients experienced one or two infections during the study, including bacteremia, parainfluenza, rhinovirus, cellulitis and BK virus infection. 5) Five of 8 at-risk patients

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
	pharmacodynamics, and its impact on aGVHD, infection, relapse, and transplantation-related mortality (TRM) were assessed. Results: All patients received the planned abatacept doses, and no infusion reactions were noted. Compared with a cohort of patients not receiving abatacept (the StdRx cohort treated with cyclosporine + methotrexate), patients enrolled in the study (the ABA cohort) demonstrated significant inhibition of early CD4⁺ T cell proliferation and activation, affecting predominantly the effector memory (Tem) subpopulation, with 7- and 10-fold fewer proliferating and activated CD4⁺ Tem cells, respectively, at day +28 in the ABA cohort compared with the StdRx cohort ($P < 0.1$). The ABA patients demonstrated a low rate of aGVHD, despite robust immune reconstitution, with 2 of 10 patients diagnosed with Grade II-IV aGVHD before day ± 100, no deaths from infection, no day +100 TRM, and with 7 of 10 evaluable patients surviving (median follow-up, 16 months). Conclusions: These results suggest that costimulation blockade with abatacept can significantly affect CD4⁺ T cell proliferation and activation post-transplantation, and may be an important adjunct to standard immunoprophylaxis for aGVHD in patients undergoing unrelated-donor HCT.	had CMV reactivation, all of whom were responsive to ganciclovir. There were no cases of primary CMV infection and no CMV invasive disease. 6) No patients developed high-level EBV reactivation. One patient developed low-level EBV reactivation without PTLD; and testing for EBV DNA became negative by PCR after treatment with 4 weekly doses of rituximab. One additional patient developed EBV-positive plasmacytoid hyperplasia of the tongue on day 62 post-transplantation, which occurred in the absence of EBV viremia and during corticosteroid treatment for GVHD; the lesion subsequently regressed without treatment or reduction of immunosuppression, and without appearance of any other evidence of PTLD. 7) No adenoviremia or clinically manifest adenoviral disease occurred. 8) Three patients died: 2 patients, who underwent HCT with minimum residual disease, suffered relapse and died (at day +121 and day +147). Another patient died from transplantation-related causes (cholestatic liver disease thought to stem partly from GVHD, steroid myopathy, and traumatic pancreatitis from a fall) at day +453 post-transplantation; the other 7 patients were disease-free survivors with a median follow-up of 475 days. The most frequently reported adverse events in this study were infections, including both bacterial and viral infections, none of which resulted in death. The incidences of CMV reactivation (62.5%) and EBV infections (20%) in this study were within

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
⁴⁹Sarita Rani Jaiswal et al. T cell costimulation blockade promotes transplantation tolerance in combination with sirolimus and post-transplantation cyclophosphamide for haploidentical transplantation in children with severe aplastic anemia. <i>Transplant Immunology</i> 43–44 (2017) 54–59.	Introduction: We and others have previously described our experience with high dose post-transplantation cyclophosphamide (PTCy) based approach in patients with severe aplastic anemia (SAA) in both children and adults. In our hands, a very high incidence of early alloreactivity in the form of acute GVHD or post-transplant hemophagocytic syndrome (PTHPS) was noted in younger children with SAA using peripheral blood stem cell graft. Costimulation blockade (COSBL) with CTLA4lg has been effective in inducing transplantation tolerance in preclinical studies. We hypothesized that COSBL with abatacept prior to graft infusion would take care of the predominant alloreactive T cell population and a minority of COSBL resistant T cells which might be activated during the 72 h window could be effectively eliminated by PTCy. In addition, a combination of sirolimus and abatacept might enhance transplantation tolerance through the regulatory T cell pathway, which are unaffected by PTCy due to increased expression of aldehyde dehydrogenase. Methods: Ten patients between the age of 4 and 21 years received a haploidentical HSCT from January 2015 to May 2016 in the study protocol (COSBL group). A retrospective cohort of 10 patients who were treated on PTCy based protocols was analysed for comparison (CONTROL group). The conditioning regimen comprised of Fludarabine, low dose Cy	the published range; there was no clinically manifest CMV invasive disease or clinically important disorders caused by EBV. Two patients had disease relapse and died, but it was not possible to assess their association with abatacept use due to the small sample size and lack of a control arm in this study. Ten patients were treated with abatacept (COSBL group); a retrospective cohort of 10 patients, who were treated with PTCy per established protocols, was analysed for comparison (CONTROL group). The key observations were: 1) Nine patients in the COSBL group achieved neutrophil and platelet engraftments at 14 and 15 days respectively. (The article did not provide information about the patient who did not achieve primary engraftment) There were no secondary graft failures in either group. 2) The incidence of CMV reactivation was 80% in the CONTROL group and 30% in the COSBL group; two patients in the CONTROL group had EBV and adenovirus infections and the only patient with aGVHD in the COSBL group experienced adenovirus infection. 3) The incidence of transplant related mortality (TRM) was 11% in the COSBL group with an overall survival of 88.9% ± 10.5% vs 50 ± 15.8% in the CONTROL group; in COSBL group, one patient died due to invasive fungal infection after developing Grade 3 aGVHD at day +28; in the CONTROL group, 3 patients with aGVHD died from related complication between days 52 and 225 and one patient died due to infection complications at day 225 after

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
⁵⁰ Sarita Rani Jaiswal, et al. CTLA4Ig Primed Donor Lymphocyte Infusion: A Novel Approach to Immunotherapy after Haploidentical Transplantation for	and Melphalan along with Antithymocyte Globulin (ATG). GVHD prophylaxis consisted of PTcy at 50 mg/kg on days + 3 and 4 with sirolimus from day - 7 (with trough levels of 8–14 ng/ml on Day 0) until nine months. GVHD prophylaxis in the CONTROL group comprised of Cyclosporine (CSA) and mycophenolate mofetil (MMF). In study group, CSA and MMF were replaced with Abatacept (10 mg/kg on days -1, + 5, +20, +35 and then every 4 weeks until day + 180).	development of severe cGVHD. 4) Eight of the patients in the COSBL group were GVHD-free and disease-free at one-year post-transplant compared to three patients in the CONTROL group. As compared to the control group, the abatacept group had lower rates of infections and TRM. One abatacept recipient died due to invasive fungal infection, which could be associated with the development of severe aGVHD in this patient. One abatacept recipient did not achieve primary engraftment, since no additional information was provided about this patient, possible causes for the event cannot be assessed.
Results: Nine patients engrafted in the COSBL group, compared to all 10 patients (median 14 vs 13 days) treated on PTcy protocols without abatacept (CONTROL group). The incidence of acute GVHD was 10.5% in the COSBL group compared to 50% in the CONTROL group (p = 0.04). Chronic GVHD (12.5% vs 56%, p = 0.02) and CMV reactivation (30% vs 80%, p = 0.03) were also reduced in the COSBL group. T and NK cell subset analysis revealed higher CD56brightCD16– NK cells in the CONTROL group (p = 0.004), but similar CD56dimCD16+ NK cells in both groups at day + 30. Tregs (CD4+ CD25+ CD127dim/– FoxP3 +) were markedly higher in the COSBL group at day + 30 (8.4% vs 1.1%) and the trend was maintained through day + 90 (p < 0.01). The GVHD and Disease-free survival at one year in the COSBL group was 80% vs. 30% in the CONTROL group (p = 0.05).	As compared to the control group, the abatacept group had lower rates of infections and TRM. One abatacept recipient died due to invasive fungal infection, which could be associated with the development of severe aGVHD in this patient. One abatacept recipient did not achieve primary engraftment, since no additional information was provided about this patient, possible causes for the event cannot be assessed.	
Conclusion: Our preliminary findings suggest that COSBL in combination with PTcy and sirolimus might augment transplantation tolerance in children with SAA, probably due to synergistic effect on early recovery of Tregs.	CTLA4Ig attenuates T cell activation by co-stimulation blockade, but natural killer (NK) cells are not only resistant to CTLA4Ig, they also may demonstrate better anti-leukemia effect in the presence of CTLA4Ig. To explore this phenomenon we used sequential CTLA4Ig primed donor	In this single arm study, 30 patients were treated with abatacept. The key observations were: 1) All patients engrafted both neutrophils and platelets by a median of 15 days. Twenty-nine patients without disease progression (DP) had donor

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
Advanced Leukemia. Biol Blood Marrow Transplant 25 (2019) 673-682.	lymphocyte infusion (DLI) after post-transplant cyclophosphamide-based haploidentical transplantation. Methods: Thirty patients with advanced leukemia (14 patients had myeloid malignancies and 16 patients had acute lymphoblastic leukemia) received CTLA4Ig (abatacept) on day -1 and subsequently on days +7, +21, and +35, followed 12 hours later by DLI of 1×10^6 CD3+ T cells/kg containing .1 to 3.27×10^6/kg CD56+ NK cells, with low dose cyclosporine for 60 days. The conditioning regimen consisted of fludarabine 30 mg/m² for 5 days, i.v. busulfan 9.6 mg/kg over 3 days, and melphalan 140 mg/m². PTCy was administered 64 hours after infusion of the graft at 50 mg/kg twice at 24-hour intervals along with mesna. Results: The incidences of acute GVHD, chronic GVHD and nonrelapse mortality (NRM) were 6.7%, 21%, and 4.5%, respectively, with disease progression of 23.3% and overall survival of 79% at 18 months. Patients without disease progression had a significant early surge in CD56dimCD16+ NK cells with lower NKG2A expression. CTLA4Ig primed DLI was associated with an upregulation of CD86 in mature NK cells that was not witnessed with CTLA4Ig administration alone. Conclusion: CTLA4Ig primed DLI resulted in early proliferation of mature NK cells with cytotoxic potential enabling early institution of adoptive immunotherapy to mitigate the risk of relapse in advanced leukemia with reduced GVHD and NRM.	chimerism of over 95% by day +30. 2) The incidence of post engraftment infections was extremely low (4.5%; 95% CI, .1 to 8.9). 3) The only patient who received CTLA4Ig-DLI who died from nonrelapse cause succumbed to a febrile illness of unknown etiology after she had returned to her home on day +240. 4) Seven patients had DP at a median of 90 days (range, 28 to 135); the probabilities of progression-free survival (PFS) and overall survival were 75.8% (95% CI, 67.8 to 83.8) and 79.5% (95% CI, 72.0 to 88.0), respectively, after a median follow-up of 18 months (range, 11.5 to 44). Limited safety data were provided in this article; it was mentioned that the infection rate was very low (4.5%) and that no patient died due to infection, but no details of these infections were provided. The PFS in this study appeared to be much higher than that among the patients bearing a similar disease risk profile who were treated with PTCy-based haploidentical HSCT (without abatacept) in an earlier study cited in this article (75% after 18 months' follow-up, vs 37% after 1 year's follow-up)⁵¹. One patient died due to a febrile illness of unknown etiology after she had returned to her home on day +240, which was considered unlikely to be associated with abatacept use since death occurred over 200 days after the last dose of abatacept.
⁵²Sarita Rani Jaiswal et al. CTLA4Ig-based reduced intensity conditioning and donor lymphocyte infusions for	Introduction: CTLA4Ig-primed donor lymphocyte infusions (DLIs) have been found to promote natural killer (NK) cell-mediated anti-leukemia effect following haploidentical	In this single arm study, 12 patients were treated with abatacept. The key observations were: 1) No infusion-related reactions. 2) All patients achieved

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
haploidentical transplantation in refractory aggressive B-cell lymphoma relapsing after an autograft: Early results from a pilot study. <i>Experimental Hematology</i> 2019;77:26-35.	hematopoietic cell transplantation (HCT). Incorporation of CTLA4lg in conditioning aided long-term remission in myeloma probably by blocking the CD28-CD86 pro-survival pathway when combined with CTLA4lg-primed DLI. We explored a similar approach in 12 patients (8-65 years) who had refractory aggressive B-cell lymphoma (R-ABCL) following autologous HCT. Methods: Patients less than 65 years of age with R-ABCL were enrolled in this study between January 2015 and May 2018, if they possessed a suitable haploidentical family donor and were not deemed fit for myeloablative conditioning. The reduced-intensity conditioning (RIC) regimen consisted of fludarabine 30 mg/m²/day x 5 days, cyclophosphamide 15 mg/m² x 2 days and 3 Gy of total-body irradiation. CTLA4lg (Abatacept) was administered at 10 mg/kg on days -15, -8, -1, +7, +21, and +35. The graft source was mobilized peripheral blood stem cells. A DLI at 1x 10⁶/kg was administered 12 hours following CTLA4lg on day +7 and at 5x 10⁶/kg on days +21 and +35 in the absence of GVHD. PTCy was administered on days +3 and +4 at 50 mg/kg, followed by cyclosporine with a trough level of 75-150 ng/mL tapered between days +60 and +90. Results: Two patients developed chronic GVHD. Only 3 patients had disease-progression at 100 days posttransplant with a progression-free and GVHD-free survival at 2 years of 75%. A higher expression of CD80 in tumor cells and a greater proliferation of CD56dim CD16+ NK cells were observed at days +30 and +60 in patients with progression-free survival. Conclusion: We hypothesize that CTLA4lg, with a greater avidity for CD80, probably interferes with the anti-apoptotic effect mediated through this pathway, and together with early proliferation of mature NK cell when used in conjunction	neutrophil engraftment and platelet engraftment at medians of 15 days and 14 days, respectively. 3) Three patients had disease progression; of these, 2 succumbed to progressive disease, and another showed partial response to DLI and was alive until day +265, when he was lost to follow-up; the remaining patients were disease free at 100 days and all subsequent assessments. 4) At a median follow-up of 765 days (range: 375-1738), 9 patients were alive and free of disease. The actuarial progression-free and GVHD-free survival at 2 years was 75%. There were no nonrelapse mortalities (NRMs) in this cohort. 4) Four patients had CMV reactivation, and two patients developed late onset viral pneumonia at 9 and 11 months, respectively; all recovered with treatment. In this study, 4 out of 12 patients (33%) had CMV infection, a frequency consistent with that in the published literature. Two patients experienced episodes of viral pneumonia that were considered unlikely to be associated with abatacept use, since neither event began until about 8 months after last dose. All infected patients recovered with treatment. There were no NRMs, and PFS at 2 years was 75%, both better than the corresponding rates of 30% NRMs and 31% PFS reported in the same patient population in an earlier study⁵³ (mentioned in this article) in which abatacept was not used.

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Study Summary	Safety Summary and Assessment
⁵⁴Pooja Khandelwal et al. Graft Versus Host Disease Prophylaxis With Abatacept Reduces Severe Acute Graft Versus Host Disease in Allogeneic Hematopoietic Stem Cell Transplant for Beta Thalassemia Major with Busulfan, Fludarabine, and Thiotepa. Transplantation 2020 May 25.	with DLI, this approach might provide a curative option for patients with R-ABCL. Introduction: We hypothesized that the addition of 4 doses of abatacept to our standard acute GVHD (aGVHD) prophylaxis would reduce the incidence of day+100 severe aGVHD in children with transfusion dependent beta- thalassemia major undergoing a myeloablative allogeneic HSCT, without impacting engraftment. Methods: Twenty-four children with beta-thalassemia major received abatacept at a dose of 10 mg/kg intravenously on days -1, +5, +14 and +28 after HSCT in addition to calcineurin inhibitors and methylprednisolone. Outcomes were compared to 8 beta thalassemia patients who received standard aGVHD prophylaxis. Results: Neutrophils engrafted at a median of 10.5 days (range 9-15 days) in the standard aGVHD prophylaxis cohort and 11 days (range 8-14 days) in the abatacept cohort (p=0.6). Platelets engrafted at a median of 16 days (range 12-81 days) in the standard aGVHD prophylaxis cohort and 18 days (range 13-100 days) in the abatacept cohort (p=0.06). No patient had Grades III- IV aGVHD by day+100 in the abatacept cohort compared to 4 patients (50%) in the standard aGVHD prophylaxis group (p=0.001). Six patients in the abatacept cohort had chronic GVHD (2 severe cases) compared to 2 patients (1 severe case) in the standard aGVHD prophylaxis cohort (p=1). Twenty patients had viral reactivation in the abatacept cohort, 16 of which were asymptomatic while 4 had viral disease (BK hemorrhagic cystitis n=4) while 5 patients in the standard aGVHD cohort had viral reactivation (p=0.2) and 3 patients had viral disease (CMV pneumonitis n=1, BK hemorrhagic cystitis n=1, disseminated adenovirus n=1) (p=0.3). Asymptomatic EBV viremia occurred in 3 children in	In this study, 24 patients received 4 doses of abatacept in addition to standard aGVHD prophylaxis and 8 patients received standard aGVHD prophylaxis only. The key observations were: 1) No patients experienced infusion related adverse effects to abatacept. 2) There was no difference in engraftment between the 2 groups. No patients in either group had primary or secondary graft failure. 3) Patients in the abatacept cohort had lower rates of TA-TMA, likely due to lower rates of aGVHD. 4) Viral viremia rate was numerically higher in abatacept group compared to standard aGVHD prophylaxis group (83% vs 62.5%); however, the rate of viral disease was numerically lower in abatacept group compared to standard aGVHD prophylaxis group (16.7% vs 37.5%); all of the EBV viremia (50%) and CMV viremia (62.5%) in abatacept recipients were asymptomatic and they were managed successfully. 5) Thalassemia-free survival after HSCT was 100% in the abatacept cohort compared to 62.5% in the standard cohort at last follow. The study demonstrates that addition of 4 doses of abatacept to standard acute GVHD prophylaxis is well tolerated and results in significant reduction of day+100 severe acute GVHD in patients with beta-thalassemia major undergoing an HSCT conditioned with busulfan, fludarabine, and thiotepa.

Table 46: Summary of Study and Safety Results for Abatacept from the Literature

Publication	Safety Summary and Assessment
	the standard aGVHD prophylaxis group compared to 12 children in the abatacept group (p=0.7). CMV viremia occurred in 4 patients in the standard GVHD prophylaxis group compared to 15 patients in the augmented GVHD prophylaxis group (p=0.2). Adenovirus incidence was low at 1 patient in the standard acute GVHD prophylaxis cohort and none in the abatacept cohort (p=0.3). BK viremia occurred in 3 patients in the standard acute GVHD prophylaxis cohort and in 5 patients in the abatacept cohort (p=1). No patient in either cohort developed posttransplant lymphoproliferative disease (PTLD). Bacterial infections occurred in 5 patients in the abatacept cohort and 4 patients in the standard acute GVHD prophylaxis cohort; all the patients were successfully treated with intravenous antibiotics. Transplant associated thrombotic microangiopathy (TA-TMA) occurred in 1 patient in the abatacept cohort and 4 patients in the standard acute GVHD cohort. All patients in the abatacept cohort are alive and thalassaemia-free at a median follow up of 853 days (range 365- 1715 days) after HSCT, while 5 patients (62.5%) in the standard cohort are alive and thalassaemia-free at a median follow up of 1931 days (range 207-3620 days) after HSCT (p=0.007). Causes of death were disseminated adenoviremia leading to multiorgan failure (n=1), disseminated Aspergillus infection (n=1) and CMV pneumonitis (n=1), all related to underlying GVHD in standard acute GVHD prophylaxis cohort. Conclusions: Adding abatacept to our routine GVHD prophylaxis reduced the incidence of day+100 severe acute GVHD without impacting engraftment or survival.

FDA Assessment:

FDA agrees with the Applicant's safety review approach. As mentioned in comments above, the core of the safety analysis is derived from comparison of patient's randomized to abatacept versus placebo treatment in the 8/8 cohort of IM101311. The Applicant

165

Version date: January 2020 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

proposed to pool the two cohorts of abatacept treated patients (combining AE rate tabulation for the 8/8 abatacept treated patients with 7/8 abatacept treated patients). However, FDA looked at pooled rates and at the AE rates for each of the individual arms and determined that while most AEs rates were similar between the cohorts, some granularity would be lost with bulk pooling. Therefore, we recommended that AE rates for each treatment cohort be presented in the label if they occurred in >10% of patients and occurred >2% more frequently with abatacept treatment than with placebo. These cutoffs greatly focused the AE analysis by removing AEs with high incidence due to the transplantation process and that did not show an increased rate with abatacept exposure.

To aid in the assessment of safety, the Applicant conducted a literature review of abatacept aGVHD prophylaxis. FDA agrees with the Applicant's notes for the individual studies and has the following comments. We note that the indications for transplantation covered many benign and malignant hematologic indications including severe aplastic anemia, thalassemia major, severe sickle cell disease, refractory aggressive B cell malignancies, and high-risk hematologic malignancies. The types of transplantation also included all types of allogeneic transplantation including matched related donors, matched unrelated donors, mismatched unrelated donors, cord blood donors, and haploidentical donors. Concomitant medications for transplant conditioning and GVHD prophylaxis varied widely with some studies combining the use of abatacept with ATG, alemtuzumab, post-transplant cyclophosphamide, or combination of these medications. Lastly, it is important to note that abatacept treatment also varied widely between studies with some studies giving several doses prior to stem cell infusion, some studies dosing the same as ABA2, and some studies extending abatacept treatment until day 180 after transplantation. These studies combined add an additional 147 abatacept-treated patients for safety consideration. Importantly, despite the wide variation of indication, graft type, conditioning regimen, abatacept treatment regimen, and concomitant medications, the addition of abatacept did not produce new safety concerns in these patients beyond the normal expected adverse reactions expected given the unique clinical scenarios presented. Looking beyond novel safety concerns from this literature review is not feasible given the heterogeneity previously discussed.

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Table 47: Safety Population, Size, and Denominators

Safety Database for the Study Drug ¹		
Individuals exposed to the Abatacept+CNI+MTX in this development program for the indication under review		
Clinical Trial Group	Abatacept+CNI+MTX	Placebo
Controlled trial conducted for this indication (IM101311)²	116	69
Individuals exposed to the Abatacept in RA		
Controlled trial conducted for RA using abatacept IV (IM101023, IM101043, IM101031, IM101029, IM101100, IM101101 and IM101102)	Abatacept 2367	Placebo 1352

¹ *study drug* means the drug being considered for approval.

² to be used in product's labeling

Table 48: Extent of Exposure to Study Medication in the Treatment Period - IM101311

	8/8 MUD Cohort			7/8 MMUD Cohort
	Abatacept (N = 73)	Placebo (N = 69)	Total (N = 142)	Abatacept (N = 43)
Number of Infusions				
1	0	1 (1.4)	1 (0.7)	1 (2.3)
2	2 (2.7)	0	2 (1.4)	0
3	2 (2.7)	7 (10.1)	9 (6.3)	0
4	69 (94.5)	61 (88.4)	130 (91.5)	42 (97.7)
Mean (SD)	3.9 (0.36)	3.9 (0.46)	3.9 (0.41)	3.9 (0.46)
Median (Range)	4.0 (2 - 4)	4.0 (1 - 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)	85.7 (4.51)
Median (Range)	86.0 (64 - 87)	86.0 (57 - 88)	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].

Source (ADaM dataset): Table S.4.10.1 (ADEX, 8/8, number of infusions); Table S.4.11.1 (ADEX, 8/8, number of days); Table S.4.10.2.1 (ADEX, 7/8, number of infusions) and Table S.4.11.2.1 (ADEX, 7/8, number of days) in the IM101311 primary CSR

Table 49: Summary of Methotrexate Dose Received - IM101311

Study Day	MTX Dose Received	8/8 MUD Cohort			7/8 MMUD Cohort
		Abatacept (N = 73)	Placebo (N = 69)	Total (N = 142)	Abatacept (N = 43)
Day 1	Full	73 (100.0)	67 (97.1)	140 (98.6)	41 (95.3)
	Partial	0	2 (2.9)	2 (1.4)	2 (4.7)
	None	0	0	0	0
Day 3	Full	72 (98.6)	67 (97.1)	139 (97.9)	41 (95.3)
	Partial	1 (1.4)	1 (1.4)	2 (1.4)	1 (2.3)
	None	0	1 (1.4)	1 (0.7)	1 (2.3)
Day 6	Full	70 (95.9)	63 (91.3)	133 (93.7)	40 (93.0)
	Partial	2 (2.7)	4 (5.8)	6 (4.2)	1 (2.3)
	None	1 (1.4)	2 (2.9)	3 (2.1)	2 (4.7)
Day 11	Full	59 (80.8)	55 (79.7)	114 (80.3)	34 (79.1)
	Partial	8 (11.0)	11 (15.9)	19 (13.4)	3 (7.0)
	None	6 (8.2)	3 (4.3)	9 (6.3)	6 (14.0)

Source (ADaM dataset): Table S.4.16.5.1 (ADCM, 8/8 cohort) and Table S.4.16.5.2 (ADCM, 7/8 cohort) in the IM101311 Primary CSR

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

Table 50: Summary of Calcineurin Inhibitor and Sirolimus Levels Over Time: 8/8 Cohort As Treated Analysis Population

Study Day		Abatacept		Placebo		Total	
		N = 73	N = 69	N = 69	N = 142		
DAY -1	TACROLIMUS LEVEL (NG/ML)	n	28	24	52		
	MEAN (SD)	10.93 (6.532)	11.26 (3.699)	11.08 (5.366)			
	MEDIAN (RANGE)	9.40 (3.0 - 40.0)	12.10 (3.5 - 19.1)	10.80 (3.0 - 40.0)			
	n	2	2	4			
DAY 5	CYCLOSPORINE LEVEL (NG/ML)	MEAN (SD)	119.00 (16.971)	196.50 (30.406)	157.75 (49.054)		
	MEDIAN (RANGE)	119.00 (107.0 - 131.0)	196.50 (175.0 - 218.0)	153.00 (107.0 - 218.0)			
	n	56	56	112			
	MEAN (SD)	10.19 (4.019)	10.36 (3.428)	10.28 (3.719)			
	MEDIAN (RANGE)	9.25 (1.5 - 22.5)	10.05 (3.0 - 20.8)	9.75 (1.5 - 22.5)			
	n	11	9	20			
DAY 35	CYCLOSPORINE LEVEL (NG/ML)	MEAN (SD)	231.25 (108.505)	317.17 (148.632)	269.92 (131.989)		
	MEDIAN (RANGE)	221.30 (108.0 - 448.6)	292.90 (155.0 - 628.9)	239.00 (108.0 - 628.9)			
	n	57	56	113			
	MEAN (SD)	8.89 (3.772)	9.61 (3.633)	9.24 (3.705)			
	MEDIAN (RANGE)	8.10 (1.2 - 16.8)	9.10 (3.2 - 21.6)	8.90 (1.2 - 21.6)			
	n	13	8	21			
	MEAN (SD)	225.15 (123.379)	375.81 (85.614)	282.55 (131.603)			
	MEDIAN (RANGE)	194.00 (10.0 - 401.0)	341.25 (284.0 - 542.0)	317.00 (10.0 - 542.0)			
	n	0	1	1			
	MEAN (SD)		2.500 (-)	2.500 (-)			
DAY 63	TACROLIMUS LEVEL (NG/ML)	MEAN (SD)	8.68 (4.371)	8.67 (3.039)	8.68 (3.778)		
	MEDIAN (RANGE)	7.40 (1.6 - 29.1)	8.20 (2.3 - 14.5)	7.80 (1.6 - 29.1)			
	n	11	7	18			
	MEAN (SD)	239.25 (98.957)	354.59 (110.139)	284.10 (115.712)			
	MEDIAN (RANGE)	249.00 (95.0 - 464.0)	388.70 (200.5 - 530.0)	276.50 (95.0 - 530.0)			
	n	0	5	5			
DAY 100	TACROLIMUS LEVEL (NG/ML)	MEAN (SD)	5.340 (2.9695)	5.600 (1.00 - 9.20)	5.340 (2.9695)		
	MEDIAN (RANGE)		5.600 (1.00 - 9.20)	5.600 (1.00 - 9.20)			
	n	44	45	89			
	MEAN (SD)	7.78 (6.630)	6.92 (2.882)	7.35 (5.081)			
	MEDIAN (RANGE)	6.55 (1.3 - 46.5)	6.20 (2.9 - 15.3)	6.40 (1.3 - 46.5)			
	n	8	4	12			
	MEAN (SD)	210.08 (109.908)	205.65 (137.105)	208.60 (113.219)			
	MEDIAN (RANGE)	182.00 (107.0 - 463.0)	194.80 (77.0 - 356.0)	182.00 (77.0 - 463.0)			
	n	1	2	3			
	MEAN (SD)	3.500 (-)	6.850 (5.4447)	5.733 (4.3085)			
DAY 180	TACROLIMUS LEVEL (NG/ML)	MEAN (SD)	3.500 (3.50 - 3.50)	6.850 (3.00 - 10.70)	3.500 (3.00 - 10.70)		
	MEDIAN (RANGE)						
	n	32	23	55			
	MEAN (SD)	5.10 (4.022)	7.36 (5.062)	6.05 (4.582)			
	MEDIAN (RANGE)	4.15 (0.4 - 16.5)	6.30 (0.3 - 18.3)	5.30 (0.3 - 18.3)			
	n	3	3	6			
	CYCLOSPORINE LEVEL (NG/ML)	MEAN (SD)	126.33 (109.510)	148.00 (114.582)	137.17 (100.942)		

169

Version date: January 2020 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Table 50: Summary of Calcineurin Inhibitor and Sirolimus Levels Over Time: 8/8 Cohort As Treated Analysis Population

Study Day	Abatacept		Placebo		Total	
	N = 73	N = 69	N = 69	N = 142		
DAY 270	MEDIAN (RANGE)	128.00 (16.0 - 235.0)	183.00 (20.0 - 241.0)	155.50 (16.0 - 241.0)		
	n	3	2	5		
	MEAN (SD)	7.000 (4.6936)	3.350 (0.2121)	5.540 (3.8760)		
DAY 270	MEDIAN (RANGE)	9.300 (1.60 - 10.10)	3.350 (3.20 - 3.50)	3.500 (1.60 - 10.10)		
	n	25	14	39		
	MEAN (SD)	6.64 (3.753)	4.59 (3.117)	5.90 (3.635)		
DAY 270	MEDIAN (RANGE)	6.50 (0.6 - 13.7)	4.00 (0.3 - 10.5)	6.20 (0.3 - 13.7)		
	n	1	1	2		
	MEAN (SD)	35.00 (-)	129.00 (-)	82.00 (66.468)		
DAY 270	MEDIAN (RANGE)	35.00 (35.0 - 35.0)	129.00 (129.0 - 129.0)	82.00 (35.0 - 129.0)		
	n	2	4	6		
	MEAN (SD)	5.600 (2.9698)	5.100 (1.0614)	5.267 (1.5832)		
DAY 365	MEDIAN (RANGE)	5.600 (3.50 - 7.70)	5.050 (3.90 - 6.40)	5.050 (3.50 - 7.70)		
	n	22	13	35		
	MEAN (SD)	5.08 (2.685)	5.05 (3.482)	5.07 (2.955)		
DAY 365	MEDIAN (RANGE)	5.35 (0.4 - 11.1)	5.40 (0.7 - 11.4)	5.40 (0.4 - 11.4)		
	n	0	1	1		
	MEAN (SD)		174.00 (-)	174.00 (-)		
DAY 365	MEDIAN (RANGE)		174.00 (174.0 - 174.0)	174.00 (174.0 - 174.0)		
	n	4	6	10		
	MEAN (SD)	4.525 (1.4315)	5.917 (3.6690)	5.360 (2.9459)		
DAY 365	MEDIAN (RANGE)	4.400 (3.10 - 6.20)	5.050 (2.50 - 11.50)	4.450 (2.50 - 11.50)		
	n					
	MEAN (SD)					

n is the number of subjects with non-missing measurements.

Source (ADaM dataset): Table S.4.16.3.1 (ADLB: PARAMCD=TACR,CYCLOS,SIROL) in the IM101311 CSR

Table 51: Summary of Calcineurin and Sirolimus Inhibitor Levels Over Time: 7/8 Cohort Treated Analysis Population

Study Day		Abatacept N = 43	
DAY -1	TACROLIMUS LEVEL (NG/ML)	n	11
		MEAN (SD)	10.30 (4.164)
		MEDIAN (RANGE)	9.60 (3.1 - 16.9)
	CYCLOSPORINE LEVEL (NG/ML)	n	2
		MEAN (SD)	141.85 (18.314)
		MEDIAN (RANGE)	141.85 (128.9 - 154.8)
DAY 5	TACROLIMUS LEVEL (NG/ML)	n	25
		MEAN (SD)	10.06 (3.756)
		MEDIAN (RANGE)	9.80 (4.0 - 21.2)
	CYCLOSPORINE LEVEL (NG/ML)	n	12
		MEAN (SD)	313.22 (137.338)
		MEDIAN (RANGE)	331.95 (95.0 - 548.4)
DAY 28	TACROLIMUS LEVEL (NG/ML)	n	28
		MEAN (SD)	10.03 (4.968)
		MEDIAN (RANGE)	8.85 (4.2 - 28.4)
	CYCLOSPORINE LEVEL (NG/ML)	n	13
		MEAN (SD)	286.30 (113.884)
		MEDIAN (RANGE)	265.20 (115.0 - 490.9)
DAY 35	TACROLIMUS LEVEL (NG/ML)	n	27
		MEAN (SD)	7.81 (2.684)
		MEDIAN (RANGE)	8.10 (2.1 - 12.6)
	CYCLOSPORINE LEVEL (NG/ML)	n	13
		MEAN (SD)	282.42 (108.822)
		MEDIAN (RANGE)	267.00 (132.0 - 502.7)
DAY 63	TACROLIMUS LEVEL (NG/ML)	n	25
		MEAN (SD)	8.76 (3.652)
		MEDIAN (RANGE)	8.90 (2.8 - 17.3)
	CYCLOSPORINE LEVEL (NG/ML)	n	11
		MEAN (SD)	270.28 (111.295)
		MEDIAN (RANGE)	272.60 (80.0 - 433.8)
DAY 100	TACROLIMUS LEVEL (NG/ML)	n	28
		MEAN (SD)	7.21 (4.054)
		MEDIAN (RANGE)	7.30 (1.6 - 19.6)
	CYCLOSPORINE LEVEL (NG/ML)	n	7
		MEAN (SD)	221.70 (129.525)
		MEDIAN (RANGE)	200.70 (70.2 - 400.4)
DAY 180	TACROLIMUS LEVEL (NG/ML)	n	17
		MEAN (SD)	6.86 (3.797)
		MEDIAN (RANGE)	6.10 (1.7 - 13.7)
	CYCLOSPORINE LEVEL (NG/ML)	n	2
		MEAN (SD)	170.55 (124.804)
		MEDIAN (RANGE)	170.55 (82.3 - 258.8)
	SIROLIMUS LEVEL (NG/ML)	n	1
		MEAN (SD)	10.400 (-)
		MEDIAN (RANGE)	10.400 (10.40 - 10.40)
DAY 270	TACROLIMUS LEVEL (NG/ML)	n	18
		MEAN (SD)	7.61 (3.713)
		MEDIAN (RANGE)	7.50 (0.3 - 15.4)
	CYCLOSPORINE LEVEL (NG/ML)	n	2
		MEAN (SD)	130.80 (2.970)
		MEDIAN (RANGE)	130.80 (128.7 - 132.9)
	SIROLIMUS LEVEL (NG/ML)	n	3
		MEAN (SD)	9.167 (8.2282)
		MEDIAN (RANGE)	7.200 (2.10 - 18.20)
DAY 365	TACROLIMUS LEVEL (NG/ML)	n	13
		MEAN (SD)	4.77 (2.079)
		MEDIAN (RANGE)	5.10 (0.3 - 8.2)
	CYCLOSPORINE LEVEL (NG/ML)	n	4
		MEAN (SD)	150.48 (102.763)
		MEDIAN (RANGE)	179.00 (3.0 - 240.9)
	SIROLIMUS LEVEL (NG/ML)	n	5
		MEAN (SD)	4.180 (2.3669)
		MEDIAN (RANGE)	3.800 (1.20 - 7.80)

n is the number of subjects with non-missing measurements.

Source (ADaM dataset): Table S.4.16.3.2 (ADLB: PARAMCD=TACR,CYCLOS,SIROL) in the IM101311 CSR

The Applicant's Position:

In 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), and the median exposure was 86.0 days for each treatment group. In the single-arm 7/8 MMUD cohort, 43 of the 46 enrolled subjects received abatacept, and the median exposure was 86.0 days (Table 35). The majority of total subjects received a full MTX dose at Days 1, 3, 6, and 11 (range: 80.3% - 98.6%); Table 36. Summary of calcineurin inhibitor and sirolimus trough concentrations for 8/8 MUD and 7/8 MMUD cohort is provided in Table 37 and Table 38, respectively.

FDA Assessment:

The FDA generally agrees with the Applicant's position. The IM101311 study data sets include sufficient patients that were treated per protocol after randomization to assess the safety of the addition of abatacept to a standard aGVHD prophylaxis regimen. Importantly, 69/73 (94.5%) and 42/43 (97.7%) of abatacept treated patients received all four planned doses for the 8/8 cohort and the 7/8 cohort, respectively. Since this trial only included 4 planned doses of abatacept, the high completion rate of these doses per protocol ensures that the safety analysis reflect the results of the study intervention.

We note that 56 days were added to the Applicant's calculation of Days of Exposure [(date of the last infusion in the treatment period - date of the first infusion in the treatment period +1) +56]. This appears to account for pharmacologic exposure to abatacept following dosing. Accounting for only days on active treatment, median exposure was the length of the treatment period (i.e., 30 days).

Relevant characteristics of the safety population:

The Applicant's Position: Key baseline characteristics for the 8/8 MUD cohort and 7/8 MMUD cohort are presented in Table 14 and Table 15, respectively.

FDA Assessment:

FDA agrees with the Applicant's position. The baseline characteristics are representative for patients aged 6 and up with a high-risk malignancies who have been deemed candidates to undertake the rigors of stem cell transplant. It is notable that while most patients were white in all 3 cohorts that the 7/8 cohort included higher proportion of African American and Hispanic patients. This also reflects the clinical difficulty of finding matched donors for patients that are not of a non-Hispanic white background.

Adequacy of the safety database:

The Applicant's Position:

The population studied in IM101311 adequately represents the target population, including demographic, disease, and other baseline characteristics. The safety events reported in this study were consistent with those expected in a population of patients with hematologic malignancies undergoing stem cell transplantation;^{55,56,57,58,59,60} review of those events did not identify any unexpected safety concerns among abatacept-treated patients. The safety database for the aGVHD prophylaxis indication was supplemented by a large safety database of 2367 abatacept-treated patients in RA and JIA.

FDA Assessment:

8.2.3 **The number of patients and the duration of follow up included in the safety database are adequate to provide a reasonable estimate of the adverse reactions over time for the indicated population. FDA disagrees with the Applicant that there were no unexpected safety concerns among abatacept-treated patients, as adverse reactions were identified with the addition of abatacept to the treatment regimen. See sections below for more information. Adequacy of Applicant's Clinical Safety Assessments**

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

See Section 8.1.2. Data review and quality control checks were implemented by the IM101311 Study Committee and consisted of site monitoring visits guided by the SMP to review source documents against the eCRF and data validation checks of the eCRF.

FDA Assessment:

The quality of the safety data submitted was adequate to allow substantial primary review.

Categorization of Adverse Event

The Applicant's Position:

Adverse events in IM101311 were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 CTCAE version 4.03, by system organ class and preferred term.

FDA Assessment:

FDA evaluated the mapping of verbatim AE terms to MedDRA terms and disagreed with approximately 10% of mappings. The specificity of the verbatim terms was lost during initial mapping due to a systemic error. This was addressed with the Applicant in response to an information request by recoding the discrepant AE terms to maintain the specificity expressed in the verbatim terms. The ADAE.xpt dataset submitted on September 1, 2021 reflects the corrected PTs. Grouping of terms was explored but was not required to adequately explore safety signals. This was because common AE were reported and mapped to PTs that did not require grouping to adequately characterize common adverse events. Therefore, grouped terms were not utilized for the current safety analysis.

Terms that referred directly to relapse or progression of the underlying hematologic malignancy or GVHD were excluded from FDA's safety analyses. Treatment-emergent adverse events (TEAEs) excluded events that started before the start of the study drug or that started more than 30 days after the last dose of abatacept. However, for the bulk of the safety analyses, the Applicant proposed to analyze safety beyond the treatment-emergent period to include AEs that occurred until the day 180 visit (per the SAP, this time was up to day 225 after transplantation). Thus, FDA confirmed safety results of these "extended" TEAEs out to day 225. AEs were summarized by maximum grade per patient.

Routine Clinical Tests

The Applicant's Position:

Routine monitoring of safety lab analytes was performed for all patients per protocol, to include hematologic, biochemical, metabolic, hepatic and renal functional, serologic, and viral nucleic acid testing. These were part of routine, standard of care pre- and post-transplant monitoring of candidates with hematologic malignancies undergoing HSCT (Section 3.4 and Table 2 in the ABA2 (IM101311) study protocol).

FDA Assessment:

FDA agrees with the Applicant's position. The clinical context of HSCT necessitates intensive clinical monitoring for all patients, and this data was adequately collected to assess the risks of serious safety events.

8.2.4 Safety Results

Data:

Table 52: Summary of Safety Results During the Day 180 Analysis Period - As Treated Population - IM101311

	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)

Table 52: Summary of Safety Results During the Day 180 Analysis Period - As Treated Population - IM101311

	8/8 MUD Cohort		7/8 MMUD Cohort
	Abatacept (N = 73)	Placebo (N = 69)	Abatacept (N = 43)
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 ^a up to Day 100	0.98 (0.95, 1.00)	0.98 (0.95, 1.00)	0.95 (0.80, 0.99)
Platelet recovery ^b 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 (up to Day 225) (95%CI)			
CMV viremia	39 (53.4)	30 (43.5)	16 (37.2)
CMV invasive disease	7 (9.6)	2 (2.9)	1 (2.3)
PTLD	1 (1.4) ^c	0 (0)	2 (4.7)
Other pre-specified infections	27 (37.0)	22 (31.9)	21 (48.8)
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 ^d	7 (9.6)	8 (11.6)	2 (4.7)
Autoimmune Disorders	0	2 (2.9)	1 (2.3)
Infusion Reactions			
Peri-infusional AEs	9 (12.3)	11 (15.9)	5 (11.6)

^a Defined as the first of 3 consecutive days following the nadir that the absolute neutrophil count (ANC) is at least 500/mm³. Subjects will be censored at date of Day 100 assessment

^b Defined as the first day that the platelet count is at least 20 x 10⁹/L without a transfusion in the preceding 7 days. Subjects will be censored at date of Day 100 assessment

^c A second subject was identified as PTLD on study team adjudication post-database lock, and so is not reported in this table

^d All malignancy-related events refer to relapse of the primary malignancy. No therapy-related or other secondary malignancies occurred.

Source (ADaM dataset): **8/8 Cohort:** Table S.6.1.1.1.S (ADAE), Table S.5.17.1 (ADTTE [PARAMCD = NRD100], neutrophil recovery), Table S.5.18.1 (ADTTE [PARAMCD = PRD100], platelet recovery), Table S.5.22.1.S (ADTTE [PARAMCD = CMVVIRE, CMVINVA, PTLD, OTHINFC], Cumulative Incidence of Infections and Immune Related Events), Table S.6.2.1.1.S (ADAE, Infection), Table S.6.7.1.1.S (ADAE [SMQ01NAM, SMQ01CD], Malignancy), Table S.6.14.1.1.S (AE [CQ01NAM, CQ01CD], autoimmune disorder), and Table S.6.8.1.1.S (ADAE [CQ02NAM, CQ02CD], Peri-infusional AEs). **7/8 Cohort:** Table S.6.1.1.2.S (ADAE), Table S.5.22.2 (ADTTE [PARAMCD = CMVINVA, CMVVIRE, OTHINFC, PTLD], Cumulative Incidence of Infections and Immune Related Events); Table S.5.17.2.1 (ADTTE [PARAMCD = NRD100], neutrophil recovery), Table S.5.18.2.1 (ADTTE [PARAMCD = PRD100], platelet recovery), Table S.6.2.1.2.S (ADAE, Infection). Table S.6.7.1.2.S (ADAE [SMQ01NAM, SMQ01CD], Malignancy), Table S.6.14.1.2.S (AE [CQ01NAM, CQ01CD], autoimmune disorder), and Table S.6.8.1.2.S (ADAE [CQ02NAM, CQ02CD], Peri-infusional AEs) in the IM101311 CSR.

Deaths

The Applicant's Position:

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 (Table 52).

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); Appendix 1 in the Summary of Clinical safety [SCS] (ADaM dataset: ADAE in the IM101311 primary CSR).

The fatality rate in abatacept-treated subjects was lower compared to that in placebo group. Major causes of deaths reported in abatacept-treated subjects were underlying malignancy recurrence and GVHD, which were expected in the study population and reported with lower rates compared to placebo.

None of the reported deaths in either Cohort were attributed to a fatal adverse drug reaction. No fatal adverse drug reactions were reported in either of the abatacept-treated groups of study IM101311.

- In the 7 of 8 MMUD Cohort: One CTC AE severity Grade 3 (serious) event of "ALLERGIC REACTION" (term not otherwise specified) was reported as in association with the first protocol-specified infusion of abatacept in a 7 of 8 matched URD HSCT recipient ((b) (6)) and resulted in discontinuation of the patient from any further dosing. Pre-specified peri-infusional reactions were reported for 4 other subjects with verbatim terms of "infusion related reaction", "hypotension", "nausea" and "vomiting" (n=1 each), of Grade 2-3 severity; none were associated with discontinuation from abatacept as study drug.
- In the 8 of 8 MUD Cohort: 9 abatacept-treated patients experienced pre-specified peri-infusional events of Grade 2-3 severity. In the 8 of 8 MUD Cohort: 9 abatacept-treated patients experienced pre-specified peri-infusional events of Grade 2-3 severity. These included "infusion-related reaction" (not otherwise specified; n=2) and nausea (n=7). 12 placebo-treated patients experienced pre-specified peri-infusional events of Grade 2-4 severity. These included nausea (n=5), "infusion-related reaction (not otherwise specified) and "hypotension" (n=3 each), and "dyspnea" (n=1).

FDA Assessment:

FDA performed an assessment of deaths in patients enrolled on Study IM101311.ABA2. We looked at this in two ways. First, we assessed the deaths of patients until the day 180 visit. Per the SAP, this time was up to day 225 after transplant. As discussed above, we found that deaths were greater in the 8/8 placebo-treated cohort (13/69) than in the 8/8 abatacept-treated cohort (5/73). We also noted 2 deaths in the 7/8 abatacept-treated cohort to this time point. FDA Root cause assessment of deaths was in overall agreement with the Applicant but was simplified to one of three categories: death related to GVHD, death from intercurrent illness, or death related to relapse of primary disease. We found that for the 8/8 placebo-treated cohort patients had died from either GVHD (n=6), intercurrent illness (n=2), or primary disease (n=5). For the 8/8 abatacept-treated cohort, we found that patients had died from either intercurrent illness (n=1) or primary disease (n=5). Lastly, for the 7/8 abatacept-treated cohort, we found that patients had died from GVHD (n=2). It is important to note that no patient died within 30 days of

abatacept treatment. One patient that received placebo died 28 days after last administration of placebo infusion.

FDA also assessed root cause of death for the deaths that occurred up until the day 180 visit (day 225 from transplant) and including any adverse event that began prior to day 225 that ultimately became a grade 5 event. This includes the patients just discussed but adds 10 more events that started prior to day 225 but resulted in the patient's death after day 225. Total deaths for each cohort were (17/69) for the 8/8 placebo-treated cohort, (8/73) for the 8/8 abatacept-treated cohort, and (5/43) for the 7/8 abatacept-treated cohort. We found that for the 8/8 placebo-treated cohort patients had died from either GVHD (n=7), intercurrent illness (n=2), or primary disease (n=8). For the 8/8 abatacept-treated cohort, we found that patients had died from either GVHD (n=2), intercurrent illness (n=1) or primary disease (n=5). Lastly, for the 7/8 abatacept-treated cohort, we found that patients had died from either GVHD (n=3) or primary disease (n=2).

Serious Adverse Events (All Causality)

The Applicant's Position:

In the 8/8 MUD cohort, the overall frequencies of all-causality SAEs were similar in the abatacept group (71.2% [52/73]) and the placebo group (65.2% [45/69]); Table 40. This was also the case for SAEs reported up to Day 365; (54 [74.0%]) versus (49 [71.0%]); Table 53.

The most frequently reported SAEs, in the 8/8 MUD cohort, with abatacept use ($\geq 5\%$ of subjects) were pneumonia, pyrexia, GI disorder, diarrhea, nausea, respiratory failure, hypoxia, hypotension, hepatobiliary disease, and acute kidney injury (AKI). Imbalances ($\geq 3\%$ more frequently in abatacept-treated subjects compared to placebo) were observed in the incidence of SAEs of pyrexia (19.8% vs 15.9%), GI disorder (13.8% vs 1.4%), pneumonia (7.8% vs 1.4%), diarrhea (6.0% vs 2.9%), hepatobiliary disease (6.9% vs 2.9%), and AKI (6.9% vs 1.4%). Review of these SAEs did not identify any unusual event pattern or increased event severity with abatacept use compare to placebo.

In the 7/8 MMUD cohort, during the Day 180 analysis period, any-Grade all-causality SAEs were reported in 29 (67.4%) subjects and the most frequently reported SAEs were pyrexia (12 subjects, 27.9%), GI disorder (7 subjects, 16.3%), and pneumonia (5 subjects, 11.6%). As expected, there was a slight increase in the number of SAEs reported up to Day 365 (33 [76.7%]) compared to that reported in the 180 day analysis period.

FDA Assessment:

FDA performed an analysis of all-grade treatment-emergent SAEs and all-grade SAE's that occurred within the 225-day (day 180 visit) safety window. FDA noted TESAE's (occurred within 30 days of last dose of abatacept or placebo) in (35/69, 51%) for the 8/8 placebo-treated cohort, (34/73, 47%) for the 8/8 abatacept-treated cohort, and (16/43, 37%) for the 7/8 abatacept-treated cohort.

For the 225-day analysis period, FDA noted extended TESAEs (45/69, 65%) for the 8/8 placebo-treated cohort, (52/73, 71%) for the 8/8 abatacept-treated cohort, and (29/43, 67%) for the 7/8 abatacept-treated cohort. The tabulation of Serious AEs that occurred during the 225-day analysis period and occurred in at least 5% of abatacept-treated patients and with $\Rightarrow 2\%$ frequency in abatacept treated patients than in placebo-treated patients are shown in Table 53

below. One difference to note from the Applicant’s tabulation of serious AEs is that the Applicant has the category of GI disorder. As mentioned above, the initial ADAE dataset contained approximately 10% of verbatim to PT coding that FDA did not agree with, and many coded events of GI GVHD as GI toxicity without specifying the diagnosis of GVHD. FDA tabulation presented in Table 53 does not include GVHD AEs.

Table 53: Summary of extended TESAEs on Study ABA2 through day 225

PT	ABATACEPT (N= 116)		PLACEBO (N= 69)	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Pyrexia	23	20	11	16
Pneumonia	9	8	1	1.4
Acute kidney injury	8	7	1	1.4
Diarrhoea	7	6	2	2.9
Hypoxia	6	5	2	2.9
Nausea	6	5	2	2.9

Source: FDA analysis using adae.xpt

Discontinuations Due to Adverse Effects

The Applicant’s Position:

Adverse events leading to discontinuation were reported for one patient in the 7 of 8 MMUD Cohort and for 2 and 5 patients in the abatacept and placebo treatment groups of the 8 of 8 MUD Cohort of study IM101311:

In the 8 of 8 MUD Cohort:

- **Abatacept group:** Following the second (Day 5) infusion of abatacept, one subject was discontinued on Day 6 due to development of a “lung infection” of Grade 3 intensity that was assessed as possibly related to study drug. The patient did not receive the remaining 2 protocol specified infusions of abatacept. A second patient was discontinued after the third abatacept infusion, due to development of lower gastrointestinal aGVHD on Day 13 that was assessed as of Grade 4 intensity and not related to study drug; this patient did not receive the final (Day 28) abatacept infusion.
- **Placebo group:** 5 patients were discontinued for the following reasons:
 - Headache and dyspnea of Grade 3 intensity, both on Day 5 and unlikely related;
 - Cutaneous aGVHD (Grade 3, Day 20), fever and dehydration (Grade 3, Days 20 and 24, respectively) and recurrence of primary malignancy (CLL) (Grade 4, Day 25), all assessed as unlikely related.
 - Hyperacute gastrointestinal GVHD (Grade 3) on Day 4, unlikely related;
 - Hypotension (Grade 3) on Day 30, unlikely related;
 - Urinary tract infection (Grade 3) on Day 1, unlikely related.

- **In the 7 of 8 MMUD Cohort:** Subject (b) (6) experienced delirium and hypotension, both of Grade 3 severity on study days 28 and 29, respectively, for which he was discontinued from abatacept. A second Subject (b) (6), who experienced an “allergic reaction” associated with the first infusion of abatacept, did not receive the remaining 3 doses but this patient was not formally discontinued from assigned therapy in the database and does not appear as a discontinuation due to an adverse event in data report rl-ae-disc7-s.sas.

There was no trend detected for the AEs that resulted in abatacept discontinuation (Table S.6.19.1.1.S [AdaM dataset: ADAE] and Table S.6.19.1.2.S [AdaM dataset: ADAE] in the IM101311 primary CSR).

FDA Assessment:

FDA agrees with the Applicant’s position. Most patients completed abatacept or placebo treatments without dose discontinuation due to an AE. By administration records, 61/69 (88%) of 8/8 placebo-treated patients, 69/73 (95%) of 8/8 abatacept-treated patients, and 42/43 (98%) of 7/8 abatacept-treated patients received all 4 of the intended doses of study drug.

Based on FDA’s analysis, 2 of 116 patients (1.7%) treated with abatacept on Study IM101311 discontinued abatacept due to an adverse reaction. One patient on the abatacept 8/8 arm discontinued due to pneumonia and one patient on the abatacept 7/8 arm discontinued due to an allergic reaction. On review of the patient narrative for the patient who discontinued due to delirium and hypotension, these AEs were found to precede the last scheduled dose of abatacept, and thus, were not considered adverse reactions. The AEs appeared to be due to large doses of opiates.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant’s Position:

The majority of subjects received all 4 infusions of study drug (Table S.4.10.1 [AdaM dataset: ADEX] and Table S.4.10.2.1 [AdaM dataset: ADEX] in the IM101311 primary CSR. There were no AEs with dose interruptions. There was only one AE with dose reduction in the 7/8 cohort (abatacept treated) had an AE of infection leading to dose reduction. But in the exposure data, this subject took 1000 mg for all 4 doses, so there is no record of dose reduction. This could be due to an issue in reporting.

The FDA’s Assessment:

FDA agrees with Applicant’s assessment. Most patients received all 4 of the intended doses of abatacept. Therefore, abatacept administration was not associated with substantial toxicity leading to either dose interruptions/reductions or discontinuations.

Significant Adverse Events

The Applicant’s Position:

The evaluation of the safety of treatment with abatacept+SOC aGVHD prophylaxis in unrelated-donor HSCT for hematologic malignancy included engraftment related events infections and immune related events.

Engraftment related events:

In Study IM101311, no subject in either treatment group experienced non-engraftment or graft rejection (Table S.5.19.1 [AdaM dataset: ADSL] and Table S.5.19.2 [AdaM dataset: ADSL] in the IM101311 Primary CSR). 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.⁶¹

Infection and immune-related events

CMV/EBV viremia: 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 39.7% of subjects treated with abatacept and 30.4% 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.

The cumulative incidences of infection and immune-related events at Day 180 and at Day 365 in the 7/8 MMUD cohort 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

Table S.5.22.1.S (AdaM dataset: ADTTE (PARAMCD=CMVVIRE,CMVINVA,EBVVIRE,PTLD,OTHINFC) 8/8 cohort and Table S.5.22.2 (AdaM dataset: ADTTE (PARAMCD=CMVVIRE,CMVINVA,EBVVIRE,PTLD,OTHINFC), 7/8 cohort, in the IM101311 CSR.

In general, the intensity of CMV reactivation events was assessed as Grade 3, with a few Grade 4 events. All EBV reactivation events were assessed as Grade 3. (Data available from the Principal Investigator).

PTLD: Four subjects experienced PTLD during the study; all of them were pediatric subjects (age < 18 years). The only 2 cases of PTLD in the 8/8 MUD cohort were reported from among the 73 patients randomized to the abatacept treatment group, corresponding to an incidence of 2.7%. One subject, whose pre-transplant EBV serology was positive, was diagnosed on Study Day 87 following presentation 3 days earlier with cervical and submandibular lymphadenopathy that proved to be EBV-positive PTLD upon histologic examination; the event, which was assessed as of Grade 3 (severe) intensity and probably related to study drug, resolved completely with the treatment of rituximab. A second subject, a 9-year old female, whose EBV serology was also positive pre-transplant, was only identified as PTLD after study-team adjudication post database lock, and therefore was not captured in the summary table or included in the AE listing as a case of PTLD. Source (AdaM dataset): Table S.5.24.1.S (ADTTE [PARAMCD=CMVVIRE,CMVINVA,EBVVIRE,PTLD,OTHINFC]) and Table S.5.24.2 (ADTTE [PARAMCD=CMVVIRE,CMVINVA,EBVVIRE,PTLD,OTHINFC]) in the IM101311 CSR.

Two cases of PTLD were also reported in abatacept-treated subjects in the 7/8 MMUD cohort: One subject, an 11-year old female whose pre-transplant EBV serology was positive, experienced EBV reactivation on Study Day 87 associated with fever and bilateral cervical lymphadenopathy that, upon histologic examination on Day 94, proved to be due to EBV-positive, monomorphic PTLD. The event resolved completely with PTLD-directed combination therapy; this event was assessed as of Grade 3 (severe) intensity and probably related to study drug. The second subject was a 12-year old female whose pre-transplant EBV serology was negative, was seen in clinic on Study Day 47 complaining of cough and had an EBV DNA titer of 14,980 IU/mL at the time with no findings on chest CT. After subsequently developing persistent headache and fever, she was admitted on Day 54 and was found on lumbar puncture to have a CSR EBV DNA titer of 600 IU/mL. A lymph node biopsy revealed findings consistent with EBV PTLD positive, monomorphic PTLD. The event, which was assessed as probably unrelated to study drug and of Grade 3 (severe) intensity, resolved completely with PTLD-directed combination therapy.

In Study IM101841, Occurrence of PTLD after transplant was an exploratory outcome and was collected up to the first 100 and 180 days after transplant among the subset of patients with available CRF data. Given the small sample size, only the incidence of PTLD during these 2 time periods was reported. There were no cases of PTLD reported at Day 100 or at Day 180 in the primary objective 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

Due to all the events of PTLD occurring in abatacept-treated subjects and biological plausibility, there is a possibility that abatacept use could be associated with an increased risk of PTLD in the setting of HSCT. The available evidence suggested that the risk could be mitigated by anti-viral prophylaxis for a longer period (eg. 6 months post-transplant).

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). The event outcomes were reported in 7 cases, all of which resolved with antiviral therapy. 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 in the setting of HSCT. Source (AdaM dataset): Table S.5.24.1.S (ADTTE [PARAMCD=CMVVIRE,CMVINVA,EBVVIRE,PTLD,OTHINFC]) and Table S.5.24.2 (ADTTE (PARAMCD=CMVVIRE,CMVINVA,EBVVIRE,PTLD,OTHINFC) in the IM101311 CSR.

All of events are Grade 3 or 4 in intensity (data available from the principal investigator).

Other Adverse Events of Special Interest

Other Aes of special interest included infections, malignancy, autoimmune disorders, and infusion

reactions.

Infections and Infestations: There was no increase in frequency for overall Aes of infections with abatacept use compared to placebo (69% vs 76.8%). Also, abatacept use was not associated with increased event intensity of infections compared to placebo, and no patient died due to infections. However, in the placebo group, 5 subjects died due to infections, including 4 events of sepsis. The most frequently ($\geq 10\%$) 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%).

In the 8/8 MUD cohort, 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. 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. Source (AdaM dataset): Table S.6.2.1.1.S (ADAE [ANL03FL]), Table S.6.2.2.1.S (ADAE [ANL03FL]), and Table S.6.2.1.2.S (ADAE [ANL03FL]) in the IM101311 Primary CSR.

Malignancy: All of Aes of malignancies reported in abatacept-treated subjects were recurrence of underlying hematological malignancies. There was no increase in the AE frequency of the malignancies with abatacept use compared to placebo. Source (AdaM dataset): Table S.6.7.1.1.S (ADAE [SMQ01CD]) and Table S.6.7.1.2.S (ADAE [SMQ01CD]) in the IM101311 Primary CSR.

Autoimmune Disorders:

The identification and analysis of potential autoimmune disorder-related Aes in study IM101311 was based on a prospectively defined set of preferred terms included in a custom Standard MedDRA Query (cSMQ) developed throughout the Orencia clinical development program; this list of autoimmune event related cSMQs is maintained at and updated periodically by BMS, and is available upon request. TEAEs reported to the clinical database were selected based on the autoimmune event related cSMQ terms and tabulated.

- **In the 8 of 8 MMUD Cohort**, 2 placebo treated patients were reported to have experienced potential autoimmune-related Aes. The first, of Grade 3 intensity, was reported only as “autoimmune disorder” in a 40 year-old male and was assessed as possibly related to study drug; the other, of Grade 4 intensity, was reported as “idiopathic thrombocytopenic purpura” in a 48 year-old female, and was assessed as unlikely to be related to study drug. These events occurred on study Days 146 and 220, respectively.
 - No potential autoimmune disorder related Aes were reported in any abatacept treated patient in the 8 of 8 MMUD Cohort.
 - **In the 7 of 8 MMUD Cohort**, 2 abatacept treated patients were reported to have experienced Aes potentially related to autoimmune disorders; both were reported as “autoimmune hemolytic anemia”: One event, of moderate (Grade 2) intensity, occurred in a 76 year-old male patient and was assessed as unlikely to be related to study drug; the other, of Grade 4 intensity, was reported in a 12 year-old male and was assessed as possibly related to study drug. These events occurred on study Days 306 and 189, respectively.

Based on the above noted review of the safety data, there was no evidence suggesting that abatacept use was associated with an increased risk of autoimmune disorders.

Source (AdaM dataset): Table S.6.14.1.1.S (ADDAE [CQ01CD]) and Table S.6.14.1.2.S (ADDAE [CQ01CD]) in the IM101311 Primary CSR.

Infusion Reactions: Peri-infusional AEs were reported in 9 (12.3%) of subjects treated with abatacept, which was similar to that observed with the placebo treatment (11 subjects ([15.9%]). Among the abatacept treated subjects, nausea was the most frequently reported peri-infusional AE (7 [9.6%]), vomiting and hypotension (1 [1.4%] each), and 1 (1.4%) infusion related reaction. In the placebo group, peri-infusional AEs reported were nausea (5 [7.2%]), infusion related reaction (3 [4.3%]), hypotension (2 [2.9%]), vomiting, and dyspnoea (1 [1.4%], each).

Source (AdAM dataset): Table S.6.8.1.1.S (ADAE [CQ02NAM, CQ02CD]) and Table S.6.8.1.2.S (ADAE [CQ02NAM, CQ02CD]) in the IM101311 Primary CSR.

FDA Assessment:

FDA agrees with the Applicant's assessment of significant adverse events. We note that primary engraftment was achieved for all patients in both the abatacept and the placebo treated groups. Additionally, we concur that the median time until platelet and neutrophil recovery was comparable for abatacept versus placebo treated patients, (day 21 vs 22) and (day 18 vs 18), respectively. Viral reactivation by surveillance testing, which is a known risk/consequence of allogeneic transplant, was slightly higher with abatacept treatment. CMV viremia was noted in 47.4% of abatacept-treated patients versus 43.5% of placebo. However, the incidence of CMV invasive disease was noticeably higher in the pooled abatacept treated patients (9% vs 3%) versus placebo by day 365.

EBV viremia was noted in 39.7% of abatacept-treated patients versus 30.4% of placebo. Furthermore, the rate of PTLD, a potential sequelae of EBV reactivation, was noticeably higher in the pooled abatacept treated patients versus placebo (3% vs 0%), respectively. It was notable that 3 of 4 PTLD cases occurred at a single pediatric transplant center that discontinued prophylaxis at day 30 post-transplant. After this was noted, a protocol amendment was made to standardize post-transplant EBV prophylaxis.

Given the increased incidence of CMV invasive disease and PTLD that was noted on trial, the USPI has been updated to include viral reactivation of CMV and EBV in section 5.7 of warnings and precautions. This section instructs clinicians to monitor for viral reactivation and to provide EBV prophylaxis for 6 months post-transplant and to consider CMV prophylaxis based on risk of infection/reactivation.

FDA agrees that overall infections and infestations are not increased with abatacept use. While viral reactivation was higher with abatacept use, as noted above, bacteremia was seen at a higher rate in the placebo group (15% vs 25%, all abatacept vs placebo). It is unclear why the abatacept group would have a lower rate of bacteremia, but this effect balanced with the higher rate of viral reactivation to make overall infections similar between treatments.

The only malignancies reported were for relapse of primary disease. No second malignancies were observed in this trial.

Infusion reactions, defined as any AE occurring within 24 hours of an infusion, were balanced between treatments with no clear signal for abatacept-related infusion reactions.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 54: Intensity of Adverse Events Reported in ≥ 2% of Subjects During the Treatment Period: 8/8 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	5 (6.8)	67 (91.8)	1 (1.4)	0	73 (100.0)
Investigations	0	0	1 (1.4)	67 (91.8)	0	0	68 (93.2)
Neutrophil count decreased	0	0	7 (9.6)	52 (71.2)	0	0	59 (80.8)
White blood cell count decreased	0	0	5 (6.8)	45 (61.6)	0	0	50 (68.5)
Platelet count decreased	0	0	3 (4.1)	39 (53.4)	0	0	42 (57.5)
Lymphocyte count decreased	0	0	3 (4.1)	36 (49.3)	0	0	39 (53.4)
CD4 lymphocytes decreased	0	0	7 (9.6)	3 (4.1)	0	0	10 (13.7)
Alanine aminotransferase increased	0	0	6 (8.2)	2 (2.7)	0	0	8 (11.0)
Blood bilirubin increased	0	0	8 (11.0)	0	0	0	8 (11.0)
Aspartate aminotransferase increased	0	0	4 (5.5)	0	0	0	4 (5.5)
Urine output decreased	0	0	2 (2.7)	2 (2.7)	0	0	4 (5.5)
Activated partial thromboplastin time prolonged	0	0	3 (4.1)	0	0	0	3 (4.1)
Forced expiratory volume decreased	0	0	2 (2.7)	1 (1.4)	0	0	3 (4.1)
Blood creatinine increased	0	0	1 (1.4)	1 (1.4)	0	0	2 (2.7)
Electrocardiogram QT prolonged	0	0	2 (2.7)	0	0	0	2 (2.7)
Metabolism and nutrition disorders	0	0	55 (75.3)	9 (12.3)	0	0	64 (87.7)
Dehydration	0	0	28 (38.4)	0	0	0	28 (38.4)
Decreased appetite	0	0	21 (28.8)	0	0	0	21 (28.8)
Obesity	0	0	14 (19.2)	3 (4.1)	0	0	17 (23.3)
Hypokalaemia	0	0	12 (16.4)	4 (5.5)	0	0	16 (21.9)
Hyperglycaemia	0	0	12 (16.4)	2 (2.7)	0	0	14 (19.2)
Hypophosphataemia	0	0	13 (17.8)	1 (1.4)	0	0	14 (19.2)
Hypermagnesaemia	0	0	10 (13.7)	0	0	0	10 (13.7)
Hyponatraemia	0	0	8 (11.0)	0	0	0	8 (11.0)
Acidosis	0	0	3 (4.1)	0	0	0	3 (4.1)
Hypertriglyceridaemia	0	0	3 (4.1)	0	0	0	3 (4.1)
Hypocalcaemia	0	0	3 (4.1)	0	0	0	3 (4.1)
Hyperkalaemia	0	0	1 (1.4)	1 (1.4)	0	0	2 (2.7)
Hypernatraemia	0	0	2 (2.7)	0	0	0	2 (2.7)
Gastrointestinal disorders	0	0	57 (78.1)	4 (5.5)	0	0	61 (83.6)
Stomatitis	0	0	49 (67.1)	3 (4.1)	0	0	52 (71.2)

Table 54: Intensity of Adverse Events Reported in ≥ 2% of Subjects During the Treatment Period: 8/8 Cohort As Treated Analysis Population

SYSTEM ORGAN CLASS (SOC) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
PREFERRED TERM (PT) (%)							
Gastrointestinal disorder	0	0	9 (12.3)	1 (1.4)	0	0	10 (13.7)
Nausea	0	0	10 (13.7)	0	0	0	10 (13.7)
Diarrhoea	0	1 (1.4)	7 (9.6)	0	0	0	8 (11.0)
Abdominal pain	0	0	6 (8.2)	0	0	0	6 (8.2)
Colitis	0	0	2 (2.7)	0	0	0	2 (2.7)
Mouth haemorrhage	0	0	2 (2.7)	0	0	0	2 (2.7)
Oral pain	0	0	2 (2.7)	0	0	0	2 (2.7)
Blood and lymphatic system disorders	0	0	56 (76.7)	2 (2.7)	0	0	58 (79.5)
Anaemia	0	0	48 (65.8)	0	0	0	48 (65.8)
Febrile neutropenia	0	0	35 (47.9)	0	0	0	35 (47.9)
Infections and infestations	0	0	42 (57.5)	3 (4.1)	0	0	45 (61.6)
Infection	0	0	32 (43.8)	1 (1.4)	0	0	33 (45.2)
Device related infection	0	0	10 (13.7)	0	0	0	10 (13.7)
Enterocolitis infectious	0	0	4 (5.5)	0	0	0	4 (5.5)
Urinary tract infection	0	0	3 (4.1)	0	0	1 (1.4)	4 (5.5)
Pneumonia	0	0	2 (2.7)	1 (1.4)	0	0	3 (4.1)
Upper respiratory tract infection	0	0	3 (4.1)	0	0	0	3 (4.1)
Skin infection	0	0	2 (2.7)	0	0	0	2 (2.7)
Vascular disorders	0	0	29 (39.7)	3 (4.1)	0	0	32 (43.8)
Hypertension	0	0	26 (35.6)	2 (2.7)	0	0	28 (38.4)
Hypotension	0	0	6 (8.2)	1 (1.4)	0	0	7 (9.6)
Respiratory, thoracic and mediastinal disorders	0	0	15 (20.5)	4 (5.5)	1 (1.4)	0	20 (27.4)
Epistaxis	0	0	12 (16.4)	0	0	0	12 (16.4)
Hyposmia	0	0	3 (4.1)	1 (1.4)	0	0	4 (5.5)
Dyspnoea	0	0	1 (1.4)	2 (2.7)	0	0	3 (4.1)
Respiratory failure	0	0	0	3 (4.1)	0	0	3 (4.1)
Pulmonary oedema	0	0	2 (2.7)	0	0	0	2 (2.7)
General disorders and administration site conditions	3 (4.1)	1 (1.4)	9 (12.3)	2 (2.7)	0	0	15 (20.5)
Pyrexia	3 (4.1)	0	3 (4.1)	0	0	0	6 (8.2)
Pain	0	0	4 (5.5)	0	0	0	4 (5.5)
Adverse event	0	0	0	2 (2.7)	0	0	2 (2.7)
Fatigue	0	0	2 (2.7)	0	0	0	2 (2.7)
Musculoskeletal and connective tissue disorders	0	0	14 (19.2)	0	0	0	14 (19.2)
Back pain	0	0	6 (8.2)	0	0	0	6 (8.2)
Muscular weakness	0	0	4 (5.5)	0	0	0	4 (5.5)

Table 54: Intensity of Adverse Events Reported in ≥ 2% of Subjects During the Treatment Period: 8/8 Cohort As Treated Analysis Population

SYSTEM ORGAN CLASS (SOC) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
PREFERRED TERM (PT) (%)	0	0	3 (4.1)	0	0	0	3 (4.1)
Pain in extremity	0	0	3 (4.1)	0	0	0	3 (4.1)
Nervous system disorders	1 (1.4)	0	13 (17.8)	0	0	0	14 (19.2)
Peripheral sensory neuropathy	0	0	6 (8.2)	0	0	0	6 (8.2)
Headache	0	0	4 (5.5)	0	0	0	4 (5.5)
Posterior reversible encephalopathy syndrome	0	0	2 (2.7)	0	0	0	2 (2.7)
Renal and urinary disorders	0	0	12 (16.4)	2 (2.7)	0	0	14 (19.2)
Acute kidney injury	0	0	7 (9.6)	1 (1.4)	0	0	8 (11.0)
Chronic kidney disease	0	0	4 (5.5)	2 (2.7)	0	0	6 (8.2)
Haematuria	0	0	2 (2.7)	0	0	0	2 (2.7)
Psychiatric disorders	0	0	9 (12.3)	0	0	0	9 (12.3)
Anxiety	0	0	4 (5.5)	0	0	0	4 (5.5)
Delirium	0	0	4 (5.5)	0	0	0	4 (5.5)
Mental status changes	0	1 (1.4)	2 (2.7)	0	0	0	3 (4.1)
Immune system disorders	0	0	4 (5.5)	1 (1.4)	0	0	5 (6.8)
Graft versus host disease in gastrointestinal tract	0	0	1 (1.4)	1 (1.4)	0	0	2 (2.7)
Graft versus host disease in skin	0	0	2 (2.7)	0	0	0	2 (2.7)
Skin and subcutaneous tissue disorders	0	0	5 (6.8)	0	0	0	5 (6.8)
Rash maculo-papular	0	0	3 (4.1)	0	0	0	3 (4.1)
Injury, poisoning and procedural complications	0	1 (1.4)	3 (4.1)	0	0	0	4 (5.5)
Infusion related reaction	0	1 (1.4)	1 (1.4)	0	0	0	2 (2.7)
Treatment Group: Placebo N = 69							
TOTAL SUBJECTS WITH AE	0	0	2 (2.9)	62 (89.9)	5 (7.2)	0	69 (100.0)
Investigations	0	0	2 (2.9)	67 (97.1)	0	0	69 (100.0)
Neutrophil count decreased	0	0	2 (2.9)	58 (84.1)	0	0	60 (87.0)
Platelet count decreased	0	0	2 (2.9)	53 (76.8)	0	0	55 (79.7)
White blood cell count decreased	0	0	5 (7.2)	46 (66.7)	0	0	51 (73.9)
Lymphocyte count decreased	0	0	6 (8.7)	40 (58.0)	0	0	46 (66.7)
Alanine aminotransferase increased	0	0	17 (24.6)	3 (4.3)	0	0	20 (29.0)
Aspartate aminotransferase increased	0	0	9 (13.0)	0	0	0	9 (13.0)
Blood bilirubin increased	0	0	6 (8.7)	1 (1.4)	0	0	7 (10.1)
CD4 lymphocytes decreased	0	0	5 (7.2)	1 (1.4)	0	0	6 (8.7)
Weight decreased	0	0	6 (8.7)	0	0	0	6 (8.7)

Table 54: Intensity of Adverse Events Reported in ≥ 2% of Subjects During the Treatment Period: 8/8 Cohort As Treated Analysis Population

SYSTEM ORGAN CLASS (SOC) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
PREFERRED TERM (PT) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
Blood alkaline phosphatase increased	0	0	3 (4.3)	0	0	0	3 (4.3)
Blood creatinine increased	0	0	2 (2.9)	0	0	0	2 (2.9)
Gamma-glutamyltransferase increased	0	0	1 (1.4)	1 (1.4)	0	0	2 (2.9)
Metabolism and nutrition disorders	0	0	54 (78.3)	11 (15.9)	0	0	65 (94.2)
Dehydration	0	0	29 (42.0)	0	0	0	29 (42.0)
Decreased appetite	0	0	25 (36.2)	0	0	0	25 (36.2)
Hypokalaemia	0	0	16 (23.2)	2 (2.9)	0	0	18 (26.1)
Obesity	0	0	11 (15.9)	7 (10.1)	0	0	18 (26.1)
Hyperglycaemia	0	0	16 (23.2)	0	0	0	16 (23.2)
Hypophosphataemia	0	0	13 (18.8)	0	0	0	13 (18.8)
Hyperkalaemia	0	0	9 (13.0)	2 (2.9)	0	0	11 (15.9)
Hyponatraemia	0	0	7 (10.1)	1 (1.4)	0	0	8 (11.6)
Hypermagnesaemia	0	0	7 (10.1)	0	0	0	7 (10.1)
Glucose tolerance impaired	0	0	4 (5.8)	0	0	0	4 (5.8)
Hypoalbuminaemia	0	0	3 (4.3)	1 (1.4)	0	0	4 (5.8)
Hypertriglyceridaemia	0	0	3 (4.3)	0	0	0	3 (4.3)
Hypocalcaemia	0	0	3 (4.3)	0	0	0	3 (4.3)
Hypernatraemia	0	0	2 (2.9)	0	0	0	2 (2.9)
Hyperuricaemia	0	0	2 (2.9)	0	0	0	2 (2.9)
Blood and lymphatic system disorders	0	0	58 (84.1)	3 (4.3)	0	0	61 (88.4)
Febrile neutropenia	0	0	46 (66.7)	1 (1.4)	0	0	47 (68.1)
Anaemia	0	0	37 (53.6)	1 (1.4)	0	0	38 (55.1)
Gastrointestinal disorders	0	0	56 (81.2)	3 (4.3)	1 (1.4)	0	60 (87.0)
Stomatitis	0	0	47 (68.1)	1 (1.4)	0	0	48 (69.6)
Diarrhoea	0	0	13 (18.8)	0	0	0	13 (18.8)
Gastrointestinal disorder	0	0	12 (17.4)	0	0	0	12 (17.4)
Nausea	0	0	10 (14.5)	1 (1.4)	0	0	11 (15.9)
Abdominal pain	0	0	10 (14.5)	0	0	0	10 (14.5)
Malabsorption	0	0	3 (4.3)	0	0	0	3 (4.3)
Mouth haemorrhage	0	0	3 (4.3)	0	0	0	3 (4.3)
Vomiting	0	0	2 (2.9)	0	0	0	2 (2.9)
Colitis	0	0	2 (2.9)	0	0	0	2 (2.9)
Gastroesophageal reflux disease	0	0	2 (2.9)	0	0	0	2 (2.9)
Lower gastrointestinal haemorrhage	0	0	1 (1.4)	0	1 (1.4)	0	2 (2.9)
Proctalagia	0	0	2 (2.9)	0	0	0	2 (2.9)
Infections and infestations	0	0	42 (60.9)	3 (4.3)	1 (1.4)	0	46 (66.7)
Infection	0	0	30 (43.5)	1 (1.4)	0	0	31 (44.9)
Device related infection	0	0	9 (13.0)	0	0	0	9 (13.0)
Enterocolitis infectious	0	0	9 (13.0)	0	0	0	9 (13.0)
Urinary tract infection	0	0	6 (8.7)	0	0	0	6 (8.7)

Table 54: Intensity of Adverse Events Reported in ≥ 2% of Subjects During the Treatment Period: 8/8 Cohort As Treated Analysis Population

SYSTEM ORGAN CLASS (SOC) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
PREFERRED TERM (PT) (%)							
Pneumonia	0	0	4 (5.8)	0	1 (1.4)	0	5 (7.2)
Sepsis	0	0	0	3 (4.3)	1 (1.4)	0	4 (5.8)
Bacteraemia	0	0	2 (2.9)	0	0	0	2 (2.9)
Skin infection	0	0	2 (2.9)	0	0	0	2 (2.9)
Upper respiratory tract infection	0	0	2 (2.9)	0	0	0	2 (2.9)
Vascular disorders	0	0	32 (46.4)	1 (1.4)	0	0	33 (47.8)
Hypertension	0	0	24 (34.8)	0	0	0	24 (34.8)
Hypotension	0	0	13 (18.8)	1 (1.4)	0	0	14 (20.3)
Capillary leak syndrome	0	0	3 (4.3)	0	0	0	3 (4.3)
Respiratory, thoracic and mediastinal disorders	0	0	20 (29.0)	3 (4.3)	0	0	23 (33.3)
Epistaxis	0	0	6 (8.7)	0	0	0	6 (8.7)
Hypoxia	0	0	6 (8.7)	0	0	0	6 (8.7)
Dyspnoea	0	0	3 (4.3)	0	0	0	3 (4.3)
Aspiration	0	0	2 (2.9)	0	0	0	2 (2.9)
Pharyngeal inflammation	0	0	2 (2.9)	0	0	0	2 (2.9)
Respiratory failure	0	0	0	2 (2.9)	0	0	2 (2.9)
General disorders and administration site conditions	4 (5.8)	2 (2.9)	8 (11.6)	2 (2.9)	1 (1.4)	0	17 (24.6)
Pyrexia	4 (5.8)	2 (2.9)	1 (1.4)	0	0	0	7 (10.1)
Fatigue	0	0	5 (7.2)	0	0	0	5 (7.2)
Pain	0	0	3 (4.3)	0	0	0	3 (4.3)
Oedema peripheral	0	1 (1.4)	1 (1.4)	0	0	0	2 (2.9)
Immune system disorders	1 (1.4)	0	13 (18.8)	1 (1.4)	0	0	15 (21.7)
Graft versus host disease in skin	0	0	8 (11.6)	0	0	0	8 (11.6)
Graft versus host disease	1 (1.4)	0	2 (2.9)	0	0	0	3 (4.3)
Acute graft versus host disease in skin	0	0	2 (2.9)	0	0	0	2 (2.9)
Graft versus host disease in gastrointestinal tract	0	0	1 (1.4)	1 (1.4)	0	0	2 (2.9)
Nervous system disorders	1 (1.4)	0	10 (14.5)	1 (1.4)	1 (1.4)	0	13 (18.8)
Headache	0	1 (1.4)	6 (8.7)	0	0	0	7 (10.1)
Encephalopathy	0	0	1 (1.4)	0	1 (1.4)	0	2 (2.9)
Nervous system disorder	0	0	2 (2.9)	0	0	0	2 (2.9)
Seizure	0	1 (1.4)	1 (1.4)	0	0	0	2 (2.9)
Renal and urinary disorders	0	0	12 (17.4)	1 (1.4)	0	0	13 (18.8)
Acute kidney injury	0	0	5 (7.2)	0	0	0	5 (7.2)
Chronic kidney disease	0	0	4 (5.8)	0	0	0	4 (5.8)

Table 54: Intensity of Adverse Events Reported in ≥ 2% of Subjects During the Treatment Period: 8/8 Cohort As Treated Analysis Population

SYSTEM ORGAN CLASS (SOC) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
PREFERRED TERM (PT) (%)							
Cystitis noninfective	0	0	2 (2.9)	0	0	0	2 (2.9)
Haematuria	0	0	1 (1.4)	1 (1.4)	0	0	2 (2.9)
Renal disorder	0	0	2 (2.9)	0	0	0	2 (2.9)
Urinary incontinence	0	0	2 (2.9)	0	0	0	2 (2.9)
Musculoskeletal and connective tissue disorders	0	0	9 (13.0)	0	0	0	9 (13.0)
Arthralgia	0	0	3 (4.3)	0	0	0	3 (4.3)
Back pain	0	0	2 (2.9)	0	0	0	2 (2.9)
Pain in extremity	0	0	2 (2.9)	0	0	0	2 (2.9)
Skin and subcutaneous tissue disorders	0	0	8 (11.6)	1 (1.4)	0	0	9 (13.0)
Rash maculo-papular	0	0	5 (7.2)	0	0	0	5 (7.2)
Pruritus	0	0	2 (2.9)	0	0	0	2 (2.9)
Hepatobiliary disorders	0	0	5 (7.2)	1 (1.4)	0	0	6 (8.7)
Hepatobiliary disease	0	0	4 (5.8)	1 (1.4)	0	0	5 (7.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	2 (2.9)	2 (2.9)	0	4 (5.8)
Acute lymphocytic leukaemia recurrent	0	0	1 (1.4)	0	0	0	1 (1.4)
Psychiatric disorders	0	0	3 (4.3)	1 (1.4)	0	0	4 (5.8)
Anxiety	0	0	2 (2.9)	0	0	0	2 (2.9)
Insomnia	0	0	2 (2.9)	0	0	0	2 (2.9)
Injury, poisoning and procedural complications	0	2 (2.9)	1 (1.4)	0	0	0	3 (4.3)
Infusion related reaction	0	2 (2.9)	1 (1.4)	0	0	0	3 (4.3)
Reproductive system and breast disorders	0	0	3 (4.3)	0	0	0	3 (4.3)
Menorrhagia	0	0	3 (4.3)	0	0	0	3 (4.3)

Includes data from the first dose date of study medication up to 56 days after the last dose date of study medication.

Source (AdAM dataset): Table S.6.12.1.1.5 (ADAE) in the IM101311 Primary CSR

Table 55: Intensity of Adverse Events Reported during the Treatment Period: 7/8 Cohort Treated Analysis Population

SYSTEM ORGAN CLASS (SOC) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
PREFERRED TERM (PT) (%)							
Hypoaalbuminaemia	0	0	1 (2.3)	0	0	0	1 (2.3)
Hypocalcaemia	0	0	1 (2.3)	0	0	0	1 (2.3)

Treatment Group: Abatacept N = 43

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table 55: Intensity of Adverse Events Reported during the Treatment Period: 7/8 Cohort Treated Analysis Population

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
Vascular disorders	0	0	22 (51.2)	0	0	0	22 (51.2)
Hypertension	0	0	19 (44.2)	0	0	0	19 (44.2)
Hypotension	0	0	6 (14.0)	0	0	0	6 (14.0)
General disorders and administration site conditions	5 (11.6)	0	5 (11.6)	0	0	0	10 (23.3)
Pyrexia	5 (11.6)	0	3 (7.0)	0	0	0	8 (18.6)
Fatigue	0	0	2 (4.7)	0	0	0	2 (4.7)
Respiratory, thoracic and mediastinal disorders	0	0	10 (23.3)	0	0	0	10 (23.3)
Epistaxis	0	0	4 (9.3)	0	0	0	4 (9.3)
Hypoxia	0	0	3 (7.0)	0	0	0	3 (7.0)
Pleural effusion	0	0	2 (4.7)	0	0	0	2 (4.7)
Atelectasis	0	0	1 (2.3)	0	0	0	1 (2.3)
Laryngeal inflammation	0	0	1 (2.3)	0	0	0	1 (2.3)
Pulmonary oedema	0	0	1 (2.3)	0	0	0	1 (2.3)
Respiratory disorder	0	0	1 (2.3)	0	0	0	1 (2.3)
Sleep apnoea syndrome	0	0	1 (2.3)	0	0	0	1 (2.3)
Immune system disorders	0	0	8 (18.6)	1 (2.3)	0	0	9 (20.9)
Graft versus host disease in skin	0	0	6 (14.0)	1 (2.3)	0	0	7 (16.3)
Acute graft versus host disease in skin	0	0	3 (7.0)	0	0	0	3 (7.0)
Hypersensitivity	0	1 (2.3)	0	0	0	0	1 (2.3)
Nervous system disorders	0	0	7 (16.3)	1 (2.3)	0	0	8 (18.6)
Headache	0	0	4 (9.3)	0	0	0	4 (9.3)
Nervous system disorder	0	0	1 (2.3)	0	0	0	1 (2.3)
Peripheral motor neuropathy	0	0	1 (2.3)	0	0	0	1 (2.3)
Peripheral sensory neuropathy	0	0	1 (2.3)	0	0	0	1 (2.3)
Posterior reversible encephalopathy syndrome	0	0	0	1 (2.3)	0	0	1 (2.3)
Syncope	0	0	1 (2.3)	0	0	0	1 (2.3)
Renal and urinary disorders	0	0	7 (16.3)	0	0	0	7 (16.3)
Acute kidney injury	0	1 (2.3)	1 (2.3)	0	0	0	2 (4.7)
Chronic kidney disease	0	0	2 (4.7)	0	0	0	2 (4.7)
Haematuria	0	0	2 (4.7)	0	0	0	2 (4.7)
Urinary tract pain	0	0	2 (4.7)	0	0	0	2 (4.7)
Cystitis haemorrhagic	0	0	1 (2.3)	0	0	0	1 (2.3)
Cystitis noninfective	0	0	1 (2.3)	0	0	0	1 (2.3)
Nephrolithiasis	0	0	1 (2.3)	0	0	0	1 (2.3)

Table 55: Intensity of Adverse Events Reported during the Treatment Period: 7/8 Cohort Treated Analysis Population

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	TOTAL
Renal disorder	0	0	1 (2.3)	0	0	0	1 (2.3)
Musculoskeletal and connective tissue disorders	0	0	4 (9.3)	0	0	0	4 (9.3)
Back pain	0	0	2 (4.7)	0	0	0	2 (4.7)
Arthralgia	0	0	1 (2.3)	0	0	0	1 (2.3)
Osteonecrosis	0	0	1 (2.3)	0	0	0	1 (2.3)
Psychiatric disorders	0	0	3 (7.0)	0	0	0	3 (7.0)
Delirium	0	0	2 (4.7)	0	0	0	2 (4.7)
Anxiety	0	0	1 (2.3)	0	0	0	1 (2.3)
Confusional state	0	0	1 (2.3)	0	0	0	1 (2.3)
Mental status changes	0	1 (2.3)	0	0	0	0	1 (2.3)
Injury, poisoning and procedural complications	0	0	2 (4.7)	0	0	0	2 (4.7)
Infusion related reaction	0	0	1 (2.3)	0	0	0	1 (2.3)
Vascular access complication	0	0	1 (2.3)	0	0	0	1 (2.3)
Skin and subcutaneous tissue disorders	0	0	2 (4.7)	0	0	0	2 (4.7)
Rash maculo-papular	0	0	2 (4.7)	0	0	0	2 (4.7)
Cardiac disorders	0	0	1 (2.3)	0	0	0	1 (2.3)
Angina pectoris	0	0	1 (2.3)	0	0	0	1 (2.3)
Supraventricular tachycardia	0	0	1 (2.3)	0	0	0	1 (2.3)
Ear and labyrinth disorders	0	0	1 (2.3)	0	0	0	1 (2.3)
Middle ear inflammation	0	0	1 (2.3)	0	0	0	1 (2.3)
Hepatobiliary disorders	0	0	1 (2.3)	0	0	0	1 (2.3)
Cholecystitis	0	0	1 (2.3)	0	0	0	1 (2.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (2.3)	0	0	0	1 (2.3)
Post-transplant lymphoproliferative disorder	0	0	1 (2.3)	0	0	0	1 (2.3)
Reproductive system and breast disorders	0	0	1 (2.3)	0	0	0	1 (2.3)
Menorrhagia	0	0	1 (2.3)	0	0	0	1 (2.3)

Includes data from the first dose date of study medication up to 56 days after the last dose date of study medication.

Source (AdAM dataset): Table S.6.12.1.2.5 (ADAE)

Table 56: Frequently Reported Adverse Events (in at Least 10 Percent of Subjects in Any Treatment Group) During the Day 180 Analysis Period

PREFERRED TERM (PT) (%)	Abatacept 8/8 Cohort (N=73)	Abatacept 7/8 Cohort (N=43)	Abatacept Combined (N=116)	Placebo 8/8 Cohort (N=69)
Total Subjects With	73 (100.0)	43 (100.0)	116 (100.0)	69 (100.0)
Neutrophil count decrease	60 (82.2)	33 (76.7)	93 (80.2)	60 (87.0)
Stomatitis	53 (72.6)	28 (65.1)	81 (69.8)	49 (71.0)
White blood cell count decreased	50 (68.5)	28 (65.1)	78 (67.2)	51 (73.9)
Platelet count decreased	45 (61.6)	26 (60.5)	71 (61.2)	55 (79.7)
Febrile neutropenia	38 (52.1)	27 (62.8)	65 (56.0)	49 (71.0)
Anaemia	50 (68.5)	24 (55.8)	74 (63.8)	39 (56.5)
Lymphocyte count decreased	41 (56.2)	22 (51.2)	63 (54.3)	47 (68.1)
Infection	35 (47.9)	21 (48.8)	56 (48.3)	36 (52.2)
Hypertension	31 (42.5)	21 (48.8)	52 (44.8)	26 (37.7)
Dehydration	36 (49.3)	9 (20.9)	45 (38.8)	30 (43.5)
Decreased appetite	21 (28.8)	17 (39.5)	38 (32.8)	25 (36.2)
Hypokalaemia	20 (27.4)	8 (18.6)	28 (24.1)	22 (31.9)
Alanine aminotransferase increased	11 (15.1)	12 (27.9)	23 (19.8)	24 (34.8)
Obesity	17 (23.3)	9 (20.9)	26 (22.4)	18 (26.1)
Gastrointestinal disorder	19 (26.0)	9 (20.9)	28 (24.1)	14 (20.3)
Hyperglycaemia	15 (20.5)	11 (25.6)	26 (22.4)	16 (23.2)
Hypotension	13 (17.8)	9 (20.9)	22 (19.0)	16 (23.2)
Hypophosphataemia	16 (21.9)	5 (11.6)	21 (18.1)	16 (23.2)
Pyrexia	11 (15.1)	12 (27.9)	23 (19.8)	13 (18.8)
Diarrhoea	16 (21.9)	4 (9.3)	20 (17.2)	15 (21.7)
Device related infection	14 (19.2)	4 (9.3)	18 (15.5)	13 (18.8)
Abdominal pain	8 (11.0)	7 (16.3)	15 (12.9)	13 (18.8)
Nausea	12 (16.4)	3 (7.0)	15 (12.9)	12 (17.4)
Aspartate aminotransferase increased	7 (9.6)	8 (18.6)	15 (12.9)	11 (15.9)
Hyponatraemia	11 (15.1)	6 (14.0)	17 (14.7)	9 (13.0)
Blood bilirubin increased	10 (13.7)	4 (9.3)	14 (12.1)	11 (15.9)
Epistaxis	12 (16.4)	5 (11.6)	17 (14.7)	7 (10.1)
Hypoxia	7 (9.6)	8 (18.6)	15 (12.9)	9 (13.0)
Pneumonia	9 (12.3)	8 (18.6)	17 (14.7)	7 (10.1)
Acute kidney injury	11 (15.1)	4 (9.3)	15 (12.9)	7 (10.1)
CD4 lymphocytes decreased	10 (13.7)	6 (14.0)	16 (13.8)	6 (8.7)
Hypermagnesaemia	13 (17.8)	2 (4.7)	15 (12.9)	7 (10.1)
Graft versus host disease in skin	5 (6.8)	8 (18.6)	13 (11.2)	8 (11.6)
Enterocolitis infectious	6 (8.2)	3 (7.0)	9 (7.8)	11 (15.9)
Headache	5 (6.8)	4 (9.3)	9 (7.8)	8 (11.6)

Table 56: Frequently Reported Adverse Events (in at Least 10 Percent of Subjects in Any Treatment Group) During the Day 180 Analysis Period

PREFERRED TERM (PT) (%)	Abatacept 8/8 Cohort (N=73)	Abatacept 7/8 Cohort (N=43)	Abatacept Combined (N=116)	Placebo 8/8 Cohort (N=69)
Hyperkalaemia	3 (4.1)	1 (2.3)	4 (3.4)	13 (18.8)
Hepatobiliary disease	6 (8.2)	3 (7.0)	9 (7.8)	7 (10.1)
Respiratory failure	5 (6.8)	3 (7.0)	8 (6.9)	8 (11.6)
Urinary tract infection	5 (6.8)	5 (11.6)	10 (8.6)	6 (8.7)
Chronic kidney disease	8 (11.0)	3 (7.0)	11 (9.5)	4 (5.8)
Upper respiratory tract infection	8 (11.0)	1 (2.3)	9 (7.8)	4 (5.8)
Weight decreased	1 (1.4)	4 (9.3)	5 (4.3)	7 (10.1)
Sepsis	0	4 (9.3)	4 (3.4)	7 (10.1)

Includes data from the first dose date up to Day 180 visit post-transplantation.

MedDRA version: 23.1

Source: Table 3 in the CO (module 2.5), (AdaM dataset: ADAE)

Table 57: Proposed Adverse Drug Reaction Table for US Prescribing Information

(b) (4)

The Applicant's Position:

In both the 8/8 MUD cohort and the 7/8 MMUD cohort, treatment emergent Aes occurred in all (100%) subjects (Table 43 and Table 44).

Adverse drug reactions (ADRs) were selected based on a threshold incidence of Aes ($\geq 10\%$ in abatacept-treated subjects and $\geq 2\%$ than placebo) and clinical assessment by the BMS medical reviewer. The Aes occurring in 10% or more of subjects and at least 2% more frequently in abatacept-treated compared to placebo-treated subjects were anemia (63.8% vs 56.5%), hypertension (44.8% vs 37.7%), gastrointestinal disorder (24.1% vs 20.3%), epistaxis (14.7% vs 10.1%), pneumonia (14.7% vs 10.1%), CD4 lymphocytes decreased (13.8% vs 8.7%), acute kidney injury (12.9% vs 10.1%), and hypermagnesaemia (12.9% vs 10.1%) (Table 45).

Six of the 8 Aes (anemia, gastrointestinal disorder, epistaxis, CD4 lymphocytes decreased, acute kidney injury, hypermagnesaemia) were rejected as ADRs on the basis of the lack of a known, biologically plausible underlying mechanism and because medical assessment did not support a causal relationship to abatacept. These Aes are common events among patients with HM undergoing HSCT. Most occurred shortly after completion of pre-transplant conditioning therapy, which was the likely the cause of these events. For the remaining 2 Aes, hypertension and pneumonia, an association with abatacept is possible considering the known safety profile of abatacept in the setting of HSCT (Table 45).

The mechanism of action of abatacept does not involve depletion of CD4 cells (rather it involves blocking the CD28:CD80/86 interaction); therefore, there is a lack of known biologically plausible mechanism. Flow data support this. In the publication by Koura et al. (BBMT 2013)²⁸, which described the outcomes of the first 10 patients treated with abatacept on the ABA1 feasibility trial, it was noted reduced proliferation of CD4+ T cells at Days 21 and 28 compared to a separate cohort of patients receiving

CNI/MTX (but not enrolled on the ABA1 trial). However, the exposure to abatacept resulted in a decrease in CD4+ T cell counts compared to these controls only at one time-point after transplant (Day 28 and at all other timepoints including Day 100), there was no difference in the CD4+ T cell counts in abatacept treated patients and controls. Moreover, in the ABA2 Trial,⁶² flow cytometric analysis of total T cell-, total CD4+ and total CD8+ T cell- reconstitution also did not detect significant differences in the abatacept or placebo cohorts.

FDA Assessment:

FDA performed an independent analysis of adverse events and generated tabulations that agree with the Applicant's tabulations. It is notable that given the clinical context of stem cell transplant, 100% of patients treated with abatacept or placebo developed a grade 3 or higher adverse event, (i.e. the transplant itself generated a high background rate of adverse events). To focus only on AEs related to abatacept treatment, AEs that occurred in at least 10% of patients and in 2% more abatacept-treated patients than placebo were subsetted from the full AE data set. Also, GVHD was not tabulated as an AE since it was more carefully tracked as part of the primary efficacy analysis.

Table 58 shows the results of the FDA AE analysis. As noted, this tabulation only shows the AEs that worsened with abatacept treatment. It excluded many AEs that were better with abatacept treatment or that were equivocal (+/- 2%) to placebo rates. Additionally, FDA analysis of AEs differs from the Applicant's due to the recoding of gastrointestinal disorders to the more specific GI GVHD based on the reported verbatim terms and the exclusion of GVHD events from AE tabulation. This strategy for focusing on relevant AEs is the same that has been employed for other FDA labels where a study treatment is given in the context of intensive backbone therapy. Therefore, these AEs were included in the label revision for abatacept. Overall, the treatment was well tolerated with the major safety concern relating to viral reactivation as already discussed above.

Table 58 FDA tabulated common (≥10% with >2% difference compared to placebo) extended TEAEs through Day 225 on Study ABA2

	Abatacept 7/8 (n=43)		Abatacept 8/8 (n=73)		Placebo 8/8 (n=69)		All Abatacept (n=116)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Anaemia	24 (56%)	24 (56%)	50 (68%)	50 (68%)	39 (57%)	39 (57%)	74 (64%)	74 (64%)
Hypertension	21 (49%)	21 (49%)	31 (42%)	31 (42%)	26 (38%)	26 (38%)	52 (45%)	52 (45%)
Cytomegalovirus infection	11 (26%)	11 (26%)	23 (32%)	23 (32%)	15 (22%)	15 (22%)	34 (29%)	34 (29%)
Pyrexia	12 (28%)	4 (9%)	14 (19%)	7 (10%)	14 (20%)	3 (4%)	26 (22%)	11 (9%)
Epistaxis	5 (12%)	5 (12%)	12 (16%)	12 (16%)	7 (10%)	7 (10%)	17 (15%)	17 (15%)
Pneumonia	8 (19%)	8 (19%)	9 (12%)	9 (12%)	6 (9%)*	6 (9%)	17 (15%)	17 (15%)
CD4 lymphocytes decreased	6 (14%)	6 (14%)	10 (14%)	10 (14%)	6 (9%)	6 (9%)	16 (14%)	16 (14%)
Hypermagnesaemia	2 (5%)	2 (5%)	13 (18%)	13 (18%)	7 (10%)	7 (10%)	15 (13%)	15 (13%)

ORENCIA (abatacept)

Acute kidney injury	4 (9%)	3 (7%)	11 (15%)	11 (15%)	7 (10%)	7 (10%)	15 (13%)	14 (12%)

Source: FDA analysis using adae.xpt, adsl.xpt

*Note: The USPI presents all-grade and Grade 3-4 AEs. Given one death due to pneumonia on the placebo 8/8 arm, the USPI notes an all-grade incidence of pneumonia of 7 (10%) in this arm.

Laboratory Findings

Data:

Table 59: Mean Serum Electrolyte and CO₂ Concentrations by Treatment Group and Study Day – IM101311

Serum Analyte	Study Day 5		Study Day 100		Study Day 180		Study Day 365	
	Abatacept	Placebo	Abatacept	Placebo	Abatacept	Placebo	Abatacept	Placebo
8/8 MUD Cohort As Treated Analysis Population								
Sodium, mmol/L	140 (N = 49)	138 (N = 53)	138 (N = 44)	139 (N = 47)	139 (N = 47)	139 (N = 43)	139 (N = 38)	139 (N = 40)
Potassium, mmol/L	4.2 (N = 49)	4.2 (N = 52)	4.2 (N = 44)	4.2 (N = 46)	4.0 (N = 47)	4.1 (N = 43)	4.0 (N = 38)	4.0 (N = 39)
Chloride, mmol/L	105 (N = 49)	106 (N = 52)	104 (N = 44)	105 (N = 46)	105 (N = 47)	105 (N = 42)	104 (N = 38)	104 (N = 39)
CO ₂ , mEq/L	25 (N = 49)	24 (N = 52)	25 (N = 44)	25 (N = 46)	25 (N = 47)	26 (N = 41)	27 (N = 38)	26 (N = 39)
7/8 MMUD Cohort Treated Analysis Population								
Serum Analyte	Study Day 5 (N = 32)		Study Day 100 (N = 31)		Study Day 180 (N = 30)		Study Day 365 (N = 29)	
Sodium, mmol/L	139		139		138		138	
Potassium, mmol/L	NA		4.1		4.0		4.0	
Chloride, mmol/L	106		105		105		104	
CO ₂ , mEq/L	25		25		24		25	

Abbreviations: MMOL/L = millimoles per litre; MEQ/L = milliequivalents per litre NA = not applicable
 Source (AdaM dataset): Table S.7.5.1.S (ADLB) and Table S.7.5.2.S (ADLB)

The Applicant’s Position:

Instructions for reporting abnormal laboratory values as adverse events were included in the protocol. There were no separate summaries of laboratory abnormalities according to pre-specified criteria. As stated in the SAP, the underlying condition, the transplantation, and the background medication affect most of the laboratory parameters, which was the reason why clinically meaningful abnormality criteria were not pre-specified.

Frequently reported Aes of laboratory abnormalities during the Day 180 Analysis Period (those reported for least 10% of the subjects in any treatment group) are included in Table 45.

Mean changes from baseline concentrations of laboratory analytes were generally modest in size and within the expected physiologic range of variation between determinations at successive study visits. The few, larger changes from baseline that were observed occurred at isolated study visits and were not consistent with progressive abnormalities in hematologic, biochemical, hepatic functional, or metabolic status. Changes in mean whole blood or serum analyte concentrations over time are summarized individually below for the 180-day treatment period (Study Day 0 through Day 180) and Day 365 in Table 43.

FDA Assessment:

FDA performed an independent analysis of laboratory values. This analysis is somewhat limited since the trial was not initially designed to collect this information robustly. The results of new or worsening labs after transplant are tabulated below in Table 60. Again, as in the above AE analysis, the transplant procedure is responsible for a high expected background of laboratory abnormalities. Perhaps surprisingly, the rate of laboratory AEs was not significantly worsened with abatacept treatment despite a difference in labs reported as AEs. One caveat to the analysis was the high rate of missing baseline and reference range values for many patients.

Table 60 FDA Common (≥10%) Abnormal Laboratory Tabulation through Day 225 on Study ABA2

	7/8 ABATACEPT (n=43)*		8/8 ABATACEPT (n=73)*		8/8 PLACEBO (n=69)*	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
ALT elevation	62%	23%	78%	10%	89%	30%
AST elevation	54%	8%	66%	5%	80%	8%
T Bili elevation	27%	5%	36%	10%	43%	13%
Hypernatremia	14%	0%	12%	3%	13%	0%
Hyperkalemia	45%	5%	27%	0%	27%	7%
Hyperglycemia	55%	18%	71%	18%	73%	21%
Hypoalbuminemia	26%	0%	30%	0%	29%	0%
Anemia	42%	13%	65%	28%	55%	26%
Leukopenia	69%	66%	84%	84%	77%	77%
Thrombocytopenia	87%	77%	85%	83%	93%	91%
Hypokalemia	41%	14%	41%	15%	56%	7%
Hyponatremia	27%	14%	45%	15%	47%	9%
*Patients with available labs for analysis varied for the lab and the treatment group, ranging from (n=19-43) for 7/8 Abatacept patients, (n=30-65) for 8/8 Abatacept patients, and (n=35-65) for 8/8 Placebo patients. Source: FDA analysis using adlb.xpt, adsl.xpt						

Vital Signs

The Applicant’s Position:

Blood pressure:

- **Systolic blood pressure (SBP):** At baseline prior to HSCT, mean SBP was similar across treatment groups, at 119 mm Hg in each of the abatacept treatment groups and 117 mm Hg in the 8 of 8 MUD placebo group. Thereafter, between study Days 5 and 365, mean SBP ranged from 119-124 mm Hg in the abatacept 8 of 8 treatment group, from 117 to 122 mm Hg in the abatacept 7 of 8 MMUD group, and from 117-124 mm Hg in the 8 of 8 MUD placebo group. No progressive upward or downward trend in mean blood pressure was discernible in any of the 3 treatment groups over

time.

- **Diastolic blood pressure (DBP):** At baseline prior to HSCT, mean DBP was 71, 70, and 68 mm Hg in the abatacept 8 of 8 MUD, abatacept 7 of 8 MMUD, and placebo 8 of 8 MUD, respectively. On Day 5, mean DBP decreased to 62 mm Hg in the abatacept 8 of 8 MUD treatment group, and remained in the range of 71-78 mm Hg thereafter. Similar decreases in mean DBP were not observed in the remaining two groups at Day 5. Between Days 5 and 365, mean DBPs remained in the range of 69-76 mm Hg in the abatacept 7 of 8 MMUD treatment group and between 71 and 78 mm Hg in the placebo 8 of 8 MUD treatment group. Mean DBP fluctuated upward slightly with increasing time post-transplant, particularly in the abatacept and placebo treatment groups of the 8 of 8 Cohort, and were 77, 72, and 75 mm Hg, in the abatacept 8 of 8 MUD, abatacept 7 of 8 MMUD, and placebo 8 of 8 MUD groups, respectively at the Day 365 study visit.
- **Heart rate:** Between study Days –1 (pre-transplant) to 365, mean heart rate ranged from 86-91/min, 84-94/min, and 84-92 mm Hg in the abatacept 8 of 8 MUD, abatacept 7 of 8 MMUD, and placebo 8 of 8 MUD treatment groups, respectively. No progressive upward or downward trend in mean heart rate was noted in any of the 3 treatment groups over time.
- **Respiratory rate:** Between study Days –1 and 365, mean respiratory rate ranged from 17-18/min, 18-24/min, and 17-21/min in the abatacept 8 of 8 MUD, abatacept 7 of 8 MMUD, and placebo 8 of 8 MUD treatment groups, respectively. Overall, mean respiratory rates remained stable in all groups.
- **Body temperature:** Mean body temperatures remained stable at 36-38°C throughout the study across treatment groups. Across study visits, individual minimum and maximum temperature readings ranged between 34.8°C-38.6°C, 35.1°C-39.9°C, and 35.3°C-40.1°C in the abatacept 8 of 8 MUD, abatacept 7 of 8 MMUD, and placebo 8 of 8 MUD treatment groups, respectively.

Program Source: BMS_GBS Oencia\WYA33451\Biostatistics\Production\Tables\EBR310\rt-vs-sum-
ebr310.sas 29JUL2021:09:54 (AdaM dataset: not mapped – vital sign data in SDTM.VS)

FDA Assessment

FDA agrees with the Applicant's assessment.

Electrocardiograms (ECGs):

The Applicant's Position:

An ECG was obtained for each study participant at the pre-transplant study visit. No ECG recordings were obtained thereafter, except as clinically indicated for individual patients.

FDA Assessment

The FDA agrees with the Applicants' position. Electro cardiology adverse events were not a safety issue with study treatment and has not been noted to be an issue with chronic use for the approved rheumatology indications.

QT intervals:

Neither QT nor QTc interval duration was routinely monitored during this clinical trial, unless clinically indicated for individual patients.

The Applicant's Position:

Not applicable

FDA Assessment

FDA agrees with the Applicant's position.

Immunogenicity

The Applicant's Position:

See Section 6.3.1

FDA Assessment:

See section 6.3.1 for FDA discussion of immunogenicity.

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Risks to be Included in the Warning and Precaution Section

The Applicant's Position:

The Sponsor proposes to include viral reactivation and prevention measures specifically for the use of abatacept when added to a standard of care regimen for "prophylaxis of aGVHD after unrelated HSCT" in the Warning and Precaution section of the US Prescribing Information (USPI).

In Study IM101311, the incidence of PTLD was higher among abatacept treated subjects compared to placebo (3.4% vs 0) and all the events were associated with EBV infection. The risk could be mitigated by early detection of EBV infection/reactivation and with a more prolonged course of anti-viral prophylaxis (eg. 6 months post-transplant). The incidence of CMV invasive disease was also higher among abatacept treated subjects compared to placebo (6.9% vs 2.9%). All the patients who experienced CMV invasive disease were CMV serology positive at baseline. The risk could be mitigated by early detection of CMV infection/reactivation and with antiviral CMV prophylaxis. PTLD and CMV invasive disease are clinically significant events. Since the incidence of both events was higher with abatacept treatment compared to placebo and given the biological plausibility, the association between these events and abatacept use is possible.

FDA Assessment:

FDA agrees with the Applicant's proposal to include viral reaction in the warnings and precautions section of the USPI. This section will detail the risk of these observed events in the IM101311 trial, recommend post-transplant monitoring, and prophylaxis against viral reactivation.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable.

FDA Assessment:

FDA agrees with the Applicant's position, not applicable.

8.2.7 Safety Analyses by Demographic Subgroups

Table 61: Serious Adverse Events Reported during the Day 180 Analysis Period by Subgroups

Subgroup	Abatacept 8/8 Cohort	Abatacept 7/8 Cohort	Abatacept Combined	Placebo 8/8 Cohort
Age				

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]

ORENCIA (abatacept)

≤ 21 Years	16/18 (88.9%)	17/18 (94.4%)	33/36 (91.7%)	13/17 (76.5%)
> 21 Years	36/55 (65.5%)	12/25 (48.0%)	48/80 (60.0%)	32/52 (61.5%)
< 18 Years	12/14 (85.7%)	16/16 (100%)	28/30 (93.3%)	10/13 (76.9%)
≥ 18 Years	40/59 (67.8%)	13/27 (48.1%)	53/86 (61.6%)	35/56 (62.5%)
< 65 Years	46/66 (69.7%)	26/38 (68.4%)	72/104 (69.2%)	38/57 (66.7%)
≥ 65 Years	6/7 (85.7%)	3/5 (60.0%)	9/12 (75.0%)	7/12 (58.3%)
Gender				
Female	20/32 (62.5%)	12/16 (75.0%)	32/48 (66.7%)	21/32 (65.6%)
Male	32/41 (78.0%)	17/27 (63.0%)	49/68 (72.1%)	24/37 (64.9%)
Race				
White	44/63 (69.8%)	19/31 (61.3%)	63/94 (67.0%)	39/61 (63.9%)
Black or African American	2/3 (66.7%)	6/7 (85.7%)	8/10 (80%)	2/2 (100%)
American Indian or Alaskan Native	1/1 (100%)	1/1 (100%)	2/2 (100%)	0/0
Asian	3/4 (75.0%)	1/2 (50.0%)	4/6 (66.7%)	1/2 (50.0%)
Other	1/1 (100%)	0/0	1/1 (100%)	1/2 (50.0%)
Unknown	1/1 (100%)	2/2 (100%)	3/3 (100%)	2/2 (100%)
Geographic Region				
North America	52/73 (71.2%)	29/43 (67.4%)	81/116 (69.8%)	45/69 (65.2%)
Type of Malignancy				
AML	18/30 (60.0%)	9/15 (60.0%)	27/45 (60%)	12/22 (54.5%)
MDS	9/15 (60.0%)	6/11 (54.5%)	15/26 (57.7%)	7/12 (58.3%)
ALL	18/20 (90.0%)	7/8 (87.5%)	25/28 (89.3%)	16/22 (72.7%)
CML	1/1 (100%)	4/4 (100%)	5/5 (100%)	4/5 (80.0%)

Source: AdaM Dataset: ADAE

The Applicant's Position:

The incident rates of SAEs were comparable between genders, and among different race groups. Subjects younger than 18 years had numerically more SAEs than those who were older than 18 years. Similarly, subjects younger than 21 years had numerically more SAEs than those who were older than 21. Subjects with ALL appeared to have more SAEs than those with AML and MDS.

FDA Assessment:

FDA agrees with the Applicant's analysis that there were more extended TESAEs in the younger abatacept treated patients. Analysis of the most common extended TESAEs in the less than 18 years abatacept-treated group is presented in the Table 51. The table has been formatted to focus only on extended TESAEs that occurred in >5% of abatacept treated patients <18 years of age and does not include TESAEs that occurred more commonly in the other demographic categories. As can be seen in Table 51, pyrexia is the TESAE that occurred much more frequently in this group compared to the others. It is likely that this difference alone is responsible for much of the numerical increase that was seen above. To investigate the occurrence of pyrexia in these patients, FDA further analyzed pyrexia as an extended TESAE by age across cohorts of ABA2. As can be seen in Table 52, the signal for pyrexia TESAE is driven exclusively by the high occurrence rate in the patients <18 years from the abatacept 7/8 cohort. The balanced occurrence of this TESAE between the 8/8 abatacept and 8/8 placebo patients would argue against an abatacept specific effect in pediatric patients. It is unclear what might have led to the high TESAE rate of pyrexia in the <18 years 7/8 abatacept-treated patients. However, it is important to consider that this cohort was open-label. The increased of TESAEs with ALL is likely

due to the higher pediatric representation in this disease group (49% of ALL patients were less than 21).

Table 62 Most Common Extended TESAEs through Day 225 in Patients <18 years (>5% incidence) on Study ABA2

PT	age ≥ 18		age < 18	
	Abatacept (n=86)	Placebo (n=56)	Abatacept (n=30)	Placebo (n=13)
Pyrexia	8 (9%)	8 (14%)	15 (50%)	3 (21%)
Diarrhoea	3 (3%)	2 (4%)	4 (13%)	0 (0%)
Sepsis	0 (0%)	6 (11%)	4 (13%)	1 (7%)
Pneumonia	6 (7%)	1 (2%)	3 (10%)	0 (0%)
Upper respiratory tract infection	1 (1%)	1 (2%)	3 (10%)	0 (0%)
Acute respiratory distress syndrome	3 (3%)	2 (4%)	2 (7%)	0 (0%)
Anaemia	2 (2%)	0 (0%)	2 (7%)	0 (0%)
Decreased appetite	1 (1%)	1 (2%)	2 (7%)	0 (0%)
Dehydration	2 (2%)	1 (2%)	2 (7%)	0 (0%)
Device related infection	2 (2%)	1 (2%)	2 (7%)	0 (0%)
Dyspnoea	2 (2%)	1 (2%)	2 (7%)	0 (0%)
Epstein-Barr virus infection reactivation	0 (0%)	1 (2%)	2 (7%)	0 (0%)
Hypotension	4 (5%)	3 (5%)	2 (7%)	1 (7%)
Myositis	0 (0%)	0 (0%)	2 (7%)	0 (0%)
Nausea	4 (5%)	2 (4%)	2 (7%)	0 (0%)
Post transplant lymphoproliferative disorder	0 (0%)	0 (0%)	2 (7%)	0 (0%)
Respiratory failure	5 (6%)	7 (13%)	2 (7%)	0 (0%)

Source: FDA analysis using adae.xpt

Table 63 Pyrexia Extended TESAЕ through Day 225 by age and treatment group on Study ABA2

PT= Pyrexia, Serious =Y	7/8 ABATACEPT (n=43)	8/8 ABATACEPT (n=69)	8/8 PLACEBO (n=73)
18 or older	2/27 (7%)	9/59 (15%)	8/56 (14%)
less than 18	12/16 (75%)	3/14 (21%)	3/13 (23%)

Source: FDA analysis using adae.xpt

8.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:

Approximately 108 publications containing clinical and nonclinical data that mentioned abatacept or CTLA4-Ig use in SCT were identified and reviewed. The publications retrieved include full-length

manuscripts, brief reports, and abstracts presented at scientific meetings. Of these publications, 9 presented safety data reported on abatacept use in prevention of GVHD following SCT, and all of them were from clinical studies; 3 were meeting abstracts,^{38,44,45} and the other 6 were full-length manuscripts.^{46,48,49,50,52,54} A summary of the publications is provided in Table 35.

Safety Assessment and Conclusions

In the 9 publications of abatacept use in prevention of GVHD following SCT (Table 35), a total of 147 patients received abatacept for GVHD prevention 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 and abatacept use in SCT was considered to be well-tolerated.

In 5 of the publications in which infusion-related events were mentioned, none of the abatacept recipients were reported to have experienced infusion-related events.^{44,45, 48, 52, 54}

Rates of infections, especially those attributed to CMV and EBV, were presented in these publications. The reported incidences for EBV viremia/infection and CMV reactivation were 0-50%^{44 46, 48, 49, 54} and 30-67%^{45,48,49}, respectively, which are within the range of previously published data for stem cell transplant populations (0.1-63% for EBV viremia⁶³ and 30-70% for CMV reactivation⁶⁴). Frequencies of clinically important, virus-related diseases were also reported in several of these publications, notably those for, EBV-PTLD (0-10%^{38,44, 48, 54}) and CMV disease (0-4.3%^{38,44, 48, 54}), both of which were also within the range of previously published data for stem cell transplantation (EBV-PTLD 0.5-17%,⁶⁵ CMV disease ~5%⁶⁶). In publications with study control arms, the incidences of EBV or CMV infections in the abatacept-treatment arms in most studies were comparable to or lower than those in the corresponding control arms,^{44,45, 49} except for one study, in which numerically higher frequencies of asymptomatic EBV viremia and CMV viremia were observed in the abatacept group compared with the control group (50% vs 37.5% and 62.5% vs 50%, respectively)⁵⁴. Additionally, no abatacept recipient died from an EBV or CMV infection. For infections other than EBV and CMV (eg, BK viremia, bacterial and fungal infections), the reporting rates were relatively low (up to 20%)^{46,48,49,50, 54} compared with that of EBV/CMV infections. These infections were well-managed, and only 1 fatal outcome was reported, an abatacept-treated patient, due to an invasive fungal infection that followed the onset of Grade 3 aGVHD.⁴⁹

Regarding donor cell engraftment in abatacept-treated recipients, 6 publications reported no engraftment failure.^{38, 45, 48,50, 52, 54} In 3 remaining publications, 3 engraftment failures were reported: one patient experienced secondary graft loss and recovered following re-transplantation⁴⁴ a second patient experienced secondary graft rejection concomitant with CMV-reactivation and recovered following re-transplantation;⁴⁶ a third patient did not achieve primary engraftment by Day 28 post-transplantation, but no information on the subsequent clinical course was provided.⁴⁹ In the case of the patient with secondary graft rejection concomitant with CMV infection reactivation, the CMV infection may have contributed to development of graft rejection; the risk factors in the other 2 cases of engraftment failure could not be assessed due to the limited information amount of information provided.

In the 9 publications referenced above, the diseases under study that required SCT were sickle cell disease (N = 3)^{38,44, 46}, severe aplastic anemia (N = 1)⁴⁹, hematologic malignancies (N = 4)^{45, 48, 50 52}, and beta thalassemia major (N = 1)⁵⁴. For the patient population with sickle cell disease, disease free survival in all 3 studies ranged from 92.9-100% after 2 to 5 years of follow-up. In the study of patients transplanted for severe aplastic anemia, overall survival was 89% at 1 year post-transplantation in the abatacept group compared with 50% in the control group. For the studies in patients with hematologic

malignancies, mortality rates varied from 20-30% with follow-up duration from 6-24 months; the reported causes of death were mainly disease relapse/progression. The non-relapse/progression free survival or overall survival rates in abatacept recipients were higher than those reported in the active control group⁴⁵ or similar patient populations that did not receive abatacept treatment, as described in the publications.^{50, 52} In the study of patients transplanted for beta thalassemia major, thalassemia-free survival was 100% after a median duration of follow-up of 853 days after HSCT in the abatacept group compared with 62.5% after a median duration of follow-up of 1931 days after HSCT in the control group.

Based on the review of the above publications, no major safety concern was identified in association with the use of abatacept for prophylaxis of GVHD in stem cell transplantation.

Safety Summary from Rheumatoid Arthritis Studies

The safety results presented in this section represent on-treatment AE data, from the first dose date up to Day 84, in adult RA subjects who were treated with IV abatacept or placebo and enrolled in the following double-blind placebo-controlled studies that are included in the abatacept-integrated safety database: IM101023,⁶⁷ IM101043,⁶⁸ IM101031,⁶⁹ IM101029,⁷⁰ IM101100,⁷¹ IM101101,⁷² and IM101102.⁷³

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.

FDA Assessment:

FDA agrees with the Applicant's assessment of the literature and of the established safety profile from rheumatoid arthritis studies. Additional FDA discussion of abatacept use from the literature review is detailed in section 8.2.1 above.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

There were no findings related to human carcinogenicity for abatacept in Study IM101311.

FDA Assessment:

FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

The Applicant's Position:

No pregnancies were reported in abatacept-treated subjects in Study IM101311. There is no new information to report for use of abatacept in pregnancy or lactation.

FDA Assessment:

FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

The Applicant's Position:

See section 10. There is no information on effects on growth.

FDA Assessment:

FDA agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

No SAEs of overdose were reported in abatacept-treated subjects in Study IM101311. Drug abuse potential and withdrawal or rebound was not studied for abatacept.

FDA Assessment:

The FDA agrees with the Applicant's position.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Based on the postmarketing experience with ORENCIA, the following adverse reactions were identified and are included in the current USPI: vasculitis (including cutaneous vasculitis and leukocytoclastic vasculitis), new or worsening psoriasis, non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma), and angioedema reactions. The USPI also states that during postmarketing experience with intravenous ORENCIA, systemic infusion reactions were similar to that seen in the clinical trial experience with intravenous ORENCIA with the exception of one case of fatal anaphylaxis, and postmarketing reports of systemic injection reactions (e.g., pruritus, throat tightness, dyspnea) have occurred following the use of subcutaneous ORENCIA. There are not any recent safety concerns from post-marketing experience that are not already reflected in the current USPI.

FDA Assessment:

FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

As the aGVHD prophylaxis indication is very different from the indications for which abatacept is currently approved, it is anticipated that the events reported in the postmarket setting will differ. The proposed USPI includes Adverse Reactions specific to patients undergoing unrelated-donor HSCT and a Warning & Precaution regarding CMV and EBV reactivation in aGVHD prophylaxis after HSCT. It is expected that increased cases of toxicities, such as CMV and PTLD, will be observed in the postmarket setting for the aGVHD prophylaxis indication relative to the currently approved indications. The Sponsor will perform signal detection activities by indication to identify any new safety concerns specific to the different indications.

FDA Assessment:

FDA agrees with the Applicants position.

8.2.11 Integrated Assessment of Safety

Data:

The following table includes a safety summary for the events occurring up to and including 56 days after the last dose. The 56 days represent approximately 4 times the half-life of abatacept in humans.

Table 64: Summary of Safety Results During the Treatment Period (Up to and including 56 days after the last dose of Abatacept/Placebo) - As Treated Population - IM101311

	8/8 MUD Cohort		7/8 MMUD Cohort
	Abatacept (N = 73)	Placebo (N = 69)	Abatacept (N = 43)
30-day mortality, n (%)	0	0	0
60-day mortality, n (%)	0	2 (2.9)	0
On-treatment deaths, n (%)	1 (1.4%)	2 (2.9%)	0 (0.0%)
AEs with death as outcome, n(%)	1 (1.4%)	2 (2.9%)	0 (0.0%)
AEs, n (%)	73 (100%)	69 (100%)	43 (100%)
Grade 3+ AEs, n (%)	73 (100%)	69 (100%)	43 (100%)

Table 64: Summary of Safety Results During the Treatment Period (Up to and including 56 days after the last dose of Abatacept/Placebo) - As Treated Population - IM101311

	8/8 MUD Cohort		7/8 MMUD Cohort
	Abatacept (N = 73)	Placebo (N = 69)	Abatacept (N = 43)
SAEs, n (%)	34 (46.6%)	35 (50.7%)	16 (37.2%)
AEs leading to discontinuation of treatment	2 (2.7%)	5 (7.2%)	1 (2.3%)
Treatment-related AEs, n (%)	62 (84.9%)	61 (88.4%)	37 (86.0%)
Treatment-related SAEs, n (%)	12 (16.4%)	15 (21.7%)	5 (11.5%)

Source: Appendix 5.3.1, 5.3.2.1.1, 6.8.1.S, 6.8.2.S; Supplemental tables: S.6.3.3.1.S, S.6.3.3.2.S, S.6.12.1.1.S, S.6.12.1.2.S, S.6.19.1.1.S, S.6.19.1.2.S (ADaM dataset: ADAE)

Source: Appendix 5.3.1, 5.3.2.1.1, 6.8.1.S, 6.8.2.S; Supplemental tables: S.6.3.3.1.S, S.6.3.3.2.S, S.6.12.1.1.S, S.6.12.1.2.S, S.19.1.1.S, S.19.1.2.S (ADaM dataset: ADAE); Program Source: BMS_GBS
 Orencia\WYA33451\Biostatistics\Production\Tables\EBR310\rt-dt-death-ebr310.sas 29JUL2021:08:29 [ADaM dataset: ADAE].

Table 65: Adverse Events Summary during the Post-transplantation Analysis Period -IM101311

	8/8 MUD Cohort		7/8 MMUD Cohort
	Abatacept (N = 73)	Placebo (N = 69)	Abatacept (N = 43)
Deaths, n (%)	14 (19.2)	17 (24.6)	8 (18.6)
SAEs, n (%)	54 (74.0)	49 (71.0)	33 (76.7)
Drug-related SAEs, n (%)	22 (30.1)	23 (33.3)	11 (25.6)
Discontinued due to SAEs, n (%)	0	1 (1.4)	0
AEs, n (%)	73 (100.0)	69 (100.0)	43 (100.0)
Drug-related AEs, n (%)	64 (87.7)	62 (89.9)	39 (90.7)
Discontinued due to AEs, n (%)	2 (2.7)	5 (7.2)	1 (2.3)

Source: Table S.6.1.2.1.S (ADaM dataset: ADAE, 8/8 cohort); Table S.6.1.2.2.S (ADaM dataset: ADAE, 7/8 cohort)

The Applicant's Position:

In IM101311, the safety events reported were consistent with those expected in a population of patients with hematologic malignancies undergoing stem cell transplantation; review of those events did not identify any unexpected safety concerns among abatacept-treated patients.

There was no death in the first 30 days of the study in any cohort. During the first 60 days of the study, there were 2 deaths in the placebo arm (2.9%) in the 8/8 cohort, but no death in the abatacept arm of the 8/8 cohort or the 7/8 cohort. During the Treatment Period (up to and including 56 days after the last dose of Abatacept/Placebo), there was no on-treatment death in the 7/8 cohort. One subject died in the on-treatment period in the abatacept group (1.4%) vs. 2 in the placebo group (2.9%) in the 8/8 cohort. Fatal treatment-emergent adverse events are the same as on-treatment deaths. All subjects had at least one treatment emergent AE which was grade 3 or above (100%). Treatment emergent SAEs occurred in 16 subjects (37.2%) in the 7/8 cohort, 34 subject in the abatacept arm (46.6%), and 35 subjects in the placebo arm (50.7%) of the 8/8 cohort. One subject discontinued due to treatment emergent adverse events in the 7/8 cohort (2.3%). Two subjects discontinued due to treatment emergent adverse events in the abatacept arm (2.7%) vs. 5 in the placebo arm (7.2%) in the 8/8 cohort.

During the 180-day treatment period post HSCT, all subjects in both treatment groups of the 8/8 MUD cohort, and all of the abatacept-treated subjects in the 7/8 MMUD cohort, experienced 1 or more AEs.

As expected in a study population undergoing HSCT, the most frequently reported AEs in both treatment groups were those related to myelosuppression (anemia, neutropenia, and thrombocytopenia) and side effects of the chemotherapeutic drugs used as part of the peri-HSCT conditioning regimens, notably secondary infection (69-76%), stomatitis (71-73%), dehydration (43-49%), and decreased appetite (29-36%). Although the frequency of SAEs was numerically higher among abatacept-treated versus placebo-treated subjects, the frequency of subjects with drug-related SAEs was similar between these treatment groups. Further, the incidence of engraftment-related events was similar between these treatment groups. These findings suggest that the well-established safety profile of abatacept, when used in the treatment of rheumatic disease, was overshadowed by the more frequent, more serious AEs known to be associated with the underlying hematologic malignancies in this population of HSCT recipients, and their clinical management. The safety profile of abatacept at Day 365 remained consistent with the findings up to Day 180, including the retrospectively collected data (AEs, SAEs, GVHD and Clinical Labs) requested by the FDA (Table 54 and Table 48).

The incidence rates of relapse were comparable between the abatacept and placebo groups in the 8/8 MUD cohort of the IM101311 study (10% vs. 13%); the relapse rates were the same in the CNI+MTX+abatacept group and the CNI+MTX group in the IM101841 study (9%). These results indicate that abatacept treatment did not negatively impact the graft versus tumor effect in HSCT.

The incidence of CMV viremia and CMV invasive disease were higher among abatacept treated subjects.

All evaluable cases of CMV disease were successfully treated to resolution with standard therapies.

The overall incidence of malignancy-related AEs was similar among abatacept- and placebo-treated subjects. Of note, the 4 cases of PTLD in the study were reported among those treated with abatacept; 2 in the 7/8 MMUD Cohort and 2 in the 8/8 MUD Cohort. All four events resolved with treatment. Further inquiry into these events led to a protocol amendment stipulating the administration of acyclovir prophylaxis through day 180 for all study participants. Following this change in supportive care, no additional cases of PTLD were reported in subjects enrolled in Study IM101311. Additionally, there were no cases of PTLD reported at Day 100 or at Day 180 in the primary objective cohort of Study IM101841.

In summary, with the above exceptions, the overall safety profile of abatacept-treated subjects in each of the study cohorts was similar to that of placebo treated 8/8 MUD subjects, and treatment with abatacept did not adversely affect rates of engraftment.

FDA Assessment:

FDA analysis of safety event rates differed with the Applicant's because of the use of an updated adae.xpt file after FDA identified incorrect verbatim to preferred term coding. FDA TEAE and TESAE rates derived from the updated adae.xpt file are presented in the sections above. FDA agreed with Applicant's attribution of cause of death as noted above. The overall safety profile for abatacept use in Study ABA2 (IM101311) is presented in Table 66 below.

Table 66 Safety summary of Study ABA2

	Abatacept 7/8	Abatacept 8/8	Placebo 8/8	All Abatacept
	N= 43	N= 73	N=69	N=116

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Total deaths	12 (28%)	24 (33%)	29 (42%)	36 (31%)
Death by day 100	0 (0%)	1 (1%)	5 (7%)	1 (1%)
Death by day 180	1 (2%)	2 (3%)	11 (16%)	3 (3%)
Death by day 225	2 (5%)	5 (7%)	13 (19%)	7 (6%)
Fatal AEs any time post-HSCT	8 (19%)	14 (19%)	20 (29%)	22 (19%)
Fatal AEs by day 225	5 (12%)	8 (11%)	17 (25%)	13 (11%)
Fatal TEAEs*	0 (0%)	1 (1%)	5 (7%)	6 (5%)
All grade TEAEs	43 (100%)	73 (100%)	69 (100%)	116 (100%)
Gr ≥ 3 TEAEs	43 (100%)	73 (100%)	69 (100%)	116 (100%)
SAEs any time post-HSCT	33 (77%)	54 (74%)	49 (71%)	87 (75%)
SAEs by day 225	29 (67%)	52 (71%)	45 (65%)	81 (70%)
TESAEs*	16 (37%)	34 (47%)	35 (51%)	50 (43%)
All-cause discontinuation	8 (19%)	14 (19%)	18 (26%)	22 (19%)
TEAE* with discontinuation	1 (2%)	2 (3%)	5 (7%)	3 (3%)
*AE within 30 days of abatacept treatment				
Source: FDA analysis using adae.xpt, adsl.xpt				

The safety profile from the Study IM101311 is line with expected adverse events from the patient population being studied (patients with high-risk heme malignancies undergoing allogeneic stem cell transplantation). Abatacept treatment did not induce any new safety events that would be unexpected in this population. Extended treatment-emergent adverse reactions increased with abatacept treatment included anemia, hypertension, CMV reactivation/CMV infection, pyrexia, pneumonia, epistaxis, CD4 lymphocytes decreased, hypermagnesemia, and acute kidney injury. Serious adverse reactions increased with abatacept treatment included pyrexia, pneumonia, acute kidney injury, diarrhea, hypoxia, and nausea.

As noted above by the Applicant and FDA, the rate of EBV and CMV viral reactivation were increased with abatacept use compared to the rate observed in the placebo-treated patients. Moreover, PTLD and invasive CMV disease, potential consequences of EBV and CMV reactivation, respectively, were increased with abatacept use. Therefore, FDA agrees with the Applicants' proposed inclusion of these risks in the warnings and precautions section of the USPI. It should be noted that despite this increased risk of viral reactivation, all cases were successfully treated.

Overall, abatacept treatment was well tolerated with most patients completing the 4 infusions peri-transplant. The addition of abatacept to the transplant regimen was well tolerated with very few treatment emergent adverse reactions (TEARs) increasing over the background rate and many actually decreasing with abatacept treatment. The identified risk of viral reactivation is already a risk post-transplant and standard monitoring, prophylaxis, and treatment strategies are already in place to deal with this transplant related adverse event. Given an increased risk with abatacept treatment, labeling will include risk mitigation strategies.

Overall, FDA agrees with the Applicant that based on the totality of efficacy and safety data, the benefit/risk profile of abatacept in addition to CNI and MTX for the prophylaxis of aGVHD for patients undergoing matched or 1 allele mismatched unrelated donor stem cell transplant is favorable and supports regular approval of abatacept for this indication.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

Please refer to the integrated assessment of effectiveness for Study IM101311 and Study IM101841 in section 8.1.7.

8.4. Conclusions and Recommendations

FDA Assessment:

The review team was able to verify or clarify the efficacy and safety endpoints as provided by the Applicant. The review team recommends regular approval of the sBLA.

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

X

X

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

Primary Clinical Reviewer

Clinical Team Leader

210

Version date: January 2020 (ALL NDA/BLA reviews)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

9 Advisory Committee Meeting and Other External Consultations

FDA Assessment:

This application was not presented to the Oncologic Drugs Advisory Committee or any other external consultants.

10 Pediatrics

The Applicant's Position:

In Study IM101311, there were 30 abatacept treated subjects in the 6-17 year age group when the 2 cohorts (8/8 MUD and 7/8 MMUD) are combined. Twenty-seven (19%) randomized subjects in the 8/8 MUD cohort were 6 to 17 years old; 14 were randomized to abatacept and 13 were randomized to placebo. In the single-arm 7/8 MMUD cohort, 16 (37%) randomized subjects were 6 to 17 years old.

Efficacy

Post-hoc analysis results from IM101311 study showed numerically higher severe GFS and OS rates in the abatacept treatment arm compared to placebo.

At 180 days post-transplant (abatacept vs. placebo), the severe GFS rates were 100% vs. 85% (Table 67).

In the single-arm 7/8 MMUD cohort, at 180 days post-transplant, the severe GFS rate was 94 (Table 67).

Table 67: Summary of Efficacy Results During the Day 180 Analysis Period in Pediatric Subgroup (< 18 Years)

	8/8 MUD Cohort		7/8 MMUD Cohort
	Abatacept (N= 14)	Placebo (N= 13)	Abatacept (N=16)
Grade III-IV aGVHD Free Survival			
GFS Events (n/N, %)	0/14	2/13 (15.4%)	1/16 (6.3%)
Survival Rate (95% CI)	1.00 (1.00, 1.00)	0.85 (0.51, 0.96)	0.94 (0.63, 0.99)
Hazard Ratio vs. Comparator Group (95% CI)	NA (NA, NA)		
P-Value (Log-Rank Test)	p = 0.1343		NA
Grade II-IV aGVHD Free Survival			
GFS Events (n/N, %)	6/14 (42.9%)	5/13 (38.5%)	8/16 (50.0%)
Survival Rate (95% CI)	0.57 (0.28, 0.78)	0.62 (0.31, 0.82)	0.50 (0.25, 0.71)
Hazard Ratio vs. Comparator Group (95% CI)	1.18 (0.36, 3.86)		
P-Value (Log-Rank Test)	0.7948		NA
Overall Survival up to Day 180			
OS Events (n/N, %)	0/14	1/13 (7.7%)	1/16 (6.3%)
Survival Rate (95% CI)	1.00 (1.00, 1.00)	0.92 (0.57, 0.99)	0.94 (0.63, 0.99)
Hazard Ratio vs. Comparator Group (95% CI)	NA (NA, NA)		
P-Value	p = 0.2994		NA

8/8 cohort (Tables in the CO [module 2.5]): (Table 9 [ADaM Dataset: ADTTE(G34FS180)]; (Table 11 [ADaM Dataset: ADTTE(OS180)], ADaM Dataset: ADTTE(G34FS%)); (Table 10 (ADaM Dataset: ADTTE(G34FS180)) (Table 12 [ADaM

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
ORENCIA (abatacept)

Dataset: ADTTE(OS180) 180, G24FS180, OS180). **7/8 cohort** (Tables in the CO [module 2.5]): (Table 10 (ADaM Dataset: ADTTE(G34FS180)); (Table 12 [ADaM Dataset: ADTTE(OS180)]) in the IM101311 primary CSR.

Safety:

The types of AEs reported in the 6-17 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.

Any-Grade, all causality AEs were reported in all (100%) abatacept treated subjects. Drug-related AEs were similar in subjects <18 years of age (n=30) and subjects ≥18 years of age (n=86).

- The most frequently reported AEs in subjects <18 years of age in the combined abatacept group (n=30) 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%); infection and decreased appetite 13 (43.3%) each
- 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% vs 61.6%. This was primarily attributable to the higher rate of pyrexia in the pediatric group.
 - SAEs reported in more than 2 subjects < 18 years of age were: pyrexia 15 (50.0%), diarrhea and sepsis in 4 (13.3%) each, and pneumonia, upper respiratory tract infection and GI disorder in 3 (10.0%) each.

Other Events of Interest: Pediatric versus Adult Subjects Treated with Abatacept

- All 4 PTLD events reported the study occurred in pediatric subjects (< 18 years). All of the PTLD events were associated with EBV infection and manifested as lymphadenopathy without extra-nodal organ involvement. All of the events resolved with treatment. 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 following implementation of this protocol amendment.

FDA Assessment:

The FDA agrees with the Applicant's assessment. The small numbers for patients and events for the efficacy analysis above prevents statistical conclusions from this subset of patients. However, the observed trends were consistent with the complete analysis discussed in section 8, with the exception that Grade II-IV GFS was lower on the abatacept arm. Grade III-IV GFS at day 180, however, was greater on the abatacept arm compared to the placebo arm.

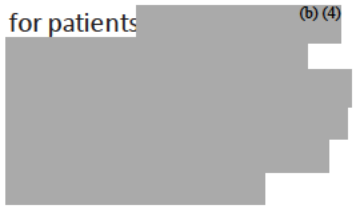
We agree with results of the pediatric safety analysis. The higher rates of SAE observed in the abatacept-treated pediatric population was completely driven by a high reported rate of pyrexia in the abatacept-treated 7/8 cohort of pediatric patients. This was discussed in detail in the safety section above. We also agree with the assessment of PTLD. The occurrence of a cluster of cases at one transplant center drove most of the PTLD signal. Interesting, comparison of standard practice likely suggested both the need and remedy for the PTLD signal. While that transplant center's standard of care to stop EBV prophylaxis at day 30 might have been sufficient for other aGVHD prophylaxis regimens, their cluster of PTLD suggested that the short of duration was insufficient when abatacept is given. The trial also suggests that the remedy for this is to continue EBV prophylaxis until day 180. After standardization of this recommendation across trial sites, no additional cases of PTLD were noted. Hence, this warning and

prevention strategy was incorporated into the updated label.

As noted in sections 6 and 8, extension of the pediatric indication to patients aged 2 to <6 was incorporated into this review. The basis for extrapolation of efficacy was on the inclusion of pediatric patients 6 and up in the Study IM101131 and the similar biology of transplant and aGVHD in patients 2 to <6 as those 6 and older. Safety of abatacept use in patients of this age was demonstrated as part of the abatacept approval for polyarticular juvenile idiopathic arthritis, albeit with a different dosing regimen and administration route.

11 Labeling Recommendations

Data: The table below summarizes changes to the proposed United States Prescribing Information (USPI). See the final approved USPI for ORENCIA (abatacept) accompanying the approval letter for more information.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
HIGHLIGHTS	Proposed updates to appropriate sections.	FDA generally agreed but provided some edits.
INDICATIONS AND USAGE (1.4)	Addition of indication for ORENCIA for patients  (b) (4)	FDA modified to describe the indication - for the prophylaxis of acute graft versus host disease, in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.
DOSAGE AND ADMINISTRATION (2.4)	Addition of recommended dosage information in prophylaxis for aGVHD is provided in the USPI.	FDA updated this section to include a dosage recommendation of 15 mg/kg on the day before transplantation, followed by a 12 mg/kg dose on Day 5, 14, and 28 after transplantation for pediatric patients 2 to less than 6 years old. In addition, FDA added recommendations for antiviral prophylaxis treatment for EBV reactivation and CMV infection/reactivation.
WARNINGS AND PRECAUTIONS FOR USE (5.7)	Addition of viral reactivation in aGVHD prophylaxis after HSCT.	FDA generally agreed and added cross-references to section 2.4 for prophylaxis for CMV and EBV.
ADVERSE REACTIONS (6.1)	Addition of safety data from the IM101311 study, including: a brief description of the study; reporting period; a brief summary of the most commonly reported adverse reactions; a table of the most common adverse reactions; a brief summary of infections and infusion reactions.	Formatting changed to remove separated numbered subsections for clinical trials information for separate indications; all clinical trials data included in 6.1 with separate headings for each patient population. The clinical trial data for the aGVHD patient population updated to align with OOD practices for presentation of adverse reaction

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
		data in section 6.1.
IMMUNOGENICITY (6.2)	Addition of immunogenicity information from the IM101311 study, including incidence rate of anti- abatacept antibodies and neutralizing antibodies against abatacept.	FDA added more detailed information concerning the impact of ADA on PK, safety, and efficacy of abatacept in patients with aGVHD.
PEDIATRIC USE (8.4)	Addition of safety and effectiveness of ORENCIA for prophylaxis of moderate to severe aGVHD in URD HSCT in patients 6 to 17 years of age from the IM101311 study.	FDA updated to include extrapolation information for pediatric patients aged 2 to less than 6 years of age based on pharmacokinetic modeling data demonstrating that abatacept exposure is expected to be similar between pediatric patients aged 2 to less than 6 years following 15 mg/kg on the day before transplantation, followed by a 12 mg/kg dose on Day 5, 14, and 28 after transplantation with that of older pediatric patients treated with the 10 mg/kg dose on the day before transplantation, followed by 10 mg/kg on Day 5, 14, and 28 after transplantation, and that the course of disease is sufficiently similar between younger and older pediatric patients to allow extrapolation of data from older to younger pediatric patients. FDA moved data concerning in utero Orencia exposure to a Clinical Considerations subheading within section 8.1.
PHARMACOKINETICS (12.3)	Addition of PK data from the IM101311 study.	FDA generally agreed but edited to add a PK parameters table including Cmax, Cmin, t1/2, Vd, CL comparing the 7/8 and 8/8 cohorts. FDA also added %CV for Cmin and %difference in clearance based on pop PK analysis.
CLINICAL STUDIES (b) (4)	Addition of efficacy information from the IM101311 study, including: a brief description of the study design and treatment groups; (b) (4)	FDA added a demographics table for each treatment group (7/8, 8/8 abatacept, and 8/8 placebo). FDA removed (b) (4)

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
	(b) (4)	(b) (4)

The Applicant's Position:

The current approved Orencia indications are for anti-rheumatic disease (RA, PsA and JIA) and the Sponsor intends that these patients will remain as the largest consumer of Orencia. When drafting the proposed labeling language, the Sponsor took care to include the most comprehensive data, including all pertinent efficacy and safety information to inform a highly skilled and knowledgeable prescriber of the information needed to effectively use the 4-dose regimen of abatacept to prevent aGVHD in the appropriate patient. Likewise, effort was made in crafting the language to differentiate the new data relating to aGVHD from that already approved in the Orencia label, as these patient populations and prescribers are vastly divergent. To that end, the new Warnings and Precautions section on CMV and EBV reactivation is intentionally called out for attention to the Hematologist/Transplant Physician as applicable to aGVHD prophylaxis after HSCT. (b) (4)

(b) (4)

FDA Assessment:

FDA modified the USPI as described in the table above. (b) (4)

(b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

FDA Assessment:

The risk of abatacept can be adequately managed in the post-market setting through product presentation and labeling. There are no additional risk management strategies required beyond the recommended packaging and labeling.

13 Postmarketing Requirements and Commitment

FDA Assessment:

A postmarketing requirement will be issued to ensure the safety of the proposed pediatric dose for patients aged 2 to <6 since the proposed regimen is based on population PK modeling and the safety of that dose has yet to be investigated. The Applicant has agreed to the following PMR.

- Conduct a clinical trial to further characterize the known serious risk of infections with abatacept in patients age 2 to less than 6 years and to characterize the pharmacokinetics (PK) of abatacept to verify the population PK predicted optimal dosing regimen of abatacept (15 mg/kg as a 60-minute intravenous infusion on Day -1, followed by 12 mg/kg on Days 5, 14, and 28 after transplantation) in pediatric patients age 2 to less than 6 years for the prophylaxis of acute graft versus host disease, in combination with a calcineurin inhibitor and methotrexate, undergoing hematopoietic stem cell transplantation from a matched or 1 allele-mismatched unrelated donor.

Final Protocol Submission:	06/2022
Trial Completion:	06/2026
Final Report Submission:	12/2026

Provide the datasets with the final report.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

X

19 Appendices

19.1. References

The Applicant's References: References are located at the end of this document in Section 19.6.

FDA Assessment:

FDA References:

Gastwirth J, Krieger A, Rosenbaum P. Dual, 1998, Simultaneous Sensitivity Analysis for Matched Pairs. *Biometrika*. 1998; 85:907–920.

Horowitz MM, Przepiorka D, Bartels P, Buell DN, Zhang MJ, Fitzsimmons WE, Erdman J, Huang C, Hodosh E, Maher R, Wingard JR. Tacrolimus vs. cyclosporine immunosuppression: results in advanced-stage disease compared with historic controls treated exclusively with cyclosporine. *Biol Blood Marrow Transplant*. 1999;5(3):180-6.

Koura D, Horan J, Langston A, Qayed M, Mehta A, Khoury H, Harvey R, Suessmuth Y, Couture C, Carr J, Crizzle A, Johnson H, Cheeseman J, Conger J, Robertson J, Stempora L, Johnson B, Garrett A, Kirk A, Larsen C, Waller E, Kean L, 2013, In Vivo T Cell Costimulation Blockade with Abatacept for Acute Graft-versus-Host Disease Prevention: A First-in-Disease Trial, *Biol Blood Marrow Transplant*, 19: 1638-1649.

Rosenbaum, Paul R, 2002, Sensitivity to hidden bias In *Observational studies*, pp. 105-170. Springer, New York, NY, 2002.

Sorrer ML, Maris M, Storb R, Baron F, Sandmaier B, Maloney D, Storer B, 2005, Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT, *Blood*, 106(8): 2912-2919.

VanderWeele, T. J., and P. Ding, 2017, Sensitivity analysis in observational research: Introducing the E-value, *Annals of Internal Medicine* 167: 268–274.

Weisdorf DJ, Hurd D, Carter S, Howe C, Jensen LA, Wagner J, Stablein D, Thompson J, Kernan NA, Prospective grading of graft-versus-host disease after unrelated donor marrow transplantation: a grading algorithm versus blinded expert panel review. *Biol Blood Marrow Transplant* 2003;9:512-8.

19.2. Financial Disclosure

The Applicant's Position:

Financial interests or arrangements with clinical investigators have been disclosed in the table below. Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the IM101311 clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators*.

FDA Assessment:

Covered Clinical Study (Name and/or Number):* IM101311

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>109</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

Not applicable

FDA Assessment:

FDA agrees.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The Applicant's Position:

Abatacept PK and Immunogenicity Methods

PK method:

A validated⁷⁴ sandwich ELISA method was used for the measurement of BMS-188667 concentrations in human serum at [REDACTED]^{(b) (4)}. The assay uses a monoclonal anti-CTLA4 antibody (7F8) as the capture reagent and a biotinylated monoclonal anti-CTLA4 antibody (11D4) as detection reagent, with streptavidin HRP as the secondary detector. A summary of the method validation parameters is provided in Table 68.

Table 68: Summary of Bioanalytical Method Validation for the Measurement of Serum Concentrations of BMS-188667

BMS DCN number/CRO Method Validation Number	Species/Matrix	LLOQ (ng/mL)	ULOQ (ng/mL)	QC	Precision (%) ^a	Accuracy (%) ^a
930051030/ (b) (4)	Human/ Serum	1.00 ng/mL	30.0 ng/mL	Intra-Assay	≤19.0	-15.7 to 2.0
				Inter-assay	≤8.6	-6.3 to -4.0

DCN = document control number; LLOQ= lower limit of quantification; QC = quality control sample; ULOQ= upper limit of quantification.

^a Precision and accuracy are for analytical QCs.

Immunogenicity method:

A bridging electro-chemiluminescence assay was used to assess the presence of anti-BMS-188667 (anti-abatacept) antibodies in human serum. The assay was fully validated (930040817)⁷⁵ at (b) (4). Biotin-labeled BMS-188667 and ruthenium (Sulfo-tag)-labeled BMS-188667 are used to form a complex with anti-abatacept antibodies and enable their capture and detection. Table 69 lists the sensitivity and drug tolerance of the method.

Table 69: Sensitivity and Drug Tolerance of Method (b) (4) for the detection of anti-abatacept antibodies

BMS DCN number/CRO Method Validation Number	Species/Matrix	Sensitivity	Drug Tolerance
930040817/ (b) (4)	Human/Serum	48.8 ng/mL ^a	250 ng/mL of anti-BMS-188667 antibody can be detected in the presence of at least 40 µg/mL of BMS-188667

CRO = contract research organization; DCN = document control number

^a in undiluted serum in the absence of free drug

Neutralizing antibody (NAb) method:

An in vitro cell based bioassay was used to assess the presence of neutralizing antibodies to abatacept in human serum. The method was validated (DCN 930103655)^{76,77,78} by (b) (4), Ltd. This assay uses two cell lines, Jurkat T-cells and Daudi B-cells. The Jurkat T-cells are transfected with a luciferase gene under the control of an IL-2 promoter. When the Jurkat T-cells are co-stimulated by Daudi B-cells in the presence of anti-CD3, this activates the IL-2 promoter which in turn produces luciferase protein. In the presence of BMS-188667 the interaction between Jurkat T-cells and Daudi B-cells is blocked and produces a dose-dependent decrease in luciferase expression. The presence of NABs restores the luciferase signal. Table 50 lists the summary of sensitivity and drug tolerance in this NAb method.

Table 70: Sensitivity and Drug Tolerance of Method (b) (4) for the Detection of neutralizing antibodies to BMS-188667

BMS DCN number/CRO Method Validation Number	Species/Matrix / Patient Population	Sensitivity with Positive Control ^a	Drug Tolerance
930103655/ (b) (4)	Human/Serum/ Normal	3.75 µg/mL ⁴	5 µg/mL of 11D4 with 0.25 µg/mL of abatacept ³ 20 µg/mL of 11D4 with 5 µg/mL of abatacept ³
930103655/ (b) (4)	Human/Serum/ Lupus	2.5 µg/mL ⁵	5 µg/mL of 11D4 with 0.25 µg/mL of abatacept ⁴ 20 µg/mL of 11D4 with 10 µg/mL of abatacept ⁴

CRO = contract research organization; DCN = document control number

^aAnti-human CTLA4 mouse monoclonal antibody, clone 11D4

Data:

Population Pharmacokinetic Analysis: The PPK analysis was conducted using data collected after intravenous (IV) administration of abatacept to 386 adult subjects with rheumatoid arthritis (RA) (Studies IM103002, IM10110, IM101101, IM101102, IM101029, and IM101031), 184 pediatric subjects with juvenile idiopathic arthritis (JIA) (Study IM101033), and 115 pediatric or adult subjects receiving URD HSCT due to HM (Study IM101311). Subjects in Study IM101311 were divided into 2 cohorts based on the number (7/8 or 8/8) of human leukocyte antigen matches recorded in the Center for International Blood & Marrow Transplant Research registry. After exclusion of 208 flagged samples and 144 observations below the lower limit of quantification, a total of 4,873 observations were used for analysis. A total of 19 subjects with JIA and 7 subjects receiving URD HSCT due to HM developed anti-drug antibodies (ADA).

Exposure-response Analysis: The ER analyses of efficacy endpoints, time to severe aGFS and time to OS up to Day 180 post-transplantation after initiation of treatment with abatacept (in subjects for whom abatacept exposure measures were available) or placebo was conducted with data from subjects (N = 185) aged 6 to 76 years with HM at risk for acute graft versus host disease (aGVHD; referred to as GVHD throughout) in Study IM101311.

The ER safety analyses of the time to first infection, regardless of seriousness, up to Day 180 post-transplantation, time to first invasive CMV, and time to first CMV viremia were conducted with data from subjects (N = 185) aged 6 to 76 years with HM at risk for GVHD in Study IM101311 administered abatacept (for whom abatacept exposure measures were available) or placebo.

METHODS:

Population Pharmacokinetic Analysis: A 2-compartment, zero-order IV infusion, and first-order elimination model previously developed using data collected in subjects with RA and subjects with JIA served as the basis for this analysis. The model describing abatacept PK in the pooled dataset was developed in 5 steps. First, the previously established base PPK model was re-estimated using the pooled set of GVHD, JIA, and RA data. Second, the effect of subject disease and other selected covariates on abatacept elimination clearance (CL) and volume of the central compartment (VC) were independently assessed prior to inclusion in a full multivariable model. Given the large number of covariates evaluated as predictors of PK variability, a single round of forward selection was used to select the statistically significant covariates using an alpha level of 0.01 for inclusion in the full model. The covariates that were statistically evaluated were age, gender, race, baseline body weight (BWT), baseline calculated glomerular filtration rate (CGFR), baseline aspartate transferase (AST), baseline

alanine, baseline total bilirubin, baseline concomitant methotrexate use, and disease status (GVHD, JIA, and RA; referred to as “disease” throughout). Additional covariates with more than 10% of missing values (baseline albumin, baseline concomitant corticosteroid use, baseline nonsteroidal anti-inflammatory drugs, baseline GVHD prophylaxis, conditioning regimen, and ADA status) were only graphically evaluated. Third, a reduced model was determined by performing backward elimination on covariates added to the model during the first round of forward selection. Fourth, a sensitivity analysis was performed to assess the effect of Study IM101311 cohort on abatacept CL and VC using a second round of forward selection. Finally, the final PPK model was identified after backward elimination on covariates added to the model during the second round of forward selection.

Model evaluation was conducted using prediction-corrected visual predictive check (VPC) methods. The final PPK model and Bayesian estimates of PK parameters were used to simulate the following abatacept exposures after a hypothetical single 1-hour infusion of 10 mg/kg (capped at a maximum of 1,000 mg): peak serum concentration following the first dose (C_{max1}), minimum concentration following the first dose (C_{min1}) and time-averaged serum concentration following the first dose (C_{av1}). Exposures were compared across disease sub-populations, Study IM101311 cohorts, and ADA status in various subsets of the analysis populations.

Exposure-response Efficacy Analysis: Time to Severe aGFS up to Day 180 Post-Transplantation and Overall Survival: The E-R relationships between abatacept exposure and the time to first severe aGFS up to Day 180 post-transplantation and OS were described by separate semi-parametric Cox proportional hazards (CPH) models and included assessments of the effect of covariates on the E-R relationships. Abatacept exposure measures following the first and last dose (area under the concentration-time curve [AUC_t], minimum concentration [C_{min}], peak serum concentration [C_{max}], and time-averaged serum concentration [C_{av}]) were tested to identify the best summary measure of exposure for prediction of clinical outcomes. Model development was conducted in 3 stages. First, the relationship between abatacept exposure and time-to-event (severe aGFS up to Day 180 post-transplantation and OS) with appropriate functional forms was characterized by base CPH models. Given the large number of covariates evaluated as predictors of efficacy, 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. Second, full covariate models were developed by incorporating all the covariate predictor variables into the base CPH models. Last, the final models were obtained by backward elimination, retaining the statistically significant covariates that were significant at a 0.1% level, with appropriate functional forms of the covariate relationships with severe aGFS up to Day 180 post-transplantation and OS.

Covariate-parameter relationships were examined for the following covariates: age, BWT, sex, race, serum immunoglobulin G (IgG), GVHD prophylaxis, conditioning regimen, pre-transplant CMV subject/donor serostatus, pre-transplant EBV subject/donor serostatus, baseline performance status, type of graft received, cohort, and relapse of underlying malignancy to Day 180.

Model evaluation was conducted using VPC methods.

Exposure-response Safety Analyses: Exploratory graphical analysis of the relationship between the following safety endpoints and abatacept exposure measures was performed: time to first infection regardless of seriousness (the most common expected adverse event), time to first invasive CMV infection, and time to first CMV viremia. No formal E-R modeling was planned since, in previous analyses of time to first infection in subjects with JIA, no E-R was found. A Kaplan-Meier plot was created by

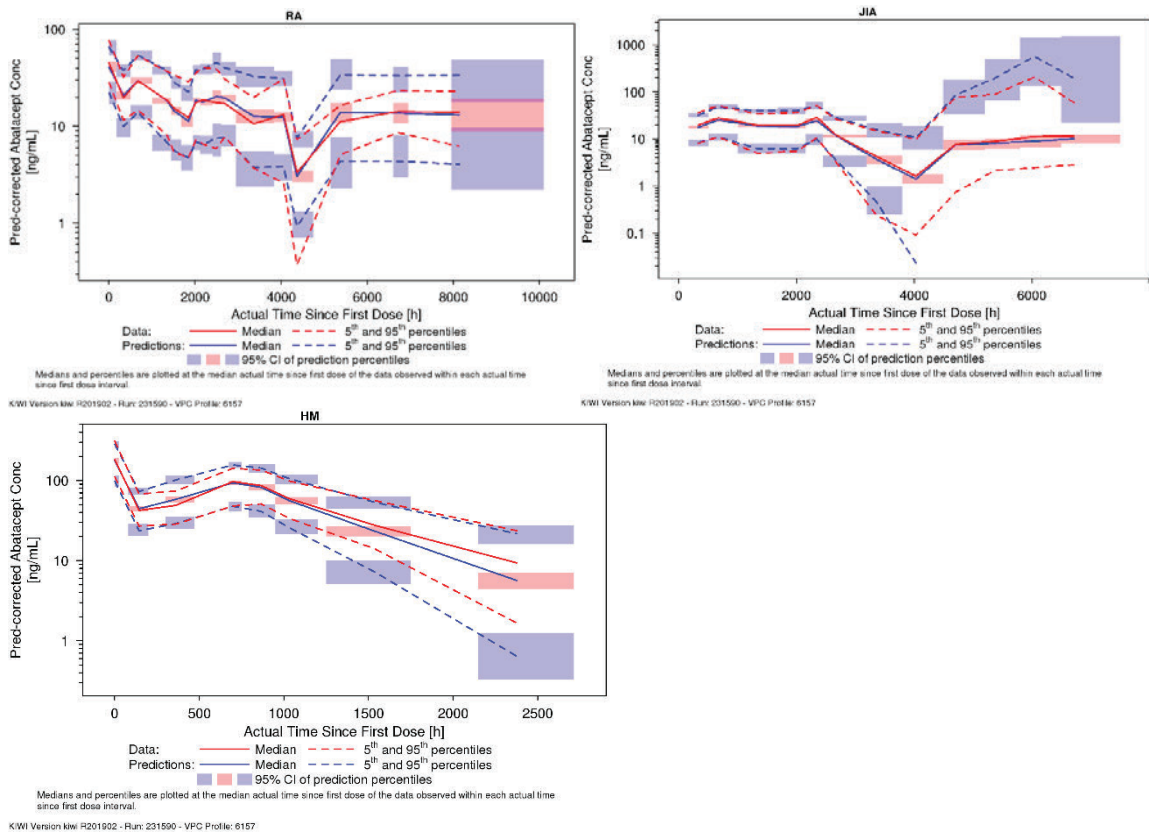
quartiles of abatacept exposure measures for the time to first safety endpoints. Boxplots of abatacept exposure measures, stratified by the occurrence of infection adverse events, were also created.

RESULTS:

Population Pharmacokinetic Analysis: The final model was a 2-compartment model with zero-order IV infusion, linear distribution and elimination parameterized in terms of CL, VC, distribution clearance, and volume of the peripheral compartment (VP). The data supported the estimation of interindividual variability on CL, VC, and VP. Residual variability was described using a combined additive and constant coefficient of variation model.

The final PPK model included effects of BWT, CGFR, AST, sex, and Study IM101311 cohorts on CL; baseline BWT and Study IM101311 Cohort 8/8 on VC; and baseline BWT on VP (Figure 1). The VPC plots show that the abatacept concentrations predicted by the final PPK model track the central tendency and variability in the observed data reasonably well. However, the abatacept concentrations collected late after the previous dose in Study IM101311 tended to be slightly underpredicted, especially after more than 1,000 hours after the previous dose.

Figure 20: Model Evaluation of Final PPK Model, by Disease Status



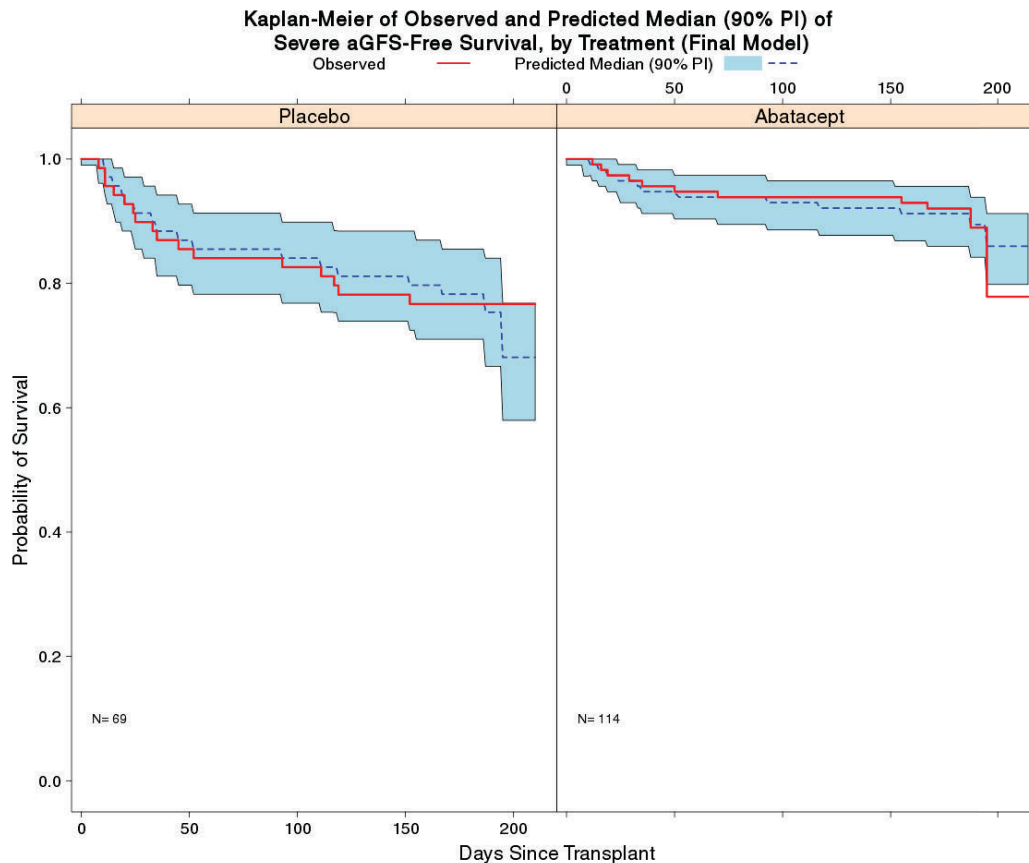
Conc: concentration; Pred: prediction

Baseline BWT and the Study IM101311 cohorts are the only variables identified as having both a statistically significant and clinically relevant influence on abatacept PK parameters and exposures. While the influence of BWT on abatacept PK was found in previous analyses and is consistent with general allometric theory, at this time it is unclear which underlying factor explains this influence on

abatacept PK. Application of the final PPK model and Bayesian estimates assuming a single 1-hour infusion of 10 mg/kg (with a cap of 1,000 mg) showed that average predicted exposures were approximately 20% lower in subjects with JIA compared to subjects with RA, from 5% to 17% higher in subjects with HM in Cohort 7/8 (except for C_{max1} which was 5% lower), and between 4% and 26% lower in subjects with HM in Cohort 8/8. On average, all exposures in subjects in Cohort 8/8 were approximately 20% lower than in subjects with HM in Cohort 7/8. Additionally, positive ADA status had no influence on C_{max1}, while decreasing the average C_{min1}, AUC_{t1}, and C_{av1} values by approximately 15% compared to exposures predicted in subjects with negative ADA status.

Exposure-response Efficacy Analysis: Time to Severe aGFS up to Day 180 Post-Transplantation: There was a significant relationship between abatacept exposure and the efficacy endpoint of time to severe aGFS up to Day 180 post-transplantation. In the CPH model, abatacept C_{min} after the last dose was the most significant predictor of the probability of time to severe aGFS up to Day 180, whereby increasing exposure (higher C_{min}) is associated with lower risk (hazard) of severe aGVHD (event). The E-R relationship for time to severe aGFS was described better by a linear function of C_{min} than a log linear function. The pre-specified covariates were estimated in the full model. 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 the full model. The covariates with a P value < 0.01 in the univariate step were estimated in the full model. The only covariate effect that met the criteria for inclusion in the full model was relapse. However, relapse was removed from the full model for time to aGFS up to Day 180 during backward elimination (P value = 0.0086). Only abatacept C_{min} after the last dose was a significant predictor of the time to severe aGFS up to Day 180 post-transplantation in subjects at risk for GVHD. The VPC plots for time to severe aGFS by quartiles of trough serum concentration at steady state (C_{minss}) revealed a trend for an over prediction bias at the lowest exposure quartile and a slight under prediction bias in the higher 2 quartiles of exposure. These trends may be due to small sample size in each quartile of exposure.

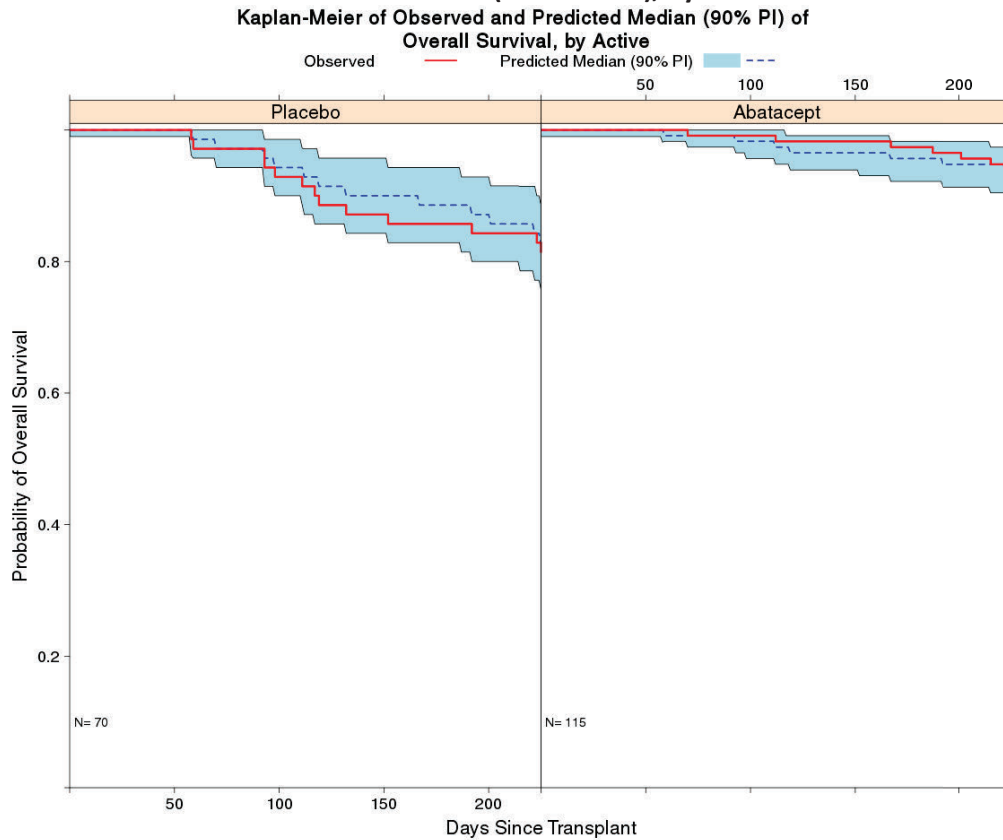
Figure 21: Model Evaluation of Time to First Severe aGFS (Final Model), by Treatment



N: number of subjects; PI: prediction interval

Exposure-response Efficacy Analysis: Time to Overall Survival: There was a significant relationship between abatacept exposure and the efficacy endpoint of time to OS. Although the exposure C_{max} after the first dose was most significant in the evaluation performed for the CPH model, C_{min} after the last dose was selected for inclusion in the OS base model since C_{min} and C_{max} were highly correlated resulting in similar Bayesian information criterion values and to maintain consistency between efficacy endpoints. In addition, C_{min} was a significant predictor of previous abatacept E-R analyses in JIA subjects. Abatacept C_{min} after the last dose and relapse of underlying malignancy were significant predictors of the probability of OS, whereby increasing exposure (higher C_{min}) is associated with lower risk (hazard) of death (event) and relapse of underlying malignancy is associated with higher risk (hazard) of death. The E-R relationship for time to OS was described better by a linear function of C_{min} than a log linear function. The pre-specified covariates were estimated in the full model. 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 the full model. The covariates with a P value < 0.01 in the univariate step were estimated in the full model. The only covariate effect that met the criteria for inclusion in the full model was relapse. After backward elimination, relapse remained in the final model for OS. Abatacept C_{min} after the last dose and relapse were significant predictors of the time to OS in subjects at risk for GVHD. The VPC plots for time to OS showed no biases.

Figure 22: Model Evaluation of Overall Survival (Final Model), by Treatment



N: number of subjects; PI: prediction interval

Exposure-response Safety Analyses: Graphical analysis of the relationship between abatacept exposures following the first and last dose (AUC, C_{min}, C_{max}, and C_{av}) and time to first infection adverse events showed no clear association between abatacept exposure and safety given the dosing regimen in Study IM101311 included in this analysis. In addition, based on graphical analyses there does not appear to be a relationship between abatacept exposure and time to invasive CMV disease or time to CMV viremia.

CONCLUSIONS:

Population Pharmacokinetic Analysis:

- The PK of abatacept in subjects with RA, JIA, and HM can be described by a linear 2-compartment model with zero-order IV infusion and first-order elimination.
- Body weight was a statistically significant covariate with a clinically relevant impact on abatacept exposures.
- Study IM101311 cohort was found to be a statistically significant covariate with a clinically relevant impact on exposures, while disease status was not identified as statistically significant.
- Subjects with HM in Cohort 7/8 of Study IM101311 had lower CL and subjects with HM in Cohort 8/8 had higher VC than non-HM subjects.
- Compared to subjects with RA, average abatacept exposures (C_{max1}, C_{min1}, AUC_{t1}, and C_{av1}) predicted from Bayesian estimates were lower in subjects with JIA, higher in subjects with HM from Cohort 7/8 (except C_{max1}), and lower in subjects with HM from Cohort 8/8.

ORENCIA (abatacept)

- The other statistically significant covariate effects (AST, CGFR, and sex on CL; sex on VC) were found to have no clinically relevant influence on abatacept exposures.

Exposure-response Efficacy Analysis:

- A Cox proportional hazards model with a linear function of Cmin after the last dose adequately described the E-R relationship for time to severe aGFS up to 180 days post-transplant in subjects administered abatacept.
- The Cmin after the last dose was a statistically significant predictor of time to severe aGFS up to 180 days post-transplant. The risk of a severe aGFS event decreased with increasing Cmin after the last dose.
- No covariates were identified to significantly influence the E-R relationship for time to severe aGFS up to 180 days post-transplant in subjects aged at least 6 years receiving URD HSCT due to HM.
- A Cox proportional hazards model with a linear function of Cmin after the last dose adequately described the E-R relationship for time to OS in subjects administered abatacept.
- The Cmin after the last dose and relapse were statistically significant predictors of time to OS. The risk of death decreased with increasing Cmin after the last dose and increased with a relapse of underlying malignancy.
- No other covariates were identified to significantly influence the E-R relationship for time to OS in subjects aged at least 6 years receiving URD HSCT due to HM.

Exposure-response Safety Analysis:

- No clear association between abatacept exposure and the occurrence of infection adverse events was found in subjects aged at least 6 years receiving URD HSCT due to HM after abatacept administration.
- No clear association between abatacept exposure and the time to invasive CMV disease or CMV viremia was found in subjects aged at least 6 years receiving URD HSCT due to HM after abatacept administration.

FDA Assessment:

19.4.1 FDA Pharmacometrics Review

19.4.1-1 Population PK Analysis

19.4.1-1.1 Population PK Summary

The Applicant's final population PK (popPK) model for IV abatacept administration adequately characterized the pharmacokinetic (PK) profile of abatacept in patients aged 6 years and older receiving unrelated donor (URD) hematopoietic stem cell transplant (HSCT) due to hematologic malignancies (HM).

Modeling and simulation support the dosing regimen of 15 mg/kg IV as a 60-minute IV infusion on Day -1 followed by 12 mg/kg on Days 5, 14, and 28 for patients with HM aged 2 to <6 years for prevention of acute Graft versus Host Disease (aGVHD). This regimen is expected to result in exposure in patients aged 2 to <6 years that is similar to the exposure in Study IM101311 patients aged 6 years and

older who received 10 mg/kg as a 60-minute IV infusion on the day before transplant (Day -1) followed by 10 mg/kg IV on Days 5, 14, and 28.

The recommended dosing regimen and predicted PK profile of IV abatacept in ages 2 to <6 years is to be verified by a postmarketing requirement (PMR) (see Section 13).

19.4.1-1.2 Summary of Applicant’s Population PK Analysis

19.4.1-1.2.1 Introduction

The two primary objectives of the Applicant’s popPK analysis were:

- To characterize the PK profile of abatacept following IV administration in subjects aged at least 6 years old receiving URD HSCT due to HM and to determine the effects of key covariates on abatacept PK parameters and exposures.
- To predict abatacept exposure in pediatric patients aged 2 to <6 years following intravenous administration for aGVHD prevention and to identify a dose to match predicted exposure in patients aged 2 to <6 years with the exposure in patients aged 6 years and older administered a 4-dose regimen of 10 mg/kg IV abatacept.

19.4.1-1.2.2 Data

The popPK dataset for the Applicant’s popPK model development included a total of 4873 observations of abatacept concentration from 685 patients. This included 934 observations from 115 patients aged 6 years and older with HM undergoing HSCT from matched human leukocyte antigen (HLA) or 1-allele-mismatched HLA URD (Study IM101311), 1857 observations from 184 patients aged 6 to <18 years with polyarticular juvenile idiopathic arthritis (pJIA) (Study IM101033), and 2082 observations from 386 patients aged 17 years and older with rheumatoid arthritis (RA) (Studies IM103002, IM101029, IM101031, IM101100, IM101101, and IM101102).

Summary statistics of patient demographics and abatacept treatment group in the popPK dataset are presented in Table 71.

Table 71. Summary of Baseline Characteristics in the Population PK Dataset

Covariate	Statistic	RA (n=386)	pJIA (n=184)	HM, 7/8 Cohort (n=42)	HM, 8/8 Cohort (n=73)	Overall (n=685)
Dose						
10 mg/kg IV	n (%)	89 (23.1%)	184 (100%)	42 (100%)	73 (100%)	388 (56.6%)
2.0 mg/kg IV	n (%)	145 (37.6%)	0	0	0	145 (21.2%)
1000 mg IV	n (%)	19 (4.9%)	0	0	0	19 (2.8%)
750 mg IV	n (%)	97 (25.1%)	0	0	0	97 (14.2%)
500 mg IV	n (%)	34 (8.8%)	0	0	0	34 (5.0%)
Sex						
Female	n (%)	277 (71.8%)	131 (71.2%)	16 (38.1%)	32 (43.8%)	456 (66.6%)
Male	n (%)	109 (28.2%)	53 (28.8%)	26 (61.9%)	41 (56.2%)	229 (33.4%)
Race/Ethnicity						
White ^a	n (%)	351 (90.9%)	142 (77.2%)	25 (59.5%)	61 (83.6%)	579 (84.5%)

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Covariate	Statistic	RA (n=386)	pJIA (n=184)	HM, 7/8 Cohort (n=42)	HM, 8/8 Cohort (n=73)	Overall (n=685)
Black or African American	n (%)	11 (2.8%)	15 (8.2%)	7 (16.7%)	2 (2.7%)	35 (5.1%)
Hispanic/Latino	n (%)	14 (3.6%)	0	7 (16.7%)	4 (5.5%)	25 (3.6%)
Asian or Pacific Islander	n (%)	9 (2.3%)	2 (1.1%)	2 (4.8%)	4 (5.5%)	17 (2.5%)
Other or Unknown	n (%)	1 (0.3%)	25 (13.6%)	1 (2.4%)	2 (2.7%)	29 (4.2%)
Baseline Age (years)	n	386	184	42	73	685
	Mean (CV%)	53.3 (22.7)	12.5 (23.2)	36.3 (63.1)	40.8 (47.8)	40 (53.8)
	Median	54	13	39.5	44	45
	Min - Max	17 - 84	6 - 17	6 - 76	6 - 71	6 - 84
Age Category	n (%)	1 (0.3%)	184 (100%)	15 (35.7%)	14 (19.2%)	214 (31.2%)
	n (%)	385 (99.7%)	0	27 (64.3%)	59 (80.8%)	471 (68.8%)
Baseline Weight (kg)	n	386	184	42	73	685
	Mean (CV%)	78.2 (26.9)	42.1 (36.3)	72.3 (38.7)	74.2 (31.5)	67.7 (38)
	Median	75.7	41.8	74.8	71.3	67.9
	Min - Max	38.1 - 186.8	14.4 - 100	22 - 127.3	23.1 - 142.7	14.4 - 186.8
Baseline eGFR ^b (mL/min/1.73m ²)	n	386	184	41	66	677
	Mean (CV%)	86.7 (33.3)	202.4 (40.2)	128.8 (40.8)	122.5 (37.6)	124.2 (57.5)
	Median	80	185	119.6	112.5	103.4
	Min - Max	37 - 245.9	82.5 - 578.2	51 - 307.7	68 - 315.2	37 - 578.2
Baseline AST (u/L)	n	386	184	40	64	674
	Mean (CV%)	20.9 (41.1)	23.6 (75.4)	32 (56.2)	26 (50)	22.8 (57.5)
	Median	19	20	27	24	20
	Min - Max	7 - 90	9 - 181	11 - 84	8 - 83	7 - 181
Baseline Albumin (g/L)	n	378	149	5	5	537
	Mean (CV%)	3.9 (7.7)	4.3 (9.3)	3.2 (12.5)	3.4 (8.8)	4 (10)
	Median	3.9	4.3	3.3	3.2	4
	Min - Max	2.7 - 4.7	3 - 5.1	2.6 - 3.5	3.2 - 3.9	2.6 - 5.1
Baseline Bilirubin (mg/dL)	n	378	149	40	64	631
	Mean (CV%)	0.4 (50)	0.4 (75)	0.6 (50)	0.6 (66.7)	0.4 (50)
	Median	0.4	0.4	0.5	0.4	0.4
	Min - Max	0.1 - 2	0.1 - 2.6	0.1 - 1.8	0.2 - 1.8	0.1 - 2.6

^aIncludes patients who were White who were reported as not having Hispanic/Latino ethnicity or who had missing/unreported ethnicity.

^beGFR for patients aged 6 to <18 years was calculated with the following equation: eGFR = 41.3 x height (m) / Scr (mg/dL). eGFR for patients aged ≥18 years was calculated with the following equation: eGFR = 186.3 x Scr^{1.154} x Age^{-0.203} x 0.742 if female x 1.212 if Black or African American.

CV = coefficient of variation; eGFR = estimated glomerular filtration rate; HLA = human leukocyte antigen; HM = hematologic malignancy; IV = intravenous; pJIA = polyarticular juvenile idiopathic arthritis; RA = rheumatoid arthritis; Scr = serum creatinine concentration.

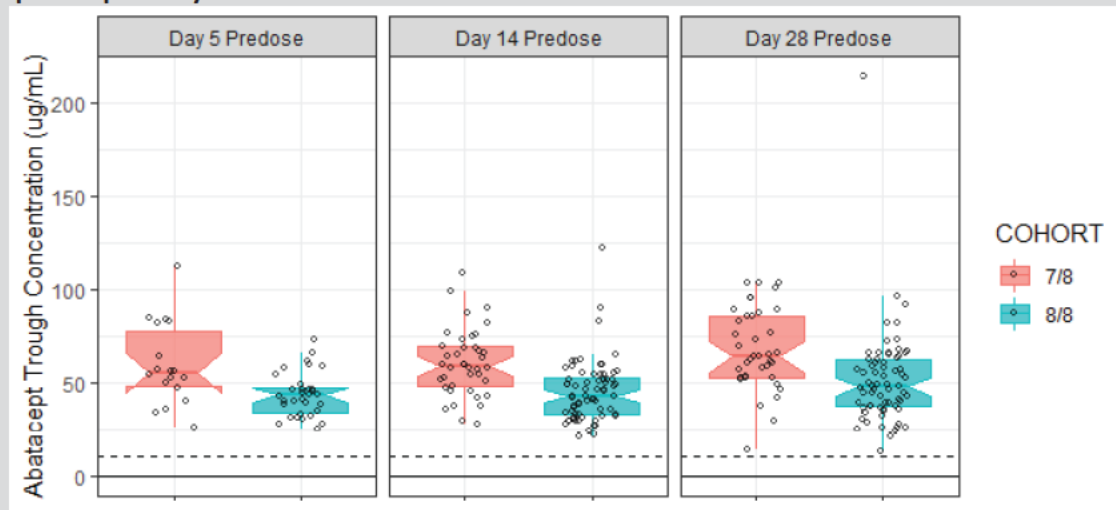
Source: Reviewer Analysis of Applicant's Datasets

19.4.1-1.2.2.1 Observed PK Concentrations Following Intravenous Abatacept Administration According to Cohort

Study IM101311 included two cohorts: Cohort 7/8 and Cohort 8/8. Cohort 7/8 included patients who had 7/8 human leukocyte antigen (HLA) matches with URD, while Cohort 8/8 included patients who had 8/8 HLA matches with URD. Cohort 8/8 randomized patients to either the active arm (abatacept + calcineurin inhibitor [CNI] + methotrexate) or placebo arm (placebo + CNI + methotrexate). Cohort 7/8 only had an active arm (abatacept + CNI + methotrexate).

Patients in Cohort 7/8 tended to have higher observed abatacept trough concentrations compared to patients in Cohort 8/8, as shown in Figure 23 and Figure 24. Descriptive statistics for observed abatacept trough concentrations within each cohort are listed in Table 4 in Section 6.2.1.

Figure 23. Study IM101311 Observed Abatacept Trough Concentrations Versus Nominal Time After Transplant up to Day 28 Predose

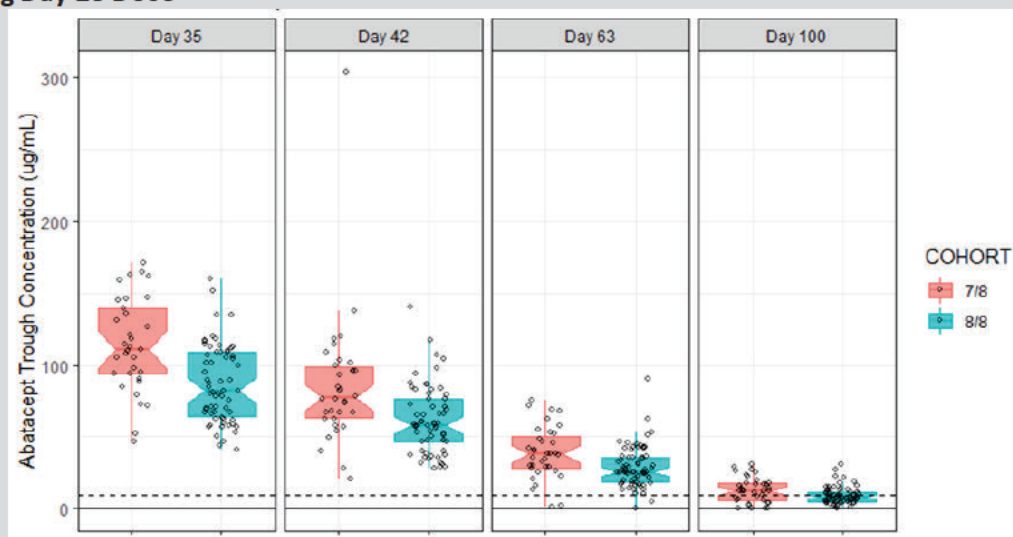


All patients received 10 mg/kg (maximum dose of 1000 mg) via IV infusion over 1 hour on the day before transplant and then on Day 5, Day 14, and Day 28 after transplant. Dashed horizontal line = 10 ug/mL. Solid horizontal line = LLOQ. BLQ observations displayed as 1/2 * LLOQ. Abatacept LLOQ = 0.001 ug/mL.

BLQ = below limit of quantification; IV = intravenous; LLOQ = lower limit of quantification.

Source: Reviewer analysis of Applicant's Study IM101311 PK Concentration Dataset ('adpc.xpt')

Figure 24. Study IM101311 Observed Abatacept Concentrations Versus Nominal Time After Transplant Following Day 28 Dose



All patients received 10 mg/kg (maximum dose of 1000 mg) via IV infusion over 1 hour on the day before transplant and then on Day 5, Day 14, and Day 28 after transplant. Dashed horizontal line = 10 ug/mL. Solid horizontal line = LLOQ. BLQ observations displayed as 1/2 * LLOQ. Abatacept LLOQ = 0.001 ug/mL.

BLQ = below limit of quantification; IV = intravenous; LLOQ = lower limit of quantification.

Source: Reviewer analysis of Applicant's Study IM101311 PK Concentration Dataset ('adpc.xpt')

19.4.1-1.2.2.2 Observed PK Concentrations Following Intravenous Abatacept Administration According to Cohort and Age Group

The limited number of pediatric patients makes it difficult to compare observed abatacept concentrations after the last dose between patients aged 6 to <13 years and 13 to <18 years. However, observed concentration tended to be higher in adults compared to pediatric patients aged 6 to <18 years within each cohort, as shown in Figure 3 and Figure 4 in Section 6.2.2.1.

The difference in PK concentration according to cohort does not appear to be explained by potential differences in age group distribution between the two cohorts.

19.4.1-1.2.3 Final Model

The Applicant's final covariate model was a 2-compartment model with zero-order IV infusion, linear distribution, and linear elimination. Inter-individual variability (IIV) was included on the parameters of clearance (CL), central volume of distribution (VC), and peripheral volume of distribution (VP). Residual variability (RV) was described by a combined additive plus constant RV model. The Applicant's parameter estimates for the final model are listed in Table 72.

Table 72. Applicant Parameter Estimates for the Final Population PK Model

Parameter	Definition	Estimate	Standard Error	RSE (%)	95% CI, Lower	95% CI, Upper	Shrinkage
CL	Clearance (L/h)	0.0250	0.000633	2.53%	0.0240	0.0260	
VC	Central Volume (L)	3.22	0.0793	2.46%	3.09	3.35	
Q	Distribution Clearance (L/h)	0.0346	0.00240	6.94%	0.0307	0.0385	
VP	Peripheral Volume (L)	5.39	0.189	3.51%	5.08	5.70	
CL _{BWT}	Power of Weight on CL	0.676	0.0375	5.55%	0.614	0.738	
VC _{BWT}	Power of Weight on VC	0.683	0.0306	4.48%	0.633	0.733	
VP _{BWT}	Power of Weight on VP	0.776	0.0476	6.13%	0.698	0.854	
CL _{AST}	Power of AST Effect	-0.120	0.0281	-23.42%	-0.0738	-0.166	
CL _{cGFR}	Power of eGFR Effect	0.187	0.0281	15.03%	0.141	0.233	
VC _{SEX}	Exponent of Sex Effect in Female	-0.117	0.0275	-23.50%	-0.0718	-0.162	
CL _{SEX}	Exponent of Sex Effect in Female	-0.0962	0.0248	-25.78%	-0.0554	-0.137	
CL _{COHORT7}	Exponent of GVHD Cohort 7/8 Effect	-0.380	0.0515	-13.55%	-0.295	-0.465	
CL _{COHORT8}	Exponent of GVHD Cohort 8/8 Effect	-0.133	0.0330	-24.81%	-0.0787	-0.187	
VC _{COHORT8}	Exponent of GVHD Cohort 8/8 Effect	0.260	0.0369	14.19%	0.199	0.321	
ETA(1)	IIV on CL (exponential)	0.0592	0.00407	6.88%	0.0525	0.0659	8.35%
ETA(2)	IIV on VC (exponential)	0.0345	0.00610	17.68%	0.0245	0.0445	41.89%
ETA(3)	IIV on VP (exponential)	0.159	0.0197	12.39%	0.127	0.191	25.93%
EPS(1)	RV (proportional)	0.0611	0.00343	5.61%	0.0555	0.0667	11.31%
EPS(2)	RV (additive)	0.00242	0.00135	55.79%	0.000199	0.00464	11.31%

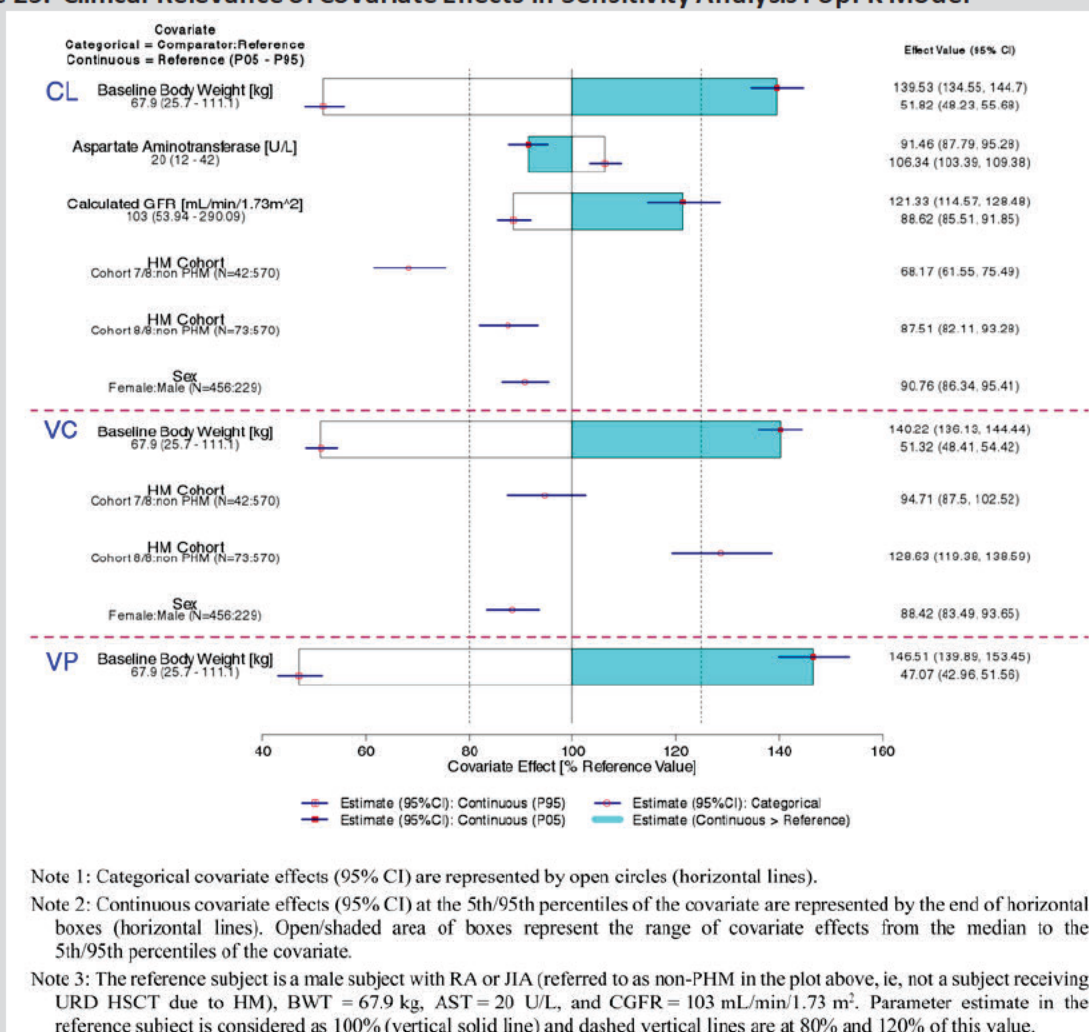
Objective Function Value = 23945.89. Condition number = 45.77.

BWT = baseline body weight; cGFR = calculated glomerular filtration rate (equal to eGFR); CI = confidence interval; eGFR = estimated glomerular filtration rate; GVHD = graft versus host disease; IIV = Inter-individual variability; RSE = relative standard error; RV = residual variability.

Source: Appendix 5.1.1.5-3 from Applicant's Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020.

Covariate effects in the final model indicated that CL was higher with increased body weight, male sex, lower AST, higher estimated glomerular filtration rate (eGFR), RA or pJIA disease status (versus HM), and Cohort 8/8 (versus Cohort 7/8). VC was higher with increased weight, male sex, and HM patients in Cohort 8/8 (versus RA patients, pJIA patients, and HM patients in Cohort 7/8). VP was higher with increased weight. The effects of body weight, HM cohort, and eGFR were predicted to have significant impact on PK parameters (Figure 25).

Figure 25. Clinical Relevance of Covariate Effects in Sensitivity Analysis PopPK Model

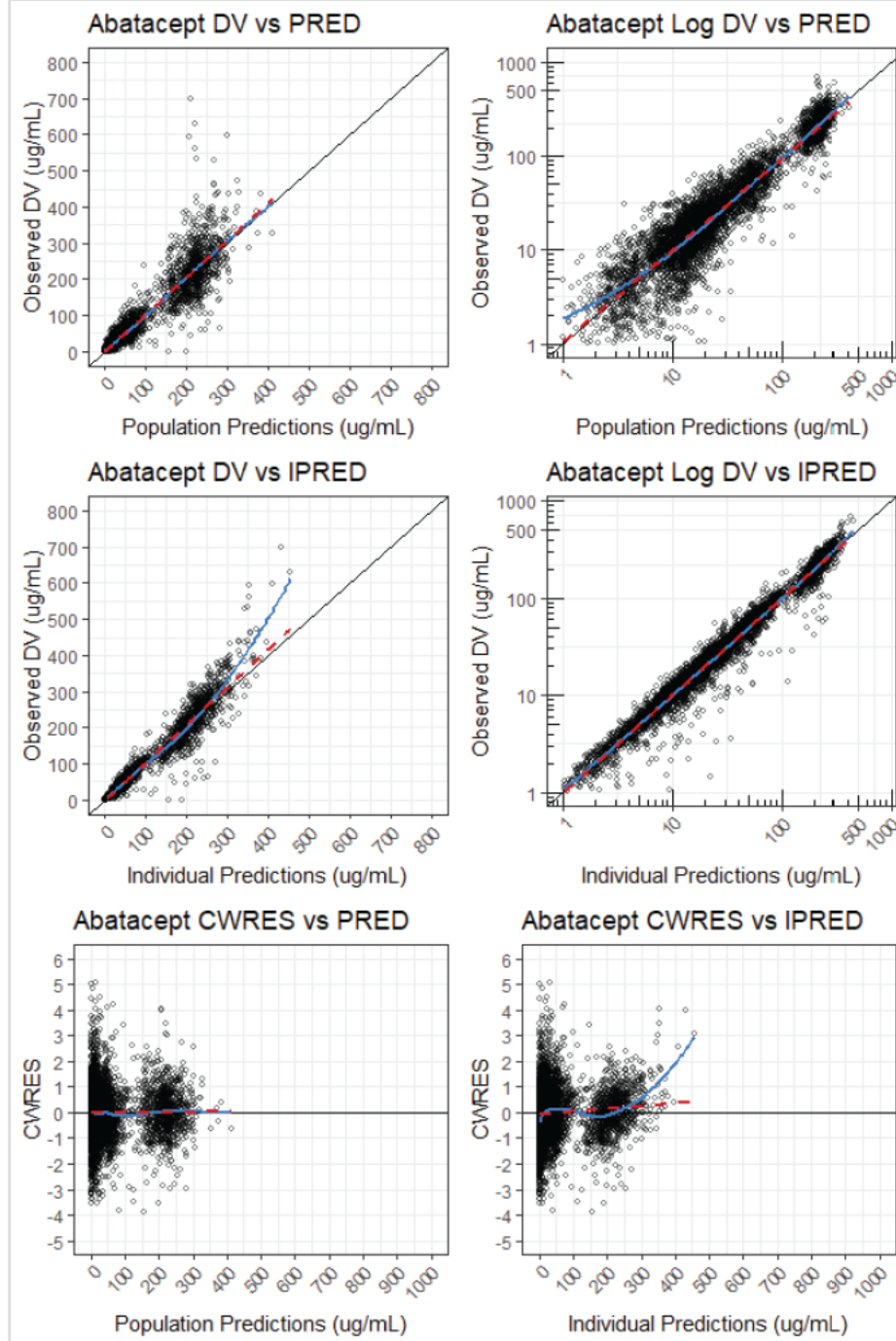


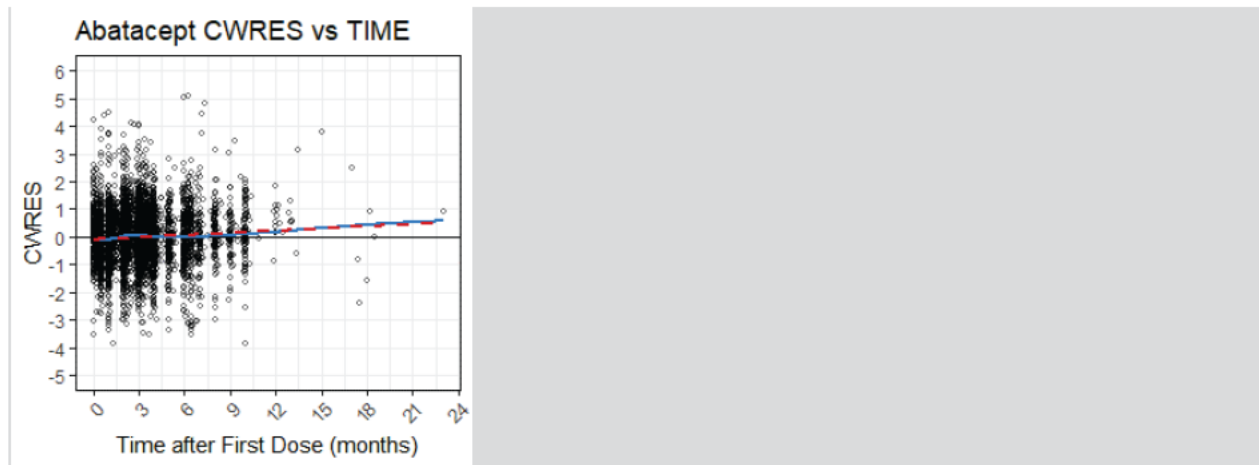
Source: Figure 5.1.1.4-1 in Applicant's Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020.

Reviewer Comments

The Reviewer was able to verify the Applicant's final model without significant discrepancies. Goodness-of-fit (GOF) plots for the Reviewer's output using the Applicant's final model are presented in Figure 26. The model had a tendency to underpredict higher abatacept concentrations (above roughly 300 ug/mL) which is visible in the plot of observed concentrations (DV) versus individual predicted concentrations (IPRED) as well as the plot of conditional weighted residual (CWRES) versus DV. For patients with HM, the model did not have any significant differences in GOF according to Study IM101311 cohort (Figure 27). The model appears to perform adequately for characterizing PK in patients with HM, although there is still a tendency to underpredict higher abatacept concentrations. This may cause some degree of underprediction for exposure parameters related to higher concentrations, such as maximum concentration (C_{max}). Concentrations close to the Applicant's PK target threshold of 10 ug/mL for maximum T-cell inhibition appear to have acceptable fit in both cohorts.

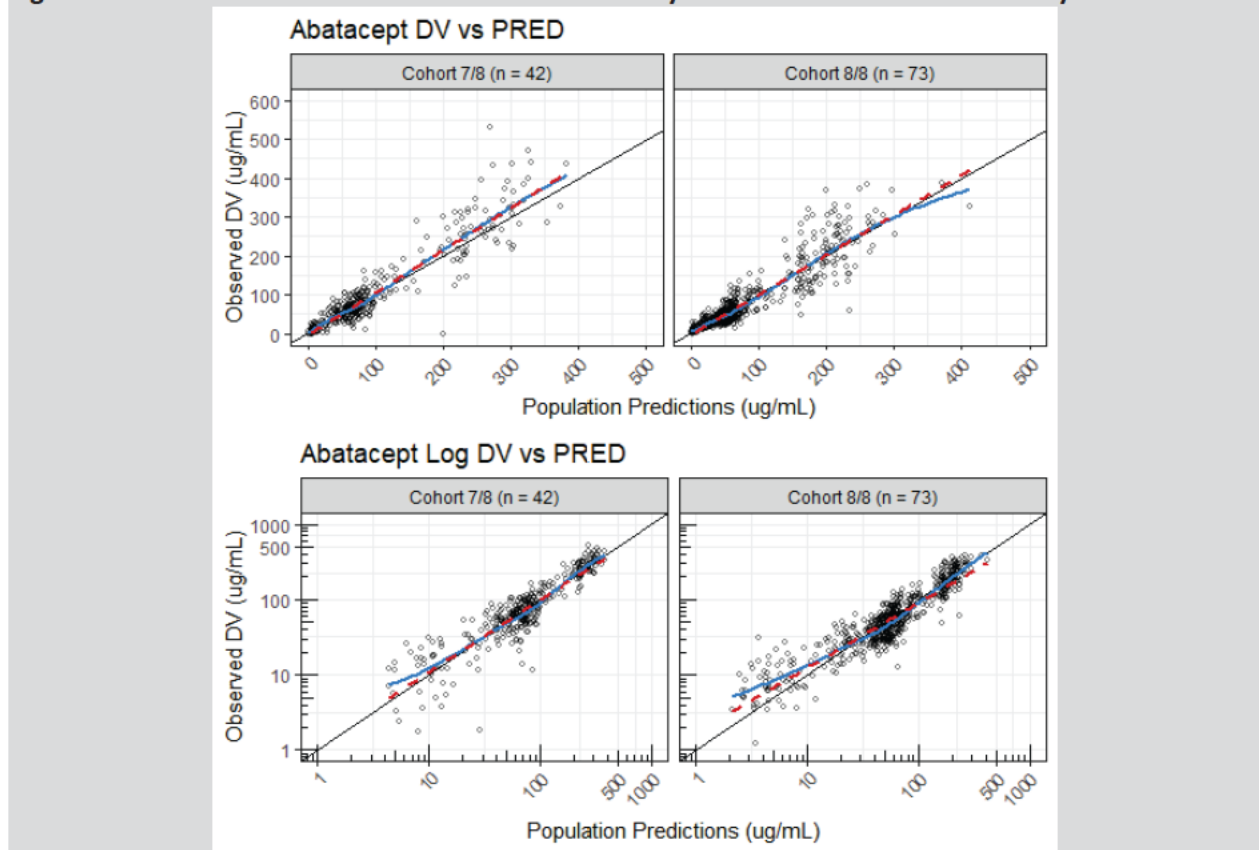
Figure 26. Goodness-of-Fit Plots for Final Model: Overall

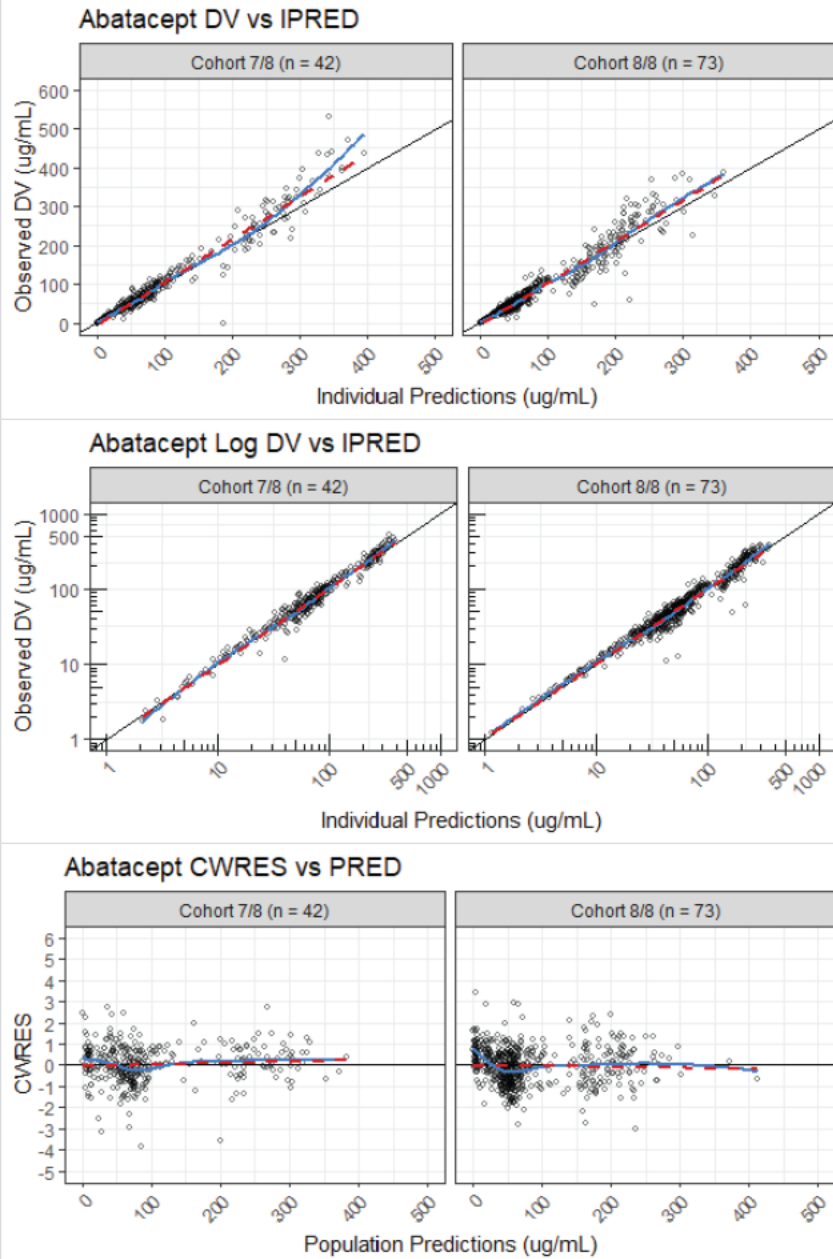




Loess in solid blue; Linear regression in dashed red. Abatacept LLOQ= 0.001 ug/mL.
CWRES = conditional weighted residual; DV = observed concentration; IPRED = individual prediction of concentration; LLOQ = lower limit of quantification; PRED = population prediction of concentration.
Source: Reviewer Analysis

Figure 27. Goodness-of-Fit Plots for Final Model: Study IM101311 Patients Stratified by Cohort





Loess in solid blue; Linear regression in dashed red. Abatacept LLOQ = 0.001 ug/mL.

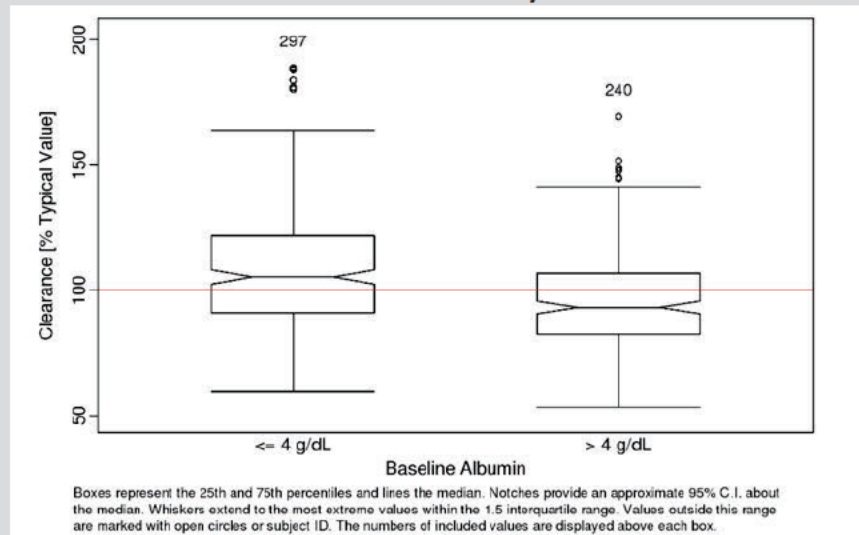
CWRES = conditional weighted residual; DV = observed concentration; IPRED = individual prediction of concentration; LLOQ = lower limit of quantification; PRED = population prediction of concentration.

Source: Reviewer Analysis

Anti-drug antibody (ADA) status was not investigated as a covariate in the popPK model due to a limited number of patients with one or more ADA-positive samples. However, individual predicted clearance appeared higher for patients with one or more ADA-positive sample compared to patients without an ADA-positive sample.

Baseline albumin was not investigated as a covariate in the model because 22% of patients were missing baseline albumin measurements. However, individual predicted clearance appeared higher for patients with low baseline albumin concentration (≤ 4 g/L) compared to those with albumin >4 g/L, as shown in Figure 28. Because only 10/115 (8.7%) patients with HM in the popPK dataset had a measured baseline albumin concentration, it is unclear if PK differences in the subgroup of patients with HM may be related to differences in albumin.

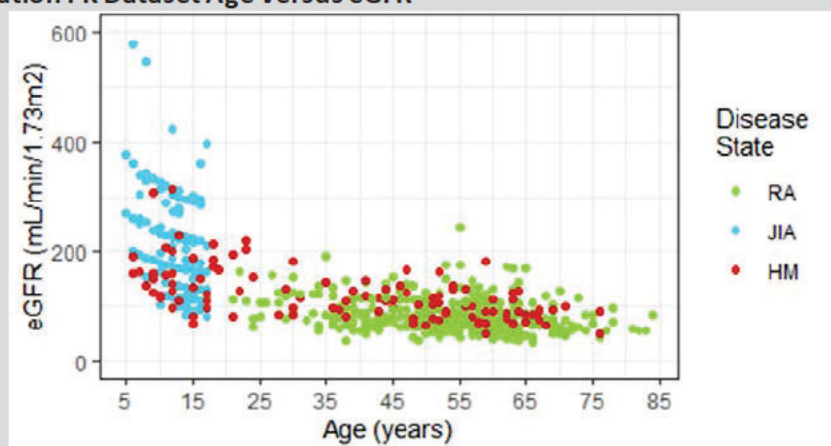
Figure 28. Distribution of Individual Predicted Clearance by Baseline Albumin Concentration



Source: Figure 5.1.1.6-1 in Applicant's Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020.

The significant covariate of eGFR on CL in the final model and the distribution of eGFR in the popPK dataset were investigated further, as abatacept is a large molecule that is not expected to undergo renal elimination. Figure 29 shows that pediatric patients 6 to <18 years tended to have higher eGFR values compared to adults.

Figure 29. Population PK Dataset Age Versus eGFR



eGFR = estimated glomerular filtration rate; HM = hematologic malignancies; JIA = juvenile idiopathic arthritis; RA = rheumatoid arthritis.

Source: Reviewer Analysis

The final popPK model included a significant covariate effect where higher abatacept clearance was associated higher eGFR. This effect is unlikely to be directly caused by the actual GFR or renal function because abatacept would not undergo renal elimination. However, the covariate effect for eGFR may be related to a correlation between eGFR and other covariates such as body size, developmental stage, or protein catabolism.

For example, eGFR in pediatric patients was correlated with body size because the pediatric eGFR equation used by the Applicant (Equation 1) incorporated height, which in turn was correlated with weight. The eGFR equation for adults (Equation 2) did not include height or weight.

Equation 1. eGFR for Patients aged <18 years

$$eGFR (mL/min/1.73m^2) = 41.3 \times height (m) / Scr (mg/dL)$$

Scr = serum creatinine with standardized assay

Equation 2. eGFR for Patients aged ≥18 years

$$eGFR (mL/min/1.73m^2) = 186.3 \times Scr^{-1.154} \times Age^{-0.203} \times F2 \times F3$$

F2 = 1.0 for men and 0.742 for women

F3 = 1.0 for non-Black subjects and 1.212 for Black subjects.

Scr = serum creatinine in mg/dL with standardized assay

Additionally, these eGFR equations may not have been optimal for accurately determining renal function for pediatric and/or adult patients with hematologic malignancies. In the popPK dataset, the highest eGFR was 578 mL/min/1.73m² and individual eGFR exceeded 250 mL/min/1.73m² in 21% of pediatric patients (46/214). However, the typical physiological upper limit of renal function in children is likely around 175 to 225 mL/min/1.73m².^{1,2} The supraphysiologic eGFR values may be a result of differences between the popPK dataset and the population from which the eGFR equation was developed. The pediatric eGFR equation utilized for the popPK dataset was developed from a sample of children with

chronic kidney disease and is thought to be most accurate for patients with eGFR between 15 and 75 mL/min/1.73m².³ This equation may over-estimate GFR values when actual GFR exceeds that range.⁴

In the final abatacept popPK model, it is not clear whether accuracy of the eGFR value is necessary because it is unclear if the effect on CL is due to a covariate that is correlated with actual GFR or a covariate that is correlated with the calculated eGFR. The effect is unlikely to be caused by the actual GFR or renal function because abatacept is not renally eliminated.

Overall, the inclusion of eGFR as a significant covariate in the popPK model is acceptable, although it should be noted that the eGFR may be acting as a surrogate covariate for a different patient characteristic with direct physiological impact on abatacept clearance.

19.4.1-1.2.4 Conclusions

The Applicant's popPK analyses and final popPK model were verified by the reviewer, with no significant discordance identified. The Applicant's popPK analysis was acceptable for the purpose of describing the PK profile of abatacept following IV administration in patients receiving URD HSCT due to HM.

19.4.1-1.3 Reviewer's Independent Population PK Analysis

19.4.1-1.3.1 Introduction

FDA conducted additional independent popPK analysis to further evaluate the Applicant's final model. In particular, the final model's inclusion of eGFR as a significant covariate on abatacept CL was investigated because younger patients tended to have higher eGFR values and the eGFR could have a significant impact on the predicted CL and exposure in virtual 2 to <6 year old patients.

The Reviewer investigated whether covariates of body size and/or age could replace the eGFR covariate effect to create a similar or improved model.

19.4.1-1.3.2 Dataset

The popPK analysis dataset "ivpk.xpt" was provided by the Applicant and included abatacept concentration data and covariates for 685 subjects.

19.4.1-1.3.3 Modeling Methods

Dataset handling and generation of diagnostics and other plots was conducted using R version 4.0.2. NONMEM version 7.3.0 or higher was used for popPK analysis.

Additional popPK model structures were tested based on the Applicant's final model. The Applicant's final popPK model file, which served as the starting point and reference for the independent review models, was provided by the Applicant as "abatacept-002586-pk-final-bis-ctl.txt."

Key models in the analysis are summarized in Table 73. Any changes from the structure of the Applicant's final model are detailed in the model description.

Table 73. Summary of Relevant Reviewer Independent Analysis Model Runs

Run	Reference	Model description	OFV	Messages and Comments
abatacept-002586-pk-final-bis	N/A	Reference; Applicant's final popPK model verified by reviewer	23945.9	Final estimates close to Applicant's provided 1st; no discrepancy identified
run001	abatacept-002586-pk-final-bis	Removed eGFR effect on CL	23990.0	Worse OFV than applicants' final model
run002	001	Added continuous age effect (pow) on CL	23981.2	Younger age assoc. w. higher CL
run003	001	Fixed WT-CL exponent to 0.75; WT-Vc exponent to 1.0	24157.0	Worse OFV
run004	003	Added continuous age effect (pow) on CL	24104.4	Worse OFV; younger age assoc. w. higher CL
run005	003	Added categorical age (ped/adult) effect on CL	24115.5	
run006	001	Added categorical age (ped/adult) effect on CL	23985.8	Power effect for continuous age has lower OFV than prop shift categorical age (ped vs adult)
run007	001	Added categorical age (<12yo/older) effect on CL	23989.8	
run008	003	Added categorical age (<12yo/older) effect on CL	24157.0	COVARIANCE STEP ABORTED
run009	001	Added categorical (ADD shift) age (ped/adult) effect on CL	N/A	ERROR IN TRANS4 ROUTINE: CL IS NEGATIVE PROGRAM TERMINATED BY OBJ; Covariance step not successful.
run013	001	Fixed WT-Vc exponent to 1.0	24104.3	Worse OFV; but not as high as run 002; slightly lower shrinkage on IIV(Vc) but higher RSE% on SEX-Vc effect
run014	013	Added continuous age effect (pow) on CL	24095.5	
run015	001	Fixed WT-CL exponent to 0.75	24056.4	
run016	015	Added continuous age effect (pow) on CL	23994.5	
run017	001	Changed WT effects to BSA effects	23955.4	Larger BSA assoc. w. higher CL; Vc; Vp
run018	017	Added continuous age effect (pow) on CL	23947.5	No 95% CIs cross zero; Younger age assoc. w. higher CL; GOF indicate very slight improvement in HM patients DV vs PRED at very low DVs (~2-5 ug/mL); largest RSE is 35.4% for age effect on CL
run019	001	Changed WT-CL effect to BSA-CL	24000.7	
run020	019	Added continuous age effect (pow) on CL	23993.2	

Run	Reference	Model description	OFV	Messages and Comments
run021	017	Added categorical (PROP shift) age (ped/adult) effect on CL	23952.7	Continuous age effect on CL appears better based on OFV
run022	017	Added categorical (PROP shift) age (<12yo/12 and up) effect on CL	23954.3	Continuous age effect on CL appears better based on OFV
run023	018	Added eGFR effect on CL	23910.7	Improved OFV compared to run 018 and reference model; Condition = 49.45; eGFR apparently contains some information leading to a lower OFV that is not captured by BSA and age effects; Age effect on CL + sex effect on CL final estimate 95% CI cross zero
run024	017	Fixed BSA effect on CL to 1.0	23958.9	No 95% CIs cross zero; fixed BSA exponent results in worse fit than when BSA effect exponent is estimated
run025	024	Added continuous age effect (pow) on CL	23948.1	No 95% CIs cross zero
run026	025	Added eGFR effect on CL	23915.4	No 95% CIs cross zero
run027	024	Added eGFR effect on CL	23919.9	No 95% CIs cross zero; Appears that age effect is not very useful here (compare with run026)
run028	023	Removed female sex effect on CL	23910.9	OFV similar to run023; Age effect on CL final estimate 95% CI includes zero; RSE on age effect is high (106%)
run029*	028	Removed age effect on CL	23911.7	No 95% CI cross zero; final estimates similar to corresponding theta #s in applicant's final model; highest RSE is 24.3% (AST effect on CL). Conclusion: using BSA as a covariate effect resulted in lower OFV than when weight was a covariate effect

* indicates best reviewer model based on OFV and certainty/error of final estimates.

The same dataset ('ivpk.xpt') was used for all listed independent model runs. OFV = objective function value.

Source: Reviewer Analysis

19.4.1-1.3.4 Model Results

Run029 was identified as the Reviewer's best and final model based on Objective Function Value (OFV), certainty in final estimates, and relative standard error of final estimates.

The Reviewer's final model had lower OFV compared to the Reviewer's run of the Applicant's final model (23911.6 versus 23945.9, respectively). The general structure was the same in both models, which was a 2-compartment model with zero-order IV infusion, linear distribution, and linear elimination. No changes were made to the structure of IIV or RV.

The Reviewer's model differed from the Applicant's model in the following ways:

1. The Reviewer's model included BSA effects on CL, VC, and VP instead of weight effects. The BSA covariate effects were centered over 1.72 m², which was the BSA calculated for the median height (157 cm) and median weight (67.9 kg) in the popPK dataset.

ORENCIA (abatacept)

2. The Reviewer's model did not include a covariate effect of female sex on CL. This was due to uncertainty in the final estimate of the effect of sex on CL, and removal of this covariate effect did not significantly impact the OFV.

Parameter estimates for the Reviewer's model are presented in Table 74. The GOF plots for the Reviewer's best model (run 029) did not appear significantly different from the GOF plots for the Reviewer's run of the Applicant's final model.

Table 74. Parameter Estimates for the Reviewer's Final Model

Parameter	Definition	Estimate	RSE (%)	95% CI	Shrinkage
CL	Clearance (L/h)	0.0251	2.30%	0.024, 0.026	-
VC	Central Volume (L)	3.18	2.10%	3.05, 3.31	-
Q	Distribution Clearance (L/h)	0.0347	6.80%	0.03, 0.039	-
VP	Peripheral Volume (L)	5.36	3.40%	5.007, 5.713	-
CL _{BSA}	Power of BSA on CL	1.16	5.90%	1.025, 1.295	-
VC _{BSA}	Power of BSA on VC	1.18	4.40%	1.078, 1.282	-
VP _{BSA}	Power of BSA on VP	1.36	5.90%	1.203, 1.517	-
CL _{AST}	Power of AST Effect on CL	-0.115	24.30%	-0.17, -0.06	-
VC _{SEX}	Exponent of Sex Effect in Female on VC	-0.0984	21.80%	-0.141, -0.056	-
CL _{COHORT7}	Exponent of GVHD Cohort 7 Effect on CL	-0.413	12.70%	-0.516, -0.31	-
CL _{COHORT8}	Exponent of GVHD Cohort 8 Effect on CL	-0.169	19.60%	-0.234, -0.104	-
VC _{COHORT8}	Exponent of GVHD Cohort 8 Effect on VC	0.231	15.80%	0.159, 0.303	-
CL _{eGFR}	Power of eGFR Effect on CL	0.186	15.80%	0.128, 0.244	-
ETA(1)	IIV on CL (exponential)	0.0597	6.90%	0.052, 0.068	8.20%
ETA(2)	IIV on VC (exponential)	0.0312	18.70%	0.020, 0.043	43.30%
ETA(3)	IIV on VP (exponential)	0.148	13%	0.110, 0.186	26.70%
EPS(1)	Residual variability (proportional)	0.0612	-5.60%	0.055, 0.068	11.10%
EPS(2)	Residual variability (additive)	0.0024	-54.70%	-0.00015, 0.00495	11.10%

Objective Function Value = 23911.646. Condition number = 27.69.

BSA = body surface area (Mosteller equation); CI = confidence interval; eGFR = estimated glomerular filtration rate; GVHD = graft versus host disease; IIV = Inter-individual variability; RSE = relative standard error.

Source: Reviewer Analysis

19.4.1-1.3.5 Conclusions

The Reviewer's independent popPK model analyses demonstrated that inclusion of the eGFR covariate on CL in the final model appears to improve model fit and that the eGFR covariate effect cannot be replaced by covariate effects of body size and/or age without causing a statistically significant increase in OFV. The eGFR covariate appears to contain information that is not captured by alternative covariates correlated with eGFR including height (used to calculate BSA) and age. The eGFR covariate effect may be related to one or more covariates that are more difficult to quantify, such as protein catabolism or body composition.

The Applicant's final popPK model appears acceptable for predicting the PK of intravenous abatacept in patients aged 2 to <6 years of age.

19.4.1-1.4 Model-Predicted Exposure

The Applicant used the final popPK model to predict abatacept concentrations in Study IM101311 patients (n=115) for the planned dosing regimen of 10 mg/kg (maximum dose of 1000 mg) over 1-hour IV infusion on the day before transplant (Day -1) and on Day 5, Day 14, and Day 28 after transplant. Concentration was simulated from the start of the first IV infusion up until Day 42 after transplant.

Reviewer Comments

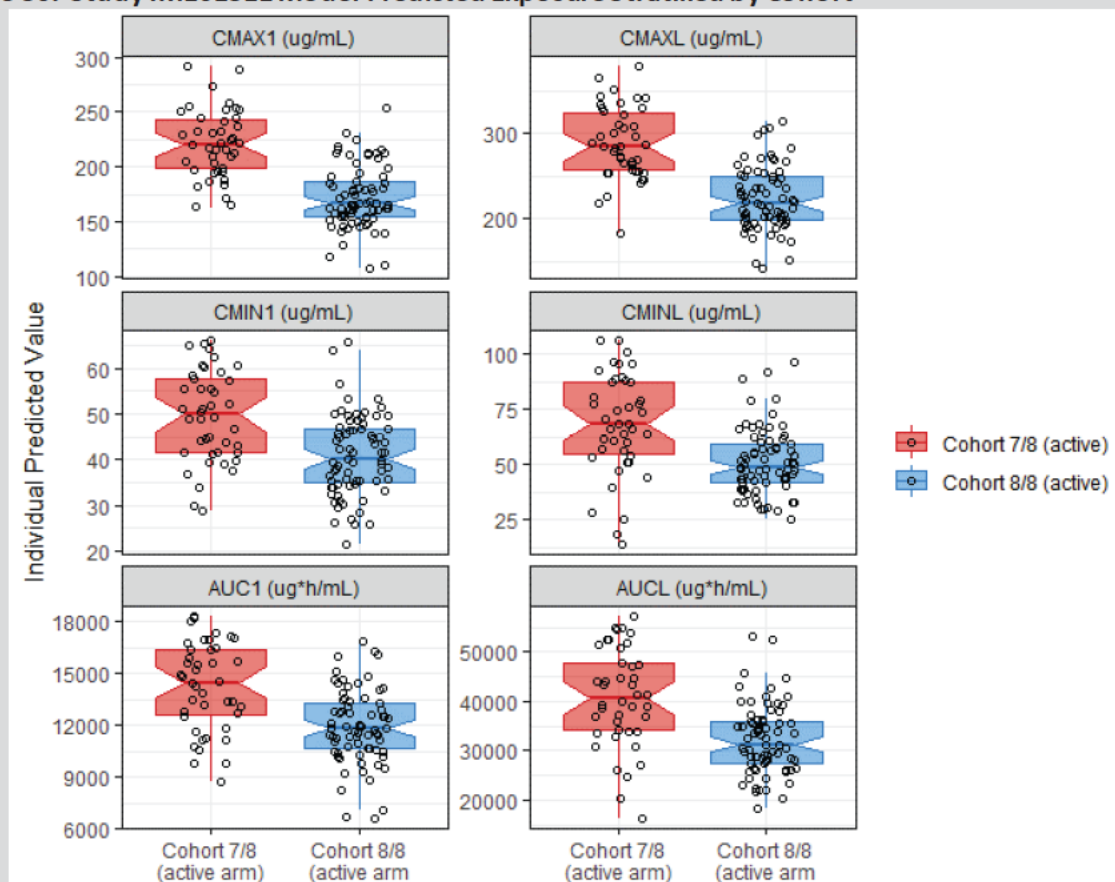
The Reviewer compared the Applicant's model-predicted exposure according to the covariates of cohort (7/8 versus 8/8), age (continuous and categorical), body weight, and sex. Cohort, body weight, and age were associated with potential differences in abatacept exposure. Although the popPK model predicted lower CL and lower VC in female patients compared to male patients, there was no significant difference in predicted abatacept exposure according to sex.

19.4.1-1.4.1 Exposure According to Cohort

Exposure for both the first and last dose tended to be higher in the 7/8 Cohort compared to the 8/8 Cohort, as shown in **Figure 30**. The 7/8 Cohort had 32% higher median predicted maximum concentration following last dose (C_{maxL}), 40% higher median predicted minimum concentration following last dose (C_{minL}), and 30% higher median predicted area under the concentration-versus-time curve after last dose (AUCL) compared to the 8/8 Cohort. This trend of higher abatacept concentrations in Cohort 7/8 compared to Cohort 8/8 was also seen in the observed abatacept trough concentration data (**Figure 23** and **Figure 24**).

Summary statistics of predicted exposure according to cohort are presented in **Table 75**.

Figure 30. Study IM101311 Model-Predicted Exposure Stratified by Cohort



All patients received 10 mg/kg (maximum of 1000 mg) abatacept via 1-hour IV infusion on the day before transplant and on Day 5, Day 14, and Day 28 after transplant.
 Active arm = abatacept + calcineurin inhibitor + methotrexate; AUC1 = AUC from 0-144 h after start of first dose; AUC1 = AUC from 0-360 h after start of last dose (696-1056 h after start of first dose); Cmax1 = maximum concentration between 0-144 h after start of first dose; CmaxL = maximum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); Cmin1 = minimum concentration between 1-144 h after start of first dose; CminL = minimum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CV = coefficient of variation; h = hours.
 Source: Reviewer Analysis of Applicant's popPK/E-R Datasets

Table 75. Summary of Individual Predicted Abatacept Exposure in the Exposure-Response Dataset

Covariate	Statistic	7/8 Cohort Active Arm (n=42)	8/8 Cohort Active Arm (n=73)
Cmax1 (ug/mL)	Geo Mean (CV%)	219.2 (14.1%)	170.1 (16.8%)
	Median	220.5	167
	Min - Max	163 - 292	107 - 254
CmaxL (ug/mL)	Geo Mean (CV%)	285.4 (15.2%)	220 (16.7%)
	Median	284.5	217
	Min - Max	182 - 379	141 - 315
Cmin1 (ug/mL)	Geo Mean (CV%)	48.5 (21.4%)	39.9 (22.4%)
	Median	49.8	40.1
	Min - Max	28.8 - 66	21.5 - 65.9

Covariate	Statistic	7/8 Cohort Active Arm (n=42)	8/8 Cohort Active Arm (n=73)
CMINL (ug/mL)	Geo Mean (CV%)	63.1 (47%)	49.2 (29.4%)
	Median	68.6	48.9
	Min - Max	14.2 - 106	25.3 - 96.3
AUC1 (ug*h/mL)	Geo Mean (CV%)	13974.6 (19.1%)	11730.6 (19%)
	Median	14450	11800
	Min - Max	8720 - 18300	6580 - 16800
AUCL (ug*h/mL)	Geo Mean (CV%)	39403.6 (28.2%)	31320.5 (22.6%)
	Median	40550	31300
	Min - Max	16200 - 57300	18400 - 53100
AUC42 (ug*h/mL)	Geo Mean (CV%)	1546 (45.9%)	1203.6 (29.2%)
	Median	1670	1200
	Min - Max	362 - 2590	625 - 2350

All patients received 10 mg/kg (maximum of 1000 mg) abatacept via 1-hour IV infusion on the day before transplant and on Day 5, Day 14, and Day 28 after transplant.

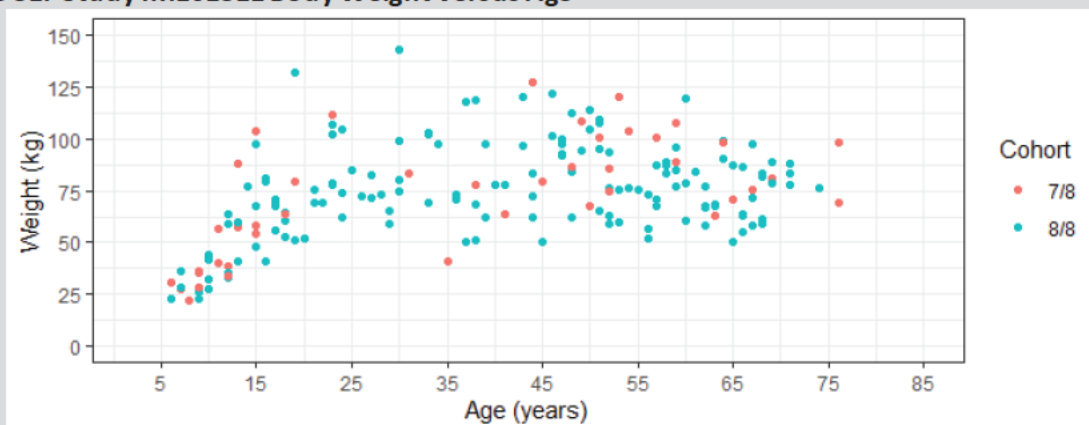
Active arm = abatacept + calcineurin inhibitor + methotrexate; AUC1 = AUC from 0-144 h after start of first dose; AUC42 = AUC from 336-360 h after start of last dose (1032-1056 h after start of first dose); AUCL = AUC from 0-360 h after start of last dose (696-1056 h after start of first dose); Cmax1 = maximum concentration between 0-144 h after start of first dose; CmaxL = maximum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); Cmin1 = minimum concentration between 1-144 h after start of first dose; CminL = minimum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CV = coefficient of variation; geo mean = geometric mean; h = hours.

Source: Reviewer Analysis of Applicant's popPK/E-R Datasets

19.4.1-1.4.2 Exposure According to Body Weight and Age Group

Age and body weight were correlated in pediatric patients (aged 6 to <18 years) in the exposure-response (E-R) dataset, as shown in Figure 31. The youngest patients tended to have the lowest body weights of all. The weight-versus-age relationship appeared relatively flat in patients aged 18 years and older.

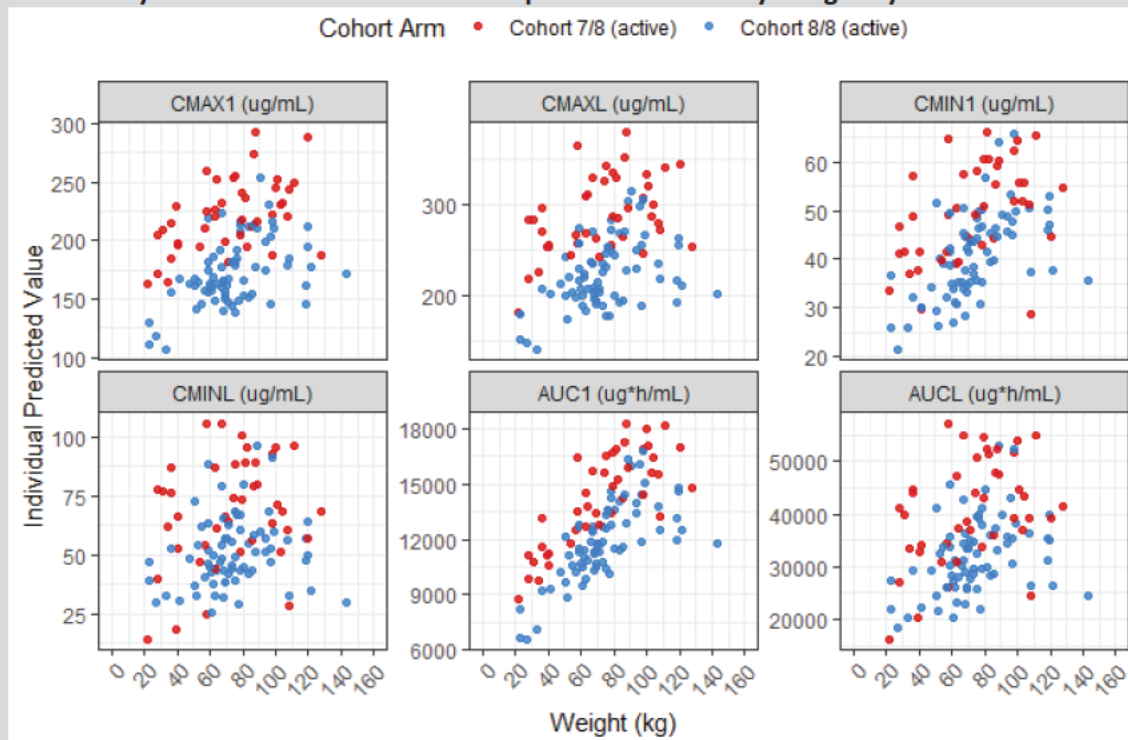
Figure 31. Study IM101311 Body Weight Versus Age



Source: Reviewer Analysis of Applicant's popPK/E-R Datasets

As expected from the popPK analysis, weight was significantly associated with exposure in the E-R dataset. Exposure also tended to be higher in Cohort 7/8 compared to 8/8 independent of body weight, as shown in Figure 32. Lower exposure was associated with lower body weight as well as younger age, which is to be expected given the association between age and weight. In particular, pediatric patients aged 6 to <13 years tended to have lower exposure than patients aged 13 to <18 years or patients aged ≥ 18 years, as shown in Figure 33.

Figure 32. Study IM101311 Model-Predicted Exposure Versus Body Weight by Cohort

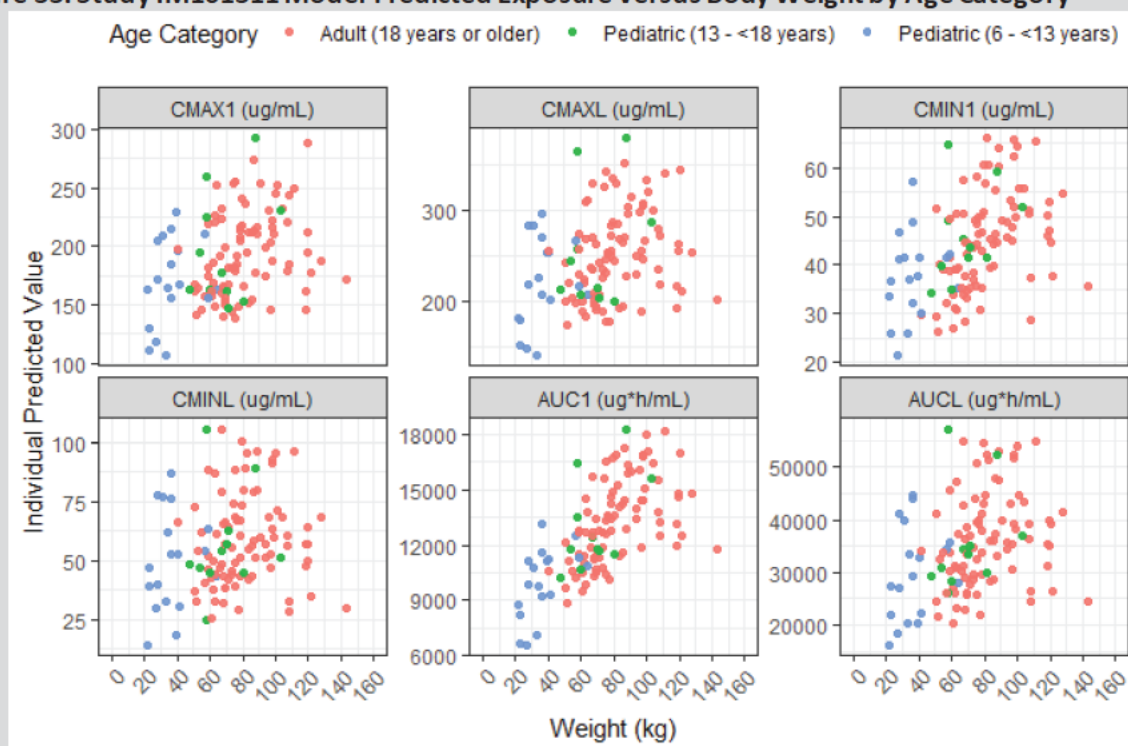


All patients received 10 mg/kg (maximum of 1000 mg) abatacept via 1-hour IV infusion on the day before transplant and on Day 5, Day 14, and Day 28 after transplant.

AUC1 = AUC from 0-144 h after start of first dose; AUCL = AUC from 0-360 h after start of last dose (696-1056 h after start of first dose); Cmax1 = maximum concentration between 0-144 h after start of first dose; CmaxL = maximum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); Cmin1 = minimum concentration between 1-144 h after start of first dose; CminL = minimum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CV = coefficient of variation; h = hours.

Source: Reviewer Analysis of Applicant's popPK/E-R Datasets

Figure 33. Study IM101311 Model-Predicted Exposure Versus Body Weight by Age Category



All patients received 10 mg/kg (maximum of 1000 mg) abatacept via 1-hour IV infusion on the day before transplant and on Day 5, Day 14, and Day 28 after transplant.

AUC1 = AUC from 0-144 h after start of first dose; AUCL = AUC from 0-360 h after start of last dose (696-1056 h after start of first dose); Cmax1 = maximum concentration between 0-144 h after start of first dose; CmaxL = maximum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); Cmin1 = minimum concentration between 1-144 h after start of first dose; CminL = minimum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CV = coefficient of variation; h = hours.

Source: Reviewer Analysis of Applicant's popPK/E-R Datasets

Even though exposure tended to be lower with younger age and lower body weight, the difference between geometric mean exposure in patients aged 6 to <13 years and patients aged 18 years and older was predicted to be <20% for the exposure parameters of Cmax and Cmin for the first dose as well as Cmax, Cmin, and AUC for the last dose. A summary of exposure according to age group is presented in Table 76.

Additionally, 100% (115/115) of patients in Study IM101311 who received abatacept (with age range of 6 years to 76 years) had a predicted concentration on Day 42 following transplant above the Applicant's suggested 10 ug/mL threshold for maximum T-cell inhibition.

Overall, there is not expected to be a clinically significant difference in exposure following the 4-dose regimen of abatacept 10 mg/kg (max of 1000 mg) between patients aged 6 to <13 years, patients aged 13 to <18 years, and patients aged 18 years and older.

Table 76. Summary of Individual Predicted Abatacept Exposure According to Age Group in the Exposure-Response Dataset

Covariate	Statistic	6 - <13 years (n=18)	13 - <18 years (n=11)	18 years and older (n=86)
C _{MAX} 1 (ug/mL)	Geo Mean (CV%)	165.6 (23.4%)	192 (23.5%)	190.6 (18.2%)
	Median	166	178	187.5
	Min - Max	107 - 229	147 - 292	139 - 289
C _{MAX} L (ug/mL)	Geo Mean (CV%)	216 (23.6%)	248.6 (23.1%)	246.9 (19%)
	Median	217.5	235	250
	Min - Max	141 - 297	199 - 379	173 - 352
C _{MIN} 1 (ug/mL)	Geo Mean (CV%)	36.6 (24.8%)	45.1 (20.4%)	44 (23.1%)
	Median	37.4	43.6	44.9
	Min - Max	21.5 - 57.3	34.2 - 64.9	26.3 - 66
C _{MIN} L (ug/mL)	Geo Mean (CV%)	45 (53.1%)	53.7 (39.1%)	56 (34.3%)
	Median	49.8	51	56.8
	Min - Max	14.2 - 87.4	25 - 106	25.3 - 106
AUC1 (ug*h/mL)	Geo Mean (CV%)	9750.8 (20.9%)	12868.5 (18.8%)	13125.2 (17.1%)
	Median	10310	11800	13150
	Min - Max	6580 - 13100	10200 - 18300	8860 - 18200
AUCL (ug*h/mL)	Geo Mean (CV%)	28563.5 (31.9%)	34759.3 (25.2%)	35246.2 (25.1%)
	Median	28700	33500	35650
	Min - Max	16200 - 44800	26000 - 57300	20300 - 55000

All patients received 10 mg/kg (maximum of 1000 mg) abatacept via 1-hour IV infusion on the day before transplant and on Day 5, Day 14, and Day 28 after transplant.

AUC1 = AUC from 0-144 h after start of first dose; AUCL = AUC from 0-360 h after start of last dose (696-1056 h after start of first dose); C_{max}1 = maximum concentration between 0-144 h after start of first dose; C_{max}L = maximum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); C_{min}1 = minimum concentration between 1-144 h after start of first dose; C_{min}L = minimum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CV = coefficient of variation; geo mean = geometric mean; h = hours.

Source: Reviewer Analysis of Applicant's popPK/E-R Datasets

19.4.1-1.4.3 Exposure According to eGFR

The popPK analysis also identified a significant covariate effect for eGFR where higher eGFR was associated with higher clearance. Higher eGFR values tended to be associated with lower abatacept exposure, as displayed in Figure 34. As discussed in Section 19.4.1-1.2.3, this may be explained by a correlation between eGFR and other covariates such as body size, developmental stage, or protein catabolism. Additionally, Figure 34 shows significant overlap between predicted exposure in patients aged 6 to <13 years and patients aged 13 years and older despite the higher average eGFR in younger patients.

Figure 34. Study IM101311 Model-Predicted Exposure Versus eGFR by Age Category



All patients received 10 mg/kg (maximum of 1000 mg) abatacept via 1-hour IV infusion on the day before transplant and on Day 5, Day 14, and Day 28 after transplant.

AUC1 = AUC from 0-144 h after start of first dose; AUCL = AUC from 0-360 h after start of last dose (696-1056 h after start of first dose); Cmax1 = maximum concentration between 0-144 h after start of first dose; CmaxL = maximum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); Cmin1 = minimum concentration between 1-144 h after start of first dose; CminL = minimum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CV = coefficient of variation; h = hours.

Source: Reviewer Analysis of Applicant's popPK/E-R Datasets

19.4.1-1.5 Exposure-Matching for Patients Aged 2 to 6 years

19.4.1-1.5.1 Introduction

The disease progression of aGVHD and response to treatment is expected to be sufficient similar in pediatric patients aged 2 to <6 years and patients aged 6 years and older, to allow for extrapolation of efficacy down to 2 years of age from patients aged 6 years and older. The final popPK model was used to determine the abatacept dose which would result in similar exposure in patients aged 2 to <6 years compared to patients aged 6 years and older receiving 10 mg/kg IV.

19.4.1-1.5.2 Virtual 2 to <6 Year Old Population Dataset

The Applicant created a virtual pediatric population containing 10,000 patients aged 2 to <6 years old with uniform age and sex distribution. Weight was simulated from age and sex based on CDC growth charts. The eGFR for all patients in the virtual pediatric dataset was set to the median value from 6 to

<13 year old IM101311 patients (159 mL/min/1.73m²). The AST for all patients in the virtual pediatric dataset was set to the median value from 6 to <13 year old IM101311 patients (29 u/L).

Reviewer Comments

The virtual population of 10,000 pediatric patients aged 2 to <6 years is generally acceptable for simulation of abatacept exposure for the indication of aGVHD prevention in this patient population. However, the fixed eGFR and AST values in the virtual population will likely underestimate the variability in abatacept CL.

19.4.1-1.5.3 Methods

The Applicant's final popPK model was used for simulation of abatacept exposure. All simulated abatacept doses were IV infused over one hour. Abatacept concentrations were simulated in the virtual 2 to <6 year population from the day before transplant (Day -1) up to Day 42 after transplant for the following dose regimens:

- 10 mg/kg IV on Days -1, 5, 14, and 28
- 12 mg/kg IV on Days -1, 5, 14, and 28
- 15 mg/kg IV on Days -1, 5, 14, and 28
- 20 mg/kg IV on Days -1, 5, 14, and 28
- 15 mg/kg IV on Day -1, followed by 10 mg/kg IV on 5, 14, and 28
- 15 mg/kg IV on Days -1 and 5, followed by 10 mg/kg IV on Days 14 and 28
- 15 mg/kg IV on Day -1, followed by 12 mg/kg IV on 5, 14, and 28
- 15 mg/kg IV on Days -1 and 5, followed by 12 mg/kg IV on Days 14 and 28

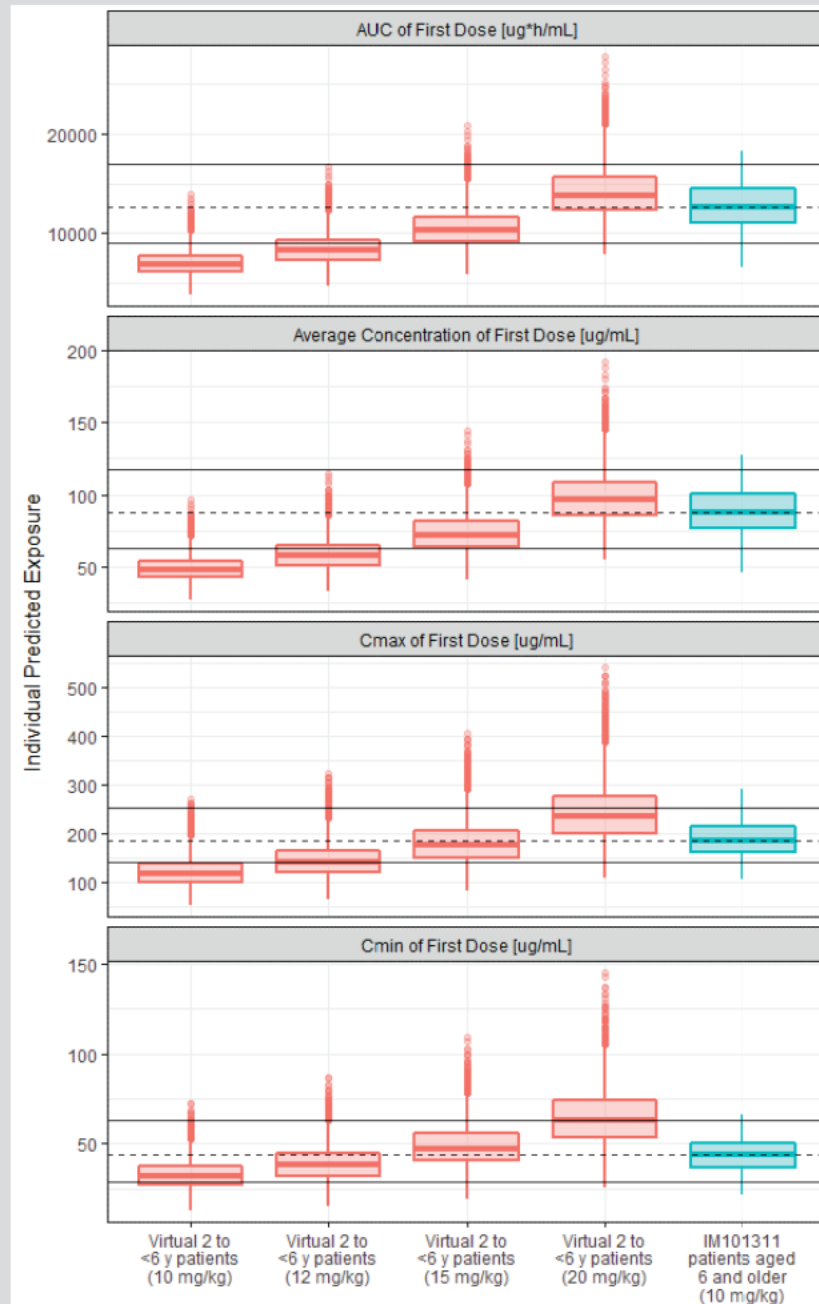
The criteria for exposure-matching specified the following:

1. Target exposures in pediatrics aged 2 to <6 years should be within the 5th and 95th percentile of exposure observed in older children (6 to <18 years of age) and adults.
2. Trough concentrations should exceed 10 ug/mL, which was the predicted threshold associated with maximal autoimmunity response based on in vitro and in vivo preclinical data.
3. Target C_{max} was not to exceed that which has been observed in Study IM101311.

19.4.1-1.5.4 Simulated Exposure Results

The Applicant's predictions of exposure for the first abatacept dose in the virtual 2 to <6 year old population and Study IM101311 patients aged 6 years and older are displayed in **Figure 35**. The simulated 15 mg/kg dose in virtual patients aged 2 to <6 years appeared to result in similar exposure compared to 10 mg/kg in Study IM101311 patients aged 6 years and older.

Figure 35. Simulated Abatacept Exposure Measures for First Dose According to Dose Level and Age Group



Study IM101311 patients included 115 patients aged 6 years and older receiving hematopoietic stem cell transplant due to hematologic malignancy. Virtual 2 to <6 year old population contained 10,000 subjects. Boxes are 25th, 50th, and 75th percentiles; whiskers are $\pm 1.58 \times \text{IQR}/\sqrt{n}$. Dashed black reference line shows the median of predicted exposure in IM101311 patients following 10 mg/kg. Solid black reference lines show 5th and 95th percentiles of predicted exposure in IM101311 patients following 10 mg/kg. Abatacept was administered on the day before transplant (Day -1) and then Days 5, 14, and 28 after transplant. AUC = area under the concentration-versus-time curve; Cmax = maximum concentration; Cmin = minimum concentration; IQR = interquartile range; y = years.

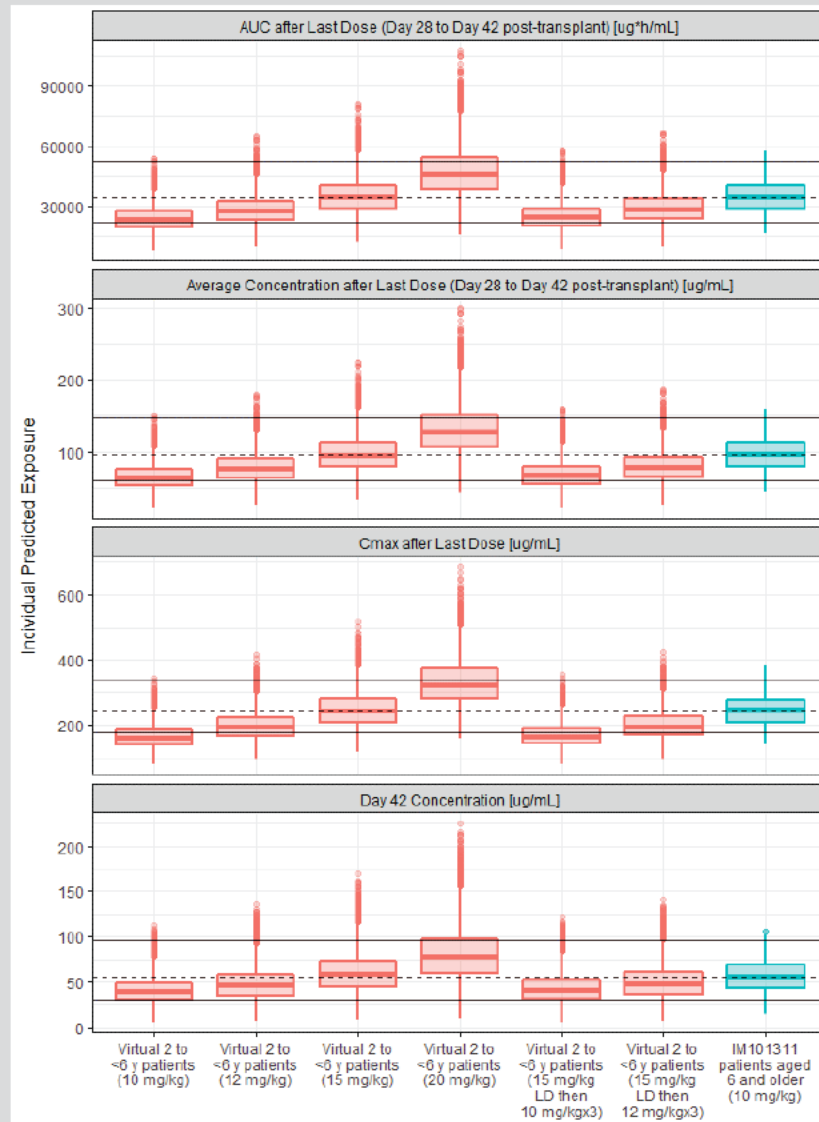
Source: Reviewer Analysis

The Applicant's predictions of exposure following the last abatacept dose (administered on Day 28 after transplantation) in the virtual 2 to <6 year old population and Study IM101311 patients aged 6 years and older are displayed in **Figure 36** and summarized in **Table 77**. Both the simulated 15 mg/kg 4-dose regimen and the 15 mg/kg loading dose followed by 12 mg/kg x3 dose regimen resulted in similar (difference in median < 20%) Day 42 concentration, AUCL, and CavL in virtual patients aged 2 to <6 years compared to 10 mg/kg in Study IM101311 patients aged 6 years and older.

Although the 15 mg/kg loading dose followed by 12 mg/kg x3 dose regimen in virtual 2 to <6 year old patients resulted in a 21% lower median C_{maxL} compared to 10 mg/kg in Study IM101311 patients, there is no significant impact on efficacy expected. Due to the mechanism of action of abatacept and E-R analysis, the minimum concentration and/or average concentration would have stronger associations with efficacy compared to C_{max}.

Exposure-matching thus supports 15 mg/kg IV on Day -1 followed by 12 mg/kg IV on Days 5, 14, and 28 for pediatric patients aged 2 to <6 years receiving HSCT from URD due to HM for the prevention of aGVHD. This dose is expected to result in similar exposure for the first dose (C_{max1}, C_{min1}, AUC₁, and Cav₁) and similar exposure following the last dose (Day 42 concentration, AUCL, and CavL) in patients aged 2 to <6 years compared to the 4-dose regimen of 10 mg/kg in patients aged 6 years and older. Exposure-matching is acceptable for this indication and patient population (see **Section 6.2.2.1**), but confirmation of PK differences in patients aged 2 to <6 years and patients aged 6 years and older is needed. This will be addressed in the PMR detailed in **Section 13**.

Figure 36. Simulated Abatacept Exposure Measures for Last Dose According to Dose Level and Age Group



Study IM101311 patients included 115 patients aged 6 years and older receiving hematopoietic stem cell transplant due to hematologic malignancy. Virtual 2 to <6 year old population contained 10,000 subjects. Boxes are 25th, 50th, and 75th percentiles; whiskers are $\pm 1.58 \times \text{IQR}/\sqrt{n}$. Dashed black reference line shows the median of predicted exposure in IM101311 patients following 10 mg/kg. Solid black reference lines show 5th and 95th percentiles of predicted exposure in IM101311 patients following 10 mg/kg.

Abatacept was administered on the day before transplant (Day -1) and then Days 5, 14, and 28 after transplant. AUC = area under the concentration-versus-time curve; Cmax = maximum concentration; IQR = interquartile range; LD = loading dose on the day before transplantation (Day -1); y = years.

Source: Reviewer Analysis

Table 77. Summary of Simulated Abatacept Exposure Measures for Last Dose According to Dose Level and Age Group

STATISTIC	Virtual 2 to <6 y Population			Study IM101311 Patients Overall 10 mg/kg	Study IM101311 Patients (By Age Subgroup)		
	15 mg/kg LD, then 10 mg/kg x3	15 mg/kg LD, then 12 mg/kg x3	15 mg/kg		6 - <13 y (10 mg/kg)	13 - <18 y (10 mg/kg)	18 y and older (10 mg/kg)
N	10000	10000	10000	115	18	11	86
AUCL (ug*h/mL)							
Geo Mean (CV%)	23815.8 (26.8%)	27898.9 (26.3%)	34022.2 (25.8%)	34059.9 (27.2%)	28563.5 (31.9%)	34759.3 (25.2%)	35246.2 (25.1%)
Geo Mean 95% CI	23693.2 - 23939	27757.8 - 28040.7	33853.3 - 34192	32420.7 - 35782	24469.9 - 33341.9	29419.4 - 41068.4	33425.2 - 37166.4
Median	24000.5	28101.5	34200	34300	28700	33500	35650
5th - 95th percentile	15322.8 - 36234.1	18138.7 - 42135.3	22300 - 51100	21840 - 52680	18070 - 44120	27200 - 54850	23575 - 52950
CAVL (ug/mL)							
Geo Mean (CV%)	66.2 (26.8%)	77.5 (26.3%)	94.5 (25.8%)	94.6 (27.2%)	79.4 (31.8%)	96.6 (25.2%)	97.9 (25.2%)
Geo Mean 95% CI	65.8 - 66.5	77.1 - 77.9	94 - 95	90.1 - 99.4	68 - 92.6	81.7 - 114.1	92.9 - 103.3
Median	66.7	78.1	95.1	95.3	79.8	93.1	99
5th - 95th percentile	42.6 - 100.7	50.4 - 117	62 - 142	60.8 - 146.6	50.1 - 122.3	75.6 - 152.5	65.5 - 147.5
CMAXL (ug/mL)							
Geo Mean (CV%)	165.5 (21.1%)	195.8 (21%)	241.3 (21%)	242 (20.6%)	216 (23.6%)	248.6 (23.1%)	246.9 (19%)
Geo Mean 95% CI	164.8 - 166.2	195 - 196.6	240.3 - 242.3	233 - 251.2	192.4 - 242.5	213.3 - 289.8	237.2 - 257.1
Median	164.4	194.6	240	245	217.5	235	250
5th - 95th percentile	118.2 - 234.3	140 - 277.1	173 - 341	179.1 - 336.8	146.9 - 286	201 - 372	188.2 - 334.8
CMINL (ug/mL)							
Geo Mean (CV%)	39.4 (41.5%)	46.1 (40.8%)	56.1 (40%)	53.9 (38.6%)	45 (53.1%)	53.7 (39.1%)	56 (34.3%)
Geo Mean 95% CI	39.1 - 39.7	45.7 - 46.5	55.7 - 56.5	50.3 - 57.7	35.1 - 57.7	41.7 - 69.2	52.1 - 60.1
Median	40.8	47.6	58	55	49.8	51	56.8
5th - 95th percentile	19.7 - 71.1	23.4 - 82.4	28.7 - 99.3	29.4 - 95.5	17.7 - 79.3	35 - 97.4	32.1 - 95.6

Abatacept was administered on the day before transplantation (Day -1), and then Day 5, Day 14, and Day 28 after transplantation.

AUCL = AUC from 0-360 h after start of last dose (696-1056 h after start of first dose); CAVL = average concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CI = confidence interval; CMAXL = maximum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CMINL = minimum concentration between 1-360 h after start of last dose (697-1056 h after start of first dose); CV = coefficient of variation; geo mean = geometric mean; LD = loading dose on Day -1; y = years.

Source: Reviewer Analysis

19.4.1-1.5.5 Updated PopPK Model and Simulation after Including SC Abatacept Data from pJIA Patients

As discussed above, the Applicant’s popPK model (Section 19.4.1-1.2.3) was developed from a dataset containing patients down to 6 years of age, and the absence of data from patients aged 2 to <6 years in the dataset may limit the model’s ability to predict exposure in that age subgroup. Upon request, the Applicant updated their popPK model by including additional PK data from 219 pJIA patients from Study IM101301 aged 2 to <18 years (including 46 patients aged 2 to <6 years) who received subcutaneous (SC) abatacept. This additional PK data was added to the existing popPK dataset (n=685 patients) resulting in an updated popPK dataset containing 904 patients total.

The updated popPK model and results are described in “BMS Response to FDA Request dated 05 November 2021” which is dated November 29, 2021. Final estimates for the updated popPK model are presented in Table 78.

Table 78. Summary of Relevant Reviewer Independent Analysis Model Runs

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 V1 (-)	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 V2 (-)	0.839	5.24		
KA	Absorption Rate Constant (1/h)	0.00705	19.2	117 %CV	39.9
F1 ^b	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	NA
Additive Component of RV		5.26E-04	66.9	F [0.001 - 700] ^a	
Minimum Value of the Objective Function = 33065.229					

^a The magnitude of residual variability (%CV) was calculated using the following equation: $(\text{SQRT}(0.0724 \times F^2 + 5.26E-04)/F) \times 100$. 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.

^b Typical value for F1 is not the absolute bioavailability. $F_{\text{Absolute}} = 1/(1 + \exp(-F1 - F1_{\text{IIV}}))$. At the reference value $F_{\text{Absolute}} = 84.9\%$. The magnitude of variability is provided on the logit scale

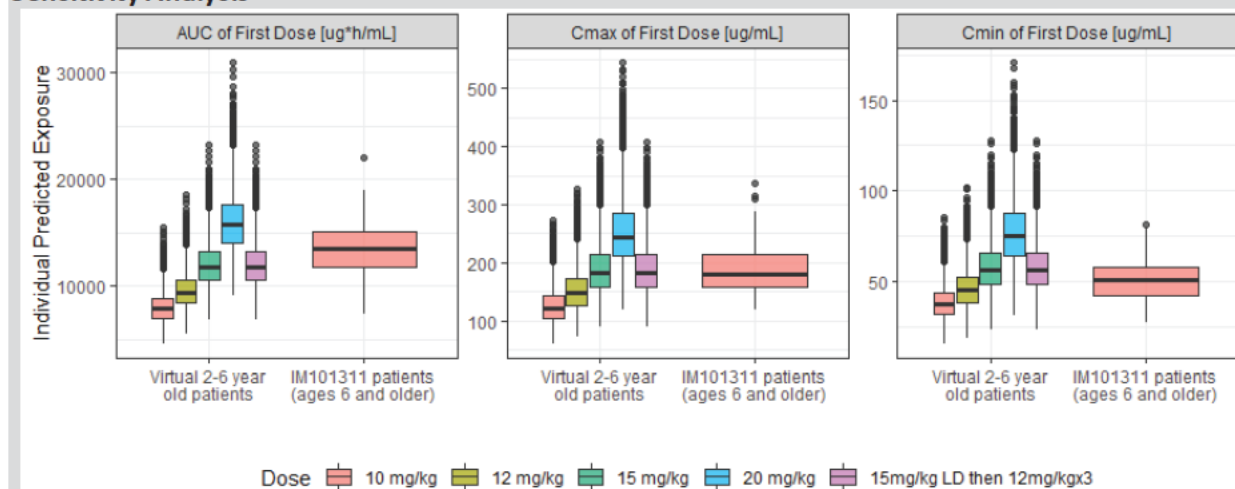
Source: Table 1.1-1 in Applicant's "BMS Response to FDA Request dated 05 November 2021" which is dated November 29, 2021.

Reviewer Comments

The Reviewer used the Applicant's updated popPK model control stream to simulate abatacept concentration up to Day 42 following abatacept 10 mg/kg on Day -1, 5, 14, and 28 in Study IM101311 patients. Exposure simulated using the updated popPK model in the virtual 2 to <6 year old population was provided by the Applicant. The virtual 2 to <6 year old population was previously described in Section 19.4.1-1.5.2.

Patients aged 2 to 6 years administered 15 mg/kg on the day before transplantation are expected to have similar exposure with first dose (C_{MAX1}, C_{MIN1}, AUC₁, and C_{AV1}) compared to patients aged 6 years and older administered 10 mg/kg on the day before transplantation (Figure 37). For exposure-matching following the last dose, patients aged 2 to <6 years administered 15 mg/kg IV on Day -1 followed by 12 mg/kg IV on Days 5, 14, and 28 are expected to have similar C_{MAXL}, C_{MINL}, AUC_L, and C_{AVL} compared to patients aged 6 years and older administered 10 mg/kg on Days -1, 5, 14, and 28 (Figure 38).

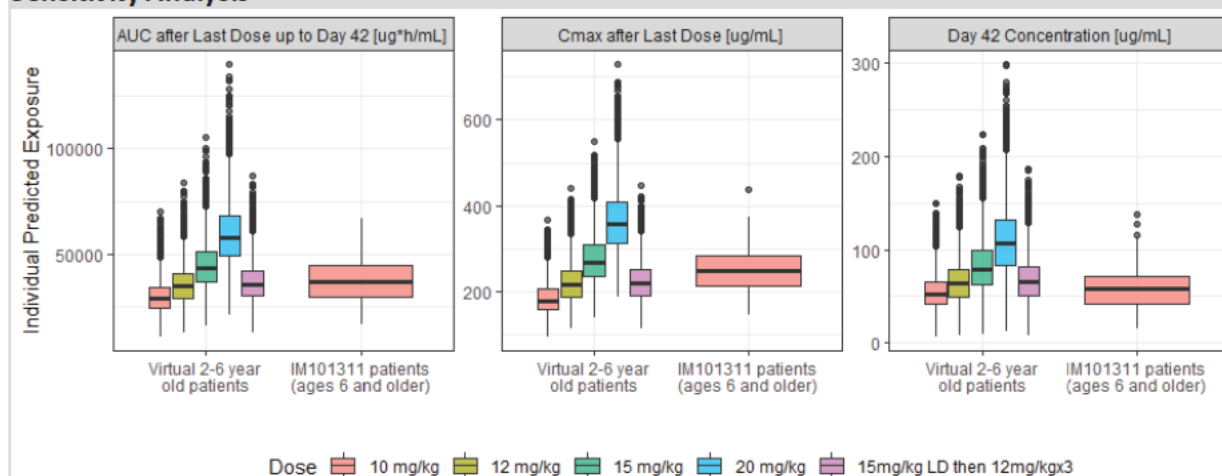
Figure 37. Simulated Abatacept Exposure after First Dose from the Updated PopPK Model for Sensitivity Analysis



Study IM101311 patients included 115 patients aged 6 years and older receiving hematopoietic stem cell transplant due to hematologic malignancy. Virtual 2 to <6 year old population contained 10,000 subjects. Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. Abatacept was administered on the day before transplantation (Day -1), and then Day 5, Day 14, and Day 28 after transplantation. AUC = area under the concentration-versus-time curve; C_{max} = maximum concentration; C_{min} = minimum concentration; LD = loading dose on the day before transplantation (Day -1).

Source: Reviewer Analysis

Figure 38. Simulated Abatacept Exposure after Last Dose from the Updated PopPK Model for Sensitivity Analysis



Study IM101311 patients included 115 patients aged 6 years and older receiving hematopoietic stem cell transplant due to hematologic malignancy. Virtual 2 to <6 year old population contained 10,000 subjects. Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. Abatacept was administered on the day before transplantation (Day -1), and then Day 5, Day 14, and Day 28 after transplantation. AUC = area under the concentration-versus-time curve; Cmax = maximum concentration; LD = loading dose on the day before transplantation (Day -1).

Source: Reviewer Analysis

In general, the updated popPK model and simulation supports the proposed dosing regimen (15 mg/kg on Day -1 followed by 12 mg/kg on Days 5, 14, and 28) in ages 2 to <6 years as the final popPK model described in detail in Section 19.4.1-1.2.3. However, certain uncertainty remains with the updated model and prediction:

- Uncertainty regarding estimates of KA and SC relative bioavailability (F1) given that the only SC PK data was from a single study in pediatric patients, and that there is no IV PK data in patients 2 to <6 years old;
- Shrinkage above 50% on the IIV on VC and IIV on the absorption rate constant (KA);
- A higher estimate for the power of weight and GFR on CL accompanied with a lower estimate for the female gender effect;
- Higher CWRES values with Study IM101033 may reflect worse model performance with IV abatacept in patients younger than 18 years.

19.4.1-1.5.6 Conclusions

The proposed dosing regimen of 15 mg/kg IV on Day -1 followed by 12 mg/kg IV on Days 5, 14, and 28 in patients aged 2 to <6 years is predicted to achieve similar exposure compared to 10 mg/kg IV on Days -1, 5, 14, and 28 in patients aged 6 years and older. Due to lack of data with IV abatacept in patients age 2 to <6 years, the model-predicted PK and recommended dosing regimen in this age group will be confirmed as part of a PMR (see Section 13).

19.4.1-2 Exposure-Response

19.4.1-2.1 Summary of Exposure-Response

The E-R analyses identified that higher abatacept concentration on Day 42 after transplant was associated with improved severe (grade III to IV) aGVHD-free survival (aGFS) up to Day 180 assessment as well as improved overall survival (OS) up to Day 180 assessment. Patients who experienced relapse of underlying malignancy had worse aGFS and worse OS compared with patients who did not experience relapse.

The exploratory E-R analyses of safety did not identify any E-R relationships for the three investigated safety events, which included invasive cytomegalovirus (CMV) disease, CMV viremia, and infection. However, as this was an exploratory analysis with limited scope, this does not rule out the possibility of other E-R safety relationships.

19.4.1-2.2 Introduction

The primary objective of the Applicant's E-R analysis was to characterize the relationship between abatacept exposure and severe aGFS as well as OS up to Day 180 post-transplantation in patients aged 6 years and older receiving URD HSCT due to HM.

The exploratory objectives of the Applicant's E-R analysis were to graphically explore the relationship between exposure and safety (time to first infection regardless of seriousness, time to first invasive CMV disease, and time to first CMV viremia) in patients aged 6 years and older receiving URD HSCT due to HM.

19.4.1-2.3 Data

The E-R dataset contained events occurring within the Day 180 analysis period, which included all events from the time of first abatacept dose up to the Day 180 assessment in each individual patient. The Day 180 assessment could take place as late as Day 225 after transplantation.

The E-R dataset for the Applicant's E-R efficacy and exploratory E-R safety contained 184 patients from Study IM101311. This included 115 patients who received abatacept + CNI + methotrexate (Cohort 7/8 or Cohort 8/8) and 69 patients who received placebo + CNI + methotrexate (Cohort 8/8 only). Patients who were administered placebo instead of abatacept were assigned abatacept exposure of zero.

Abatacept concentration was simulated up to 1056 hours after start of first infusion (Day 42 after transplant on Day 1) in patients who received abatacept. The simulation utilized the planned dosing regimen of 10 mg/kg (maximum dose of 1000 mg) via 1-hour IV infusion given at 0 hours (Day -1), 144 hours (Day 5), 360 hours (Day 14), and 696 hours (Day 28) after start of first infusion. Individual predicted minimum concentration (C_{min}), maximum concentration (C_{max}), average concentration (C_{av}), and area-under-the-concentration-versus-time curve (AUC) were determined for all subjects for the first dose and the last dose.

The minimum concentration after last dose (C_{minL}) was calculated as the minimum concentration between 1 and 360 hours after start of last dose (which was 697 and 1056 hours after start of first dose), and so C_{minL} was equal to the concentration on Day 42 after transplant.

Average concentration for the first dose (C_{av1}) was calculated by dividing AUC from time 0 to 144 hours after first dose (AUC₁) by 144 hours, and average concentration for the last dose (C_{avL}) was calculated by dividing AUC from time 696 to 1056 hours after first dose (AUC_L) by 360 hours. The average concentration on Day 42 (C_{av42}) was calculated by dividing the AUC from time 1032 to 1056 hours after start of first dose (AUC₄₂) by 24 hours.

Summary statistics of patient characteristics and demographics in the E-R dataset are presented in Table 79. The 7/8 Cohort appears to have a slightly lower proportion of pediatric patients compared to the 8/8 Cohort (27/42 patients [64.3%] versus 115/142 patients [81.0%], respectively). However, neither the range nor median values of age and body weight differed significantly between cohorts. Although the majority of patients in each cohort were White, the 7/8 Cohort included a higher proportion of patients in non-White subgroups of race (12/42 patients [28.6%]) compared to the 8/8 Cohort (18/142 patients [12.7%]). In particular, the proportion of Black or African American patients was higher in the 7/8 Cohort (7/42 patients [16.7%]) compared to the 8/8 Cohort (5/142 patients [3.5%]). There were also imbalances in conditioning regimen and the CNI used for aGVHD prophylaxis between cohorts, as well as a slightly higher incidence of underlying malignancy relapse up to Day 180 assessment in the 8/8 Cohort compared to the 7/8 Cohort. One or more of these imbalances may have contributed to safety and/or efficacy outcomes.

Table 79. Summary of Baseline Patient Characteristics in the Exposure-Response Dataset

Covariate	Statistic	7/8 Cohort (Abatacept)	8/8 Cohort (Abatacept Arm)	8/8 Cohort (Placebo Arm)
Baseline Age (years)	n	42	73	69
	Mean (CV%)	36.3 (63.1)	40.8 (47.8)	39.9 (50.9)
	Median	39.5	44	40
	Min - Max	6 - 76	6 - 71	7 - 74
Age Category				
Adult (≥18 years)	n (%)	27 (64.3%)	59 (80.8%)	56 (81.2%)
Pediatric (≥6 to <18 years)	n (%)	15 (35.7%)	14 (19.2%)	13 (18.8%)
Sex				
Female	n (%)	16 (38.1%)	32 (43.8%)	32 (46.4%)
Male	n (%)	26 (61.9%)	41 (56.2%)	37 (53.6%)
Baseline Weight (kg)	n	42	73	69
	Mean (CV%)	72.3 (38.7)	74.2 (31.5)	75.4 (29.8)
	Median	74.8	71.3	76.7
	Min - Max	22 - 127.3	23.1 - 142.7	26.3 - 131.7
Race				
White	n (%)	30 (71.4%)	63 (86.3%)	61 (88.4%)
Black or African American	n (%)	7 (16.7%)	3 (4.1%)	2 (2.9%)
Asian/Pacific Islander	n (%)	2 (4.8%)	4 (5.5%)	2 (2.9%)
American Indian/Alaska Native	n (%)	1 (2.4%)	1 (1.4%)	0
Other	n (%)	0	1 (1.4%)	2 (2.9%)
Unknown	n (%)	2 (4.8%)	1 (1.4%)	2 (2.9%)

Covariate	Statistic	7/8 Cohort (Abatacept)	8/8 Cohort (Abatacept Arm)	8/8 Cohort (Placebo Arm)
Baseline Performance Score				
Missing/unknown	n (%)	13 (31.0%)	28 (38.4%)	31 (44.9%)
50	n (%)	0	1 (1.4%)	0
60	n (%)	3 (7.1%)	4 (5.5%)	5 (7.2%)
70	n (%)	3 (7.1%)	2 (2.7%)	5 (7.2%)
80	n (%)	10 (23.8%)	19 (26%)	11 (15.9%)
90	n (%)	8 (19%)	18 (24.7%)	13 (18.8%)
100	n (%)	5 (11.9%)	1 (1.4%)	4 (5.8%)
Conditioning Regimen				
Busulfan and cyclophosphamide	n (%)	12 (28.6%)	28 (38.4%)	21 (30.4%)
Busulfan and fludarabine	n (%)	8 (19%)	7 (9.6%)	2 (2.9%)
Melphalan and fludarabine	n (%)	11 (26.2%)	18 (24.7%)	20 (29%)
Total body irradiation and chemotherapy	n (%)	11 (26.2%)	20 (27.4%)	26 (37.7%)
GVHD Prophylaxis				
Cyclosporine	n (%)	15 (35.7%)	11 (15.1%)	11 (15.9%)
Tacrolimus	n (%)	27 (64.3%)	62 (84.9%)	58 (84.1%)
Type of Graft Received				
Bone marrow	n (%)	20 (47.6%)	33 (45.2%)	26 (37.7%)
Cytokine mobilized peripheral blood	n (%)	22 (52.4%)	40 (54.8%)	43 (62.3%)
Relapse of Underlying Malignancy up to Day 180 Assessment				
No relapse	n (%)	39 (92.9%)	64 (87.7%)	58 (84.1%)
Relapse	n (%)	3 (7.1%)	9 (12.3%)	11 (15.9%)

Abatacept arm = abatacept + calcineurin inhibitor + methotrexate. Placebo arm = placebo + calcineurin inhibitor + methotrexate.

CV = coefficient of variation.

Source: Reviewer Analysis of Applicant's E-R Datasets

Summary statistics of patient characteristics and demographics in the E-R dataset according to each quartile of predicted C_{min}L are presented in Table 80. Due to the lower clearance predicted in Cohort 7/8 compared to Cohort 8/8, most of the patients in the highest C_{min}L quartile (Q4) were from Cohort 7/8. The active arm of Cohort 8/8 had a larger number of patients compared to Cohort 7/8, and the majority of patients in Q1, Q2, and Q3 are from Cohort 8/8. Although there was no clear trend in the proportion of pediatric patients across quartiles, lower exposure was associated with lower median age, and lower median weight, consistent with the popPK findings described above (Figure 33).

Additionally, there may be imbalances in conditioning regimen and type of graft received across C_{min}L exposure quartiles. These covariates may have impacted safety and efficacy outcomes independent of an association with abatacept exposure.

Table 80. Summary of Patient Characteristics in the Exposure-Response Dataset Stratified by Minimum Concentration Following Last Dose up to Day 42 After Transplant

Covariate	Statistic	Placebo (n=69)	C _{min} L Q1 (n=29)	C _{min} L Q2 (n=29)	C _{min} L Q3 (n=28)	C _{min} L Q4 (n=29)
Cohort and Arm						

NDA/BLA Multi-disciplinary Review and Evaluation [BLA 125118 S-240]
 ORENCIA (abatacept)

Covariate	Statistic	Placebo (n=69)	CminL Q1 (n=29)	CminL Q2 (n=29)	CminL Q3 (n=28)	CminL Q4 (n=29)
Cohort 7/8 (active)	n (%)	0	5 (17.2%)	6 (20.7%)	9 (32.1%)	22 (75.9%)
Cohort 8/8 (active)	n (%)	0	24 (82.8%)	23 (79.3%)	19 (67.9%)	7 (24.1%)
Cohort 8/8 (placebo)	n (%)	69 (100%)	0	0	0	0
Age (years)	Mean (CV%)	39.9 (50.9)	36.7 (59.9)	34.9 (57)	42.6 (46.9)	42.5 (49.6)
	Median	40	41	38	45	50
	Min - Max	7 - 74	6 - 71	9 - 71	12 - 76	6 - 69
Age Category						
Adult (18 years and older)	n (%)	56 (81.2%)	20 (69%)	19 (65.5%)	24 (85.7%)	23 (79.3%)
Pediatric (6 - <18 years)	n (%)	13 (18.8%)	9 (31%)	10 (34.5%)	4 (14.3%)	6 (20.7%)
Sex						
Female	n (%)	32 (46.4%)	13 (44.8%)	13 (44.8%)	7 (25%)	15 (51.7%)
Male	n (%)	37 (53.6%)	16 (55.2%)	16 (55.2%)	21 (75%)	14 (48.3%)
Baseline Weight (kg)	Mean (CV%)	75.4 (29.8)	65.4 (44.2)	71.1 (32.1)	80.6 (27)	77 (31.9)
	Median	76.7	62.9	67.3	76.5	80.3
	Min - Max	26.3 - 131.7	22 - 142.7	23.1 - 119.1	33.9 - 120	28.4 - 127.3
Race Category						
White	n (%)	61 (88.4%)	26 (89.7%)	22 (75.9%)	23 (82.1%)	22 (75.9%)
Black or African American	n (%)	2 (2.9%)	2 (6.9%)	4 (13.8%)	0	4 (13.8%)
Asian	n (%)	2 (2.9%)	1 (3.4%)	3 (10.3%)	2 (7.1%)	0
American Indian or Alaska Native	n (%)	0	0	0	1 (3.6%)	1 (3.4%)
Other	n (%)	2 (2.9%)	0	0	1 (3.6%)	0
Unknown	n (%)	2 (2.9%)	0	0	1 (3.6%)	2 (6.9%)
Baseline eGFR^a (mL/min/1.73m²)	n	0	27	27	26	27
	Mean (CV%)	N/A	137.6 (39.2)	122.4 (34.3)	117 (38.7)	122.2 (42.7)
	Median	N/A	121	115.9	101.2	110.2
	Min - Max	N/A	71 - 315.2	68 - 208.6	51 - 219.4	65.8 - 307.7
Baseline Performance Score						
50	n (%)	0	1 (3.4%)	0	0	0
60	n (%)	5 (7.2%)	1 (3.4%)	2 (6.9%)	1 (3.6%)	3 (10.3%)
70	n (%)	5 (7.2%)	1 (3.4%)	1 (3.4%)	0	3 (10.3%)
80	n (%)	11 (15.9%)	7 (24.1%)	5 (17.2%)	14 (50%)	3 (10.3%)
90	n (%)	13 (18.8%)	7 (24.1%)	9 (31%)	5 (17.9%)	5 (17.2%)
100	n (%)	4 (5.8%)	1 (3.4%)	3 (10.3%)	1 (3.6%)	1 (3.4%)
Missing/unknown	n (%)	31 (44.9%)	11 (37.9%)	9 (31%)	7 (25%)	14 (48.3%)
Conditioning Regimen						
Busulfan and cyclophosphamide	n (%)	21 (30.4%)	12 (41.4%)	11 (37.9%)	9 (32.1%)	8 (27.6%)
Busulfan and fludarabine	n (%)	2 (2.9%)	2 (6.9%)	4 (13.8%)	3 (10.7%)	6 (20.7%)
Melphalan and fludarabine	n (%)	20 (29%)	6 (20.7%)	4 (13.8%)	9 (32.1%)	10 (34.5%)
TBI and chemotherapy	n (%)	26 (37.7%)	9 (31%)	10 (34.5%)	7 (25%)	5 (17.2%)
GVHD Prophylaxis						
Cyclosporine	n (%)	11 (15.9%)	9 (31%)	6 (20.7%)	4 (14.3%)	7 (24.1%)
Tacrolimus	n (%)	58 (84.1%)	20 (69%)	23 (79.3%)	24 (85.7%)	22 (75.9%)
Type of Graft Received						
Bone marrow	n (%)	26 (37.7%)	17 (58.6%)	18 (62.1%)	7 (25%)	11 (37.9%)

Covariate	Statistic	Placebo (n=69)	CminL Q1 (n=29)	CminL Q2 (n=29)	CminL Q3 (n=28)	CminL Q4 (n=29)
Cytokine mobilized peripheral blood	n (%)	43 (62.3%)	12 (41.4%)	11 (37.9%)	21 (75%)	18 (62.1%)
Relapse of Underlying Malignancy up to Day 180						
No relapse	n (%)	58 (84.1%)	29 (100%)	23 (79.3%)	27 (96.4%)	24 (82.8%)
Relapse	n (%)	11 (15.9%)	0	6 (20.7%)	1 (3.6%)	5 (17.2%)

^aBaseline eGFR was merged according to subject ID from popPK dataset and thus the placebo arm does not have eGFR data.

CminL = Minimum concentration after last dose up to Day 42 after transplant; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; N/A = not available; Q = quartile; TBI = total body irradiation.

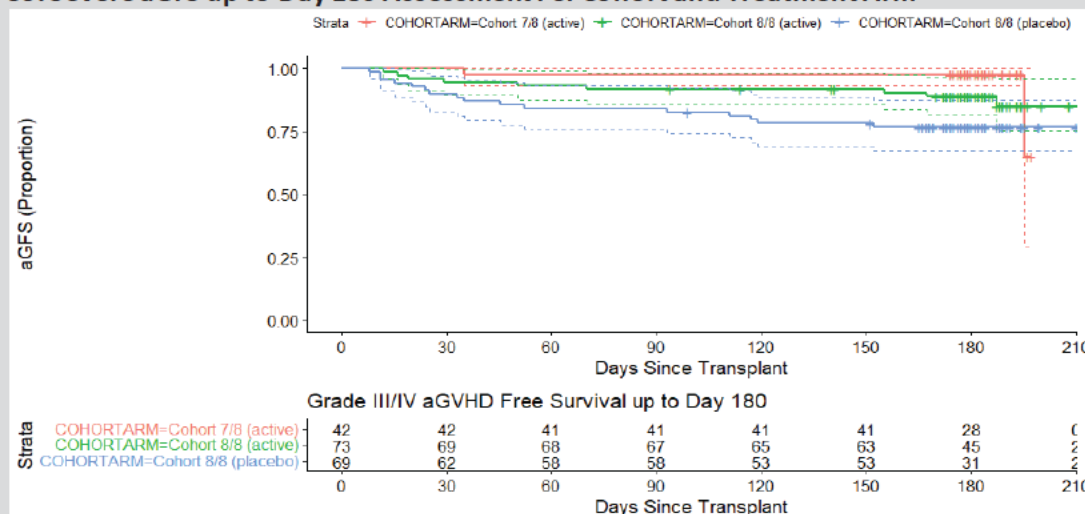
Source: Reviewer Analysis of Applicant's E-R Datasets

19.4.1-2.4 Exposure-Response Analyses of Efficacy

19.4.1-2.4.1 Observed Severe (Grade III/IV) aGFS up to Day 180 Post transplantation

Severe aGFS up to Day 180 assessment in Cohort 7/8 and Cohort 8/8 patients included in the E-R dataset is displayed in Figure 39. Patients in Cohort 8/8 treated with abatacept appeared to have improved aGFS compared to patients in Cohort 8/8 treated with placebo. The limited number of patients and events as well as the lack of placebo arm in the 7/8 Cohort make it difficult to assess the impact of abatacept on severe aGFS.

Figure 39. Severe aGFS up to Day 180 Assessment Per Cohort and Treatment Arm



Active = Abatacept + calcineurin inhibitor + methotrexate; aGFS = aGVHD-free survival; aGVHD = acute graft versus host disease; placebo = placebo + calcineurin inhibitor + methotrexate.

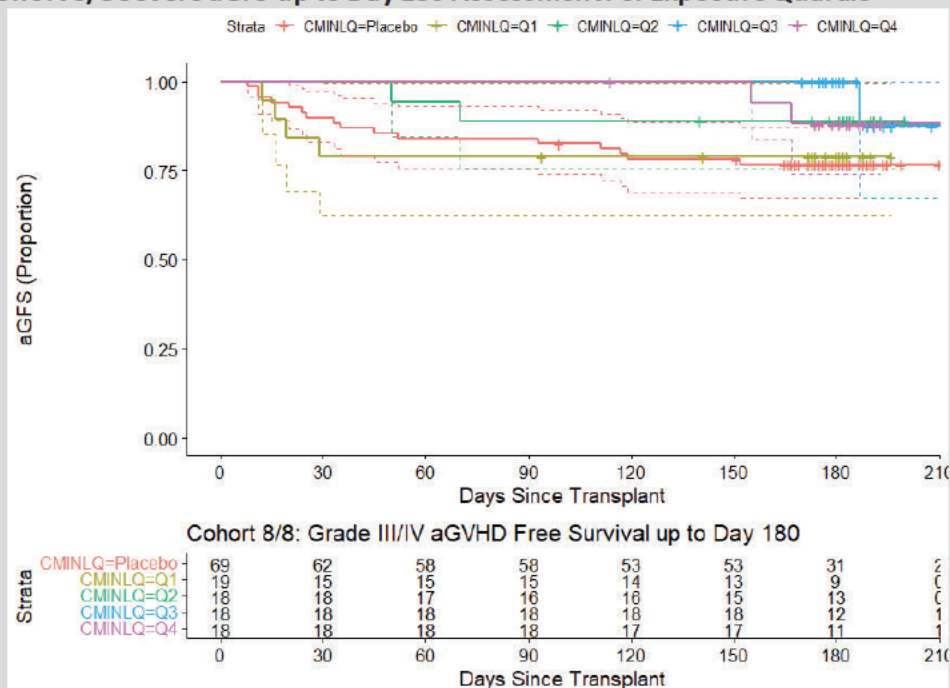
Source: Reviewer Analysis of Applicant's E-R efficacy dataset ('s311eff.xpt')

Observed severe aGFS according to CminL quartile in Cohort 8/8 and Cohort 7/8 is displayed in Figure 40 and Figure 41, respectively. The number of events per cohort and per abatacept exposure quartile within each cohort is described in Table 81.

In Cohort 8/8, the lowest exposure quartile (Q1) appears to have worse aGFS than the higher exposure quartiles and worse aGFS in the first few months after transplant than the placebo arm. Differences in baseline disease characteristics could potentially contribute to the differences in aGFS. Interpretation of results in Cohort 8/8 may also be limited by the relatively small number of patients and events.

There is potentially worse aGFS for the lowest exposure quartile in Cohort 7/8, but the relatively limited number of patients per quartile (n=10 to 11) and the limited number of events (2 events observed in 42 patients total) make it difficult to determine the significance of this association.

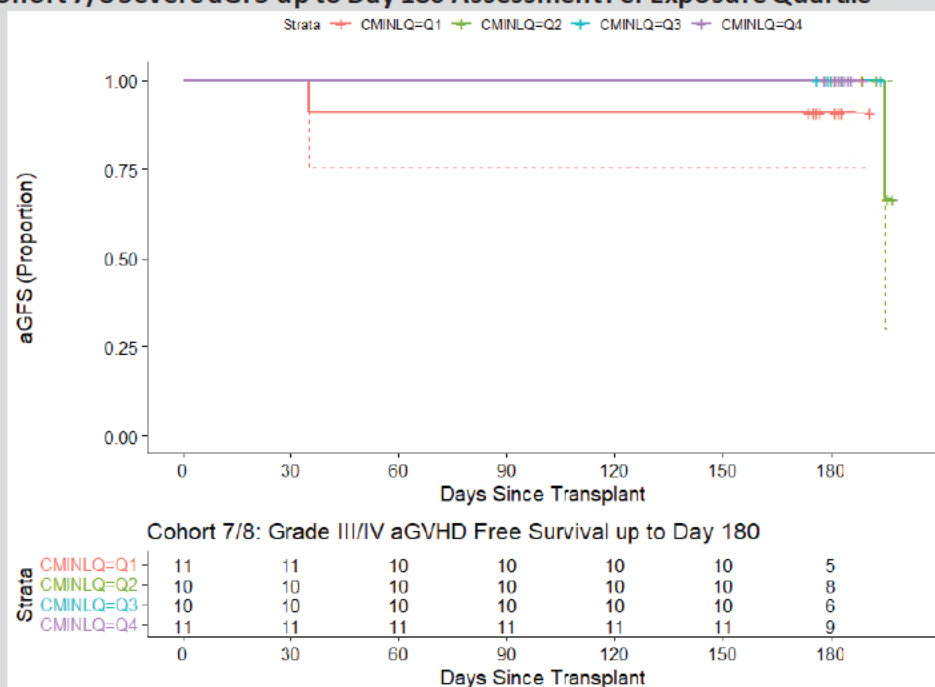
Figure 40. Cohort 8/8 Severe aGFS up to Day 180 Assessment Per Exposure Quartile



aGFS = aGVHD-free survival; aGVHD = acute graft versus host disease; CminL = minimum concentration following last dose up to Day 42 after transplant; Q = quartile; Q4 = highest abatacept exposure.

Source: Reviewer Analysis of Applicant's E-R efficacy dataset ('s311eff.xpt')

Figure 41. Cohort 7/8 Severe aGFS up to Day 180 Assessment Per Exposure Quartile



aGFS = aGVHD-free survival; aGVHD = acute graft versus host disease; CminL = minimum concentration following last dose up to Day 42 after transplant; Q = quartile; Q4 = highest abatacept exposure.

Source: Reviewer Analysis of Applicant's E-R efficacy dataset ('s311eff.xpt')

Table 81. Severe aGFS Events up to Day 180 Assessment Per Cohort and Exposure Quartile

Cohort	CminL Quartile	Total patients (n)	Patients with Severe aGFS event (n [%])
Cohort 7/8	Quartile 1	11	1 (9.1%)
	Quartile 2	10	1 (10.0%)
	Quartile 3	10	0
	Quartile 4	11	0
Cohort 8/8	Placebo	69	17 (24.6%)
	Quartile 1	19	4 (21.1%)
	Quartile 2	18	2 (11.1%)
	Quartile 3	18	1 (5.6%)
	Quartile 4	18	3 (16.7%)

Severe aGFS event = Grade III to IV aGVHD or death. Quartile 1 = lowest abatacept exposure.

aGFS = aGVHD-free survival; aGVHD = acute graft versus host disease; CminL = minimum concentration following last dose up to Day 42 after transplant.

Source: Reviewer Analysis of Applicant's E-R efficacy dataset ('s311eff.xpt')

19.4.1-2.4.2 Modeling of Severe (Grade III/IV) aGFS up to Day 180 Assessment

The Applicant created a Cox Proportional Hazard model for aGFS up to Day 180 assessment. The base model for aGFS included abatacept CminL as the only covariate. Increased CminL was associated with improved severe aGFS. Covariate analysis investigated potential associations between efficacy and age,

body weight, baseline serum IgG, sex, race (White versus not White), GVHD prophylaxis, conditioning regimen, pre-transplant CMV status, pre-transplant CMV donor status, type of graft received, relapse of underlying malignancy to Day 180, and cohort. Backwards elimination was used to determine the final model.

The Applicant’s final model included the effect of CminL, and higher CminL was associated with improved aGFS. The Applicant’s final model parameter estimates are presented in Table 82. Observed and model-predicted survival are presented by exposure quartile in Figure 42.

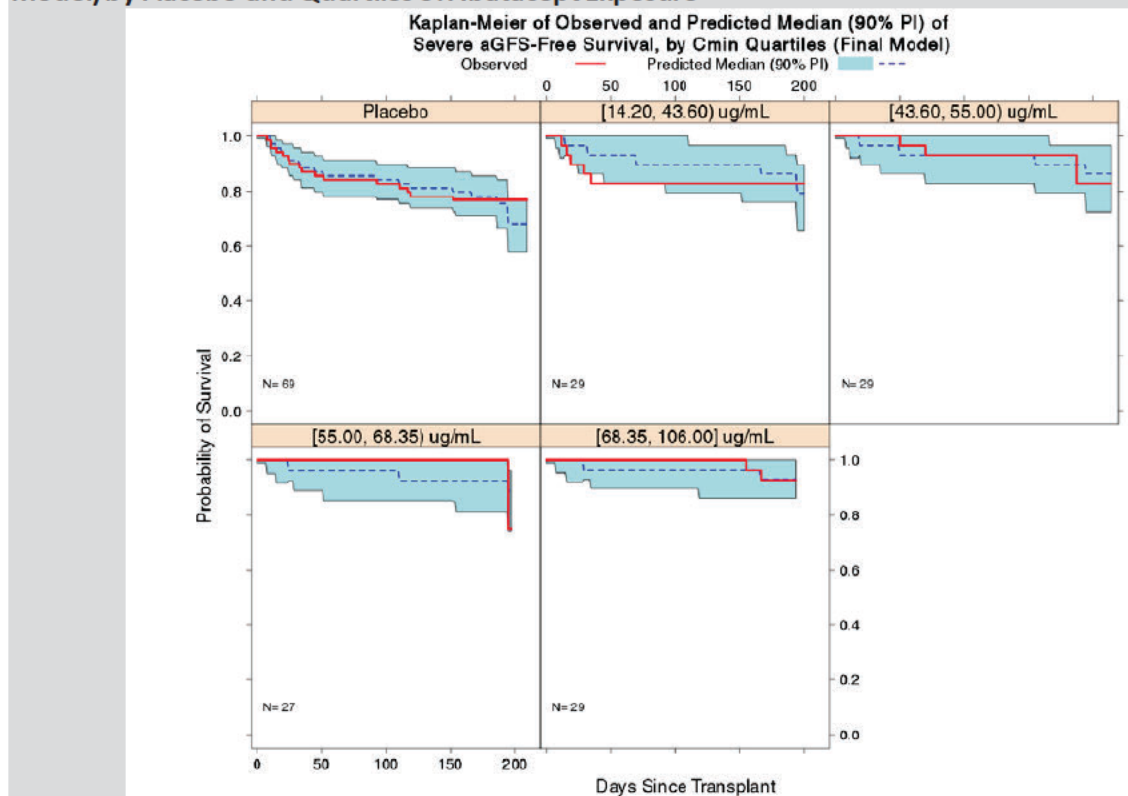
Table 82. Parameter Estimates of Exposure-Response Efficacy for Time to First Severe aGFS up to Day 180 Assessment (Applicant’s Final Model)

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)

Note: Final model was identical to the base model for time to first severe aGFS.

aGFS = aGVHD-free survival; aGVHD = acute graft versus host disease; CI = confidence interval; CminL = minimum concentration following last dose up to Day 42 after transplant; RSE = relative standard error; SE = standard error. Source: Table 5.2.1.1-1 in Applicant’s Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020.

Figure 42. Model Evaluation of Time to First Severe aGFS up to Day 180 Assessment (Applicant’s Final Model) by Placebo and Quartiles of Abatacept Exposure



aGFS = aGVHD-free survival; aGVHD = acute graft versus host disease; Cmin = minimum concentration following last dose up to Day 42 after transplant; PI = prediction interval.

Source: Figure 5.2.2-3 in Applicant's Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020.

Reviewer Comments

There appears to be some discordance between the observed and model-predicted aGFS around Day 200 (see Figure 42 above). There also appears to be worse observed aGFS compared to model-predicted survival up to approximately Day 50 in the lowest exposure quartile. The 90% prediction interval aGFS also overlaps significantly across exposure quartiles.

The Applicant's E-R analysis utilized exposure quartiles determined from data from both cohorts. Even though cohort was not a statistically significant covariate in the E-R model, patients in Cohort 7/8 tended have higher exposure compared to Cohort 8/8.

When the Reviewer performed stepwise covariate search according to the Applicant's methods, the final model retained the covariates of CminL and relapse of underlying malignancy. The final model parameter estimates are presented in Table 83. CminL is statistically significant, but the magnitude of effect on severe aGFS appears to be smaller compared to the effect of relapse.

Table 83. Parameter Estimates of Exposure-Response Efficacy for Time to First Severe aGFS up to Day 180 Assessment (Reviewer's Final aGFS Model)

Variable	Coefficient	SE	P value	Hazard Ratio	Lower 95% CI HR	Upper 95% CI HR
Relapse of underlying malignancy up to Day 180 assessment	1.068	0.4204	0.0111	2.9098	1.2765	6.6329
CminL	-0.015	0.0067	0.0205	0.9847	0.9700	1.0000

aGFS = aGVHD-free survival; aGVHD = acute graft versus host disease; CI = confidence interval; CminL = minimum concentration following last dose up to Day 42 after transplant; HR = hazard ratio; SE = standard error.

Source: Reviewer analysis

When Cohort (8/8 versus 7/8) was added as a covariate to the model displayed in Table 83, neither CminL nor Cohort were significant, as shown in Table 84.

Table 84. Parameter Estimates of Exposure-Response Efficacy for Time to First Severe aGFS up to Day 180 Assessment (Reviewer Independent aGFS Model #1)

Variable	Coefficient	SE	P value	Hazard Ratio	Lower 95% CI HR	Upper 95% CI HR
Relapse of underlying malignancy up to Day 180 assessment	1.051	0.4186	0.0121	2.8591	1.2587	6.4943
CminL	-0.0118	0.0073	0.1064	0.9883	0.9700	1.0000
Cohort (8/8 versus 7/8)	0.7791	0.8014	0.3310	2.1795	0.4500	10.4800

aGFS = aGVHD-free survival; aGVHD = acute graft versus host disease; CI = confidence interval; CminL = minimum concentration following last dose up to Day 42 after transplant; HR = hazard ratio; SE = standard error.

Source: Reviewer analysis

Finally, in order to remove potential confounding according to cohort from the model, the Reviewer performed stepwise covariate search with E-R data in Cohort 7/8 (n=42) and Cohort 8/8 (n=73 administered abatacept and n=69 administered placebo) separately. For Cohort 8/8, treatment (abatacept or placebo) was added as a covariate for investigation. Final estimates for Cohort 8/8 are shown in Table 85 and relapse status was the only covariate significantly associated with aGFS in the final Cohort 8/8 model. For Cohort 7/8, no covariates remained after stepwise search which is likely related to the very limited number of aGFS events (2 events in 42 patients up to Day 180 assessment).

Table 85. Parameter Estimates of Exposure-Response Efficacy for Time to First Severe aGFS up to Day 180 Assessment in Cohort 8/8 Only (Reviewer Independent aGFS Model #2)

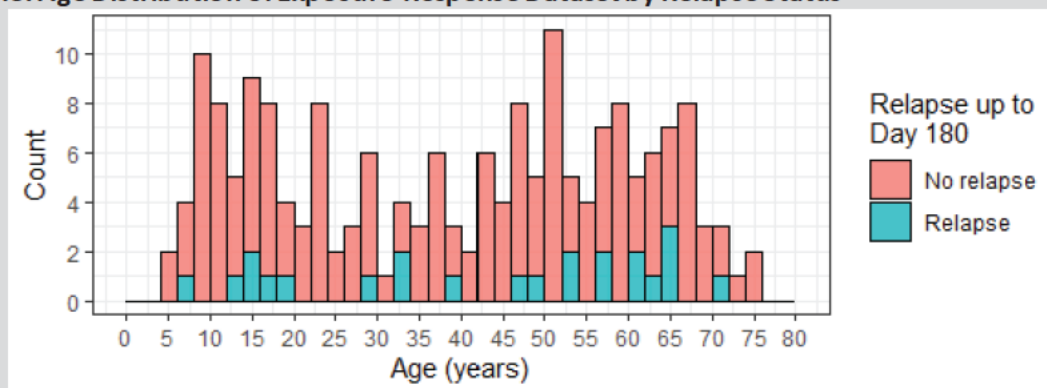
Variable	Coefficient	SE	P value	Hazard Ratio	Lower 95% CI HR	Upper 95% CI HR
Relapse of underlying malignancy up to Day 180 assessment	1.172	0.4199	0.00525	3.2289	1.4177	7.3539

aGFS = aGVHD-free survival; aGVHD = acute graft versus host disease; CI = confidence interval; HR = hazard ratio; SE = standard error.

Source: Reviewer analysis

The Reviewer models indicated that relapse of underlying malignancy up to Day 180 assessment was a significant predictor of worse aGFS. Relapse status did not appear to be correlated with age (Figure 43) and so the worse aGFS in patients with relapse was not explained by age. Additionally, when exposure (AUC1, AUCL, AUC42, Cmax1, CmaxL, Cmin1, and CminL) was compared according to relapse status within each cohort, patients with relapse did not have significantly different exposure compared to patients without relapse.

Figure 43. Age Distribution of Exposure-Response Dataset by Relapse Status



Source: Reviewer Analysis of Applicant's E-R Datasets

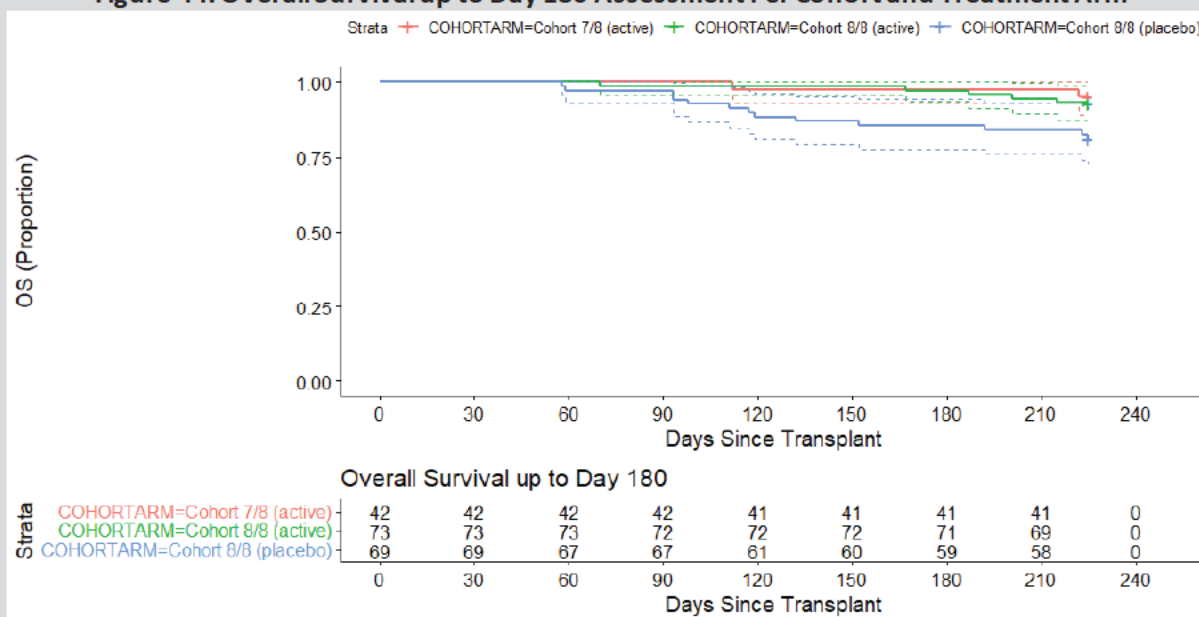
Relapse status up to Day 180 assessment appeared significantly more important than abatacept exposure for predicting aGFS. Although increased abatacept exposure is associated with modestly improved aGFS, this effect may be confounded by imbalance in baseline patient characteristics across exposure quartiles, as shown in Table 80. When cohort is incorporated into the model, the covariate effect of CminL is no longer significant. The ability to characterize the E-R relationship may also be limited by the relatively small number of patients and limited number of events (29 aGFS events

recorded for aGFS up to Day 180 assessment in a total of 184 patients administered abatacept or placebo).

19.4.1-2.4.3 Observed Overall Survival up to Day 180 Post-transplantation

Overall survival up to approximately Day 180 assessment (which could occur up to Day 225 after transplant) in Cohort 7/8 and the active and placebo arms of Cohort 8/8 are displayed in Figure 44. Patients in Cohort 8/8 treated with abatacept appeared to have some improvement in OS compared to patients treated with placebo. The limited number of patients and events as well as the lack of placebo arm in the 7/8 Cohort make it difficult to assess the impact of abatacept on OS.

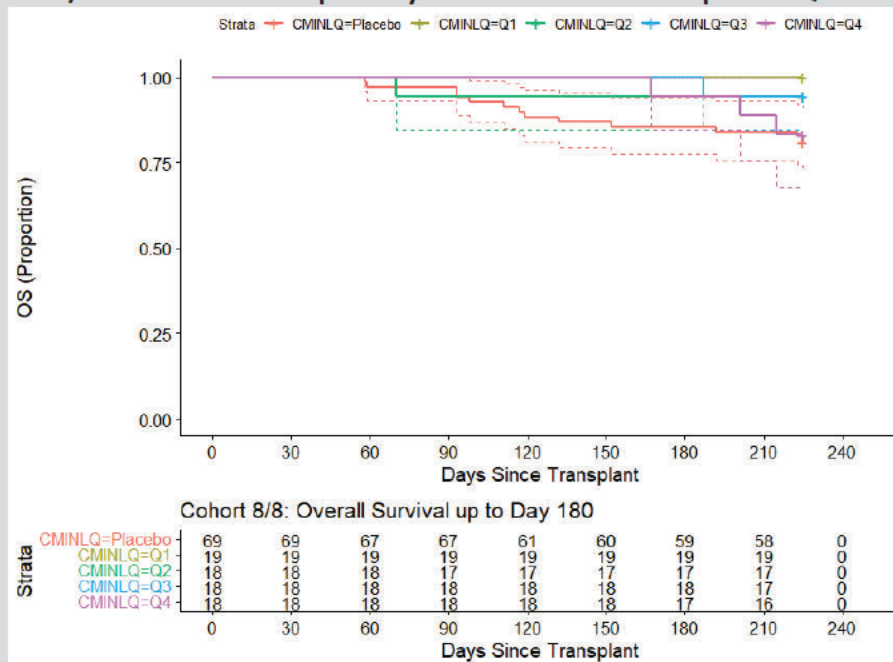
Figure 44. Overall Survival up to Day 180 Assessment Per Cohort and Treatment Arm



Active = Abatacept + calcineurin inhibitor + methotrexate; OS = overall survival; placebo = placebo + CNI + MTX.
 Source: Reviewer Analysis of Applicant's E-R efficacy dataset ('s311os.xpt')

Observed OS up to Day 180 assessment in each cohort is displayed according to CminL quartile and placebo for Cohort 8/8 and Cohort 7/8, respectively, in Figure 45 and Figure 46. The number of events per cohort and per abatacept exposure quartile within each cohort is described in Table 86. There are no clear trends in OS across exposure quartiles in either Cohort 7/8 or Cohort 8/8, but assessment is limited by the relatively small number of patients with OS events before the Day 180 assessment.

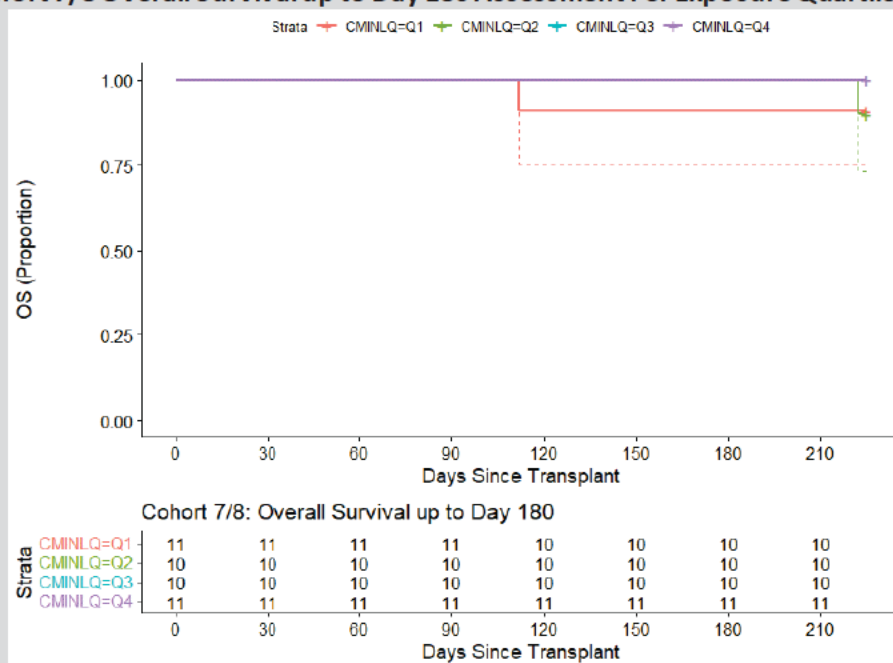
Figure 45. Cohort 8/8 Overall Survival up to Day 180 Assessment Per Exposure Quartile



CminL = minimum concentration following last dose up to Day 42 after transplant; OS = overall survival; Q = quartile; Q4 = highest abatacept exposure.

Source: Reviewer Analysis of Applicant's E-R efficacy dataset ('s311os.xpt')

Figure 46. Cohort 7/8 Overall Survival up to Day 180 Assessment Per Exposure Quartile



CminL = minimum concentration following last dose up to Day 42 after transplant; OS = overall survival; Q = quartile; Q4 = highest abatacept exposure.

Source: Reviewer Analysis of Applicant's E-R efficacy dataset ('s311os.xpt')

Table 86. Overall Survival Events up to Day 180 Assessment Per Cohort and Exposure Quartile

Cohort	CminL Quartile	Total patients (n)	Patients with death event (n [%])
Cohort 7/8	Quartile 1	11	1 (9.1%)
	Quartile 2	10	1 (10.0%)
	Quartile 3	10	0
	Quartile 4	11	0
Cohort 8/8	Placebo	69	13 (18.8%)
	Quartile 1	18	0
	Quartile 2	18	1 (5.6%)
	Quartile 3	18	1 (5.6%)
	Quartile 4	18	3 (16.7%)

Quartile 1 = lowest abatacept exposure. Quartile 4 = highest abatacept exposure.
 CminL = minimum concentration following last dose up to Day 42 after transplant.
 Source: Reviewer Analysis of Applicant's E-R efficacy dataset ('s311os.xpt')

19.4.1-2.4.4 Modeling of Overall Survival up to Day 180 Assessment

The Applicant created a Cox Proportional Hazard model for OS up to Day 180 assessment. The base model for OS included abatacept CminL as the only covariate. Increased CminL was associated with lower risk of death. Covariate analysis investigated potential associations between efficacy and age, body weight, baseline serum IgG, sex, race (White versus not White), GVHD prophylaxis, conditioning regimen, pre-transplant CMV status, pre-transplant CMV donor status, type of graft received, relapse of underlying malignancy to Day 180, and cohort. Backwards elimination was used to determine the final model.

The Applicant's final model included the effect of CminL and relapse of underlying malignancy. Higher CminL was associated with improved OS. Relapse was associated with worsened OS. Final model parameter estimates are presented in Table 87.

The Applicant's model incorporating CminL and relapse status appears to adequately predict OS in patients treated with placebo and patients treated with abatacept. However, OS up to Day 180 assessment was above 80% in all CminL quartiles and the placebo arm. The 90% prediction intervals for each abatacept exposure quartile in Figure 47 also show significant overlap across quartiles.

Table 87. Parameter Estimates of Exposure-Response Efficacy for Overall Survival up to Day 180 Assessment (Applicant's Full/Final Model)

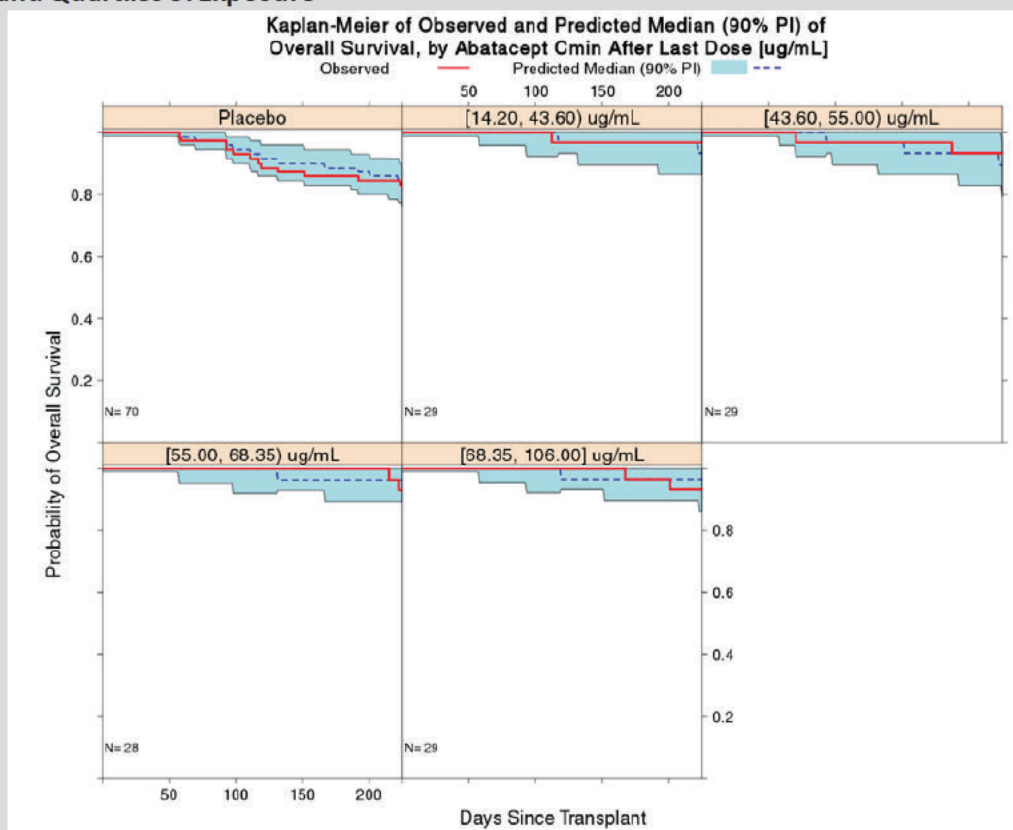
Variable ^a	Coefficient	SE	RSE	P value	Hazard Ratio	Lower 95% CI	Upper 95% CI	Hazard Ratio (95% CI)
Abatacept Cmin After the Last Dose [µg/mL]	-0.01607	0.007772	48.38	0.03872	0.9841	0.9692	0.9992	0.9841 (0.9692, 0.9992)
Relapse	1.868	0.4517	24.18	3.54E-05	6.475	2.672	15.69	6.475 (2.672, 15.69)

^a Reference values: Relapse=No.

CI = confidence interval; Cmin = minimum concentration following last dose up to Day 42 after transplant;
 RSE = relative standard error; SE = standard error.

Source: Table 5.3.1.2-1 in Applicant's Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020.

Figure 47. Model Evaluation of Overall Survival up to Day 180 Assessment (Applicant's Final Model) by Placebo and Quartiles of Exposure



Cmin = minimum concentration following last dose up to Day 42 after transplant; PI = prediction interval.

Source: Figure 5.3.2-3 in Applicant's Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020.

Reviewer Comments

Similar to the Applicant's aGFS analysis, the Applicant's final OS model did not include cohort even though patients in Cohort 7/8 tended have higher exposure compared to Cohort 8/8.

When the Reviewer performed stepwise covariate search according to the Applicant's methods, the final model retained the covariates of CminL and relapse of underlying malignancy. The final model parameter estimates are presented in Table 88 and showed no discrepancy with the Applicant's final model for OS.

Table 88. Parameter Estimates of Exposure-Response Efficacy for Time to Overall Survival up to Day 180 Assessment (Reviewer Independent OS Model)

Variable	Coefficient	SE	P value	Hazard Ratio	Lower 95% CI HR	Upper 95% CI HR
Relapse of underlying malignancy up to Day 180 assessment	1.857	0.4518	0.00004	6.4036	2.6400	15.5200
CminL	-0.0162	0.00778	0.03713	0.9839	0.9690	0.9990

CI = confidence interval; CminL = minimum concentration following last dose up to Day 42 after transplant; HR = hazard ratio; SE = standard error.

Source: Reviewer analysis

The efficacy endpoint of OS up to Day 180 assessment improved with higher abatacept concentration on Day 28 following transplantation and with the absence of relapse up to Day 180 assessment. As discussed in Section 19.4.1-2.4.2, relapse status did not appear to be associated with age or with exposure.

19.4.1-2.5 Exposure-Response Analyses of Safety

The Applicant conducted exploratory E-R safety analyses for the following safety events: time to first invasive CMV disease, time to first CMV viremia, and time to first infection.

19.4.1-2.5.1 Invasive CMV Disease

The incidence of invasive CMV disease during Study IM101311 was slightly higher in patients who received abatacept (10/115 [8.7%]) compared to patients who received placebo (2/70 [2.9%]). However, incidence of invasive CMV disease did not appear to be associated with abatacept CmaxL. Table 89 summarizes incidence of invasive CMV disease according to abatacept CmaxL quartile. Time to invasive CMV disease did not differ significantly in the abatacept arm compared to the placebo arm. There was also no apparent relationship between time to invasive CMV disease and any abatacept exposure metric, as demonstrated with abatacept CmaxL in Figure 48.

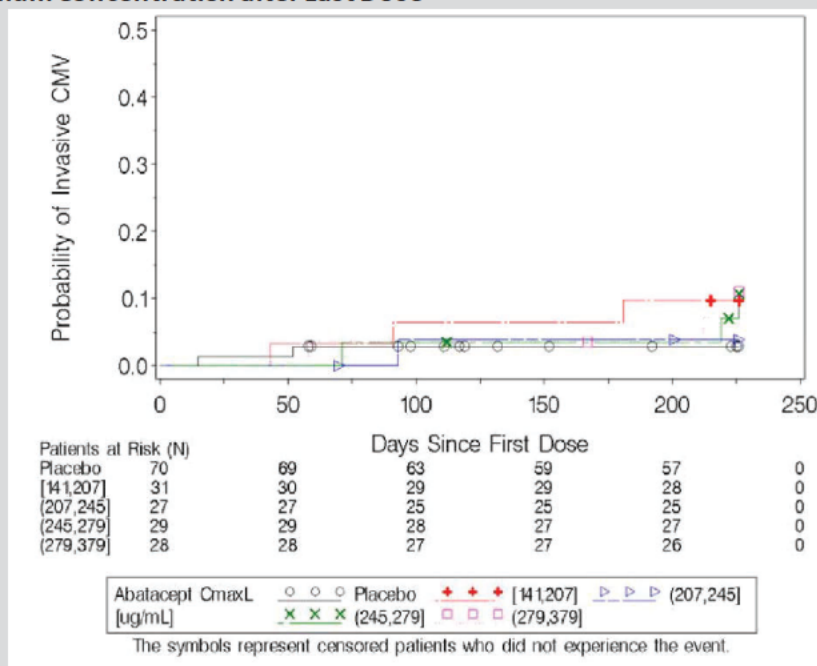
Table 89. Exposure-Response Dataset Incidence of Invasive CMV Disease up to Database Lock According to Predicted Maximum Concentration after Last Dose

	Placebo	CmaxL Q1 (141 - 207 ug/mL)	CmaxL Q2 (208 - 245 ug/mL)	CmaxL Q3 (246 - 274 ug/mL)	CmaxL Q4 (279 - 379 ug/mL)
Total number of patients (N)	69	31	27	28	29
Any Grade Invasive CMV Disease [n (%)]	2 (2.9%)	4 (12.9%)	1 (3.7%)	3 (10.7%)	3 (10.3%)

CmaxL = Predicted Cmax following Day 28 dose; CMV = cytomegalovirus; Q = quartile.

Source: Reviewer Analysis of Applicant's time-to-event dataset ('adtte.xpt') and E-R dataset ('s311eff.xpt').

Figure 48. Probability of Invasive CMV Disease during the Day 180 Analysis Period by Quartiles of Abatacept Maximum Concentration after Last Dose



Note: this figure contains data from one patient in Cohort 7/8 who received placebo.
 CmaxL = Predicted Cmax following last abatacept dose on Day 28; CMV = cytomegalovirus.
 Source: Figure 5.4-4 in Applicant's Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020.

19.4.1-2.5.2 CMV Viremia

The observed incidence of CMV viremia during Study IM101311 was similar in patients who received abatacept (54/115 [47.0%]) and patients who received placebo (31/70 [44.3%]). There were also no apparent trends with incidence of CMV viremia and abatacept CmaxL quartile, as summarized in Table 90.

Time to CMV viremia did not differ significantly in the abatacept arm compared to the placebo arm. Time to CMV viremia did not appear to be associated with increasing abatacept exposure quartile for any exposure metric. The Kaplan-Meier plot for time to CMV viremia by abatacept Cmax1 quartile is shown in Figure 49.

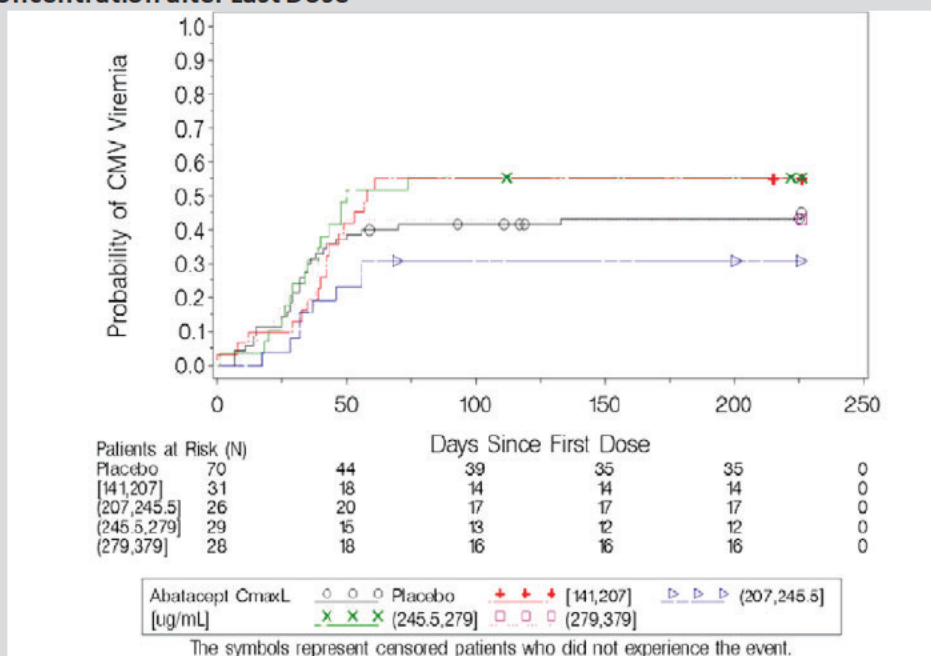
Table 90. Exposure-Response Dataset Incidence of CMV Viremia up to Database Lock According to Predicted Maximum Concentration after Last Dose

	Placebo	CmaxL Q1 (141 - 207 ug/mL)	CmaxL Q2 (208 - 245 ug/mL)	CmaxL Q3 (246 - 274 ug/mL)	CmaxL Q4 (279 - 379 ug/mL)
Total number of patients (N)	69	31	27	28	29
Any Grade CMV Viremia [n (%)]	30 (43.5%)	17 (54.8%)	9 (33.3%)	16 (57.1%)	12 (41.4%)

CmaxL = Predicted Cmax following Day 28 dose; CMV = cytomegalovirus; Q = quartile.

Source: Reviewer Analysis of Applicant's time-to-event dataset ('adtte.xpt') and E-R dataset ('s311eff.xpt').

Figure 49. Probability of CMV Viremia during the Day 180 Analysis Period by Quartiles of Abatacept Maximum Concentration after Last Dose



Note: this figure contains data from one patient in Cohort 7/8 who received placebo.
 C_{maxL} = Predicted C_{max} following last abatacept dose on Day 28; CMV = cytomegalovirus.
 Source: Figure 5.4-6 in Applicant's Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020.

19.4.1-2.5.3 Infection

For the E-R analysis, the Applicant states that incidence of infection was 15/116 (12.9%) in patients who received abatacept and 8/70 (11.4%) in patients who received placebo (Table 5.4-1 in Applicant's Population Pharmacokinetic and Exposure-Response Report dated March 26, 2020). Per the Applicant's analysis, time to first infection did not appear to differ in patients who received abatacept versus placebo. Time to infection also did not appear to be associated with any abatacept exposure metric.

Reviewer Comments

The Applicant's reported incidence of infection for E-R safety analysis is significantly lower than the reported incidence of infection per the Applicant's Study IM101311 primary clinical study report (Table 91). The Applicant's E-R safety analysis for infection appears to use under-reported incidence of infection and could not be verified.

Table 91. Study IM101311 Adverse Events Reported during the Day 180 Analysis Period

System Organ Class (SOC) Preferred Term (PT)	Statistic	8/8 Cohort: Placebo (n=69)	8/8 Cohort: Abatacept (n=73)	7/8 Cohort: Abatacept (n=43)
Infections and infestations	n (%)	53 (76.8 %)	50 (68.5 %)	30 (69.8 %)
Infection	n (%)	36 (52.2 %)	35 (47.9 %)	21 (48.8 %)

System Organ Class (SOC) Preferred Term (PT)	Statistic	8/8 Cohort: Placebo (n=69)	8/8 Cohort: Abatacept (n=73)	7/8 Cohort: Abatacept (n=43)
Device Related Infection	n (%)	13 (18.8 %)	14 (19.2 %)	4 (9.3 %)
Enterocolitis infectious	n (%)	11 (15.9 %)	6 (8.2 %)	3 (7.0 %)
Pneumonia	n (%)	7 (10.1 %)	9 (12.3 %)	8 (18.6 %)
Upper respiratory tract infection	n (%)	4 (5.8 %)	8 (11.0 %)	1 (2.3 %)
Urinary tract infection	n (%)	6 (8.7 %)	5 (6.8 %)	5 (11.6 %)
Sepsis	n (%)	7 (10.1 %)	0	4 (9.3 %)

Table includes PT within SOC of infections and infestations with $\geq 5\%$ incidence during the Day 180 analysis period. Source: Table S.6.2.1.1.S (Cohort 8/8) and Table S.6.2.1.2.S (Cohort 7/8) in Applicant's Study IM101311 Primary Clinical Study Report.

The Reviewer used the recorded incidence of infections and infestations in the Applicant's 'adae.xpt' dataset and predicted exposure values from the Applicant's E-R efficacy dataset ('s311eff.xpt') to compare incidence by abatacept exposure quartile. No apparent trend was identified in incidence of infections and infestations across the predicted abatacept exposure quartiles, as shown in Table 92.

Table 92. Exposure-Response Dataset Incidence of Infection during the Day 180 Analysis Period According to Predicted Maximum Concentration after Last Dose

	Placebo	C _{max} L Q1 (141 - 207 ug/mL)	C _{max} L Q2 (208 - 245 ug/mL)	C _{max} L Q3 (246 - 274 ug/mL)	C _{max} L Q4 (279 - 379 ug/mL)
Total number of patients (N)	69	31	27	28	29
Infections and Infestations, Any Grade [n (%)]	53 (76.8%)	25 (80.6%)	18 (66.7%)	20 (71.4%)	16 (55.2%)

C_{max}L = Predicted C_{max} following Day 28 dose; Q = quartile.

Source: Reviewer Analysis of Applicant's AE dataset ('adae.xpt') and E-R dataset ('s311eff.xpt').

19.4.1-2.5.4 Reviewer's Independent Exposure-Response Analyses of Safety

As part of the FDA review, the Reviewer investigated additional safety events for potential associations with abatacept exposure. Quartiles of exposure (C_{max}L) were calculated separately within Cohort 8/8 and Cohort 7/8, as TEAE incidence may have differed by cohort and Cohort 7/8 tended to have higher abatacept exposure compared to the abatacept arm of Cohort 8/8.

The Applicant's safety analyses determined that stomatitis, infection, hypertension, dehydration, decreased appetite, obesity, gastrointestinal (GI) disorder, and hyperglycemia were the most frequently reported ($\geq 20\%$ of subjects) TEAEs with abatacept not based on lab values. The incidence of these TEAEs across exposure quartiles are reported in Table 93. Multiple lab-derived TEAEs such as decreased white blood cell count, decreased platelet count, febrile neutropenia, anemia, decreased lymphocyte count, and hypokalemia were also frequently reported, but the Reviewer did not analyze these or any other lab-derived TEAEs for potential E-R relationships.

Table 93. Incidence of Select Common Treatment Emergent Adverse Events during the Day 180 Analysis Period According to Maximum Concentration after Last Dose Quartile

	Placebo	CmaxL Q1	CmaxL Q2	CmaxL Q3	CmaxL Q4
Total patients (n)	69	31	27	28	29
CmaxL Range (ug/mL)	N/A	141 - 207	208 - 245	246 - 274	279 - 379
Abdominal pain	13 (18.8%)	4 (12.9%)	3 (11.1%)	5 (17.9%)	3 (10.3%)
Acute graft versus host disease in skin	3 (4.3%)	3 (9.7%)	1 (3.7%)	4 (14.3%)	0
Acute kidney injury	7 (10.1%)	2 (6.5%)	2 (7.4%)	8 (28.6%)	2 (6.9%)
Decreased appetite	25 (36.2%)	10 (32.3%)	7 (25.9%)	16 (57.1%)	5 (17.2%)
Dehydration	30 (43.5%)	12 (38.7%)	13 (48.1%)	10 (35.7%)	10 (34.5%)
Device related infection	13 (18.8%)	8 (25.8%)	3 (11.1%)	5 (17.9%)	2 (6.9%)
Diarrhoea	15 (21.7%)	6 (19.4%)	6 (22.2%)	5 (17.9%)	3 (10.3%)
Enterocolitis infectious	11 (15.9%)	4 (12.9%)	0	1 (3.6%)	4 (13.8%)
Epistaxis	7 (10.1%)	7 (22.6%)	5 (18.5%)	1 (3.6%)	3 (10.3%)
Gastrointestinal disorder	14 (20.3%)	11 (35.5%)	6 (22.2%)	3 (10.7%)	7 (24.1%)
Graft versus host disease in skin	8 (11.6%)	4 (12.9%)	0	6 (21.4%)	3 (10.3%)
Hyperglycaemia	16 (23.2%)	8 (25.8%)	4 (14.8%)	10 (35.7%)	4 (13.8%)
Hypertension	26 (37.7%)	15 (48.4%)	9 (33.3%)	17 (60.7%)	11 (37.9%)
Hypotension	16 (23.2%)	3 (9.7%)	7 (25.9%)	6 (21.4%)	6 (20.7%)
Hypoxia	9 (13%)	2 (6.5%)	5 (18.5%)	2 (7.1%)	6 (20.7%)
Infection	36 (52.2%)	17 (54.8%)	11 (40.7%)	15 (53.6%)	12 (41.4%)
Nausea	12 (17.4%)	3 (9.7%)	7 (25.9%)	4 (14.3%)	0
Obesity	18 (26.1%)	3 (9.7%)	5 (18.5%)	8 (28.6%)	10 (34.5%)
Pneumonia	7 (10.1%)	3 (9.7%)	5 (18.5%)	5 (17.9%)	4 (13.8%)
Pyrexia	13 (18.8%)	7 (22.6%)	4 (14.8%)	7 (25%)	5 (17.2%)
Stomatitis	49 (71%)	26 (83.9%)	19 (70.4%)	16 (57.1%)	19 (65.5%)

Lab-derived TEAEs not included in this table. TEAEs with <10% incidence in patients treated with abatacept are not included in this table. Adverse event refers adverse event preferred term with to any grade severity.

CmaxL = Predicted Cmax following last abatacept dose on Day 28; N/A = not applicable; Q = quartile.

Source: Reviewer analysis of Applicant's E-R dataset ('s311eff.xpt') and Study IM101311 adverse event dataset ('adae.xpt')

Limited numbers of patients in each exposure quartile make it difficult to draw strong conclusions. However, patients with higher CmaxL quartile may have experienced increased incidence of hypotension and obesity. None of the other TEAEs reported in Table 93 appeared to be associated with increased CmaxL in the overall E-R dataset.

No major E-R safety issues have been identified with exposure of abatacept for the indication of aGVHD prevention in this review; however, the E-R safety profile of abatacept has not been fully characterized or investigated.

19.4.1-3 Listing of analyses codes and output files

Codes and output files for this review are listed with location in Table 94.

Table 94. Analysis Codes and Output Files

File Name	Description	Location
PPK_Dataset_Exploration.rmd and .docx	R markdown code and output for evaluation of the Applicant's popPK dataset; Code for Table 71, Figure 29 .	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PPK
PK_Dataset_Exploration.rmd and .docx	R markdown code and output for evaluation of the Applicant's Study IM101311 'adpc.xpt' dataset of PK concentrations; Code for Table 4, Figure 3, Figure 4, Figure 23, Figure 24 .	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PK
ivpk.csv, abatacept-002586-pk-final-bis.mod, and abatacept-002586-pk-final-bis.lst	Dataset, control stream, and output for Reviewer's run of the Applicant's final popPK model submitted with the Applicant's PopPK and E-R Report dated March 26, 2020.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PPK\Sponsor_Final_PPK\mfe_abatacept-002586-pk-final-bis_001
Reviewer_GOF_for_Sponsor_Final_Model.rmd and .docx	R markdown code and output for GOF plots of Reviewer's run of the Applicant's final popPK model; Code for Figure 26, Figure 27 .	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PPK\Sponsor_Final_PPK\mfe_abatacept-002586-pk-final-bis_001
.lst and .mod files for run001-run029	Dataset, control streams, and outputs for Reviewer's independent popPK analysis (see Table 73).	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PPK\Indep_Reviewer_PPK
pirana_sum_run028.txt	Summary table of independent reviewer final estimates; Source for Table 74 .	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PPK\Indep_Reviewer_PPK\pirana_reports
Reviewer_GOF_run029.rmd and .docx	R markdown code and output for GOF plots of Reviewer's independent analysis final popPK model (run029).	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PPK\Indep_Reviewer_PPK
ER_Dataset_Exploration_Subgroup_Analysis.rmd and .docx	R markdown code and output for evaluation of the Applicant's Study IM101311's311eff.xpt' E-R dataset; Code for Table 75, Table 76, Table 79, Table 80, Figure 30, Figure 31, Figure 32, Figure 33, Figure 34, Figure 43 .	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\ER
Applicant_PredExposure_Age2to6.rmd and .docx	R markdown code and output for summarizing final popPK model predicted exposure; Code for summary in Table 77 .	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PPK\IndivPred_Age2to6_Exposure
Applicant_PredExposure_Age2to6_LoadingDoseSims.rmd and .docx	R markdown code and output for summarizing final popPK model predicted exposure for dosing	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PPK

	scenarios with loading dose(s); Code for summary in Table 77, Figure 35, Figure 36.	K\IndivPred_Age2to6_Exposure\ApplicantModel_ApplicantDataset_LoadingDoseSims
IndivPredExposure_UpdatedPPKModel_study331_and_virtual2to6.rmd and .docx	R markdown code and output for summarizing UPDATED popPK model predicted exposure; Code for Figure 37, Figure 38.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\PPK\Updated_IVSC_PopPK_22NovModel\IndivPredExposure_Study311_Updated
ER_aGFS_Day180_Analysis.rmd and .docx	R markdown code and output for evaluation of aGFS up to Day 180; Code for Table 81, Table 83, Table 84, Table 85, Figure 39, Figure 40, Figure 41.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\ER
ER_OS_Day180_Analysis.rmd and .docx	R markdown code and output for evaluation of OS up to Day 180; Code for Table 86, Table 88, Figure 44, Figure 45, Figure 46.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\ER
ER_Safety_TTEdata set_Analysis.rmd and .docx	R markdown code and output for evaluation of Applicant's exploratory E-R safety analyses; Code for Table 89, Table 90.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\ER\Safety
ER_Safety_AEdatas et_Analysis.rmd and .docx	R markdown code and output for evaluation of additional safety TEAE events; Code for Table 92, Table 93.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Abatacept_BLA125118_S240_REK\ER\Safety

19.4.1-4 Pharmacometrics References

1. Hjorth L, Wiebe T, Karpman D. Hyperfiltration evaluated by glomerular filtration rate at diagnosis in children with cancer. *Pediatr Blood Cancer*. 2011 May;56(5):762-6. Epub 2011 Jan 16.
2. Grönroos M, Bolme P, Winiarski J, et al. Long-term renal function following bone marrow transplantation. *Bone Marrow Transplant*. 2007; 39: 717–723.
3. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009; 20: 629-37.
4. Millisor VE, Roberts JK, Sun Y, et al. Derivation of new equations to estimate glomerular filtration rate in pediatric oncology patients. *Pediatr Nephrol*. 2017; 32(9): 1575-1584.

19.5. Additional Safety Analyses Conducted by FDA

FDA Assessment:
 Not applicable.

19.6. LIST OF REFERENCES

- 1 Bunin N, Carston M, Wall D, et al. Unrelated marrow transplantation for children with acute lymphoblastic leukemia in second remission. *Blood* 2002;99:3151-7.
- 2 Bunin NJ, Davies SM, Aplenc R, et al. Unrelated donor bone marrow transplantation for children with acute myeloid leukemia beyond first remission or refractory to chemotherapy. *J Clin Oncol* 2008;26:4326-32.
- 3 Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood* 2007;110:4576-83.
- 4 Shaw PJ, Kan F, Woo Ahn K, et al. Outcomes of pediatric bone marrow transplantation for leukemia and myelodysplasia using matched sibling, mismatched related, or matched unrelated donors. *Blood* 2010;116:4007-15.
- 5 Woolfrey A, Klein JP, Haagenson M, et al. HLA-C Antigen mismatches are associated with worse outcomes in unrelated donor peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant* 2011.
- 6 Ochs L, Shu XO, Miller J, et al. Late infections after allogeneic bone marrow transplantations: comparison of incidence in related and unrelated donor transplant recipients. *Blood* 1995;86:3979-86.
- 7 Jagasia M, Arora M, Flowers ME, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood* 2012;119:296-307.
- 8 Parkman R and Weinberg K. Immune reconstitution following hematopoietic cell transplantation. In: Appelbaum F, Forman S, Negrin R, Blume K, eds. *Thomas' Hematopoietic Cell Transplantation*. Fourth ed. Hoboken, NJ: Wiley-Blackwell 2008.
- 9 Ferrara J and Antin J. The pathophysiology of graft-versus-host disease. In: Appelbaum F, Forman S, Negrin R, Blume K, eds. *Thomas' Hematopoietic Cell Transplantation*. Fourth ed. Hoboken, NJ: Wiley-Blackwell 2008.
- 10 Faraci M, Bertaina A, Luksch R, et al. Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease after Autologous or Allogeneic Hematopoietic Stem Cell Transplantation in Children: a retrospective study of the Italian Hematology-Oncology Association-Hematopoietic Stem Cell Transplantation Group. *Biol Blood Marrow Transplant* 2019;25:313-20.
- 11 Majhail NS, Chitphakdithai P, Logan B, et al. Significant improvement in survival after unrelated donor hematopoietic cell transplantation in the recent era. *Biol Blood Marrow Transplant*. 2015;21:142-50.
- 12 Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med* 2010;363:2091-101.
- 13 McDonald-Hyman C, Turka LA, Blazar BR et al. Advances and Challenges in Immunotherapy for Solid Organ and Bone Marrow Transplantation. *Sci Transl Med*. 2015 March 25; 7(280).
- 14 Champlin RE, Passweg JR, Zhang MJ, et al. T-cell depletion of bone marrow transplants for leukemia from donors other than HLA-identical siblings: advantage of T-cell antibodies with narrow specificities. *Blood* 2000;95:3996-4003.
- 15 Wagner JE, Thompson JS, Carter SL, et al. Effect of graft-versus-host disease prophylaxis on 3-year disease-free survival in recipients of unrelated donor bone marrow (T-cell Depletion Trial): a multi-centre, randomised phase II-III trial. *Lancet* 2005;366:733-41.
- 16 Bacigalupo A, Lamparelli T, Bruzzi P, et al. Antithymocyte globulin for graft-versus-host disease prophylaxis in transplants from unrelated donors: 2 randomized studies from Gruppo Italiano Trapianti Midollo Osseo (GITMO). *Blood* 2001;98:2942-7.
- 17 Jacobsohn DA, Vogelsang GB. Acute graft versus host disease. *Orphanet J Rare Dis*. 2007; 2:35.
- 18 Garnett C, Apperley JF, and Pavlu J. Treatment and management of graft-versus-host disease: improving response and survival. *Ther Adv Hematol* (2013);4(6):366–378
- 19 Olavarria E, Siddique S, Griffiths MJ, et al. Posttransplantation imatinib as a strategy to postpone the requirement for immunotherapy in patients undergoing reduced-intensity allografts for chronic myeloid leukemia. *Blood*. 2007;110:4614-4617.

- 20 Ram R, Gafter-Gvili A, Yeshurun M et al. Prophylaxis regimens for GVHD: systemic review and metaanalysis. Bone Marrow Transplantation 2009; 43: 643-653.
- 21 Chhabra S, Liu Y, Hemmer MT et al. Comparative analysis of calcineurin inhibitor-based methotrexate and mycophenolate mofetil-containing regimens for prevention of graft versus host disease after reduced intensity conditioning allogeneic transplantation. Biol Blood Marrow Transplant 2019; 25: 73-85.
- 22 Bailen R, Kwon M, Pascual-Cascon MJ et al. Post-transplant cyclophosphamide for GVHD prophylaxis compared to ATG-based prophylaxis in unrelated donor transplantation. Ann Hematol 2021; 100:541-533.
- 23 Linsley PS and Nadler SG. The clinical utility of inhibiting CD28-mediated costimulation. Immunol Rev 2009; 229:307–321.
- 24 Module 2.7.2 Summary of Clinical Pharmacology Studies. Bristol Myers Squibb Company, 2014. Document Control Number 930008811.
- 25 Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005;353:1114-23.
- 26 Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med 2003;349:1907-15.
- 27 Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008;372:383-91.
- 28 Koura DT, Horan JT, Langston AA, et al. In vivo T cell costimulation blockade with abatacept for acute graft-versus-host disease prevention: a first-in-disease trial. Biol Blood Marrow Transplant. 2013;19(11):1638-49.
- 29 Primary Clinical Study Report for IM101311. Abatacept Combined with a Calcineurin Inhibitor and Methotrexate for Graft Versus Host Disease Prophylaxis. Bristol-Myers Squibb Company, 2021. Document Control No. 930167273.
- 30 Calore J, Fadrowski C, Weiner R. Enzyme immunoassay for the quantitation of fixed process human CTLA4Ig Fusion Protein (BMS-188667) in human serum. Bristol-Myers Squibb Company, 1995. Document Control No. 910050896.
- 31 Dong H, Weiner R. Quantitative determination of BMS-188667 in human rheumatoid arthritis serum by an enzyme-linked immunosorbent assay (cross validation). Bristol-Myers Squibb Company, 1999. Document Control No. 910074383.
- 32 Validation of an Electrochemiluminescent (ECL) Immunoassay for the Detection of Anti-BMS-188667 Antibodies in Lupus Patient Serum. Bristol-Myers Squibb Company, 2019. Document Control No. 930044056.
- 33 Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012; 120:2454-65.
- 34 Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995; 15:825-8.
- 35 Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005; 11:945-56)
- 36 Przepiorka D, Weisdorf D, Martin P, et al., 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995; 15:825-8.
- 37 The University of Chicago Hematopoietic Malignancies Cancer Risk Team; How I diagnose and manage individuals at risk for inherited myeloid malignancies. Blood 2016; 128 (14): 1800–1813.
- 38 30Chaudhury S, Volonte B, Rangarajan H, et al. Abatacept for Gvhd Prophylaxis after Hematopoietic Cell Transplantation (HCT) for Pediatric Sickle Cell Disease (SCD): A Sickle Cell Transplant Advocacy and Research Alliance (STAR) Trial. Abstracts / Biol Blood Marrow Transplant 26 (2020)S8-S74.
- 39 Styczynski J, Van der Velden W, Fox C, et al. Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth

- European Conference on Infections in Leukemia (ECIL-6) guidelines. *Haematologica* 2016 Volume 101(7):803-811.
- 40 Cho S, Lee D, Kim H. Cytomegalovirus Infections after Hematopoietic Stem Cell Transplantation: Current Status and Future Immunotherapy. *Int. J. Mol. Sci.* 2019, 20, 2666.
- 41 Al Hamed R, Bazarbachi A, Mohty M. Epstein-Barr virus-related posttransplant lymphoproliferative disease (EBV-PTLD) in the setting of allogeneic stem cell transplantation: a comprehensive review from pathogenesis to forthcoming treatment modalities. *Bone Marrow Transplantation* (2020) 55:25–39.
- 42 De la Cámara R. CMV in Hematopoietic Stem Cell Transplantation. *Mediterr J Hematol Infect Dis* 2016, 8(1).
- 43 Sousa H, Boutolleau D, Ribeiro J, et al. Cytomegalovirus infection in patients who underwent allogeneic hematopoietic stem cell transplantation in Portugal: a five-year retrospective review. *Biol Blood Marrow Transplant.* 2014 Dec;20(12):1958-67.
- 44 Khoury R, Grimley M, Davies S, et al. Abatacept Decreases the Rate of Acute and Chronic GVHD in Children with Sickle Cell Disease Undergoing Matched Sibling Transplants. *Abstracts / Biol Blood Marrow Transplant* 26 (2020) S96-S255.
- 45 Patel A, Yong J. Elimination of acute GVHD with three doses of abatacept prophylaxis combined with post-transplant cyclophosphamide after myeloablative treosulfan-based conditioning in the HLA identical sibling and unrelated (10-12/12) peripheral blood stem cell donor setting: Improved safety and efficacy compared to alemtuzumab prophylaxis. *Blood*, (November 2019) Vol. 134, Supp. Supplement 1. Abstract.
- 46 Ngwube A, Shah N, Godder K, et al. Abatacept is effective as GVHD prophylaxis after unrelated donor stem cell transplantation (URD SCT) for children with severe sickle cell disease. *Blood Adv* (2020) 4 (16): 3894–3899.
- 47 Shenoy S, Eapen M, Panepinto J, et al. A Trial of Unrelated Donor Marrow Transplantation for Children With Severe Sickle Cell Disease. *Blood.* 2016 Nov 24;128(21): 2561-2567.
- 48 Koura DT, Horan JT, Langston AA, et al. In vivo T cell costimulation blockade with abatacept for acute graft-versus-host disease prevention: a first-in-disease trial. *Biol Blood Marrow Transplant.* 2013;19(11):1638-49.
- 49 Jaiswal S, Bhakuni P, Zaman S, et al. T cell costimulation blockade promotes transplantation tolerance in combination with sirolimus and post-transplantation cyclophosphamide for haploidentical transplantation in children with severe aplastic anemia. *Transplant Immunology* 43–44 (2017) 54–59.
- 50 Jaiswal S, Bhakuni P, Joy A, et al. CTLA4Ig Primed Donor Lymphocyte Infusion: A Novel Approach to Immunotherapy after Haploidentical Transplantation for Advanced Leukemia. *Biol Blood Marrow Transplant* 25 (2019) 673-682.
- 51 McCurdy S, Kanakry J, Showel M, et al. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. *Blood* (2015) 125 (19): 3024–3031.
- 52 Jaiswal S, Aiyer H, Rawat G, et al. CTLA4Ig-based reduced intensity conditioning and donor lymphocyte infusions for haploidentical transplantation in refractory aggressive B-cell lymphoma relapsing after an autograft: Early results from a pilot study. *Experimental Hematology* 2019;77:26–35.
- 53 Fenske T, Ahn K, Graff T, et al. Allogeneic transplantation provides durable remission in an subset of DLBCL patients relapsing after autologous transplantation. *British Journal of Haematology*, 2016, 174, 235–248.
- 54 Khandelwal P, Yeh R, Yu L, et al. Graft Versus Host Disease Prophylaxis With Abatacept Reduces Severe Acute Graft Versus Host Disease in Allogeneic Hematopoietic Stem Cell Transplant for Beta Thalassemia Major with Busulfan, Fludarabine, and Thiotepa. *Transplantation* 2020 May 25.
- 55 Ljungman P, Boeckh M, Hirsch HH, Josephson F, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clinical Infectious Diseases.* 2017; 64(1):87-91.
- 56 Green ML, Leisenring W, Stachel D, et al. Efficacy of a viral load based, risk-adapted, preemptive treatment strategy for prevention of cytomegalovirus disease after hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2012; 18(11):1687–1699.
- 57 Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *N Engl J Med.* 2017; 377(25):2433-2444.

- 58 Marty FM, Winston DJ, Rowley SD, et al. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. *N Engl J Med*. 2013; 369(13):1227-36
- 59 Curtis RE, Travis LB, Rowlings PA, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. *Blood*. 1999; 94(7):2208-16.
- 60 Landgren O, Gilbert ES, Rizzo JD, et al. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. *Blood*. 2009; 113(20):4992-5001.
- 61 Anasetti C, Logan BR, Lee SJ, et al. Blood and Marrow Transplant Clinical Trials Network. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med* 2012; 367(16):1487-96.
- 62 Watkins B, Qayed M, McCracken C, et al. Phase II Trial of Costimulation Blockade With Abatacept for Prevention of Acute GVHD. *Journal of Clinical Oncology* 2021; 39:1865-1877
- 63 Styczynski J, Van der Velden W, Fox C, et al. Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. *Haematologica* 2016 Volume 101(7):803-811.
- 64 Cho S, Lee D, Kim H. Cytomegalovirus Infections after Hematopoietic Stem Cell Transplantation: Current Status and Future Immunotherapy. *Int. J. Mol. Sci.* 2019, 20, 2666.
- 65 Al Hamed R, Bazarbachi A, Mohty M. Epstein-Barr virus-related posttransplant lymphoproliferative disease (EBV-PTLD) in the setting of allogeneic stem cell transplantation: a comprehensive review from pathogenesis to forthcoming treatment modalities. *Bone Marrow Transplantation* (2020) 55:25–39.
- 66 De la Cámara R. CMV in Hematopoietic Stem Cell Transplantation. *Mediterr J Hematol Infect Dis* 2016, 8(1).
- 67 Study IM101023: A Phase 3 Multi-Center, Randomized, Double-Blind Study to Evaluate Remission and Joint Damage Progression in Methotrexate-Naive Early Erosive Rheumatoid Arthritis Subjects with Abatacept Plus Methotrexate Compared with Methotrexate. Clinical study report. Bristol-Myers Squibb Company; 2008. Document Control No. 930027983.
- 68 Study IM101043: A Phase III, Multi-Center, Randomized, Double-Blind, Placebo Controlled Comparative Study of Abatacept or Infliximab in Combination with Methotrexate in Controlling Disease Activity in Subjects with Rheumatoid Arthritis Having An Inadequate Clinical Response to Methotrexate. Bristol-Myers Squibb Company; 2006. Document Control No. 930016106.
- 69 Study IM101031: A Phase III, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Use Study to Evaluate the Safety and Tolerability of BMS-188667 Administered Intravenously to Subjects with Active Rheumatoid Arthritis (RA) with or without Medical Co-Morbidities Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs) and/or Biologics Approved for RA. Bristol-Myers Squibb Company; 2005. Document Control No. 930012546.
- 70 Study IM101029: A Phase III, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of BMS-188667 in Subjects with Active Rheumatoid Arthritis on Background DMARDs Who Have Failed Anti-TNF Therapy. Bristol-Myers Squibb Company; 2005. Document Control No. 930012507.
- 71 Study IM101100: A Phase IIB, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Clinical Efficacy of Two Different Doses of BMS-188667 Administered Intravenously to Subjects with Active Rheumatoid Arthritis While Receiving Methotrexate. Bristol-Myers Squibb Company; 2005. Document Control No. 930012512.
- 72 Study IM101101: A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Safety and Clinical Efficacy of Intravenous Infusions of BMS-188667 (Abatacept, 2 mg/kg) Given Monthly in Combination with Subcutaneous Injections of Etanercept (25 mg) Given Twice Weekly to Subjects With Active Rheumatoid Arthritis. Bristol-Myers Squibb Company; 2005. Document Control No. 930012513.
- 73 Study IM101102: A Phase III, Multi-Center, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of BMS-188667 in Combination with Methotrexate vs. Methotrexate Alone in Subjects

- with Active Rheumatoid Arthritis and Inadequate Response to Methotrexate. Bristol-Myers Squibb Company; 2005. Document Control No. 930012517.
- ⁷⁴ Validation of an ELISA assay for the quantification of Abatacept (BMS-188667) in human serum (Study Report: 10BAS0278) Bristol-Myers Squibb Company, 2011. Document Control No. 930051030
- ⁷⁵ Validation of an electrochemiluminescent (ECL) immunoassay for the detection of Anti-BMS-188667 Antibodies in lupus patient serum (Study Report: (b) (4)) Bristol-Myers Squibb Company, 2009. Document Control No. 930040817
- ⁷⁶ Validation of A Cell-Based Bioassay for Determination of Neutralizing Antibodies to Abatacept (BMS-188667) in Human Serum. Method Validation Report Addendum-01. (Study Report: (b) (4)) Bristol-Myers Squibb Company, 2019. Document Control No. 930103655
- ⁷⁷ Validation of A Cell-Based Bioassay for Determination of Neutralizing Antibodies to Abatacept (BMS-188667) in Human Serum. Method Validation Report Addendum-02. (Study Report: (b) (4)) Bristol-Myers Squibb Company, 2020. Document Control No. 930103655
- ⁷⁸ Validation of A Cell-Based Bioassay for Determination of Neutralizing Antibodies to Abatacept (BMS-188667) in Human Serum. Method Validation Report. (Study Report: (b) (4)) Bristol-Myers Squibb Company, 2016. Document Control No. 930103655

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Lili Pan, PhD	OCP/DCPII	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
				Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiling Jiang -S, 0.9.2342.19200300.100.1.1=2001167656 Date: 2021.12.02 13:25:25 -05'00'
Clinical Pharmacology Team Leader	Ruby Leong, PharmD	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
				Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiling Jiang -S, 0.9.2342.19200300.100.1.1=2001167656 Date: 2021.12.02 13:30:15 -05'00'
Pharmacometrics Reviewer	Robyn Konicki, PharmD	OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
				Signature: Robyn E. Konicki -S Digitally signed by Robyn E. Konicki -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002409730, cn=Robyn E. Konicki -S Date: 2021.12.03 10:12:16 -05'00'
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
				Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2021.12.03 10:09:48 -05'00'

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15, 19.4	Select one: ☐ Authored ☒ Approved
				Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brian P. Booth -S, 0.9.2342.19200300.100.1.1=1300137436 Date: 2021.12.06 08:27:38 -05'00'
Clinical Reviewer	Joseph Wynne, MD, PhD	CDER/OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 11, 12, 13, 19	Select one: ☒ Authored ☐ Approved

Signature: Joseph P. Wynne -S
 Digitally signed by Joseph P. Wynne -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2003065031, cn=Joseph P. Wynne -S
 Date: 2021.12.13 09:03:48 -05'00'

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Jian (Jay) Zhao, PhD	OB/DBIX	Sections: 8	Select one: ☒ Authored ☐ Approved
Signature: Jian Zhao -S Digitally signed by Jian Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jian Zhao -S, 0.9.2342.19200300.100.1.1=2003071296 Date: 2021.12.07 20:40:32 -05'00'				
Statistical Team Leader	Jonathon Vallejo, PhD	OB/DBIX	Sections: 8	Select one: ☐ Authored ☒ Approved
Signature: Jonathon J. Vallejo -S Digitally signed by Jonathon J. Vallejo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002146299, cn=Jonathon J. Vallejo -S Date: 2021.12.08 14:08:48 -05'00'				
Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections: 8, 16	Select one: ☐ Authored ☒ Approved
Signature: Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369224, cn=Thomas E. Gwise -S Date: 2021.12.08 14:17:09 -05'00'				
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP	OOD/DHMI	Sections: 11	Select one: ☒ Authored ☐ Approved
Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000363858, cn=Elizabeth E. Everhart -S Date: 2021.11.22 14:45:57 -05'00'				

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SURIA YESMIN
12/15/2021 09:55:40 AM

KELLY J NORSWORTHY
12/15/2021 10:18:38 AM

ROMEO A DE CLARO
12/15/2021 10:20:28 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125118Orig1s240

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)**

Epidemiology RWE Review

Date: 29 November 2021

Reviewer: Aida Kuzucan, PhD, PharmD
Division of Epidemiology I (DEPI-I)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)

Team Leader: Steve Bird, PhD, PharmD
DEPI-I, OPE, OSE

Division Director: Simone Pinheiro, ScD
DEPI-I, OPE, OSE

Subject: Protocol and topline results for non-Interventional Study
“IM101841: A retrospective cohort study evaluating subjects who received abatacept in addition to Standard of Care (SOC) aGVHD prophylaxis, compared to subjects receiving SOC aGVHD alone, using data routinely collected in the Center for International Blood & Marrow Transplant Research (CIBMTR) database.”

Drug Name: Abatacept (ORENCIA)

Application Type/Number: IND 135013; BLA 125118 (Efficacy supplement 240)

Sponsor: Bristol-Myers Squibb (BMS)

OSE RCM #: 2021-1438

I. Introduction

The Division of Hematologic Malignancies I (DHMI) consulted the Division of Epidemiology (DEPI) to review the protocol and results of a real-world evidence (RWE) study submitted in support of a new indication for abatacept (ORENCIA). The proposed indication is for [REDACTED] (b) (4)

[REDACTED] (b) (4)

This proposed indication is supported by two studies: 1) IM101301 (ABA2), a phase 2 randomized clinical trial evaluating the efficacy of abatacept combined with calcineurium inhibitor (CNI) and methotrexate (MTX) for aGVHD prophylaxis, and 2) IM101841, a real-world retrospective study conducted in the Center for International Blood & Marrow Transplant Research (CIBMTR) database evaluating patients treated with Abatacept in addition to Standard of Care (SOC) in aGVHD prophylaxis.

This memo documents DEPI's assessment of the real-world study IM101841 protocol, topline results, and additional sensitivity analyses. DEPI defers the review of the phase 2 trial (IM101311/ABA2) submitted alongside the RWE study to the clinical and biostatistics teams.

II. Background

Abatacept, a selective modulator of T cell co-stimulation, was approved in the U.S. for adult rheumatoid arthritis in December of 2005. Additional approvals for juvenile idiopathic arthritis, and psoriatic arthritis were granted by the FDA in 2009 and 2017, respectively.¹

In October 2019, abatacept was granted breakthrough therapy designation for prevention of aGVHD based on preliminary results from the phase 2 trial IM101311 (aka ABA2).² Between June 2019 and October 2020, the FDA had type B, type C, and RWE subcommittee meetings to discuss the feasibility and evidence necessary to support an indication for the prevention of aGVHD among individuals receiving URD HSCT matched at no fewer than 7/8 human leukocyte antigens (HLA).^{3,4,5} During these meetings, a lack of equipoise in the 7/8 HLA arm led the FDA to agree to submission and review of a non-randomized registry-based study. A randomized controlled trial, like the ABA2 trial, was still deemed appropriate for evaluating aGVHD efficacy among 8/8 HLA matched HSCT recipients.^{3,4}

In April 2020, a Study May Proceed letter was sent to the Sponsor regarding a registry study accessing overall survival among 7/8 human leukocyte antigen matched transplant patients using Center for International Blood and Marrow Transplant Research (CIBMTR) data.⁶ In June 2021, topline results from

¹ Bristol-Myers Squibb Company. ORENCIA (abatacept) [label]. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125118s209lbl.pdf. Accessed November 4, 2021.

² Baird Amy C. Rev-Clinical-24(Grant Breakthrough Therapy Designation Request), Abatacept (ORENCIA). DAARTS reference ID: 4611008.

³ Chon, Wonne K. Memorandum of meeting minutes, Type C Guidance, Abatacept (BMS-188667); June 17, 2019 2:00-3:00 PM EST, DAARTS reference ID: 4455480.

⁴ Chon, Wonne K. Memorandum of meeting minutes, Type B Initial Breakthrough Therapy, Abatacept (Orencia, BMS-188667); January 13, 2020 2:00-3:00 PM EST, DAARTS reference ID: 4547178.

⁵ Chon, Wonne K. FRM-ADMIN-01 (Memorandum to File), Real World Evidence Subcommittee Meeting, Abatacept (Orencia); March 30, 2020 2:00-3:00 PM EST, DAARTS reference ID: 4582378.

⁶ Chon, Wonne K. COR-INDAD-01 (Study May Proceed), Abatacept (ORENCIA). DAARTS reference ID: 4589596.

study IM101311(ABA2) and IM101841 were submitted to the FDA.⁷ This memo documents DEPI-I's assessment of study IM101841.

III. Study Design

Study IM 1011841 is a retrospective cohort study that compares the rate of 180-day overall survival after allogeneic transplant among people who receive a CNI plus MTX for aGVHD prophylaxis with or without abatacept. Patients over 6 years of age who received their first allogeneic transplant (bone marrow or peripheral blood stem cell donor matched at 7/8 loci) from January 1st 2011 to December 31st 2018 were identified from the CIBMTR database which, due to a requirement by U.S. law, includes prospective data on every allogeneic transplant performed in the U.S. Inverse probability treatment weighting (IPTW) analysis was used to account for unequal distribution of measured confounding characteristics across cohorts. Propensity score variables included sex, disease, age, HSCT graft source, conditioning intensity, Karnofsky/Lansky performance score, and CNI type. Disease status however was not included in the propensity score in the initially submitted topline results; a covariate was added to the cox proportional hazards model to address concerns raised by the FDA regarding potential confounding by disease status.

The study included a total of 56 patients exposed to abatacept/CNI/MTX and 162 patients exposed to CNI/MTX. Complete case analysis was used to address missingness concerns; one out of 56 abatacept patients was missing donor age and was excluded from adjusted analysis. Relative to the CNI/MTX group, IPTW analysis found abatacept users had a higher rate of overall survival [death in 2% vs. 25%, HR 0.07 (95%CI:0.01,0.030)]. See Appendix Table A2 for a tabular summary of the design of study IM101841. A tabular summary of the RCT arm of study IM101311 (ABA2) is also found in Appendix Table 2A for context.

IV. Discussion

Study IM101841 used a regularly audited national registry database containing all allogeneic transplants in the U.S to evaluate the effect of aGVHD prophylaxis with abatacept on overall survival. Complete capture of HSCT transplant patients in the U.S. and their overall survival increases confidence in the generalizability of findings to the indicated population. Additional analyses using different PS models and different comparison groups also increased confidence in the observed benefit. Additional (sensitivity/supplemental) analyses were conducted to evaluate potential exposure and outcome misclassification as well as concerns regarding comparability across study arms. These and other considerations are discussed below.

Measurement of Exposure

- The duration of exposure of prophylaxis regimens were not captured. Exposure was defined based on the planned regimen reported prior to transplant. Patients may have switched or discontinued treatment temporarily or permanently. The extent of use is therefore, unclear. Analysis should be interpreted as an intention-to-treat analysis.
- Exposure misclassification other than treatment discontinuation or switching is likely not a concern. Recording of abatacept and other aGVHD prophylactic treatments were different; other treatments were chosen from a pull-down menu while abatacept had to be written in. Misclassification of abatacept users as recipients of SOC could occur if a clinician either forgot or

⁷ BristolMyers Squibb. BLA 125118 Supplement 240 (PO#53), abatacept (ORENCIA), aGVHD; June 23rd, 2021. EDR link: <\\CDSESUB1\evsprod\BLA125118\0507>

chose not to write in the medication. In a sub-study evaluating CIBMTR's ability to capture abatacept use, no misclassification of abatacept exposure among 9 randomly selected non-trial participants treated in ABA2 centers were identified. Thus, misclassification of abatacept users as standard of care is less likely.

Measurement of Outcome

- While overall survival is an important outcome measure, it may not isolate the effect of abatacept on aGVHD. Relapse, aGVHD, and infection are the leading causes of death after HSCT.⁸ Overall survival may be affected by unmeasured baseline characteristics or post-transplant care between treatment arms.
- Outcome misclassification is likely not a concern. Outcomes were determined by individual reporting physicians. The sponsor evaluated the concordance of outcomes in the CIBMTR and ABA2 trial and found negligible variation. Given the findings from this additional analysis and that the primary outcome of death is likely reported with limited variation between centers, outcome misclassification is likely not a concern.

Comparability Across Arms⁹

- Differences in trial participation could bias results in favor of abatacept. Differences in trial participation remained after IPTW; 82.4% abatacept patients were from the ABA2 trial while 13.2% of SOC patients participated in any trial. Trial participation could be associated with more frequent and higher intensity care which could lead to better overall survival.
- Confounding by center cannot be evaluated. This study excluded all SOC patients that were treated in an ABA2 participating center. As a result, no abatacept and SOC treated patients received care in the same center. A lack of overlap precludes analytic techniques for evaluating center-specific effects; it is unclear how variations in center practices might influence differences in overall survival.
- Differences in year of transplant could bias results in favor of abatacept. Relative to the SOC treatment arm, more abatacept treated patients received transplants in later follow-up years. These time-trend differences remained after PS and IPTW adjustments. Transplant outcomes have improved over time;¹⁰ time-related bias is likely away from the null.
- Differences in baseline disease status could bias results in favor of abatacept. The disease status variable in CIBMTR classifies individuals according to their ability to achieve and maintain complete remission at the time of their transplant.¹¹ After IPTW, the proportion of abatacept in "early stage" of disease was larger than in SOC (71.8% vs. 54.1%). In a communication with the sponsor, discrepancies were identified between patients' disease status captured in ABA2 and CIBMTR suggesting a potential lack of measure validity.¹² Residual confounding by disease status cannot be ruled out.

⁸ Styczyński, J., Tridello, G., Koster, L. et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. *Bone Marrow Transplant* 55, 126–136 (2020). <https://doi.org/10.1038/s41409-019-0624-z>

⁹ FDA conducted quantitative bias assessments that were inconclusive. Please refer to the assessment aid associated with this application for more details.

¹⁰ Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorrow ML, Boeckh M, Martin PJ, Sandmaier BM, Marr KA, Appelbaum FR, Storb R, McDonald GB. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010 Nov 25;363(22):2091-101. doi: 10.1056/NEJMoa1004383. PMID: 21105791; PMCID: PMC3017343.

¹¹ <https://www.cibmtr.org/manuals/fim/1/en/topic/q235-238-current-disease-status>

¹² Abatacept BMS-188667 (BLA 125118 Supplement 240) DATE: 17 SEPTEMBER 2021 Version 1.0; BMS Response to FDA Request dated 13 September 2021.

The FDA conducted additional sensitivity (quantitative bias) analyses to evaluate the impact of unmeasured/uncontrolled confounding resulting from potential differences between study arms in factors such as complete remission status at the time of transplant, treatment through clinical trial protocols versus routine care, treatment practices across centers, and treatment practices over time. These analyses estimated the *e-value*¹³ – or the minimum magnitude of association unmeasured confounders need to have with treatment and outcome to account for the observed study findings, conditional on measured covariates. A large *e-value* would increase confidence in findings because it implies considerable unmeasured/residual confounding would need to be present to account for an observed effect. In the primary IPTW analysis, an estimated *e-value* of 4.3 was necessary to negate the statistically significant overall survival benefit (*i.e.*; have the upper bound of the 95% confidence interval include 1.0), while an *e-value* of 11.6 was necessary to negate any effect observed in the abatacept arm (*i.e.*; move the point estimate to 1.0). The estimated *e-value* of 4.3 for the upper bound of the 95% confidence interval indicated that relatively large – though not insurmountable – joint confounding effects could overturn the significance of findings in the primary analyses of study IMR101841. Thus, these analyses could not conclusively rule out the impact of potential large differences in important risk factors across study arms.

¹³ VanderWeele TJ and Ding P. Sensitivity analysis in observational research: introducing the *e-value*. *Ann. Intern. Med.* 2017; 167(4): 268-274.

V. Conclusion

Study IM101841 has several strengths which include: the use of a registry containing all U.S. allogeneic transplant patients, validation sub-study analyses indicating no exposure misclassification issues, and multiple sensitivity analyses indicating robust overall survival benefits. Conclusions however should be interpreted with caution. Differences across study arms in complete remission status at the time of transplant, treatment through clinical trial protocols versus routine care, treatment practices across centers, and treatment practices over time may introduce bias. Sensitivity (quantitative bias) analyses could not conclusively rule out the impact of potential large differences in important risk factors across study arms. The extent this potential bias could diminish the comparative benefit observed in this study is unclear.

VI. References

1. Bristol-Myers Squibb Company. ORENCIA (abatacept) [label]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125118s209lbl.pdf. Accessed November 4, 2021.
2. Baird Amy C. Rev-Clinical-24(Grant Breakthrough Therapy Designation Request), Abatacept (ORENCIA). DAARTS reference ID: 4611008.
3. Chon, Wonme K. Memorandum of meeting minutes, Type C Guidance, Abatacept (BMS-188667); June 17, 2019 2:00-3:00 PM EST, DAARTS reference ID: 4455480.
4. Chon, Wonme K. Memorandum of meeting minutes, Type B Initial Breakthrough Therapy, Abatacept (Orencia, BMS-188667); January 13, 2020 2:00-3:00 PM EST, DAARTS reference ID: 4547178.
5. Chon, Wonme K. FRM-ADMIN-01 (Memorandum to File), Real World Evidence Subcommittee Meeting, Abatacept (Orencia); March 30, 2020 2:00-3:00 PM EST, DAARTS reference ID: 4582378.
6. Chon, Wonme K. COR-INDAD-01 (Study May Proceed), Abatacept (ORENCIA). DAARTS reference ID: 4589596.
7. Bristol Myers Squibb. BLA 125118 Supplement 240 (PO#53), abatacept (ORENCIA), aGVHD; June 23rd, 2021. EDR link: <\\CDSESUB1\evsprod\BLA125118\0507>
8. Styczyński, J., Tridello, G., Koster, L. et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. *Bone Marrow Transplant* 55, 126–136 (2020). <https://doi.org/10.1038/s41409-019-0624-z>
9. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, Martin PJ, Sandmaier BM, Marr KA, Appelbaum FR, Storb R, McDonald GB. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010 Nov 25;363(22):2091-101. doi: 10.1056/NEJMoa1004383. PMID: 21105791; PMCID: PMC3017343.
10. <https://www.cibmtr.org/manuals/fim/1/en/topic/q235-238-current-disease-status>
11. Abatacept BMS-188667 (BLA 125118 Supplement 240) DATE: 17 SEPTEMBER 2021 Version 1.0; BMS Response to FDA Request dated 13 September 2021.

Appendix

Table A1. Summary of Regulatory Considerations for Study IM101841¹⁴

Product Name, Approved indications	Abatacept (ORENCIA), currently approved for rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis
Regulatory purpose	<i>Evidence supporting approval of a new indication:</i> (b) (4)
Existing evidence from other sources	IM101311/ABA2 is a double-blind randomized study of HLA-matched HSCT recipients. Abatacept treatment improved severe GFS in the 8/8 cohort (89%) compared to the placebo cohort (77%). The improvement was not statistically significant at the 0.05 level (HR: 0.54, 95%CI: 0.25-1.20, P-value = 0.1223). However, numerically higher rates of moderate to severe (Gr II-IV) GFS (50% vs 30%; HR: 0.55, P-value = 0.0069), as well as OS (84% vs. 97%; HR: 0.55, P-value = 0.0281) were reported in the 8/8 HLA abatacept arm. High rates of severe GFS in the 7/8 cohort (98% [95%CI: 0.85-1]) and OS (98%[95%CI: 0.85-1.00]) were also observed in the Abatacept arm.
Regulatory need and gap	The RCT's primary analyses failed to reach statistical significance in the 8/8 cohort. This could be because of a lack of power to address a marginal benefit in a relatively small sample of patients. Lack of equipoise prohibited randomization in the 7/8 cohort; a single arm trial indicated high rates of GFS and OS. A RWE study may provide additional data informing the effect of abatacept in the population with a relatively lower prognosis (i.e. the 7/8 cohort). It may also provide an opportunity to access the magnitude of a potential benefit in the 7/8 cohort by including a comparison group.
Study objective	The main objective is to compare <u>180-day overall survival (outcome)</u> in patients who undergo <u>7/8 human leukocyte antigen (HLA)-matched hematopoietic stem cell transplantation (HSCT) (indicated population)</u> and receive prophylaxis with <u>Abatacept + CNI+MTX without ATG (exposure)</u> or <u>CNI+MTX without ATG (comparator)</u>. This outcome in study IM101841 varies from that accessed in IM101311. The outcome accessed in IM101311 was acute versus graft host disease by day 180 post-transplant. The population also varies with 8/8 matched individuals in the RCT and 7/8 matched individuals in the RWE study. A single arm of 7/8 matched individuals were studied in the pivotal trial; those were the same individuals captured in the RWE study.

¹⁴ Bristol Myers Squibb. BLA 125118 Supplement 240 (PO#53), a batacept (ORENCIA), a GVHD; June 23rd, 2021. EDR link: <\\CDSESUB1\evsprod\BLA125118\0507>

Table A2. Tabular Summary of Study Designs of IM101841 and IM101311¹⁵

Study design	RWE study (Observational) (IM 101841)	RCT (IM 101311)
Design	Observational retrospective cohort using secondary data	Randomized, double-blind, placebo-controlled trial
Data source (including calendar time of data availability and follow-up, if applicable)	The Center for international Blood Marrow Transplant Research (CIBMTR). Includes data on every allogeneic transplant performed in the U.S. (for the SCTOD, reporting as required by U.S. law). January 1, 2011 to December 31, 2018, 180-days of follow-up	Primary data collection with prespecified data collection schedule
RWE study population inclusion and exclusion criteria and RCT study population inclusion and exclusion criteria as applicable to the RWE study	Inclusion criteria: First allogeneic transplant in the United States from 01/01/2011 to 12/31/2018 Unrelated donor is HLA-matched at 7/8 loci (A, B, C, DRB1); at least 6 years of age and weighs at least 20kg; Karnofsky/Lansky performance score greater than 80% (two patients were included despite not meeting this criteria); diagnosis of AML, ALL, CML, MDS, HL, or NHL; treatment with CNI +MTX (+/- ATG and +/- abatacept) or PT-Cy without ATG for aGVHD prophylaxis; treatment with any of the following conditions regimens: total body irradiation (TBI) /cyclophosphamide (Cy), busulfan (Bu)/Cy, Bu/fludarabine (flu), Flu/Melphalan (MEL) Exclusion criteria: Any missing information on ATG, disease status at transplantation, age, gender, HSCT graft source, conditioning intensity, Karnofsky/Lansky Performance	The following exclusion criteria used in the retrospective cohort study do not apply in the RCT setting. Transplant recipients with any missing information on ATG, disease status at transplantation, age, gender, HSCT graft source, conditioning intensity, Karnofsky/Lansky Performance Score, or CNI type (only among cohorts including CNI) The following exclusion criteria were used in the RCT but not applied in the RWE setting. (superscript key for justification from sponsor below): enrollment in COG trial^a (participation in any trial was included)

¹⁵ Bristol Myers Squibb. BLA 125118 Supplement 240 (PO#53), a batacept (ORENCIA), a GVHD; June 23rd, 2021. EDR link: <\\CDSESUB1\evsprod\BLA125118\0507>

	Score, CNI type (only among cohorts including CNI) Treatment with alemtuzumab (Campath) or abatacept with ATG; cord blood grafts; diagnosis of non-MDS myeloproliferative disorders; among non-abatacept patients: patient transplanted at centers with abatacept trial patients; patients who did not consent or were treated at embargoed centers for research.	uncontrolled viral, bacterial, fungal or protozoal infection^a (infections resulting in hospitalizations were included); HIV infection^b; serious psychiatric disease^a (psychiatric disease resulting in hospitalization was included); known or inherited or constitutional predisposition to cancer;^c incompletely treated tuberculosis infection;^a pregnancy or breastfeeding;^a estimated GFR<50;^b cardiac ejection fraction <50;^a bilirubin>2x upper limit of normal or ALT>4 x upper limit of normal or unresolved veno-occlusive disease;^b pulmonary disease with FVC, FEV1, or DLCO. (Adjusted DLCO ≤ 65% (severe), FEV1 66-80% (moderate), or FEV1 ≤ 65% (severe) are captured in the HCT-CI which will be included in a sensitivity propensity score analysis. Individual components of the HCT-CI (including moderate and severe pulmonary comorbidity) are described.);^a presence of antibodies to a mismatched donor HLA antigen^d Justifications superscripts for above: not collected in CIBMTR collected only in CRF (~25% of patients) collected only for some diseases This newly collected item at CIBMTR and is unlikely to be available for the current study population
Index date	Date of 1 st allogenic transplant	Date of 1 st allogenic transplant

Follow-up and censoring	Follow-up: up to 180-days post-transplant Censoring: at time of last follow-up or at end of follow-up period (180-days) whichever occurs 1 st	Follow-up: 180 days for primary endpoint with an additional 5 years of follow-up.
Exposure definition, ascertainment, and validation	GVHD prophylaxis (CNI, MTX, ATG, PT-Cy) information was obtained through the standardized data collection form in CIBMTR. Abatacept use is not yet part of the standardized data collection form, abatacept use was captured through the following: Linking CIBMTR unique recipient ID number from patients in ABA2 study (IM101311) with those in CIBMTR database; and Using information in the “Other GVHD prophylaxis” free text field. Abatacept misclassification was assessed in a validation sub-study using a stepwise risk-based process. Three steps were planned. First, 18 randomly selected patients from 9 centers that participated in the ABA2 trial were evaluated. If any patient’s abatacept use was misclassified, an additional 42 patients would be randomly selected and evaluated in the second step. Subsequently, a third step full review of all centers would be conducted if 5/60 patients were misclassified. No treatment misclassification was identified in the first step.	Patients’ treatment were assigned at random
Comparator definition, ascertainment, and validation	GVHD prophylaxis (CNI, MTX, ATG, PT-Cy) information was obtained through the standardized data collection form in CIBMTR. No comparison patients were identified from ABA2 centers to decrease likelihood of falsely classifying abatacept users as SOC patients.	Patients’ treatment assigned at random

	Primary exposure comparison groups: CNI + MTX without ATG Secondary exposure groups are: 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	
Outcome definition, ascertainment, and validation	Primary Objective Compare overall survival (OS) at 180 days after hematopoietic stem cell transplantation (HSCT) in 7/8 human leukocyte antigen (HLA)-matched patients treated with and without abatacept in addition to SOC Secondary Objectives Stratified analysis by CNI regimen Exploratory Objectives Assess the OS at 180 days post-HSCT with/between alternative GVHD prophylaxis regimens Assess grade II-IV and grade III-IV aGVHD-free survival up to the first 100 and 180 days Assess relapse-free survival at 100 and 180 days Assess incidence of PTLD at the first 100 and 180 days Overall survival was ascertained using death dates reported in CIBMTR. Sponsor compared death dates captured in single arm ABA trial with those captured in CIBMTR. No discrepancies were identified.	Primary endpoint: Severe (Gr III-IV) aGVHD-free survival (GFS) up to Day 180 Secondary endpoint: Cumulative incidence of severe Gr III-IV aGVHD up to Day 180 post-transplantation Other endpoints: Overall Survival (OS) Disease-Free Survival (DFS) (also known as relapse-free survival [RFS]) Transplant-related mortality (TRM) Relapse rates Frequency of early onset (before day 100) aGVHD Frequency of late onset (after day 100) aGVHD Frequency of chornic GVHD Immune suppression-free survival and immune suppression free/disease-free survival GVHD Free Disease- Free survival
Key covariates: measured and unmeasured	Measured covariates: demographics: age, sex, Karnofsky/Lansky performance score, race/ethnicity Disease: ALL, AML, MDS, CML, HL+NHL Disease status: early, intermediate, advanced, HL-Chemosensitive at transplantation	Most covariates in RWE were captured in RCT. Justifications and deviations in measures were described in the protocol. Covariate reported in RCT but not RWE: Pre-transplant CMV (donor) Pretransplant CMV (recipient) Pre-transplant EBV (donor)

	Donor-related: donor age, sex-match, cytomegalovirus match, ABO mismatch, HLA matching Transplant related: conditioning regimen, conditioning intensity, stem cell source, year of transplant, time from diagnosis to transplant, CNI type Comorbidities: hematopoietic cell transplantation-comorbidity index, arrhythmia, cardiac comorbidity, cerebrovascular disease, diabetes, heart valve disease, mild hepatic comorbidity, moderate/severe hepatic comorbidity, infection, inflammatory bowel disease, obesity, peptic ulcer, psychiatric disturbance, moderate pulmonary comorbidity, severe pulmonary comorbidity, moderate/severe renal comorbidity, rheumatologic comorbidity, prior solid tumor Participation in IM101311 clinical trial participation in any clinical trial during the study period	Pre-transplant EBV (recipient) Baseline serum IGG Geographic region weight category/ weight Discontinuation of treatment
Statistical methods (primary analysis)	A propensity score predicting probability of abatacept treatment was developed. Patients were weighted by the stabilized inverse probability of receiving the treatment they received. Comparison of OS between the treatment groups was based on a weighted log-rank test using a 2-sided alpha of 0.05. Supplemental analyses were conducted using varying propensity score matching approaches. Variables considered in PS creation include sex, disease, age, HSCT graft source, conditioning intensity, Karnofsky/Lansky performance score, and CNI type. 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	Cumulative incidence was calculated. In 8/8 MUD cohort MITT subjects, the abatacept group had a numerically higher severe GFS rate up to Day 180 post-transplantation compared to the placebo group.

	that accounts for the sample weights. The estimated survival probability over time was provided by weighted Kaplan-Meier curves up to 180 days after transplant.	
Sample size	Actual: Abatacept+CNI+MTX without ATG: N=54 CNI+MTX without ATG: N=162	Actual: From 22 sites (21 sites in US and 1 site in Canada) 146 subjects were enrolled in the 8/8 MUD cohort. Five were randomized but discontinued prior to treatment. Study sample=142 73--> abatacept 69--> placebo
Methods to handle confounding, if applicable	PS, IPTW, and additional sensitivity models with varying covariates in the PS.	Randomization
Methods to handle missing data, if applicable	Only patients with non-missing treatment and propensity score variables are included in the study. One abatacept patient was missing their donor age and was excluded from adjusted analysis.	Missing data is limited with rigorous study quality control

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AIDA E KUZUCAN
11/30/2021 03:10:23 PM

STEVEN BIRD
12/02/2021 05:43:13 PM

SIMONE P PINHEIRO
12/02/2021 09:06:04 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 1, 2021

To: Suria Yesmin, MS
Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nisha Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (established name): ORENCIA (abatacept)

Dosage Form and Route: for injection for intravenous use
injection, for subcutaneous use

Application Type/Number: BLA 125118

Supplement Number: S-240

Applicant: Bristol-Myers Squibb

1 INTRODUCTION

On June 23, 2021, Bristol-Myers Squibb submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to Biologics License Application (BLA) 125118/S-240 for ORENCIA (abatacept), for injection for intravenous use and injection, for subcutaneous use. With this supplement, the Applicant proposes a new indication (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies I (DHM1) on June 29, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ORENCIA (abatacept) for injection for intravenous use and injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft ORENCIA (abatacept) PPI and IFU received on June 23, 2021, and received by DMPP and OPDP on October 26, 2021.
- Draft ORENCIA (abatacept) Prescribing Information (PI) received on June 23, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 26, 2021.
- Approved ORENCIA (abatacept) labeling dated June 17, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. We do not have any revisions for the submitted IFU, therefore it is not attached. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN W REDWOOD
11/01/2021 09:13:30 AM

NISHA PATEL
11/01/2021 09:30:29 AM

BARBARA A FULLER
11/01/2021 09:43:30 AM

LASHAWN M GRIFFITHS
11/01/2021 09:44:20 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: October 29, 2021

To: Suria Yesmin, Regulatory Project Manager
Division of Hematologic Malignancies 1 (DHM1)

Elizabeth Everhart, Associate Director for Labeling, DHM1

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for ORENCIA (abatacept) for injection, for intravenous use and ORENCIA (abatacept) injection, for subcutaneous use

BLA: 125118/S-240

In response to DHM1's consult request dated June 29, 2021, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for ORENCIA (abatacept) for injection, for intravenous use and ORENCIA (abatacept) injection, for subcutaneous use (Orencia). This supplement (S-240) provides for a new indication for (b) (4)

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling accessed from SharePoint on October 26, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

Product Labeling

Section	Statement from draft	Comment
14 Clinical Studies, 14.4 Prophylaxis of Acute Graft versus Host Disease	(b) (4)	OPDP agrees with DHM1's comment and recommendation: "To Applicant: (b) (4)

66 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NISHA PATEL
10/29/2021 04:54:21 PM

CLINICAL INSPECTION SUMMARY

Date	October 7, 2021
From	Anthony Orenca M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Joseph Wynne, M.D., Ph.D., Medical Officer Kelly Norsworthy, M.D., Medical Team Leader R. Angelo de Claro, M.D., Division Director Suria Yesmin, M.S., Project Manager Division of Malignant Hematology 1 (DHM1) Office of Oncology Drugs (OOD)
BLA	BLA 125118 S-240
Applicant	Bristol-Myers Squibb Company
Drug	Orenca® (abatacept)
NME	No
Division Classification	Inhibitor of CD28-mediated stimulatory signal immune activation and T-cell activation (immunomodulator)
Proposed Indication	Prophylaxis of moderate to severe acute graft versus host disease (aGVHD) in unrelated-donor hematopoietic stem cell transplantation (HSCT)
Review Type	Priority
Consultation Request Date	August 10, 2021
Summary Goal Date	September 22, 2021; Extended to October 15, 2021
Action Goal Date	October 22, 2021
PDUFA Date	December 22, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from an investigator-sponsored research Study IM101311 were submitted to the Agency in support of a supplemental Biologics License Application (BLA) 125118/S-240 for the drug abatacept, proposed as prophylaxis regimen with a calcineurin inhibitor and methotrexate, in subjects with moderate to severe acute graft versus host disease undergoing unrelated-donor allogeneic hematopoietic stem cell transplantation. Two clinical investigators (Amelia Langston, M.D. and Aleksandra Petrovic, M.D.) were inspected for Study IM101311. The sponsor-investigator, Leslie Kean, M.D., Ph.D., was also inspected for monitoring and oversight of the above study.

The study data derived from the above two clinical investigator sites are considered reliable. Monitoring and oversight of Study IM101311 by the sponsor-investigator appeared adequate. The study data submitted to the Agency for assessment appeared acceptable in support of the proposed indication.

II. BACKGROUND

Abatacept (BMS-188667) is a co-stimulation modulator that blocks the interaction between cluster of differentiation (CD) 80/CD86 on antigen-presenting cells, and the CD28 receptor on T cells. This interaction provides a key signal necessary for full activation of T cells. By inhibiting CD28-mediated immune activation, abatacept blocks antigen recognition and modulates the immune response to decrease T-cell activation and antibody production.

Sponsor proposes adding a labeled therapeutic biologics indication for abatacept to standard acute Graft Versus Host Disease (GVHD) prophylaxis regimen of a calcineurin inhibitor and methotrexate in subjects undergoing unrelated-donor allogeneic hematopoietic stem cell transplantation for the treatment of high-risk hematologic malignancies. Specifically, the marketing applicant proposes the following treatment indication for abatacept: (b) (4)

A single study IM101311, an investigator sponsored research, formed part of the regulatory decision for approvability of this submitted application to the Agency. Bristol-Myers Squibb Company submitted this prior approval efficacy supplement as the marketing applicant.

Study IM101311

Study IM101311 was designed to assess the utility of adding abatacept to standard acute GVHD prophylaxis regimen of a calcineurin inhibitor and methotrexate in subjects undergoing unrelated donor allogeneic HSCT for the treatment of high-risk hematologic malignancies. A total of 146 subjects were enrolled in 8/8 matched unrelated donor (MUD) cohort and 46 subjects were enrolled 7/8 mismatched unrelated donor (MMUD) cohort. All 146 subjects enrolled in the 8/8 MUD cohort of Study IM101311 were randomly assigned 1:1 to abatacept (abatacept + standard prophylaxis regimen) or placebo (standard calcineurin inhibitor + methotrexate) treatment arm.

The original protocol required all subjects enrolled into both the 8/8 MUD cohort and 7/8 MMUD cohort to be randomized to either abatacept or placebo arm. Following initiation of the study, but independent of it, a general impression began to emerge among members of the allogeneic hematopoietic stem cell transplantation transplant community that addition of abatacept to a standard of care regimen for acute GVHD 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 enrollment 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. The comparator arm for 7/8 MMUD cohort was changed to a pre-specified control cohort from the Center for International Blood and Marrow Research.

Subjects were enrolled using an online system and eligibility was confirmed by the study coordinator. After enrollment, subjects in the 8/8 MUD cohort were randomly assigned to the placebo arm (abatacept + calcineurin inhibitor) or to the investigational abatacept arm (abatacept + calcineurin inhibitor + methotrexate) of the study. Randomized subjects who never received any study medication (abatacept or placebo) were replaced, i.e., additional subjects were randomized to replace these subjects. Treating physicians were to choose a conditioning regimen that he or she determined was best suited for the individual patient and the patient's malignancy.

Study drug (abatacept or placebo) was administered intravenously (IV) at a dose of 10 mg/kg on Days -1, +5, +14, +28. Day of transplant was Day 1 of Study; there was on Day 0.

The primary study objective was to compare severe (Grade III-IV) acute GVHD free survival up to Day 180 post-transplantation between the abatacept + standard acute GVHD prophylaxis and standard acute GVHD prophylaxis regimen only in unrelated-donor hematopoietic stem cell transplantation for subjects with hematologic malignancies.

The primary efficacy endpoint was severe (Grade III-IV) GVHD free survival up to Day 180 post-transplantation. The following formed the principal groups analyzed: the abatacept + standard acute GVHD prophylaxis versus acute standard GVHD prophylaxis regimen only in unrelated donor allogeneic hematopoietic stem cell transplantation for subjects with hematologic malignancies. Sensitivity analysis were conducted for severe GVHD free survival up to Day 180 with censoring at the time of relapse.

The study enrolled 192 subjects from 22 sites (21 sites in US and 1 site in Canada). The study initiated on April 15, 2013 and completed on November 17, 2018.

In the 8/8 matched unrelated donor cohort, all 146 enrolled subjects were randomized. In the 7/8 mismatched unrelated donor cohort, of the 46 subjects enrolled, 44 were treated with study medication and transplanted; 43 subjects were treated with abatacept and 1 subject was randomized to the placebo group prior to Study Protocol Amendment 04.

III. RESULTS (by site)

1. Amelia Langston, M.D./Site 001

Emory University - Winship Cancer Institute
1365 Clifton Rd NE, Suite B3101
Atlanta, GA 30322

Inspection dates: September 7 to 21, 2021

For this study, 46 subjects were consented and screened, 41 subjects were enrolled (ten subject in the 7/8 MMUD cohort, and 31 subjects in the 8/8 MUD cohort). There were 40 study participants were randomized into the study. Of the randomized subjects, 18 died, 14 completed the treatment phase of the study, one withdrew consent, and 8 are being seen in follow-up. The study is ongoing but closed to enrollment.

Study files assessed included a review of the Institutional Review Board (IRB) approvals and informed consent documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, case report forms, and test article control records. The site audit also involved an evaluation of subject source records medical history, progress notes, laboratory results, ancillary procedures, blood sample records, adverse event and serious adverse event documentation, and subject-specific protocol deviation records.

The Center for International Blood and Marrow Transplant Research, located in Minneapolis, MN conducted monitoring of Dr. Langston's site for the duration of the study. Monitors met with study staff at Dr. Langston's clinical site both in person and remotely at the first interim monitoring visit. Following the initial monitoring visit, monitors conducted visits 2-3 times per year. Monitor's reviews included, but were not limited to: protocol required procedures, informed consent, pharmacy records, and adverse events. Audit of these monitoring reports by FDA noted that the clinical site addressed all monitors' observations and reported all deviations to the IRB and sponsor-investigator as required.

Source records were reviewed for 9 of 41 enrolled subjects. The reviewed source records included medical history, eligibility criteria, randomization, protocol-required procedures, adverse events, serious adverse events, and primary endpoints. No discrepancies were noted.

Source records for the enrolled study patients were examined and verifiable for graft versus host disease free survival efficacy data against the data line listings. No under-reporting of adverse events was found.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Aleksandra Petrovic, M.D./Site 004

Seattle Children's Hospital
1900 Ninth Ave
Seattle, WA 98101

Inspection dates: September 1 to 8, 2021

A total of 120 subjects were screened and consented, and 71 study subjects were enrolled (11 of the 7/8 MMUD cohort and 60 of the 8/8 MUD cohort). Of the randomized, all subjects completed the treatment phase of the study.

The following regulatory documents were assessed: IRB approval letters and correspondence, monitoring reports, informed consent forms, subject medical records, financial disclosure reports, case report forms, subject questionnaires and diaries, dosing records, scans, independent reviewer imaging, site signature and responsibility logs, and site training documentation. The selected subjects' records were audited for eligibility, treatment assignment and disposition, protocol adherence, adverse event reporting, efficacy data, and concomitant medications.

For Study IM101311, the Center for International Blood and Marrow Transplant Research, located in Minneapolis, MN conducted monitoring of Dr. Petrovic's study site for the duration of the study. Additional monitoring was also performed by the Fred Hutchinson University of Washington Consortium, Clinical Research Support.

A 100% review of the informed consent document forms was conducted. A total of 15 subject record files were assessed for the 8/8 matched unrelated donor (MUD), and five subject records were reviewed for the 7/8 mismatched unrelated donor (MMUD) cohorts.

Source records evaluated, as described, for the enrolled study patients were examined and verifiable, for primary endpoint data against the data line listings. No discrepancies were noted. There was no evidence of under-reporting of adverse events or protocol deviations.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. Leslie Kean, M.D., Ph.D., Sponsor-Investigator

Boston Children's Hospital
1 Blackfan Circle, Karp-8
Boston, MA 02115

Inspection dates: September 20 to 27, 2021

The inspection assessed the application sponsor-investigator research's responsibilities for the Study IM101311, a Phase 2 randomized clinical trial on behalf of the marketing applicant, Bristol-Myers Squibb Company.

The inspection included review of the trial master files, standard operating procedures, site monitoring, handling of adverse events, data collection, and how the sponsor brought non-compliant sites into compliance. Information was also obtained concerning procedures for selection of clinical investigators, monitoring procedures and frequency, and other monitoring-related activities.

Records for the following eight clinical study sites were evaluated: Site 001 (Amelia Langston, M.D.); Site 002 (Muna Qayed, M.D.); Site 003 (Nosha Farhadfar, M.D.); Site 004 (Aleksandra Petrovic, M.D.); Site 005 (Michael Grimley, M.D.); Site 006 (Sung Won Choi, M.D.); Site 009 (David A. Jacobsohn, M.D.), and Site 011 (Christine Duncan, M.D.). The FDA audit found that these sites were monitored throughout the studies, and clinical investigators carried out their responsibilities according to the FDA regulatory requirements. No evidence of under-reporting of adverse events to the Agency was found.

In general, the monitoring and oversight of Study IM101311 by Dr. Kean who conducted an investigator-sponsored research appeared adequate.

Based on the inspectional results, there were no objectionable conditions noted, and no Form FDA-483, Inspectional Observations, was issued.

{See appended electronic signature page}

Anthony Orenca, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANTHONY J ORENCIA
10/07/2021 07:21:46 PM

MIN LU
10/08/2021 09:16:36 AM

KASSA AYALEW
10/08/2021 09:58:03 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 2, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	BLA 125118/S-240
Product Name, Dosage Form, and Strength:	Orencia (abatacept) For injection, 250 mg/vial Orencia (abatacept) Injection, 125 mg/mL, 87.5 mg/0.7 mL, and 50 mg/0.4 mL Orencia Clickject (abatacept) Injection, 125 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bristol-Myers Squibb Company (BMS)
FDA Received Date:	June 23, 2021
OSE RCM #:	2021-1439
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Bristol-Myers Squibb Company (BMS) submitted a supplemental BLA 125118/S-240 for Orenzia (abatacept) For injection to update the Prescribing Information (PI) to support the addition of a new indication for Orenzia for the (b) (4)

(b) (4). We reviewed the proposed Orenzia PI, Patient Information, and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Orenzia is a selective T cell inhibitor costimulation modulator that was approved on December 23, 2005.

Orenzia is indicated for the treatment of adult rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and adult psoriatic arthritis (PsA).

It is available as 250 mg lyophilized powder in a single-dose vial, 50 mg/0.4 mL, 87.5 mg/0.7 mL, 125 mg/mL single-dose prefilled syringe, and 125 mg/mL single-dose prefilled ClickJect autoinjector.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

BMS proposed changes to the PI, to support the addition for a new indication for Orenzia for

(b) (4)

(b) (4) We performed a risk assessment of the proposed PI, Patient Information, and IFU to determine if they are acceptable from a medication error perspective. We find the IFU acceptable from a medication error perspective. We identified areas of concern in the PI and Patient Information that should be revised to improve the clarity of the information presented. Specifically, we note that the PI is missing (b) (4), contains large doses without commas, and symbols. We note the Patient Information contains abbreviations, which may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We find the IFU acceptable from a medication error perspective. We identified areas in the proposed PI and Patient Information that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the PI and Patient Information.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Highlights of Prescribing Information

1. Dosage and Administration Section

- a. Consider replacing the symbols “<” and “≥” with their intended meanings to prevent misinterpretation and confusion.
- b. The dose of 1000 mg is presented as a large dose and appears without comma to improve readability. Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100” or ten-thousands “10000”. We recommend revising the dose to include a comma, for example, to read as 1,000 instead of 1000.
- c. We recommend revising the statement, “(b) (4)
(b) (4)

(b) (4)
(b) (4) as “Administer at a 10 mg/kg dose (maximum dose 1,000 mg) as a 60-minute intravenous infusion on the day before transplantation, followed by a dose on Day 5, 14, and 28 after transplant.”

B. Prescribing Information

1. Dosage and Administration Section

- a. Section 2.1 Dosage in Adult Rheumatoid Arthritis and Section 2.4 Dosage in Prophylaxis for Acute Graft versus Host Disease
 - i. The dose of 1000 mg is presented as a large dose and appears without comma to improve readability. Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100” or ten-thousands “10000”. We recommend revising the dose to include a comma, for example, to read as 1,000 instead of 1000. In addition, we recommend making this revision throughout the entire label.

C. Patient Information

1. How should I use Orencia

- a. As currently presented, the Patient Information contains the abbreviation, “IV”. Error prone abbreviations may lead to misinterpretation and medication error. We recommend replacing the abbreviations “IV” with the intended meaning.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Orencia received on June 23, 2021 from Bristol-Myers Squibb Company (BMS).

Table 2. Relevant Product Information for Orencia													
Initial Approval Date	December 23, 2005												
Proper Name	abatacept												
Indication	Adult Rheumatoid Arthritis (RA), Polyarticular Juvenile Idiopathic Arthritis (JIA), Adult Psoriatic Arthritis (PsA), and prophylaxis for Acute Graft versus Host Disease (aGVHD) (<i>proposed</i>)												
Route of Administration	Intravenous, Subcutaneous												
Dosage Form	For injection and Injection												
Strength	250 mg/vial, 125 mg/mL, 87.5 mg/0.7 mL, and 50 mg/0.4 mL												
Dose and Frequency	• Adult RA{Subcutaneous administration}:125 mg once weekly • Adult RA {Intravenous administration} and Adult PsA <table border="1" style="margin-left: 20px;"> <thead> <tr> <th style="text-align: left;">Body Weight of Patient</th> <th style="text-align: center;">Dose</th> <th style="text-align: center;">Number of Vials</th> </tr> </thead> <tbody> <tr> <td>Less than 60 kg</td> <td style="text-align: center;">500 mg</td> <td style="text-align: center;">2</td> </tr> <tr> <td>60 to 100 kg</td> <td style="text-align: center;">750 mg</td> <td style="text-align: center;">3</td> </tr> <tr> <td>More than 100 kg</td> <td style="text-align: center;">1000 mg</td> <td style="text-align: center;">4</td> </tr> </tbody> </table> • pJIA {Intravenous administration}: Patients less than 75 kg= 10 mg/kg at weeks ^(b)₍₄₎ 2, 4, then every 4 weeks thereafter Patients 75 kg or more- Follow adult intravenous dosing regimen, not to exceed a max dose of 1000 mg	Body Weight of Patient	Dose	Number of Vials	Less than 60 kg	500 mg	2	60 to 100 kg	750 mg	3	More than 100 kg	1000 mg	4
Body Weight of Patient	Dose	Number of Vials											
Less than 60 kg	500 mg	2											
60 to 100 kg	750 mg	3											
More than 100 kg	1000 mg	4											

	• Subcutaneous Administration for Juvenile Idiopathic Arthritis in Patients 2 Years of age or older <table border="1" data-bbox="784 344 1203 705"> <thead> <tr> <th data-bbox="784 344 995 470">Body Weight of Pediatric Patient</th> <th data-bbox="995 344 1203 470">Dose (once weekly)</th> </tr> </thead> <tbody> <tr> <td data-bbox="784 470 995 562">10 to less than 25 kg</td> <td data-bbox="995 470 1203 562">50 mg</td> </tr> <tr> <td data-bbox="784 562 995 655">25 to less than 50 kg</td> <td data-bbox="995 562 1203 655">87.5 mg</td> </tr> <tr> <td data-bbox="784 655 995 705">50 kg or more</td> <td data-bbox="995 655 1203 705">125 mg</td> </tr> </tbody> </table> • Subcutaneous Administration for Adult PsA: 125 mg should be administered by subcutaneous injection once weekly without the need for an intravenous loading dose • aGVHD (proposed): 10 mg/kg dose (maximum dose of 1000 mg) administered on the day before transplantation (Day -1), followed by a dose on Day 5, 14, and 28 after transplant.	Body Weight of Pediatric Patient	Dose (once weekly)	10 to less than 25 kg	50 mg	25 to less than 50 kg	87.5 mg	50 kg or more	125 mg
Body Weight of Pediatric Patient	Dose (once weekly)								
10 to less than 25 kg	50 mg								
25 to less than 50 kg	87.5 mg								
50 kg or more	125 mg								
How Supplied	• For Injection: 250 mg lyophilized powder in a single-dose vial for reconstitution and dilution prior to intravenous infusion • Injection: 50 mg/ 0.4 mL, 87.5 mg/0.7 mL, 125 mg/mL solution in a single-dose prefilled syringe for subcutaneous use • Injection: 125 mg/mL solution in a single-dose prefilled ClickJect autoinjector for subcutaneous use								
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F)								

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 26, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Orencia. Our search identified eight previous label and labeling reviews^{a,b,c,d,e,f,g,h}, and we considered our previous recommendations to see if they are applicable for this current review.

^a Siahpoushan, M. Label and Labeling Review for Orencia (abatacept) injection BLA 125118/s-122. Silver Spring, (MD): FDA, CDER, OSE, DMEPA (US); 2011JUN1. RCM No.: 2010-2240.

^b Owens, L. Label and Labeling Review for Orencia (abatacept) injection BLA 125118/s-143. Silver Spring, (MD):FDA, CDER, OSE, DMEPA (US); 2012FEB28. RCM No.: 2011-4647.

^c McMillan, T. Label Labeling and Packaging Review for Orencia (abatacept) injection BLA 125118/s-171. Silver Spring, (MD): FDA, CDER, OSE, DMEPA (US); 2013NOV25. RCM No.: 2013-756.

^d McMillan, T. Human Factor Protocol Review for Orencia (abatacept) injection BLA 125118 and IND 09391. Silver Spring, (MD): FDA, CDER, OSE, DMEPA (US); 2014SEP17. RCM No.: 2014-1634.

^e Mehta, H. Label and Labeling and Human Factors Review for Orencia (abatacept) injection BLA 125118/S-200. Silver Spring, (MD): FDA, CDER, OSE, DMEPA (US); 2016JAN12. RCM No.: 2015-2290 and 2015-2154.

^f McMillan, T. Label, Labeling and Human Factors Results Review for Orencia (abatacept) injection BLA 125118/S-211. Silver Spring, (MD): FDA, CDER, OSE, DMEPA (US); 2017MAR14. RCM No.: 2016-2592 and 2017-20.

^g McMillan, T. Label and Labeling Review for Orencia (abatacept) injection BLA 125118/S-209. Silver Spring, (MD): FDA, CDER, OSE, DMEPA (US); 2017MAY03. RCM No.: 2016-2199.

^h McMillan, T. Label and Labeling Review for Orencia (abatacept) injection BLA 125118/S-235. Silver Spring, (MD): FDA, CDER, OSE, DMEPA (US); 2020SEP30. RCM No.: 2020-1616.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,ⁱ along with postmarket medication error data, we reviewed the following Orenzia labels and labeling submitted by Bristol-Myers Squibb Company (BMS).

- Prescribing Information, Patient Information, and Instructions for Use (Images not shown) received on June 23, 2021, available from <\\CDSESUB1\evsprod\bla125118\0507\m1\us\pas-gvhd-abata-ann.pdf>

ⁱ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLE F IVERSON
09/02/2021 04:25:57 PM

HINA S MEHTA
09/03/2021 02:28:44 PM