Summary Basis for Regulatory Action

Date:	March 26, 2021
From:	Anna Kwilas, PhD, Chair of the Review Committee, OTAT/DCGT
BLA/NDA STN:	125736/0
Applicant:	Celgene Corporation, a Bristol-Myers Squibb Company
Submission Receipt Date:	July 27, 2020
PDUFA Action Due Date:	March 26, 2021
Proper Name:	idecabtagene vicleucel
Proprietary Name:	ABECMA
Indication:	Treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Tissues and Advanced Therapies

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC Reviewer(s) • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Anna Kwilas, PhD (OTAT/DCGT/GTB) Jakob Reiser, PhD (OTAT/DCGT/GTIB) Jessica Chery, PhD (OTAT/DCGT/GTB) Bo Liang, PhD (OTAT/DCGT/GTB) Lily Koo, PhD (OCBQ/DMPQ) Steven Bowen, PhD (ORA/OMPTO/OBPO/BPIS) Scott Ballard (ORA/OMPTO/OBPO/BPOS) Lauren Lilly, PhD, MBA (ORA/OMPTO/OBPO/DBPOII/BPIB) Nimmy Matthews, PharmD (ORA/OMPTO/OBPO/BPIS) Linda Thai, MS (ORA/OMPTO/OBPO/BPIS) Debra Emerson, RPh, MS (ORA/OMPTO/OBPO/BPIS) Alice Silva, RPh, MS (ORA/OMPTO/OBPO/DBPOI/BPIB) Marie Anderson, PhD (OCBQ/DBSQC) Yen Phan, PhD (OCBQ/DBSQC)
Clinical Reviewer(s) • Clinical (Product Office) • Post marketing safety epidemiological review (OBE/DE) • BIMO	Poornima Sharma, MD (OTAT/DCEPT) Deborah Thompson, MD (OBE/DE) Anthony Hawkins (OCBQ/DIS/BMB)
Statistical • Clinical data (OBE/DB) • Non-clinical data	Mary Lin, PhD (OBE/DB/TEB)
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Shana Hardy, PhD (OTAT/DCEPT)
Clinical Pharmacology	Xiaofei Wang, PhD (OTAT/DCEPT)
Labeling • Promotional (OCBQ/APLB)	LCDR Jun Lee, PhD, PharmD (OCBQ/APLB)
Other Review(s) not captured above categories, for example: • Consults *Pharmacometrics*	Jiang Liu, PhD (CDER/OTS/OCP/DPM) Yuan Xu, PhD (CDER/OTS/OCP/DPM)
Advisory Committee Summary	No advisory committee meeting was held

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1. Introduction

Celgene Corporation submitted a Biologics License Application (BLA), STN 125736, for licensure of idecabtagene vicleucel (ide-cel, bb2121), with the proprietary name of ABECMA. ABECMA is a B cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

ABECMA is composed of genetically modified, antigen-specific, autologous T cells reprogrammed to target cells that express BCMA through transduction with a lentiviral vector (LVV) expressing a chimeric antigen receptor (CAR) targeting BCMA. The BCMA CAR is comprised of a murine extracellular single-chain variable fragment (scFv) specific for BCMA, a human CD8α hinge and transmembrane domain and the 4-1BB and CD3ζ chain T cell intracellular signaling domains. Binding of the ABECMA CAR to BCMA-expressing target cells

leads to signaling through the CD3ζ and 4-1BB domains, and subsequent CAR+ T cell activation. Antigen-specific activation results in CAR+ T cell proliferation, cytokine secretion, and lysis of BCMA-expressing cells.

This document summarizes the basis for regular approval of ABECMA. A single clinical trial, Study BB2121-MM001 (MM-001), provides the primary evidence of safety and efficacy for the BLA submission. Our recommendation for approval is based on the overall response rate, complete response rate and duration of response demonstrated in this study. The major risks of ABECMA include cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), neurologic toxicity and prolonged cytopenia, any of which can be life-threatening.

The review team recommends regular approval of this BLA with the Chemistry, Manufacturing, and Control (CMC) Postmarketing Commitment (PMC), and Clinical Postmarketing Requirement (PMR) and PMC for:

- PMC: Celgene Corporation, commits to conduct a comparability study between the (b) (4) and the (b) (4) method as per (b) (4) to provide assurance that the alternate method is equal to or greater than the assurances provided by the method for ide-cel and will provide the final study report.
- PMR: A post marketing observational study to assess the long-term safety of ABECMA, including the risk of secondary malignancies.
- PMC: A post marketing commitment to submit an integrated final report containing data from ongoing clinical trials:MM-002 and MM-003 to further characterize the efficacy and safety of ABECMA among African Americans/Blacks with multiple myeloma.

The approval of this BLA also requires a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) for the management of cytokine release syndrome (CRS) and neurologic toxicity.

2. Background

Disease Background:
Multiple myeloma is the second most common hematologic malignancy in the US, accounting for 1.8% of all cancers and 17% of all hematologic malignancies. Data from the US Surveillance, Epidemiology, and End Results (SEER) registry estimate approximately 32,270 new cases and 13,000 deaths annually in the US. It constitutes 2% of all cancer related deaths in the US.
The majority of patients with multiple myeloma will have an initial response to treatment with combination regimens, however, treatment is not curative and most of these patients ultimately relapse. In addition, some patients do not respond to the initial treatment which constitutes refractory disease. The introduction of proteasome inhibitors, immunomodulatory agents, monoclonal antibodies and stem cell transplantation has further extended median survival to 5 to 6 years. Myeloma is not considered curable with a 5-year survival rate of 54% (Cancer stat facts: Myeloma SEER 2010-2016). Patients who are refractory to major classes of available anti-myeloma therapies such as triple class refractory (refractory to a proteasome inhibitor, an immunomodulatory agent and anti-CD 38 monoclonal antibody) or penta-refractory disease

(refractory to 2 proteasome inhibitors, 2 immunomodulatory agents and anti-CD38 monoclonal antibody) demonstrate low response rates and have poor overall prognosis. Therefore, there is need for new therapies for myeloma that is refractory to main classes of agents such as anti-CD38 antibody, a proteasome inhibitor and an immunomodulatory agent.

Available Therapies:

The following are the approved therapies for the overlapping indication of relapsed or refractory (R/R) multiple myeloma who have received four prior lines of therapies including a proteasome inhibitor (PI), an immunomodulatory (IMiD) agent and an anti-CD38 monoclonal antibody therapy. These are in addition to the multiple standard of care salvage regimens which may include re-treatment with one or more of the agents that patients may have previously received:

- Selinexor, a nuclear export inhibitor in combination with dexamethasone has regular approval for treatment of penta-refractory myeloma population who has received at least four prior therapies.
- Belantamab, a BCMA-directed antibody and microtubule inhibitor conjugate received accelerated approval in relapsed or refractory population who has received 4 prior therapies including an anti-CD 38 antibody, a PI and an IMiD.
- Melphalan flufenamide, an alkylating agent, in combination with dexamethasone recently received accelerated approved in R/R myeloma patients who have received at least four prior lines of therapy with triple class refractory disease.
- Belantamab and Melphalan flufenamide are approved under accelerated approval pathway and therefore are not considered available therapies.

These are summarized below in Table 1:

Table 1: Approvals for population previously exposed to a PI, an IMiD and anti-CD38 monoclonal antibody Therapy:

Drug	Median prior lines /Refractory status	Approval	Trial Design /N	ORR (95% CI)	CR	Duration of Response (DOR) (months)
Selinexor with dexamethasone	8 Penta-refractory	Accelerated (2019) converted to Regular (2020)	Single arm Open label N=83	25% (16%, 36%)	1%	Median DOR=3.8 Range: 0.7, 8.1 95% CI :2.3, NE
Belantamab mafodotin-blmf	7 Triple-refractory	Accelerated (2020)	Single arm Open label N=97	31% (21%, 43%)	3%	73% of the responders had DOR ≥6 months Median DOR= NR* Median f/u=6.3 mths
Melphalan flufenamide with dexamethasone	6 Triple - refractory	Accelerated (2021)	Single arm Open label N=97	24% (16%, 33%)	0%	4.2 months 95% CI 3.2, 7.6

NR=Not reached, NE=Not evaluable, CR=Complete response, DOR=Duration of response

Regulatory History
IND 16664 for ABECMA, which includes the licensing study, MM-001, was allowed to proceed on October 30, 2015. ABECMA was granted orphan designation for the treatment of multiple myeloma on May 11, 2016. Breakthrough therapy designation was granted on September 19, 2017 for treatment of patients with multiple myeloma relapsed to or refractory to at least three lines of therapy including a proteasome inhibitor, an immunomodulatory agent and daratumumab.

A pre-BLA meeting was held on December 12, 2019. Original BLA 125724 was submitted for ABECMA on March 30, 2020; however, this was subject to a refusal to file (RTF) due to Chemistry, Manufacturing, and Controls related issues. A Type A meeting was held with the Applicant on May 11, 2020 to discuss the RTF. An original BLA 125736 for ABECMA was resubmitted on July 27, 2020 which was granted priority review, and filed on September 21, 2020. A Mid-cycle communication was conducted on November 19, 2020 and a Late-cycle communication was conducted on January 29, 2021.The PDUFA goal date is March 26, 2021.

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

The CMC review team concludes that the ABECMA manufacturing process and controls are capable of yielding a product with consistent quality attributes, and the CMC review team recommends approval.

Product Description
ABECMA is composed of genetically modified, antigen-specific, autologous T cells reprogrammed to target cells that express B cell maturation antigen (BCMA). Reprogramming is achieved through transduction with a lentiviral vector (LVV) expressing a chimeric antigen receptor (CAR) targeting BCMA (anti-BCMA02 CAR LVV). The BCMA CAR is comprised of a murine extracellular single-chain variable fragment (scFv) specific for BCMA, a human CD8α hinge and transmembrane domain and the 4-1BB and CD3ζ chain T cell intracellular signaling domains.

Manufacturing Summary
Patient leukapheresis material is collected at qualified apheresis centers and is shipped to the Celgene manufacturing facility (S12) to initiate ABECMA manufacturing. Upon receipt of the leukapheresis material, PBMCs are isolated (b) (4) . To initiate ABECMA manufacturing, PBMCs are (b) (4) cultured in the presence of IL-2, and anti-CD3 and anti-CD28 antibodies to stimulate T cell proliferation. The cells are then transduced with the anti-BCMA02 CAR LVV and expanded in culture until sufficient cells are available to meet dose requirements (total expansion culture time is (b) (4)). After the culture period, the T cells are harvested, washed, and immediately formulated into an infusible cryopreservation solution containing Plasma-Lyte A and CryoStor® CS10. The formulated drug product (DP) is filled into 1-8 cryopreservation bags and cryopreserved at ≤ -130°C in vapor-phase liquid nitrogen until lot release testing is complete. DP release testing is performed on the (b) (4) final formulated DP, as appropriate. The number of bags needed to meet the intended dose is based on the final cell count and CAR expression frequency. The number of bags required to meet the intended dose is shipped in a vapor-phase liquid nitrogen dry shipper to the clinical infusion center for administration back to the same patient.

The anti-BCMA02 CAR LVV is manufactured by (b) (4) . The LVV harvest is (b) (4) . The LVV is stored at (b) (4). LVV release testing is performed on the (b) (4) , as appropriate.

Manufacturing Controls

The chain of identity and chain of custody (COI/COC) are established at the time of leukapheresis collection and maintained throughout the manufacturing process to administration, by a validated computer-based system, to ensure that the patient receives the correct autologous lot.

The ABECMA manufacturing control strategy begins with a raw material and reagent qualification program consisting of source material risk assessment, vendor qualification, confirmation of the certificate of analysis and material testing. Raw materials derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents. Critical process parameters are established for unit operations based on process characterization and risk assessment studies. In-process monitoring and controls are implemented throughout the process to support process consistency.

Lot release testing is performed on material collected at appropriate stages of the manufacturing process to evaluate product safety and function. Specifically, mycoplasma testing is performed on samples taken at the time of (b) (4) . All other lot release testing (sterility, endotoxin, viability, (b) (4) , purity, identity, potency) is performed on samples taken from the final formulated DP during (b) (4) . Lot release test methods are suitably validated (except for the appearance method, which is a qualified (b) (4) assay) and DP specifications are adequate to ensure product quality and consistency.

Process Validation

Suitability of the ABECMA commercial manufacturing process was assessed at the Celgene S12 facility using healthy donor leukapheresis material. The process validation was assessed against established process parameters and predefined release criteria. The manufacturing process validation demonstrated removal of process-related impurities, including residuals associated with vector manufacturing. The anti-BCMA02 CAR LVV manufacturing process at (b) (4) was also validated. Additional validation studies, including aseptic process simulation and shipping validation studies were also performed. Shipping was validated for all shipping steps, including the (b) (4) DP.

Manufacturing Risks, Potential Safety Concerns, and Management

Product mix-up

ABECMA is an autologous product; as such, product mix-ups, either of autologous lots or with other CAR T cell products manufactured at the same facility, would result in potential risks, including infection, graft versus host disease, and lack of anti-tumor effect. The COI/COC ensures that the patient receives their autologous lot. COI/COC is established at the point of leukapheresis collection, checkpoints are indicated throughout the manufacturing process, and patient identifiers are confirmed prior to administration. The COI/COC is

maintained through integrated computer-based programs with human-readable identifiers present on all labels as well.

ABEMCA is manufactured in a multiproduct manufacturing facility. Products are spatially segregated in the facility with manufacturing of different products occurring in different rooms. Prior to transduction, the vector label is confirmed to ensure the correct LVV is used. Additionally, lot release testing confirms CAR identity and BCMA-specific activation.

Replication Competent Lentivirus (RCL)
RCL are a theoretical concern for the ABECMA manufacturing process. The likelihood of RCL generation is reduced by the anti-BCMA02 CAR LVV design: (b) (4) The final anti-BCMA02 CAR LVV and production cells are tested for RCL by (b) (4) in accordance with current FDA guidance prior to release and use in the CAR T cell manufacturing process. To date, no RCL has been detected in clinical trial lots of either the anti-BCMA02 CAR LVV or transduced cell product.

Insertional Mutagenesis
LVV integration poses a risk for insertional mutagenesis. Activation of proto-oncogenes or disruption of tumor suppressor genes has the potential to cause secondary malignancies. To mitigate the risk of insertional mutagenesis, the vector used for ABECMA manufacturing was designed to remove any known viral enhancer elements (self-inactivating design). Insertion-site analysis did not identify any areas of increased or preferred integration. CAR T cell lot release testing limits the average integrated vector copy number per transduced cell to that within the clinical trial experience.

Product Comparability Assessment
Studies to demonstrate comparability of DP manufactured using process versions (b) (4) were performed. These studies demonstrated that DP manufactured with each process were comparable. Studies to demonstrate comparability of anti-BCMA02 CAR LVV manufactured at the clinical and commercial manufacturing facilities were also performed. These studies demonstrated that anti-BCMA02 CAR LVV manufactured at the two facilities were comparable.

b. Testing Specifications

The final lot release specifications are shown in Table 2.

Table 2. ABECMA lot release specifications

Quality Parameter	Attribute	Sampling Point	Analytical Procedure	Acceptance Criteria
Appearance	Visual appearance	Final Filled DP (fresh)	Visual appearance inspection	Liquid, colorless cell suspension
Identity	CAR+ expression	Final Filled DP (cryopreserved)	(b) (4)	Anti-BCMA02 CAR+ T cells detected: (b) (4)
Purity	T cell Percentage	Final Filled DP (cryopreserved)	(b) (4)	(b) (4)
	Cell Viability Percentage	Final Filled DP (cryopreserved)	(b) (4)	(b) (4)
	CAR+ T cell Percentage	Final Filled DP (cryopreserved)	(b) (4)	(b) (4)
Potency	(b) (4)	Final Filled DP (cryopreserved)	(b) (4)	(b) (4)
Strength	Dose	Final Filled DP (cryopreserved)	Calculation [b]	300 to 460 × 10^6 CAR+T cells
Safety	(b) (4)	Final Filled DP (cryopreserved)	(b) (4)	(b) (4)
	Mycoplasma	(b) (4)	(b) (4)	None detected
	Sterility	Final Filled DP (fresh)	(b) (4)	No growth
	Endotoxin	Final Filled DP (cryopreserved)	(b) (4)	(b) (4)

b Dose is derived from cell concentration, CAR+ T cell percentage, the volume/number of product bags shipped for infusion

(b) (4)

The analytical methods and their validations and/or qualifications reviewed for the idecabtagene vicleucel drug substance and drug product were found to be adequate for their intended use, except for the outstanding issue with the following test method: (b) (4) Method for Drug Product by (b) (4). Celgene Corporation has provided a written commitment to complete a comparability study of the (b) (4) Method for Drug Product by (b) (4), as a Postmarketing Commitment (PMC).

Impurity Profile
The active ingredient in ABECMA is viable anti-BCMA02 CAR LVV transduced T cells. Overall cell viability and T cell purity were high throughout the BB2121-MM0001 clinical study. Consequently, viability and T cell purity are tightly controlled through release testing. In particular, no more than (b) (4) non-T cells are allowed in the final product. The mean transduction rate in the BB2121-MM0001 clinical study was (b) (4).

Impurities can be divided into product-related (cellular impurities derived from the leukapheresis material and non-viable cells) and process-related impurities (residual manufacturing reagents and ancillary materials that are not intended to be in the final product). Impurities were evaluated during ABECMA process characterization and process validation. Residual (b) (4) were not detected above the method limits of detection ((b) (4) respectively) in any lots tested. The primary non-T cell cellular impurities were identified as (b) (4). The ABECMA manufacturing process also consistently removed process-related impurities, including (b) (4), to safe levels and levels below the assay quantification limits. Residual (b) (4) was not detected in any of the final DPs tested. A risk assessment was performed for process-related impurities, which concluded that maximum levels of each potential impurity in the product are within toxicological acceptance limits by a substantial safety margin.

Stability
Long-term stability studies have been completed and support 12 months of storage for ABECMA when stored at ≤ -130°C in vapor phase of liquid nitrogen. The stability studies utilized DP manufactured at-scale from normal healthy donor starting material. The DPs were filled into all three sizes of the intended commercial container closure. Temperature cycling stress studies were performed and demonstrated that cell viability, CAR+ T cell percentage, and CD137 activation were stability-indicating attributes. In-use stability testing supports a post-thaw expiry of 2 hours.

c. CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is that idecabtagene vicleucel is an autologous product; as such, each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be acceptable. The facilities involved and the activities performed in the manufacture of idecabtagene vicleucel are listed in Table 3. The inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 3. Manufacturing Facilities Table for ABECMA (idecabtagene vicleucel)

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Celgene Corporation, A Bristol-Myers Squibb Company 556 Morris Avenue, Building S12 Summit, NJ 07910, US • Drug Substance (DS) and Drug Product (DP) manufacturing • DP primary and secondary packaging and labeling • DP release testing • DP storage	3004991673	080392427	Pre-License Inspection	ORA February 15-19, 2021 VAI
(b) (4) • Chimeric antigen receptor lentiviral vector (CAR LVV) manufacture	(b) (4)	(b) (4)	Pre-License Inspection	ORA (b) (4) VAI
(b) (4) • CAR LVV storage	(b) (4)	(b) (4)	Pre-License Inspection	ORA (b) (4) VAI
(b) (4) • CAR LVV release testing	(b) (4)	(b) (4)	Pre-License Inspection	ORA (b) (4) VAI

ORA conducted a pre-license inspection (PLI) of (b) (4), and its associated off-site warehouse facility in (b) (4) from (b) (4) for the manufacture of chimeric antigen receptor lentiviral vector, which is a critical component used in the manufacture of idecabtagene vicleucel. At the conclusion of the inspections, a Form FDA 483 with three observations was issued for the (b) (4) manufacturing facility and a Form FDA 483 with one observation was issued for the (b) (4) warehouse facility. The firm responded to the observations on (b) (4) and the corrective actions were found to be adequate. The inspection of each facility was classified as Voluntary Action Indicated (VAI).

ORA conducted a PLI of Celgene Corporation, a Bristol-Myers Squibb Company, in Summit, NJ from February 15-19, 2021 for the manufacture and testing of idecabtagene vicleucel drug substance and drug product. At the conclusion of the inspection, a Form FDA 483 with three observations was issued. The firm responded to the observations on March 15, 2021 and the corrective actions were found to be adequate. The inspection was classified as VAI.

ORA conducted a PLI of (b) (4) from (b) (4) for the release testing of chimeric antigen receptor lentiviral vector. At the conclusion of the

inspection, a Form FDA 483 with four observations was issued. The firm responded to the observations on March 22, 2021 and the corrective actions were found to be adequate. The inspection was classified as VAI.

e. Container/Closure System

The drug product is filled and cryopreserved (≤ -130°C) in (b) (4) cryopreservation bags supplied by (b) (4) located in (b) (4). The cryopreservation bags are 510(k) cleared for the US market ((b) (4)) and are supplied sterile in three size configurations: (b) (4) 50 ((b) (4) mL), (b) (4) 250 ((b) (4) mL), and (b) (4) 500 ((b) (4) mL). The bag and the crimped ports are made of (b) (4) and the loading tube is made of (b) (4) co-extrusion. Container closure integrity testing was performed by (b) (4) using a validated (b) (4) action test method; all acceptance criteria were met.

A dose of ABECMA is provided as a single dose for infusion in one or more cryopreservation bags. The bags containing the cryopreserved cells are thawed and visually inspected for leaks and damage prior to infusion.

f. Environmental Assessment

A request for categorical exclusion from an Environmental Assessment per 21 CFR 25.31(c) was provided in the BLA. This request and supporting information provided by Celgene is acceptable to conclude that ABECMA poses a negligible risk to the environment or to the general public. The risk of vector recombination into a replication competent form is assessed as extremely low to negligible. The potential for the lentiviral vector or ABECMA to persist in the environment is negligible. There is a potential risk for exposure of healthcare staff during product administration, but this can be effectively mitigated by universal precautions that are already established at healthcare facilities and by additional training provided by Celgene during treatment site qualification. Overall, there are no significant environmental or public health impacts posed by the lentiviral vector or by ABECMA. Categorical exclusion under 21 CFR 25.31(c) is therefore acceptable.

4. Nonclinical Pharmacology/Toxicology

In vitro co-culture studies of ABECMA and various tumor cell lines demonstrated BCMA-specific cytokine production, proliferation, and cytotoxicity. In vivo proof-of-concept (POC) studies were also conducted to evaluate the anti-tumor activity of ABECMA in a xenograft murine model of multiple myeloma. In (b) (4) mice bearing subcutaneous BCMA+ (b) (4) human multiple myeloma xenografts, intravenous administration of ABECMA demonstrated dose-dependent anti-tumor activity and improved survival compared to control mice.

In vivo distribution of ABECMA was observed in the perfused organs including the lungs, blood, bone marrow, liver and spleen in (b) (4) mice. A biphasic peak expansion of ABECMA cells was observed on Days 2 and 11 in the peripheral blood and Days 8 and 15 in analyzed tissues in tumor-bearing mice. No ABECMA-related adverse findings were reported in these studies.

No traditional genotoxicity assays and carcinogenicity assessments were performed for ABECMA. The safety of ABECMA was assessed by evaluating the integration profile of the lentiviral vector. Integration site analysis was performed for 20 clinical drug product lots. The resulting data showed that the lentiviral vector does not preferentially integrate in or near genes of concern for oncogenic transformation and is consistent with other similar vectors. Additionally, an IL-2-independent growth assay of ABECMA® generated from five patient donors and two healthy donors showed no signs of uncontrolled cellular proliferation.

No animal reproductive and developmental toxicity studies were conducted for ABECMA which is acceptable based on the product characteristics.

5. Clinical Pharmacology

The clinical pharmacology section of this application is supported by a supportive Phase 1 study and a pivotal Phase 2 study:

- A first-in-human, two-part, nonrandomized, open-label, multicenter, dosing finding Phase 1 study to evaluate the safety, efficacy, cellular kinetics/pharmacokinetics of a single dose of ABECMA in subjects with relapsed/refractory multiple myeloma (RRMM) (Study No. CRB-401, supportive study).
- An ongoing, open-label, single-arm, multicenter, Phase 2 study to determine the efficacy, safety, and cellular kinetics/pharmacokinetics of ABECMA in subjects with RRMM. ABECMA was infused to each subject at the target doses of 150, 300, and 450 x 10^6 CAR+ T cells (Study No. BB2121-MM-001).

Clinical review of the safety and efficacy of ABECMA supports the following dose range for ABECMA: 300 to 460 x 10^6 CAR-positive T cells. Considering the limited sample size for doses higher than 460 x 10^6 CAR-positive T cells, high inter-subject variability in PK parameters and lack of association between ide-cel dose and complete response (CR) rate, clinical pharmacology reviewer agrees with clinical reviewer's recommendation. Clinical pharmacology assessment of ABECMA supports approval of this dose range.

Following are important clinical pharmacology findings:

<u>General Cellular Kinetics/Pharmacokinetics</u>

- Following infusion, ABECMA proliferated and underwent rapid multi-log expansion, with the maximum peak expansion occurring at a median of 11 days across the evaluated dose range of ABECMA: 150 to 540 x 10^6 CAR+ T cells. Persistence of JCAR017 transgene was observed up to 1 year.
- Within the dose range evaluated, ABECMA exposure increased in a dose-dependent manor. However, due to high inter-subject variability in ABECMA PK profiles, there was overlap of ABECMA exposure across different dose levels. This may due to heterogenicity of ABECMA drug product composition with respect to different T cell subsets.
- ABECMA expansion after the second dose was substantially lower than ABECMA expansion after the first dose in retreated subjects.
- Exploratory multivariate regression analysis indicates that ABECMA vector copy number was positively associated with ABECMA dose normalized $AUC_{0\text{-}28d}$ and Cmax. Subjects' body

weight and the percentage of CD3+CAR+CCR7+CD27- T cell subset in the ABECMA final product were negatively associated with ABECMA dose normalized $AUC_{0\text{-}28d}$ and Cmax.

Pharmacodynamics

- After ABECMA infusion, there were transient elevations of soluble biomarkers. Peak concentrations of CRP, IFN-γ, IL-10 and IL-6 were substantially higher in responders compared to non-responders.
- Compared to subjects with no cytokine release syndrome (CRS), levels of the following immune-related soluble biomarkers were significantly elevated in subjects with any grade of CRS:
    - Within the first day after infusion: GM-CSF, IFN-γ, IL-10, IL-13, IL-2, IL-6, and IL-8
    - At the time of peak concentration: CRP, granzyme B, IL-18, IL-2Rα, IL-5, MIP-1β, TNF, and TNFSF6 (FasL)
- Compared to subjects with no neurotoxicities (NT), levels of following immune-related soluble biomarkers were significantly elevated in subjects with any grade of NT:
    - Within the first day after infusion: GM-CSF, IFN-γ, IL-10, IL-2, IL-5, IL-6, IL-8, and IL-13
    - At the time of peak concentration: ferritin, granzyme B, IFN-γ, IL-10, IL-15, IL-18, IL-2, IL-2Rα, IL-5, IL-6, IL-8, MIP-1β, and TNFα
- Baseline levels of peripheral soluble BCMA (sBCMA) were negatively corelated with overall response: non-responders had significantly higher median sBCMA concentrations compared to responders. Post-infusion, 81.4% of responders had elimination levels below LLOQ at nadir as compared to 13.51% of non-responders.
- Higher pre-infusion sBCMA levels at screening tended to be associated with any grade of CRS. After infusion of ABECMA, subjects with any grade CRS achieved lower median concentration at nadir and had a higher rate of complete elimination of sBCMA than subjects without CRS. There was no association of pre- or post-infusion sBCMA levels with any grade NT.

Dose/Exposure-Response Relationship

ABECMA Dose

- A higher dose of ABECMA was associated with a higher overall response rate (ORR), but not complete response (CR) rate. Exploratory analysis indicated that ABECMA product memory T cell status (percentage of CD3+CAR+CCR7+CD27- T cells) was negatively associated with ORR.
- A higher ABECMA dose was positively associated with incidence of any grade cytokine release syndrome (CRS).
- There was no apparent association between ABECMA dose and incidence of any grade neurotoxicities (NT).

ABECMA Exposure/Expansion

- A higher cellular expansion ($AUC_{0\text{-}28d}$, Cmax and expansion rate) of ABECMA was associated with both higher ORR and complete response (CR) rate. In addition to ABECMA

expansion, covariates such as sex (female), baseline soluble BCMA levels and usage of steroids as prior medications were potentially positively associated with a higher ORR.

- A higher cellular expansion of ABECMA was associated with any grade of CRS incidence. Additionally, potential association was indicated between pre-lymphodepletion TNFα levels and any grade of CRS incidence.
- There was no apparent association between ABECMA exposure and incidence of any grade NT.
- A higher ABECMA cellular expansion of ABECMA appeared to be associated with greater reduction in post-infusion BCMA levels.
- A higher ABECMA cellular expansion of ABECMA was associated with higher likelihood of achieving minimal residual disease (MRD) negativity.

Immunogenicity

- Less than 5% of subjects had pre-existing anti-drug antibody (ADA) before infusion of ABECMA. ADAs did not develop in the first month post-infusion. By Month 3 and Month 6 after infusion, approximately 20.6% (21 of 102 subjects) and 43.8% (35 of 80 subjects) of the subjects, respectively, were ADA-positive. The PK values in subjects with positive ADA post-infusion were comparable to PK values in the overall study population. The presence of ADA did not appear to have a clinically significant impact on PK, safety or efficacy.

Replication-competent Lentivirus (RCL) Testing

- No RCL has been detected in the blood in any ABECMA treated subjects.

6. Clinical/Statistical

The clinical review team's recommendation for regular approval of ABECMA for the treatment of adult patients with relapsed or refractory multiple myeloma after at least four prior lines of therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, is based on the clinical study, MM-001.

a. Clinical Program

Study MM-001 was a single-arm, Phase 2, multicenter study of the efficacy and safety of ABECMA in subjects with relapsed and refractory multiple myeloma who had received at least three prior lines of therapy including a proteasome inhibitor, an IMiD and an anti-CD38 antibody therapy. The primary endpoint was objective response rate (ORR), defined as rate of stringent complete response (sCR) plus complete response (CR) plus very good partial response (VGPR) plus partial response (PR) as determined by an Independent Response Committee (IRC) applying the 2016 IMWG (International Myeloma Working Group) Uniform Response Criteria. Complete response rate defined as rate of sCR plus complete response (CR) was a key secondary endpoint. Other secondary endpoints included duration of response (DOR) and MRD (minimal residual disease) negativity in the bone marrow using ClonoSEQ NGS (next generation sequencing) assay. The efficacy-evaluable population was drawn from a pool of 127 subjects with an updated data cutoff of January 14, 2020. Primary safety analyses were performed on 127 subjects who received conforming CAR T cell product in three dose cohorts that ranged from 150 – 450 $x10^6$ cells, at the primary data cutoff of October 16, 2019. Of the 127 subjects, 100 subjects were included in the primary efficacy analysis, based on the protocol specified requirement for baseline and one post-baseline efficacy assessment, and having received a

single dose of 300-460 x 10^6 CAR-positive T cells. These subjects received the CAR positive T cells following lymphodepletion with fludarabine and cyclophosphamide, and were followed for at least nine months after their first objective disease response. Bridging therapy was allowed at the investigators' discretion during product manufacturing. The study permitted a second dose at the time of disease progression; however, the protocol-specified primary efficacy analysis was based on ORR and duration of response observed following the first dose.

Efficacy Results

The majority of subjects (100/127; 79%) received the study drug at the recommended dose schedule (300-460 x 10^6 CAR-positive T cells). The efficacy data for the efficacy evaluable population (n=100) is summarized: The ORR as assessed by the independent response committee (IRC) assessment, was 72% (95% Confidence Interval [CI]: 62%, 81%) and complete response rate (comprised entirely of stringent CRs) was 28% (95% CI: 19%, 38%), with a median DOR of 11 months (95% CI: 10.3, 11.4).

Stringent CRs (sCR) tended to have substantially longer DOR (duration of response) compared to PR and VGPR subjects. At a median follow up of 10.7 months, the estimated median DOR for sCR subjects was 19 months (95% CI: 11.4, NE) and for the PR and VGPR subjects was 9.2 months (95% CI: 5.0, 10.6). Given that the median DOR for sCRs is skewed due to the small sample size of 28 subjects with wide confidence intervals and because of censoring prior to 12 months within this subgroup, we also examined the landmark analysis for DOR. This shows that an estimated 65% of the sCR subjects (95% CI: 42%, 81%) maintained a response at 12 months, an estimated 22% of VGPR subjects (95% CI:6%, 44%), and an estimated 35% of the overall responders ((95% CI : 23%,47%) remained in response at 12 months confirming that the overall durability is driven by the sCR cohort.

Efficacy results in Study MM-001 met the study objective that ORR was statistically significantly greater than the pre-specified null hypothesis threshold rate of 50% at a dose range of 300-460 x 10^6 CAR-positive T cells. In addition, CR rate, a key secondary endpoint, was statistically significantly greater than the pre-specified null hypothesis rate of 10%. Please see Table 4.

Table 4. Efficacy analysis for Study MM-001

Response	bb2121 treated at recommended Dose range 300-460 million CAR-positive T cells n=100
ORR, n (%) (CR+s CR+PR+VGPR)	72 (72%)
95% CI	62%, 81%
Stringent CR*, n (%)	28 (28%)
95% CI	19%, 38%
VGPR, n (%)	25 (25%)
95% CI	17%, 35%
Partial response, n (%)	19 (19%)
95% CI	12%, 28%
Minimal response, n (%)	0
Stable disease, n (%)	15 (15%)
Progressive disease, n (%)	7 (7%)
Not evaluable, n (%)	6 (6%)
Median follow up for DOR	10.7 months

*All CRs in the study were stringent CRs.

Table 5. MRD Negative Rate in Study MM-001:

Parameter	N (%)
MRD-negativity rate[a] in all treated subjects (n=100) 95% CI (%)	21 (21%) 13%, 30%
MRD- negative rate in patients achieving CR or stringent CR (n=28) 95% CI (%)	21 (75%) 55%, 89%

[a] MRD negativity was defined as the proportion of patients with CR or stringent CR who are MRD negative at any timepoint within 3 months prior to achieving CR or stringent CR until the time of progression or death.

Similar efficacy was noted in the triple class refractory subset (85% of the efficacy evaluable population), which is a high-risk population with an unmet need, indicating that the efficacy data are robust.

A dose response relationship was noted within the recommended dose range with numerically higher ORR, CR rate and DOR with 440-460 $x10^6$ CAR+ T cells (n=48) compared to 300-340 $x10^6$ CAR+ T cells (n=52). Overall response rate of 79% (95% CI 65%, 90%), sCR rate of 31% (95% CI, 19%, 46%) and an estimated median DOR of 11.3 months was observed with 440-460 $x10^6$ CAR+ T cells. Overall response rate of 65% (95% CI 51%, 78%), a stringent CR rate of 25% (95% CI 14%, 39%) and an estimated median DOR of 10.4 months was observed with 300-340 x 10^6 CAR+ T cells.
An additional sensitivity analysis for efficacy that evaluated ORR in all subjects who were leukapheresed (n=135), a cohort representative of the intent-to-treat population, demonstrated

that the lower bounds of the 95% CI was greater than the protocol-specified null hypothesis threshold for ORR and CR. Of the 135 patients who underwent leukapheresis, 15 additional patients achieved a response apart from the responses noted in Table 4. The IRC assessed overall response in the leukapheresis population (n=135) was 64% (95% CI: 56%, 72%) with stringent CR rate of 24% (95% CI: 17%, 32%), VGPR rate of 21% (95% CI: 14%, 29%) and PR rate of 20% (95% CI: 14%, 28%). The efficacy results include responses after receipt of products outside of the dose range of 300 to 460 x 10^6 CAR-positive T cells (dose range 279-299 and 460.2 to 518 x10^6 CAR+ T cells).

In summary, Study MM-001 represents an adequate and well-controlled trial that demonstrated high response rates and durability of CR rate. The basis of FDA's conclusion of substantial evidence of effectiveness is the magnitude of benefit primarily driven by durable complete response in a disease setting where durable complete response rates are dismal with standard of care therapies (See Table 1). Overall, the ORR of 72% and a sCR rate of 28% with 35% of all responders and 65% of sCR subjects maintaining response at 12 months indicates that the magnitude of treatment effect is substantial translating into clinical benefit. Therefore, the results support a traditional approval for ABECMA.

Given that only 12% of the efficacy evaluable population received three prior lines of therapy and 88% of the efficacy evaluable population in Study MM-001 had received 4 or more prior lines, the risk and benefit of this therapy has been established in this latter line population. Therefore, the indication statement in the prescribing information (PI) is restricted to the relapsed/refractory myeloma population who have received at least four prior lines of therapy.

Additionally, Section 14, Clinical Studies, of the label will include the following information:
a) Efficacy data for subjects treated in the recommended dose range of 300-460 x10^6 CAR+T cells..

b) ORR (overall response rate) in all subjects who were leukapheresed (n=135) in addition to the ORR in the efficacy evaluable population. This includes 15 additional subjects who received ABECMA outside of the recommended dose range and achieved a response.

c) MRD negative rate of 21% (95% CI: 13%, 30%), which was a prespecified secondary endpoint and assessed using a validated NGS (next generation sequencing) assay.

Key Review Issues
1. Missing assessments for stringent CR determination:
IMWG criteria requires concurrent assessment of biochemical data, bone marrow and imaging for determination of stringent complete responses (sCR). The primary efficacy review issue included sCR adjudication without contemporaneous bone marrow assessment. Review team re-adjudicated sCR cases to VGPR if they did not have supporting bone marrow assessments performed within 1 month of sCR determination. Review team also identified sCR response adjudications without confirmation of biochemical response with two consecutive assessments. These cases were re-adjudicated to VGPR. Applicant considered a subject as stringent CR without post-treatment assessment of a non-measurable extramedullary plasmacytoma that was present at baseline. This subject was re-adjudicated to a non-responder.

2. Determination of upper end of dose range:
With the commercial fill strategy, approximately 36% of the patients are estimated to receive lots with <400x10^6 CAR+ T cells per patient at the recommended dose range of 300-460 x10^6 CAR+ T cells. A higher upper end of the dose range (to up to 500 x10^6 CAR+ T cells) would allow for the majority of patients to receive a dose of >400x10^6 with an average dose of 451x 10^6 with the

commercial fill. To consider extending the upper end of the dose range, we examined the efficacy data from 460 to 518 $x10^6$ CAR+ T. In Study MM-001, a total of five subjects were treated at dose range of 460.2 to 518.4 $x10^6$ CAR+ T cells. Four out of five subjects responded with only one stringent CR. Stringent CR rate is an important consideration for regulatory purposes because the durability of response seen with bb2121 may be driven by the stringent CRs. Overall, efficacy review of data from subjects treated at the dose range of 460-518 $x10^6$ CAR+ T cells raises uncertainties about the reliability of the sample size and the efficacy outcome to support extending the dose range above 460 $x10^6$ CAR+ T cells. Finally, a pharmacometric analysis of the dose response relationship above 460 $x10^6$ CAR+ T cells had several limitations, including lack of a validated model, small sample size and pooling of data across studies with differences in eligibility, definition of measurable disease and schedule of assessment. Given the limited clinical data for efficacy and the unknown benefit/risk profile of a dose higher than 460x 10^6 CAR+ T cells, the clinical team does not recommend extending the upper end of the dose range beyond 460 x 10^6 CAR+T cells.

3. In Study MM-001, 73% of the study population was enrolled from the US; however, only 6% of the ABECMA treated population was African-American. To address the issue of underrepresentation of the African-American/Black population, the review team has recommended that the Applicant commit to submitting an integrated final report containing data from ongoing clinical trials MM-002 and MM-003 to characterize safety and efficacy of ABECMA among the African-American/black population in the post-marketing setting. Please refer to Section 11-c regarding this PMC.

Pharmacovigilance

Please refer to Section 11c regarding Post-Marketing Requirements and Post-Marketing Commitments.

Risk Evaluation and Mitigation Strategies (REMS)

FDA determined that a REMS is necessary to ensure that the benefits of ABECMA outweigh the serious risks of cytokine release syndrome (CRS) and neurologic toxicities (NT). The REMS includes the following Elements to Assure Safe Use (ETASU) to mitigate these risks:

- Health care settings that dispense ABECMA are specially certified.
- ABECMA is dispensed to patients only in certain health care settings.

The REMS ETASU requires Celgene Corporation, a Bristol-Myers Squibb Company, to ensure that:

- Hospitals and their associated clinics are enrolled in the ABECMA REMS Program and certified through a training program and knowledge assessments.
- Certified sites report serious cases of CRS and NT.
- Celgene Corporation maintains documentation that processes and procedures are followed for the ABECMA REMS Program.
- Celgene Corporation conducts audits to ensure that training processes and procedures are in place.
- Sites verify that a minimum of two doses of tocilizumab are available on site prior to ABECMA infusion.

Materials provided as part of the ABECMA REMS Program include:

- Hospital Enrollment Form
- Patient Wallet Card
- Training Program
- Knowledge Assessment
- Adverse Reaction Management Guide
- ABECMA REMS Program Website

Post-marketing Requirement (PMR) study

Long-term safety after treatment with ABECMA, particularly from the risk of insertional mutagenesis-related secondary malignancies, remains a concern due to the limited follow-up duration. Therefore, a safety post-marketing requirement (PMR) study is warranted under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA). The applicant is required to conduct a post-marketing, prospective, multi-center, observational study to assess the long-term safety of ABECMA and the risk of secondary malignancies occurring after treatment with ABECMA. The PMR study will include at least 1500 adult patients with multiple myeloma who have received at least four prior lines of therapies, including an immunomodulatory agent, a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody; patients will be followed for 15 years after their ABECMA infusion. The primary endpoint will be evaluation for secondary malignancy, which will include the collection and analysis of blood and/or biopsy specimens of certain malignancies for evaluation of insertional mutagenesis. Other important endpoints include the incidence and severity of CRS, neurologic toxicity (including the incidence and severity in older adults; 65 years and older), prolonged cytopenia (including the use of rescue stem cell transplantation, the outcome of hematopoietic reconstitution and survival post-transplant) and HLH/MAS.

The PMR study milestones are as follows:

Final protocol submission: May 31, 2021

Study completion: June 30, 2041

Final report submission: June 30, 2042

Post-marketing Commitment study (PMC):

Multiple Myeloma has two-three-fold higher incidence and a higher disease related mortality in the African American compared to the White population. Approximately 20% of the population diagnosed with myeloma in the US is African-American. In Study MM-001, 73% of the study population was enrolled from the US; however, only 6% of the ABECMA treated population was African-American. To address the issue of underrepresentation of the African-American/black race in the study, clinical team recommends a PMC which will include integrated data from ongoing studies MM-002 and MM-003 to further characterize the efficacy and safety of ABECMA in the African-American/Black population. The primary objective of the study is to evaluate the efficacy of ABECMA among the African-American/Black population compared to the White population and the secondary objective is safety.

The PMC study milestones are as follows:

Final analysis plan: February 28, 2023

Final report submission: November 30, 2023

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were conducted at four US clinical study sites participating in the conduct of Study: BB2121-MM-001. The inspections did not reveal any issues that impact the data submitted in support of this BLA.

c. Pediatrics

This application is exempt from PREA because it is intended for a biological product for which orphan designation has been granted.

d. Other Special Populations

ABECMA has not been studied in any special populations.

7. Safety and Pharmacovigilance

Safety:
The primary safety population for MM-001 included a total of 127 subjects who were treated with ABECMA at doses of 150.5-518.4 x10^6 CAR+T cells. All 127 subjects (100%) had at least one adverse event (AE) that occurred after the administration of ABECMA. Ninety-nine percent (n=126) experienced Grade 3 or higher events. Serious adverse events (SAEs) were observed in 85 (67%) of the subjects, and Grade 3 or higher SAEs occurred in 67 (53%) subjects. Key adverse events observed following administration of ABECMA are outlined below in Table 6. CRS was reported and graded per the Lee 2014 criteria.

Table 6. Key Adverse Events with ABECMA

Study MM-001	Any Grade N=127 n(%)	Grades ≥3 n(%)
Cytokine release syndrome (CRS)	108 (85%)	12 (9%)
Neurologic toxicity	36 (28%)	5 (4%)
Hemophagocytic lymphohistiocytosis/Macrophage activation syndrome (HLH/MAS)	5 (4%)	2 (1.6%)
Infections	89 (70%)	29 (23%)
Prolonged Cytopenia*	-	77 (61%)

*Prolonged cytopenia is defined as ≥Grade 3 neutropenia or thrombocytopenia lasting 30 days or longer after receiving ABECMA.

The following table summarizes AEs that were observed in at least 10% of subjects following ABECMA infusion.

Table 7. Most Frequent Non-Laboratory Adverse Events Following ABECMA infusion

Body System Organ Class AE	All Grades (%)	Grades 3 - 5 (Max Grade) (%)
Blood and lymphatic system disorders		
Febrile neutropenia	16	16
Cardiac disorders		
Tachycardia*	19	0
Gastrointestinal disorders		
Nausea	29	0
Diarrhea	35	1.6
Constipation	16	0
Oral pain*	12	0
Vomiting	15	0
General disorders and administration site conditions		
Fatigue*	45	3.1
Pain[*,#]	20	0
Edema[*, #]	25	0
Pyrexia	25	1.6
Chills	11	0
General physical health deterioration	11	10
Immune system disorders		
Cytokine Release Syndrome	85	9.4
Hypogammaglobulinemia[1*]	41	0.8
Infections and infestations		
Infections: pathogen unspecified[2]	51	15
Bacterial infection[2]	15	3.9
Viral infection[2]	27	9.4
Pneumonia*	17	9.4
Upper Respiratory Tract Infection (URTI)[*,#]	34	1.6
Investigations		
Weight decreased	13	1.6
Metabolism and nutrition disorders		
Decreased appetite*	22	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	45	3.1
Motor dysfunction[#,*]	11	0
Nervous system disorders		
Headache*	23	0
Encephalopathy*[,#]	26	5.5
Dizziness*	17	0.8
Tremor*	10	0
Peripheral neuropathy*	17	0.8

Body System Organ Class AE	All Grades (%)	Grades 3 - 5 (Max Grade) (%)
Psychiatric disorders		
Insomnia*	13	0
Anxiety*	12	0.8
Renal and urinary disorders		
Renal failure*	10	2.3
Respiratory, thoracic and mediastinal disorders		
Cough*	23	0
Dyspnea*	13	2.3
Skin and subcutaneous tissue disorders		
Rash*,#	14	0.8
Xerosis*#	11	0
Vascular disorders		
Hypotension*	17	0
Hypertension	11	3.1

Source: FDA Analysis adae 3.xpt AE: adverse event, SOC: system organ class, PT: preferred term
** Includes grouped terms as detailed in APPENDIX A of the Clinical Review Memo: 125736_0*
 # Encompasses more than one system organ class
1 includes both adverse reaction (GT) and laboratory based defined as IgG <500 mg/dl.
2 Applicant's high-level grouped term. Some infections included under pneumonia and upper respiratory tract infection are also included under infections classified by pathogen.

Forty-three (34%) of the 127 subjects treated with ABECMA in Study MM-001 had died as of the data cutoff of January 14 ,2020. Twenty-three (18%) deaths were due to progressive disease, 5 (4%) from unknown causes and 8 (6%) from other causes. Seven deaths (6%) were adjudicated by the FDA to be related to ABECMA. One death attributed to the product occurred within 30 days after ABECMA administration. Fatal cases of CRS, HLH/MAS, infections including bronchopulmonary aspergillosis, CMV and pneumocystis carinii pneumonia and fatal gastrointestinal bleeding in setting of severe thrombocytopenia occurred following ABECMA administration. Prolonged cytopenia refractory to stem cell rescue for hematopoietic recovery and resulting infections and bleeding complications were observed in 2.3% of patients in the safety population. Please also refer to discussion of Prolonged Cytopenia below.

CRS: CRS occurred in 108/127 subjects (85%) and Grade ≥3 events occurred in 12/127 (9%). Median time to CRS onset was 1 day (range 1 to 23 days). CRS resolved in the majority of subjects (107 out of 108, 99%) with a median time to resolution of 7 days (range 1 to 63 days). One subject had fatal CRS. The median duration of CRS in all subjects, including the one subject who died, was 7 days (range 1 to 63 days). The most common manifestations of CRS included fever, hypotension, tachycardia, chills, hypoxia, fatigue and headache. Notable Grade 3 or higher events associated with CRS included fever, hypotension, hypoxia, dyspnea, tachycardia, ARDS, atrial fibrillation, hypofibrinogenemia, metabolic acidosis, multiple organ dysfunction syndrome, pulmonary edema and hepatocellular injury. Fifty-four percent (68/127) received tocilizumab and fifteen percent (19/127) received corticosteroids for CRS management.

HLH/MAS: Five out of 127 (4%) subjects treated with ABECMA developed HLH. Two subjects had fatal HLH/MAS. Three out of five subjects had Grade 2 HLH/MAS events, which resolved. All

events of HLH had onset within 10 days of receiving ABECMA (median onset was 7 days; range: 4-9 days) and occurred in the setting of ongoing or worsening CRS. Two subjects had concurrent or overlapping neurologic toxicity with HLH/MAS. The manifestations of HLH/MAS included hypotension, hypoxia, multiple organ dysfunction, renal dysfunction and cytopenia.

Neurologic toxicity: Neurologic toxicity occurred in 36/127 (28%) subjects, with Grade ≥3 events reported in 4% of the subjects. The median time to onset of neurologic toxicity was 2 days (range 1 to 42 days). Neurologic toxicities resolved in 92% (33/36) of subjects with a median time to resolution of 5 days (range 1 to 61 days). One subject had Grade 2 neurologic toxicity (encephalopathy, delirium and urinary incontinence) ongoing at the time of death from a lower GI bleed. Two subjects had neurologic toxicity of grade 1 tremor ongoing at the time of data cut off. Median duration of neurologic toxicity was 6 days (range 1 to 578 days) in all subjects, including those with ongoing neurologic adverse events at time of death or data cutoff. The most common neurologic toxicities included encephalopathy in 20% (26/127), tremor in 9% (12/127), aphasia in 7% (9/127) and delirium in 6% (7/127) of subjects, respectively. Grade 1 seizure was reported in one subject which was self-limited. All grade 3 neurologic toxicities occurred in 65 years or older adults. Neurologic toxicities were managed with corticosteroids and antiseizure medications, either as prophylaxis or treatment, and supportive care. Neurological toxicities identified from other studies included in the BLA submission included cerebral edema, Grade 3 myelitis and Grade 3 parkinsonism post-ABECMA. These AEs have been included in the safety information of the label.

Hypogammaglobulinemia: Newly diagnosed hypogammaglobulinemia, based either on laboratory value defined as IgG <500 mg/dl post-ABECMA infusion or an adverse event, was reported in 41% (52/127) of subjects. Overall, 77/127 (61%) of ABECMA treated subjects received IVIG (intravenous immunoglobulin) therapy for serum IgG level less than 400 mg/dl as needed to maintain an IgG level above 400 mg/dl.

Prolonged cytopenia: 41% (52/127) of patients developed prolonged neutropenia and 49% (62/127) developed prolonged thrombocytopenia after ABECMA infusion. In 83% (43/52) of patients who recovered from Grade 3 or 4 neutropenia after Month 1, the median time to recovery from ABECMA infusion was 1.9 months. In 65% (40/62) of patients who recovered from Grade 3 or 4 thrombocytopenia, the median time to recovery was 2.1 months. Median time to cytopenia recovery was similar across the 300 and 450 x 10^6 dose cohort. Three subjects that received ABECMA (3/127) underwent stem cell transplantation for hematopoietic reconstitution for prolonged cytopenia. Two patients underwent autologous and one patient underwent allogeneic stem cell transplantation. Two out of the three subjects died from complications of prolonged cytopenia: lower GI bleeding and bronchopulmonary aspergillosis. The third subject recovered from neutropenia after autologous stem cell transplantation.

Dose-toxicity relationship: The 300 x10^6 CAR + T cell dose cohort included a dose range from 277 to 339 x 10^6 CAR+ T cells and the 450 x 10^6 CAR+ T cell dose cohort included a dose range from 447 to 518 x 10^6 CAR+ T cells. A higher rate of toxicity was observed in the 450 x10^6 CAR+ T dose cohort compared to the 300 x 10^6 CAR+ T cell dose cohort for overall rate of CRS (96% vs. 79%), Grade 2 CRS (40% vs. 23%), Grade 3 neurotoxicity (8% vs. 1.4%), HLH/MAS (8% vs. 1.4%) and prolonged neutropenia (49% vs.34%).

Secondary malignancies were reported post ABECMA infusion. None of the malignancies were deemed to be related to the product. However, risk of insertional mutagenesis and secondary malignancy remains a concern.

Laboratory abnormality: Grade 3 or 4 laboratory abnormalities with worsening from baseline occurring in ≥ 10% of subjects included neutropenia (96%), leukopenia (96%), lymphopenia (92%), thrombocytopenia (63%), anemia (63%), hypophosphatemia (45%), hyponatremia (10%) and prolongation of a-PTT (10%).

Although ABECMA was administered exclusively in the inpatient setting in Study MM-001, implementation of the REMS program and labelling requirements to ensure daily monitoring of patients in the outpatient setting post-approval is expected to facilitate early diagnosis and management of CRS and neurologic toxicity.

The safety database of 127 subjects is sufficient to assess the acute toxicities of ABECMA, and severity of CRS and neurologic toxicity warrant marketing authorization under the REMS program. The long-term adverse reactions require post-marketing study to evaluate the risks of secondary malignancies, particularly those associated with insertional mutagenesis.

Key Changes made to the label in reference to safety are outlined below:

1. Boxed Warning was revised to include the risk of HLH/MAS and risk of prolonged cytopenia with fatal outcome of bleeding and infection.
2. Warning and Precaution section was revised to include a separate section for HLH/MAS.
3. Safety information from other studies of ABECMA included in the PI are Grade 4 neurotoxicity with cerebral edema, Grade 3 myelitis and Grade 3 parkinsonism

8. Labeling

The proposed proprietary name, ABECMA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on August 12, 2020 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on October 15, 2020.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and package and container labeling, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

ABECMA is similar to other genetically modified autologous CAR T cell immunotherapies and did not raise new or unique scientific or regulatory issues; as a result, an advisory committee meeting was not deemed necessary.

10. Other Relevant Regulatory Issues

None

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review team recommends regular approval of ABECMA for the treatment of patients with relapsed or refractory multiple myeloma after at least four prior lines of therapies, including a proteasome inhibitor, an immunomodulatory drug and anti-CD38 monoclonal antibody.

Indication Statement: Since 88% of the population treated at the recommended dose range had received at least 4 or more prior lines of therapy, the risk and benefit of bb2121 has been not been adequately evaluated in patient who have received only 3 prior lines of therapy. Therefore, the indication will be restricted to a narrower R/R myeloma patient population who has received at least 4 prior lines of therapy. In making this recommendation, the review team considered the risk of prolonged ≥ Grade 3 cytopenia with a median recovery of 1.9-2 months with ABECMA, which may interfere with the ability to tolerate sequential anti-myeloma therapies that may be available to patients exposed to 3 prior lines of therapy

b. Benefit/Risk Assessment

ABECMA has demonstrated favorable ORR, stringent CR and DOR in subjects with R/R multiple myeloma after at least four or more lines of systemic therapy including a PI, an IMiD and anti-CD 38 monoclonal antibody.

The safety results demonstrate an acceptable safety profile when implemented with Risk Evaluation and Mitigation Strategies (REMS) with Elements to Assure Safe Use (ETASU) for the management of CRS and NT, which represent life-threatening adverse reactions. However, given the life-threatening nature of the disease in the indicated population, these adverse reactions, if managed appropriately, represent toxicities that are acceptable from a benefit-risk perspective. Thus, the overall benefit-risk profile favors approval of ABECMA in patients with multiple myeloma who have received at least four prior lines of therapies including a PI, an IMiD and anti-CD 38 monoclonal antibody.

c. Recommendation for Postmarketing Activities

1. Registry study: Marketing approval should include a safety post-marketing requirement (PMR) under Section 505(o) of the FDCA that the Applicant conduct a multicenter, prospective, observational safety study to assess the long-term safety of ABECMA and the risk of secondary malignancies. The study will use a registry design and will include 1500 adult patients with multiple myeloma who have received at least four prior lines of therapies, including an immunomodulatory agent, a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody; patients will be followed for 15 years after their ABECMA infusion. This study is observational and focuses on short-term toxicity, documenting adverse events, and long-term follow-up for evaluation of secondary malignancies, which will include blood and/or tissue work-up for these events. The primary endpoint includes the incidence and severity of secondary malignancies, CRS, neurologic toxicity (including the incidence and severity in older adults 65 years and older), prolonged cytopenia (including the use of rescue stem cell transplantation, the outcome of hematopoietic

reconstitution and survival post-transplant) and HLH/MAS. Applicant will submit annual report for prolonged cytopenia requiring rescue stem cell transplantation and secondary malignancy in the post-marketing setting. Evaluation for secondary malignancy will include the collection and analysis of blood and/or biopsy specimens of certain malignancies for evaluation of insertional mutagenesis.

The timetable for the PMR study is:

Final protocol submission: May 31, 2021

Study completion: June 30, 2041

Final report submission: June 30, 2042

The applicant agreed to the following Postmarketing Commitments (PMC):

1. Celgene Corporation, commits to conduct a comparability study between the (b) (4) and the (b) (4) method as per (b) (4) to provide assurance that the alternate method is equal to or greater than the assurances provided by the (b) (4) method for ide-cel and will provide the final study report.

Final Study Report Submission: August 31, 2021

2. Celgene Corporation commits to submit an integrated final report containing data from clinical trials MM-002 and MM-003 to further characterize the safety and efficacy of idecabtagene vicleucel among African-Americans/ Blacks with multiple myeloma. The primary objective of this analysis is to evaluate the efficacy of idecabtagene vicleucel in the subpopulation of African-Americans/Blacks with multiple myeloma compared to the subpopulation of Whites, and the secondary objective is safety.

Ensure that the representation of the African American subpopulation in the studies is reflective of the Black population in the geographical location/country. Therefore, approximately 15% of the population that is enrolled from the US should comprise of African Americans. Prespecify an analysis plan for safety and efficacy with a justification/rationale of prespecified assumptions for efficacy outcomes.

Final Analysis Plan submission: February 28, 2023

Final Report Submission: November 30, 2023